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The influence of air pollutants and temperature on the occurrence of myocardial infarctions and coronary deaths.

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Zusammenfassung

Die auslösenden Ursachen eines akuten Herzinfarkts sind oftmals nicht bekannt. Verschiedene Faktoren wie starke körperliche Anstrengung, emotionaler Stress, Ernährungsgewohnheiten, der Konsum von Kaffee und Alkohol, sexuelle Betätigung sowie Kokain- oder Marihuana-Missbrauch konnten mit der Auslösung eines Herzinfarkts in Verbindung gebracht werden. In letzter Zeit wurden als weitere akute Risikofaktoren für Herzinfarkte und koronare Todesfälle sowohl eine erhöhte Luftschadstoffbelastung als auch extreme Lufttemperaturen diskutiert. Eine Vielzahl von epidemiologischen Studien konnte einen Zusammenhang zwischen erhöhten Luftschadstoffkonzentrationen und kardiovaskulärer Morbidität und Mortalität feststellen. Weit weniger Studien untersuchten den Einfluss von extremen Temperaturen auf das Risiko von Herzinfarkten. Abhängig vom regionalen Klima wurden entweder Kälteeffekte oder Hitzeeffekte, aber auch beides, berichtet. Einige wenige Studien berücksichtigten Interaktionen zwischen Luftschadstoffen und Temperatur, allerdings war eine wechselseitige Beeinflussung nicht immer gegeben. In der vorliegenden Arbeit wird der Einfluss von Luftschadstoffen und Temperatur auf die tägliche Anzahl von Herzinfarkten über den Zeitraum von 1995 bis 2004 untersucht.

Im MONICA/KORA Herzinfarktregister wurden in diesen zehn Jahren 9801 Herzinfarktfälle bei 25-74 jährigen Einwohnern der Region Augsburg registriert. Im selben Zeitraum wurden im Studiengebiet an verschiedenen Messstationen die Massenkonzentration von Partikeln mit einem Durchmesser <10 µm (PM_{10}), Ozon (O_3), Kohlenmonoxid (CO), Stickstoffmonoxid (NO), Stickstoffdioxid (NO_2), Schwefeldioxid (SO_2) sowie meteorologische Maßzahlen gemessen. Zusätzlich wurden ab 1999 auch die Massenkonzentration von Partikeln mit einem Durchmesser <2.5 µm ($PM_{2.5}$) und die Partikelanzahlkonzentration (PNC) stellvertretend für ultrafeine Partikel ermittelt. Für PNC wurden die Werte vorangegangener Jahre anhand eines Vorhersagemodells imputiert. Zur Abschätzung sofortiger, verzögerter und kumulativer Schadstoff- und Temperatureffekte auf die tägliche Anzahl von Herzinfarkten wurden Poisson-Regressionsmodelle mit einer Adjustierung für einen globalen zeitlichen Trend, Saison und Kalendereffekte verwendet. Die Luftschadstoffmodelle wurden ferner für Temperatur adjustiert, die Temperaturmodelle für relative Luftfeuchte. Um für nichtlineare Einflüsse der Kovariablen zu kontrollieren, wurden penalisierte Regressionssplines verwendet.

Interaktionseffekte zwischen Luftschadstoffen und