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Associations between short-term exposure to particulate matter and ultrafine particles and myocardial infarction in Augsburg, Germany

Kathrin Wolf^{a,*}, Alexandra Schneider^a, Susanne Breitner^a, Christa Meisinger^{a,b}, Margit Heier^{a,b}, Josef Cyrus^{a,c}, Bernhard Kuch^{d,e}, Wolfgang von Scheidt^d, Annette Peters^{a,f}, for the KORA Study Group¹

^a Helmholtz Zentrum München, German Research Center for Environmental Health, Institute of Epidemiology II, Neuherberg, Germany

^b Central Hospital of Augsburg, MONICA/KORA Myocardial Infarction Registry, Augsburg, Germany

^c Environmental Science Center, University of Augsburg, Augsburg, Germany

^d Department of Internal Medicine I, Central Hospital of Augsburg, Augsburg, Germany

^e Department of Internal Medicine/Cardiology, Hospital of Nördlingen, Nördlingen, Germany

^f German Research Center for Cardiovascular Disease (DZHK), Partner Site Munich, Germany

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ABSTRACT

Background: Short-term exposure to increased particulate matter (PM) concentration has been reported to trigger myocardial infarction (MI). However, the association with ultrafine particles remains unclear. **Objectives:** We aimed to assess the effects of short-term air pollution and especially ultrafine particles on registry-based MI events and coronary deaths in the area of Augsburg, Germany.

Methods: Between 1995 and 2009, the MONICA/KORA myocardial infarction registry recorded 15,417 cases of MI and coronary deaths. Concentrations of PM < 10 µm (PM₁₀), PM < 2.5 µm (PM_{2.5}), particle number concentration (PNC) as indicator for ultrafine particles, and meteorological parameters were measured in the study region. Quasi-Poisson regression adjusting for time trend, temperature, season, and weekday was used to estimate immediate, delayed and cumulative effects of air pollutants on the occurrence of MI. The daily numbers of total MI, nonfatal and fatal events as well as incident and recurrent events were analysed.

Results: We observed a 1.3% risk increase (95%-confidence interval: [−0.9%; 3.6%]) for all events and a 4.4% [−0.4%; 9.4%] risk increase for recurrent events per 24.3 µg/m³ increase in same day PM₁₀ concentrations. Nonfatal events indicated a risk increase of 3.1% [−0.1%; 6.5%] with previous day PM₁₀. No association was seen for PM_{2.5} which was only available from 1999 on. PNC showed a risk increase of 6.0% [0.6%; 11.7%] for recurrent events per 5529 particles/cm³ increase in 5-day average PNC.

Conclusions: Our results suggested an association between short-term PM₁₀ concentration and numbers of MI, especially for nonfatal and recurrent events. For ultrafine particles, risk increases were notably high for recurrent events. Thus, persons who already suffered a MI seemed to be more susceptible to air pollution.

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Introduction

Ischemic heart disease which includes myocardial infarction (MI), angina pectoris, and heart failure is the leading cause of death globally. It is estimated that 55 million people died due to these causes worldwide in 2011 (<http://www.who.int/mediacentre/factsheets/fs310/en/>). Chronic risk factors for MI mainly affect the progression of atherosclerosis. Nonmodifiable risk factors are family history, male sex and advanced age. Modifiable factors are mostly lifestyle-dependent and include smoking, hyperlipidemia, psychosocial factors, abdominal obesity, history of diabetes or hypertension, physical inactivity, and chronically increased markers of inflammation (Yusuf et al., 2004; Culic, 2007).

Abbreviations: BMI, body mass index; CPC, condensation particle counter; GCV, generalized cross-validation criteria; IQR, interquartile range; KORA, Cooperative Health Research in the region of Augsburg; MI, myocardial infarction; MONICA, monitoring of trends and determinants in cardiovascular disease; RR, relative risk; PM, particulate matter; PNC, particle number concentration; STEMI, ST segment elevation MI.

* Corresponding author. Tel.: +49 89 3187 4563; fax: +49 89 3187 3380.

E-mail address: kathrin.wolf@helmholtz-muenchen.de (K. Wolf).

¹ The KORA-Study Group consists of A. Peters (speaker), J. Heinrich, R. Holle, R. Leidl, C. Meisinger, K. Strauch, and their co-workers, who are responsible for the design and conduct of the KORA studies.

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Transient risk factors have the potential to trigger plaque rupture and thrombosis followed by the onset of MI or other acute coronary syndromes. These include heavy physical exertion, emotional stress, sexual intercourse, coffee or alcohol consumption, but also air pollution. A comparative risk assessment of these transient factors showed that although the individual risk increase in association with air pollution is very small, the magnitude of the risk on a population level is considerable since many people are exposed to this trigger (Nawrot et al., 2011). Additionally, the exposure to elevated air pollution concentrations is often inevitable for the population due to its ubiquitous nature.

Results from previous studies on particulate matter with an aerodynamic diameter $<10\text{ }\mu\text{m}$ (PM_{10}) and $<2.5\text{ }\mu\text{m}$ ($\text{PM}_{2.5}$) and MI were somewhat controversial reporting positive (Peters et al., 2001; Zanobetti and Schwartz, 2005; Pope et al., 2006) but also no associations (Sullivan et al., 2005; Lanki et al., 2006; Berglind et al., 2010; Bhaskaran et al., 2011). One reason might be the small effect size which requires large study populations to reduce the standard errors. A recent review and meta-analysis combining 19 studies on PM_{10} and 13 studies on $\text{PM}_{2.5}$ found significant positive associations for both pollutants (Mustafic et al., 2012). Due to their small size ultrafine particles (aerodynamic diameter $<0.1\text{ }\mu\text{m}$) are deposited in the alveoli and may even cross the lung-blood barrier and translocate into the circulation. They derive from fresh industrial and vehicle combustion and have only a short lifetime because they agglomerate and coalesce into larger particles. Since ultrafine particles have only little effect on PM mass but contribute most to the number of particles within PM, particle number concentration (PNC) is often used as a proxy. As their surface area-to-mass ratio is much larger compared to PM_{10} and $\text{PM}_{2.5}$, their potential of carrying diverse toxic materials on the surface is high. However, studies on ultrafine particles as trigger for MI are sparse (Forastiere et al., 2005; Peters et al., 2005; von Klot et al., 2005; Lanki et al., 2006; Gardner et al., 2014) and often consider data collected over limited periods. Therefore, the objective of this analysis was to assess the effects of short-term exposure to PM_{10} , $\text{PM}_{2.5}$ and PNC on registry-based MI cases and coronary deaths in the area of Augsburg, Germany, for the period 1995–2009.

Materials and methods

MONICA/KORA myocardial infarction registry

The population-based Augsburg MI registry was founded in 1984 as part of the WHO MONICA project and since 1996 has been continued by the Cooperative Health Research in the region of Augsburg (KORA). The registry records all cases of MI and coronary deaths among persons aged 25 to 74 with a principal residence in the city of Augsburg, Southern Germany, and the two adjacent rural districts. Altogether, the study population consists of about 400,000 inhabitants aged 25 to 74 years. According to the MONICA protocol (Tunstall-Pedoe et al., 1994), hospital admissions are continuously monitored and MI patients, who survive at least 24 h, are asked for an interview concerning the event, medication and family history. If the patient deceases between the second and 28th day after admission the MI is considered as fatal, otherwise as nonfatal. Coronary deaths are fatal cases outside the hospital or within the 24 h after admission. They are identified by checking all death certificates within the regional health departments together with information of the last treating physician and/or coroner. While the MI diagnosis was clinically redefined in 2000, we used the MI diagnosis established in 1985 over the whole period for consistency (Löwel et al., 2005). The diagnostic criteria included: chest pain lasting more than 20 min that is not relieved by the administration of nitrates; Q waves on electrocardiographic examination that

suggest an evolving myocardial infarction; subsequent increases in the level of creatine kinase, aspartate aminotransferase, or lactate dehydrogenase to more than twice the upper limit of normal, or both. The study was approved by the ethics committee of the Bavarian Chamber of Physicians and performed in accordance with the Declaration of Helsinki.

Air pollution and meteorological data

Particulate air pollutant concentrations were measured at several monitoring stations in the city of Augsburg (Online Supplement Fig. 1). From 1995 to 1999, total suspended particles were measured with a β -absorption device (ESM-Andersen FH 62 I-N) at two fixed urban background sites within the city of Augsburg and scaled down by a factor of 0.83 to derive PM_{10} (von Klot et al., 2005). Afterwards, PM_{10} was directly assessed with the same devices and from 2001 on, additionally with a third monitor. Monitors were averaged with a modified APHEA procedure (Katsouyanni et al., 1996; von Klot et al., 2005). Both $\text{PM}_{2.5}$ and PNC were measured at a single urban background site located 1 km north of the city centre until 2003. The site was relocated to 1 km south of the city centre in the beginning of 2004. $\text{PM}_{2.5}$ was measured by a Tapered Element Oscillating Microbalance (TEOM model 1400A, Rupprecht and Patashnick, German distributor: MLU, Essen, Germany). PNC was obtained from 1999 to 2003 by a condensation particle counter (CPC 3022A, TSI, Aachen, Germany) and from 2004 to 2009 by a triple-instrument approach combining a Twin Differential Mobility Particle Sizer (TDMPS), and an Aerodynamic Particle Sizer (APS, model 3321, TSI Inc., USA) to measure particles between 10 and 2000 nm which is comparable to the size range of the CPC. For previous years, concentrations were predicted within a regularized linear prediction model based on the measurements for the year 2001 (Paatero et al., 2005). Measured values are indicated with PNC_m and the combined time series of measured and fitted values with PNC_{m+f} . Air temperature, relative humidity, and barometric pressure were measured at an urban background measurement station located 7 km (until 2000) and 5 km south of the city centre (from 2001 on). Until 2004, PM_{10} was only available on a 3-h basis. All other data were available on an hourly basis, and 24-h mean values were calculated if at least 75% of the hourly values were available.

Statistical analyses

Model building

Based on the literature (Forastiere et al., 2005; Zanobetti and Schwartz, 2005), we assumed a log-linear association between air pollutants and daily cases of MI and coronary deaths. We used generalized additive Quasi-Poisson models to accommodate a Poisson distribution with overdispersion. For each pollutant, a separate model was calculated for the exposure of the same day, the day before MI occurrence and up to four days before the event, and the average exposure over five days (mean concentration of same and previous four days). As potential confounders, we considered a global time trend to model long-term changes, temperature of the same and the average of the three previous days to cover the effects of hot and cold days, same day relative humidity and barometric pressure, and seasonal and weekday variations. To model nonlinear confounder effects, we used penalized regression splines to optimize the degree of smoothness. The optimal degree was then kept fix to allow a better comparability when entering the air pollutants. Model selection was based on the reduction of the generalized cross-validation criteria (GCV) and the absolute value of the sum of the partial autocorrelation function (Touloumi et al., 2004). Statistical significance was mandatory for season and weekdays which were included as indicator variables. The final model included a

Table 1
Study population in Augsburg, Germany, 1995–2009.

	Missings N (%)	Total events	Nonfatal events	Fatal events	Incident events	Recurrent events	Insufficient data ^a
No. of cases	–	15,417	8298	7119	10,699	3303	1415
Mean age (SD) [years]	–	62.7 (9.2)	60.8 (9.5)	64.9 (8.3) ^c	61.9 (9.5)	64.8 (7.8)	63.6 (9.2) ^d
Men [%]	–	73.8	77.8	71.4 ^e	72.5	78.9	71.2 ^e
Residence in the city of Augsburg [%]	–	49.9	48.6	51.5 ^e	47.8	52.7	59.6 ^e
History of							
Hypertension [%] ^b	1297 (8.4)	77.8	74.1	68.5 ^e	69.1	80.5	74.9 ^e
Diabetes mellitus [%] ^b	1316 (8.5)	34.9	31.2	40.1 ^e	31.1	44.9	53.7 ^e

^a For classifying incident or recurrent event.

^b Percentages are calculated based on observations with available information.

^c Wilcoxon rank sum test <0.001 comparing the age distribution between nonfatal and fatal events (nonparametric analogon to the *t*-test which tests the equality of two samples).

^d Kruskal–Wallis rank sum test <0.001 comparing the age distribution between incident, recurrent and events with insufficient data (nonparametric analogon to ANOVA which tests the equality of three or more samples).

^e Pearson's chi-squared test <0.001 comparing proportions in two or more samples.

regression spline with three knots for time trend, linear terms for current day temperature and the average temperature of the three previous days, season as a categorical variable (March–May, June–August, September–November and December–February) and an indicator variable for Mondays.

Besides the daily numbers of total MI, we inspected nonfatal and fatal events as well as incident and recurrent events. To check whether the effect estimates differed by personal characteristics, we assessed effect modification by age groups (25–54, 55–64 and 65–74 years of age), sex, place of residence (city vs counties), history of diabetes and hypertension using stratified analyses. We additionally stratified nonfatal MIs by smoking status (current, former, never), education (≤ 9 years vs > 9 years) as an indicator for socio-economic position, obesity ($\text{BMI} > 30 \text{ kg/m}^2$ vs $\text{BMI} \leq 30 \text{ kg/m}^2$) and medication intake before the event (anticoagulants, antihypertensives, lipid-lowering agents, nitrates, cardiac glycosides, antidiabetics) as this information was not available for most of the fatal events. Since higher risk increases have been described for ST segment elevation MI (STEMI) we further stratified by infarction type. All statistical analyses were performed with R software, version 3.0.0, package “mgcv”.

Sensitivity analysis

To explore the robustness of the results we modelled the time trend as a penalized thin plate regression spline and decreased the smoothing parameter to decrease the smoothness of the time trend function (S1). Furthermore, as time trend, season and temperature partly competed for the same effects, the model was reduced by leaving out the seasonal categories (S2). We also adjusted for influenza epidemics (S3) (Stölzel et al., 2007). To check the adjustment for weather variables additional to influenza epidemics, we reran the confounder selection and included hierarchically temperature, relative humidity and barometric pressure as penalized splines based on a reduction of GCV (S4). For each variable, exposure of same day, up to four previous days and the average of these five days were compared and the term was chosen which minimized GCV the most. Model S4 included time trend (regression spline with three knots), linear terms for current day temperature and 5-day average relative humidity, nine terms for influenza (linear or smooth functions), season, and an indicator for Mondays. As $\text{PM}_{2.5}$ was only measured from 1999 on, we recalculated the effects of PM_{10} and PNC for this shorter period to be comparable.

Results

Study population

A total of 15,417 coronary events were recorded between 1995 and 2009. Of these, 8298 were nonfatal MIs, and 7119 were fatal

Table 2

Personal characteristics, infarction type and medication intake for persons suffering from a nonfatal MI ($N = 8298$) in Augsburg, Germany, 1995–2009.

	Missings N (%)	Yes N (%) ^a	No N (%) ^a
Personal characteristics			
Education ≤ 9 years	1737 (20.9)	4813 (73.4)	1748 (26.6)
Current smoker	694 (8.4)	2845 (37.4)	–
Former smoker	694 (8.4)	2481 (32.6)	–
Never smoker	694 (8.4)	2278 (30.0)	–
$\text{BMI} \geq 30 \text{ kg/m}^2$	422 (5.1)	1912 (24.3)	5964 (75.7)
Infarction type			
STEMI	796 (9.6)	3214 (42.8)	4288 (57.2)
Medication intake			
Anticoagulants ^b	668 (8.1)	2613 (34.2)	5017 (65.8)
Antihypertensives ^c	653 (7.9)	4114 (53.8)	3531 (46.2)
Lipid lowering ^d	673 (8.1)	1569 (20.6)	6056 (79.4)
Nitrates	672 (8.1)	893 (11.7)	6733 (88.3)
Cardiac glycosides	675 (8.1)	119 (1.6)	7504 (98.4)
Antidiabetics ^e	662 (8.0)	1500 (19.6)	6136 (80.4)

BMI: body mass index; STEMI: ST segment elevation MI.

^a Percentages are calculated based on observations with available information.

^b Anticoagulants and antiplatelet drugs.

^c ACE inhibitors, angiotensin I receptor blocker, beta-blocker, calcium channel blocker, diuretics, and other antihypertensive drugs.

^d Statins and other lipid-lowering agents.

^e Insulin and other antidiabetic drugs.

MIs or coronary deaths. The proportion of incident and recurrent MIs constituted 69.4% and 21.4%, respectively. The remaining 9.2% could not be categorized in either of the subgroups because of missing information and originated mostly from coronary deaths. 62.7% of recurrent events but only 47.8% of incident MIs were fatal. Personal characteristics for all cases and MI subgroups are summarized in Table 1. Mean age was higher, and the percentage of men was lower within fatal cases than within nonfatal cases. Persons suffering from a recurrent MI were on average older and rather male than persons suffering from an incident MI. Further personal characteristics which were not available for most fatal events, infarction type and medication intake are presented for nonfatal MIs only (Table 2). While antihypertensives were taken by more than half of the persons, only 1.6% took cardiac glycosides.

Daily event numbers were quite stable over the study period with approximately three cases per day (Online Supplement Fig. 1). A smoothing function visualizes the seasonality with higher rates in winter and lower rates in summer. The yearly number of cases ranged from 956 to 1089 with a mean of 1028.

Air pollutants

Summary statistics and Spearman correlation coefficients for air pollutants and meteorology are presented in Table 3. PM_{10} and $\text{PM}_{2.5}$ showed only moderate correlation with PNC_{mf} and

Table 3

Summary statistics and Spearman correlation coefficients for particulate air pollutants and meteorology (data on 5479 consecutive days).

Variable	N in %	Mean (SD)	Min	Q1	Median	Q3	Max	IQR ^a	Spearman correlation coefficient					
									PM ₁₀	PM _{2.5}	PNC _m	PNC _{m+ff}	Temp	RH
PM ₁₀ ^b (μg/m ³)	99.4	35.8 (19.9)	3.8	21.4	32.2	45.7	203.0	24.3						
PM _{2.5} ^b (μg/m ³)	71.0	16.8 (10.5)	1.4	10.3	14.7	20.6	126.4	10.3	0.87					
PNC _m ^c (1000/cm ³)	61.1	11.2 (5.6)	2.2	7.2	10.0	13.7	44.8	6.5	0.47	0.41				
PNC _{m+ff} ^c (1000/cm ³)	90.5	12.2 (6.1)	2.2	8.0	10.9	14.8	70.3	6.8	0.53	0.41	1.00			
Mean air temperature (°C)	99.4	9.6 (8.0)	−14.9	3.3	9.9	16.0	27.9	12.7	−0.04	−0.19	−0.25	−0.35		
Relative humidity (%)	99.5	76.0 (13.1)	32.4	66.4	77.4	86.8	100.0	20.5	−0.12	−0.01	−0.07	−0.02	−0.54	
Barometric pressure (hPa)	99.3	1018.0 (8.1)	984.3	1013.0	1019.0	1024.0	1045.0	10.2	0.22	0.30	0.18	0.11	−0.02	−0.11

^a IQR: interquartile range (Q3–Q1).^b PM₁₀: particles with diameter <10 μm; PM_{2.5}: particles with diameter <2.5 μm.^c PNC_m: particle number concentration, measured values; PNC_{m+ff}: particle number concentration, measured and fitted values.

almost no correlation with meteorological parameters. Time series of PM₁₀, PM_{2.5} and PNC_{m+ff} can be found in the Online Supplement Fig. 1. All variables indicated seasonality with higher concentrations in winter.

Association of air pollutants and MI

Results of the association between daily numbers of MI and same day, previous day and 5-day average concentrations of particulate air pollutants are presented in Table 4. Percent increase in relative risk estimates and corresponding 95% confidence intervals (CI) are expressed for an interquartile range (IQR) increase in air pollutants. Most point estimates were positive, but not statistically significant. An IQR increase of same day PM₁₀ indicated increased risks for the total numbers of daily MIs as well as recurrent events. Nonfatal events showed a suggestive risk increase in association with elevated concentrations of previous day PM₁₀. No association could be observed for PM_{2.5} and daily numbers of MI except for fatal events where estimates were slightly decreased. Regarding PNC_{m+ff}, our results indicated an association between same day exposure and total MI as well as recurrent MI. The latter showed significantly increased event numbers in association with increased 5-day average PNC_{m+ff} concentrations.

Stratified risk estimates per IQR increase in same day PM₁₀ (a) and PNC (b) are presented in Fig. 1. Risks were increased for men, residents of the counties and individuals without diabetes in association with higher PM₁₀ or PNC concentrations. People without

diagnosed hypertension showed increased risk estimates for PM₁₀ while persons older than 55 years seemed to be susceptible to elevated PNC concentrations. Except for antidiabetic medication, risk estimates of PNC were generally higher for persons taking regular medication, especially for cardiac glycosides. For the latter, we observed a likewise effect modification of PM₁₀ estimates, while other medication had no influence. An effect modification by cardiac glycosides was also indicated for PM_{2.5} (Online Supplement Fig. 2). Other medication groups showed similar or slightly higher estimates for persons taking no medication.

Sensitivity analysis for selected groups, pollutants and exposure windows which showed significant or suggestive effects resulted in similar effect estimates (Fig. 2). When reducing the study period to the last eleven years, both PM₁₀ and PNC effect estimates were decreased (Online Supplement Table 1).

Discussion

This registry-based time series study investigated short-term effects of air pollutants on daily numbers of MI and coronary deaths in residents of Augsburg, Germany, aged 25 to 74 years over a period of 15 years. PNC, a proxy for ultrafine particles, was imputed for the first four years and our results indicated a delayed effect on recurrent events. Moreover, elevated PM₁₀ and PNC concentrations pointed to an immediate risk increase for all events and recurrent MIs. For PM₁₀, the risk for nonfatal MIs was increased in association with previous day exposure. PM_{2.5} measurements were

Table 4

Percent change in relative risk estimates for daily cases of MI and coronary deaths per interquartile range increase in ambient particulate matter adjusted for time trend, current day and previous 3-day average temperature, season, and Monday (1995–2009).

Group	Same day		Previous day		5-Day average ^a	
	%	(95% CI) ^b	%	(95% CI)	%	(95% CI)
PM ₁₀						
Total events	1.3	(−0.9; 3.6)	0.7	(−1.6; 3.0)	0.2	(−2.3; 2.7)
Nonfatal events	1.5	(−1.7; 4.8)	3.1	(−0.1; 6.5)	2.1	(−1.4; 5.7)
Fatal events	1.3	(−1.9; 4.7)	−1.8	(−5.0; 1.6)	−1.6	(−5.2; 2.0)
Incident events	1.1	(−1.7; 3.9)	1.0	(−1.8; 3.9)	0.0	(−3.1; 3.1)
Recurrent events	4.4	(−0.4; 9.4)	1.6	(−3.1; 6.6)	3.8	(−1.5; 9.3)
PM _{2.5} (only 1999–2009)						
Total events	−0.3	(−2.4; 1.7)	−0.6	(−2.6; 1.5)	−0.6	(−2.5; 1.4)
Nonfatal events	1.0	(−1.6; 3.7)	0.6	(−2.1; 3.3)	1.1	(−1.4; 3.7)
Fatal events	−2.5	(−5.6; 0.8)	−2.3	(−5.5; 0.9)	−3.2	(−6.3; 0.0)
Incident events	−0.7	(−3.2; 1.8)	−1.1	(−3.6; 1.4)	−1.3	(−3.7; 1.2)
Recurrent events	2.5	(−1.7; 6.9)	1.7	(−2.5; 6.1)	2.9	(−1.1; 7.1)
PNC _{m+ff}						
Total events	1.5	(−0.8; 3.7)	0.4	(−1.9; 2.8)	0.8	(−1.7; 3.4)
Nonfatal events	1.6	(−1.5; 4.8)	0.3	(−2.9; 3.6)	2.0	(−1.5; 5.8)
Fatal events	1.3	(−2.0; 4.7)	0.5	(−2.8; 4.0)	−0.5	(−4.2; 3.3)
Incident events	0.7	(−2.1; 3.5)	−0.1	(−2.9; 2.8)	−0.2	(−3.3; 2.9)
Recurrent events	4.1	(−0.6; 9.0)	3.8	(−1.1; 8.9)	6.0	(0.6; 11.7)

^a 5-Day average: mean concentration of same and 4 previous days.^b %: Percent change in relative risk, CI: confidence interval.

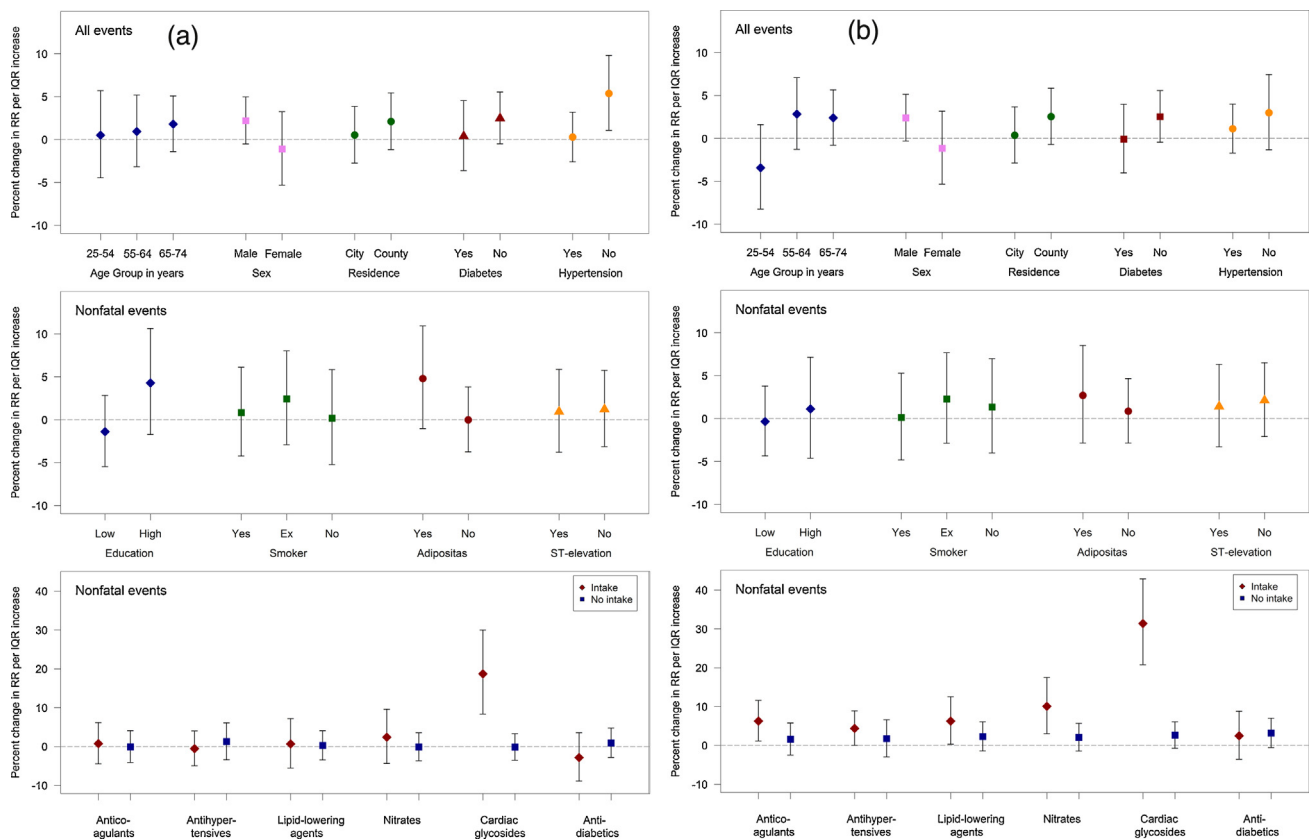


Fig. 1. Main results – percent change in relative risk (RR) for total numbers (top panel) and nonfatal events (middle and bottom panel) of daily events per interquartile range (IQR) increase in same day PM₁₀ (a) and same day PNC_{m+f} (b) adjusted for time trend, current day and previous 3-day average temperature, season, and Mondays stratified by subgroups.

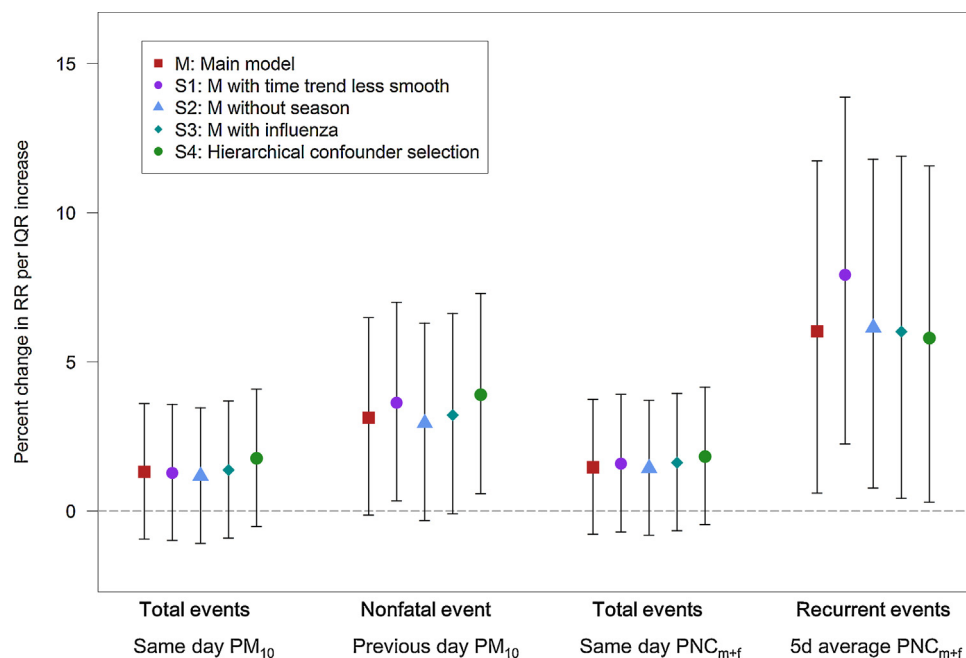


Fig. 2. Sensitivity analysis – percent change in relative risk (RR) for total, nonfatal and recurrent events per interquartile range (IQR) increase in same day PM₁₀, previous day PM₁₀, same day PNC_{m+f}, and 5-day average PNC_{m+f}, respectively. The main model (squares) was adjusted for time trend (regression spline with three knots), current day and previous 3-day average temperature (both linear), season (categorical), and an indicator for Mondays. Sensitivity models were altered according to the legend.

only available for 11 years. No significant association with either of the subgroups could be seen except for fatal events suggesting a decreased risk.

Comparison with previous studies

Several studies have investigated the association between PM₁₀ and MI or coronary deaths, though outcomes and sources of data were quite different. A recent meta-analysis combining 19 studies reported a risk increase of 0.6% (95% CI: 0.2%; 0.9%) for a 10 µg/m³ increase in same day ambient PM₁₀ concentration (Mustafic et al., 2012). For the same increment, our study yielded with 0.5% (−0.4%; 1.5%) a similar risk increase for all events. Most studies used hospital admissions that are not directly comparable to our registry data since fatal events are underrepresented. A registry-based study from England and Wales including almost 80,000 events (Bhaskaran et al., 2011) observed a harvesting effect with an immediate risk increase of 1.2% (0.3; 2.1) per 10 µg/m³ increase up to 6 h after PM₁₀ exposure and reduced numbers thereafter. Several studies using more specific study populations and daily data have indicated a similar pattern with increased rates on the same or subsequent day after increased exposure, though without reduction in event numbers thereafter (Braga et al., 2002; Forastiere et al., 2005; Zanobetti and Schwartz, 2005; Pope et al., 2006). Our results indicated a slightly decreased risk for fatal events in association with delayed PM₁₀ exposure. However, this kind of harvesting pattern was not significant and not seen in other subgroups. A meta-analysis on five European cities observed no association between PM₁₀ and hospitalization for first MI (Lanki et al., 2006), but hospital readmissions for cardiac events among MI survivors were significantly increased in the same cities (von Klot et al., 2005). Contrary results reported a longitudinal study on patients drawn from the cardiac catheterization registry in Utah, USA, which observed increased risks for incident but not recurrent events (Pope et al., 2006).

Regarding PM_{2.5}, Mustafic et al. (2012) combined 13 studies resulting in a pooled risk increase of 2.5% (1.5%; 3.6%) for a 10 µg/m³ increase in previous day concentration. We did not observe this relationship within our data potentially due to the limited time period leading to a loss of power. PM₁₀ and PNC estimates also decreased or confidence intervals increased when reducing the time series to the last 11 years for which PM_{2.5} was measured.

Only a few studies examined the influence of ultrafine particles on MI events. No association was seen between PNC and nonfatal events in an earlier study in the Augsburg region (Peters et al., 2005). A study from Rome (Forastiere et al., 2005) observed a 2.7% (0.7; 4.9%) increase of coronary deaths and the HEAPSS study reported risk increases of 0.5% (−0.4; 1.5%) for hospitalization for first MIs (Lanki et al., 2006) and of 3.9% (−0.2; 8.2%) for hospital readmissions for MI (von Klot et al., 2005) per 10,000 particles/cm³ increase of same day PNC. The effect sizes quite comply with our results with risk increases of 1.9% (−2.9; 7.0) for fatal events, 1.0% (−3.1; 5.1%) for incident events and 6.1% (−0.9; 13.5%) for recurrent events when using the same increment. However, other studies did not find associations between PNC and hospital admissions for coronary heart disease (Halonen et al., 2009), acute coronary syndrome (Belleudi et al., 2010) or cardiovascular diseases (Andersen et al., 2008).

Effect modification by personal characteristics or medication intake

The literature about the influence of personal characteristics on the association between air pollutants and MI or coronary deaths provides incoherent results and is only partly comparable due to different outcome specifications, age ranges and pre-existing

illnesses of the study populations. For all events of persons older than 54 years, we observed an increased risk in association with PNC, but not for PM₁₀ or PM_{2.5}. Other studies reported higher numbers of MI for persons older than 65 years in association with PNC (Forastiere et al., 2005) and PM_{2.5} (Pope et al., 2006), but not with PM₁₀ (Zanobetti and Schwartz, 2005; Berglind et al., 2010; Bhaskaran et al., 2011). Higher risks for males were also observed by previous studies (Zanobetti and Schwartz, 2005; Pope et al., 2006) while others could not identify any differences by sex (Forastiere et al., 2005; Berglind et al., 2010). Regarding pre-existing illnesses, pollutant effects have also been reported for individuals without diabetes (Forastiere et al., 2005) and, contrary to our results, for hypertensive patients (Forastiere et al., 2005; Pope et al., 2006). Other studies did not see an effect modification by diabetes (Zanobetti and Schwartz, 2005; Pope et al., 2006; Berglind et al., 2010) or hypertension status (Berglind et al., 2010). The higher effect estimates for residents of the counties seemed somewhat surprising at the first glance. Yet, the proportion of men and non-diabetics was significantly higher and people were older compared to the city dwellers. A recent study reporting associations with PM_{2.5} only for STEMI (Gardner et al., 2014) but not non-STEMI suggesting different underlying mechanisms how air pollution may trigger MI could not be confirmed in our analyses (nonfatal events only).

To our knowledge, no study has looked at detailed medication intake yet. We observed stronger effects for persons taking cardiac glycosides suggesting this subgroup to be more susceptible to air pollution. Cardiac glycosides increase myocardial contractility and were usually given to support cardiac function. Together with nitrates which cause vasodilation they were mostly prescribed for the treatment and prevention of angina pectoris and MI, thus reflecting a highly susceptible subgroup. However, treatments have changed over the last decades and the prescription of both drugs has significantly decreased. The intake of anticoagulants, antihypertensives, lipid-lowering agents and nitrates indicated increased risks for PNC only. Thus, the small size of ultrafine particles seems to play a role for less healthy persons.

Mechanisms

On the basis of observational and experimental studies, several putative pathways how air pollution may trigger MI have been suggested (Brook et al., 2010; Gold and Mittleman, 2013). Direct pollutant effects are hypothesized to trigger acute cardiovascular events occurring within a few hours after the exposure. These include alterations in autonomic tone by activation of pulmonary neural reflexes which might contribute to the instability of a vascular plaque or initiate cardiac arrhythmias. Further, ultrafine particles may directly interact with the cardiovascular system and affect vascular endothelium and atherosclerotic plaques as well as provoke local inflammation and oxidative stress. A study on mice (Tong et al., 2010) reported that hearts from mice exposed to ultrafine particles showed a significantly lower post-ischemic functional recovery and a greater infarct size, but no effects were seen for mice exposed to coarse particles (PM ranging from 2.5 to 10 µm in aerodynamic diameter) or PM_{2.5}. Indirect pollutant effects are supposed to evoke rather delayed and chronic cardiovascular responses. Pulmonary oxidative stress and inflammation may induce a systemic chain reaction by the release of circulating pro-oxidative and pro-inflammatory mediators from the lungs. These mediators include cytokines (e.g. interleukin-6), acute-phase reactants (e.g. fibrinogen and C-reactive protein), vasoactive hormones (e.g. endothelins), and activated leucocytes, which may trigger various adverse cardiovascular reactions. Thus, exposure to air pollutants may increase the baseline risk of MI by promoting atherosclerosis formation over the long-term, but

also may alter the risk acutely by provoking transient plaque instability.

Strengths and limitations

The main strength of this study is the validated, complete and detailed registration of all MI cases in the study region by the MON-ICA/KORA MI registry (Tunstall-Pedoe et al., 1994; Löwel et al., 2005). Further strengths are the non-linear confounder adjustment and the information on patient characteristics, infarction type and medication intake to conduct subgroup analyses.

One limitation is the different precision of time of onset. For non-fatal and fatal MIs, time of symptom onset was used and validated against the information from the medical records. For coronary deaths, time of hospital arrival or death were used instead. The age range of the registry of 25–74 years is a further limitation since especially women suffer from MIs more frequently at older ages. Regarding air pollutants, only fixed site measurements were used which poses a source for exposure misclassification as it assumes homogeneous exposure for the whole study area. Especially ultrafine particles are spatially heterogeneous and depend on distance from the roadway as they are mostly produced by local traffic. However, Forastiere et al. (2005) could show a high overall correlation for two parallel PNC measurements in Rome despite very different average values depending on distance to traffic of each monitor. Therefore, the authors consider a correlation between daily variation in outdoor concentrations and population average personal exposure as possible. Cyrus et al. (2008) investigated the temporal and spatial variation of PNC at four background sites in Augsburg, Germany and reported high correlations ($r > 0.80$). The authors concluded that the high temporal correlations of PNC across the study area implicate that in epidemiological time-series studies the use of one single ambient monitoring site is an adequate approach for characterizing exposure to ultrafine particles. A further limitation is the lack of PM_{2.5} measurements for the first four years of our study period as the results are only partly comparable to PM₁₀ and PNC estimates. Maybe the loss of power due to the reduced numbers of observations impeded the detection of effects. When reducing the PM₁₀ and PNC time series to the last 11 years, associations with MI events attenuated. Also, the retrospective PNC estimation for almost 1/3 of the days potentially biased the results. However, the correlation of fitted and measured PNC values was high ($r = 0.86$). Further, we cannot exclude that some associations might have occurred by chance due to multi-comparisons. The investigation of effect modifications might be partly only exploratory, particularly the portion of patients taking cardiac glycosides was very small.

Conclusions

Our results pointed to an association between short-term concentration of air pollutants and numbers of MI. Effect estimates for PM₁₀ were similar in size compared with findings from previous studies and indicated an association with nonfatal and recurrent events. No association could be seen for PM_{2.5} where data was only available for a shorter period. Effect estimates for PNC were notably higher for recurrent events than for incident MIs suggesting that myocardial infarction survivors may be more susceptible to ultrafine particles.

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Conflict of interest statement

The authors declare that they have no conflict of interests.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.ijheh.2015.05.002>

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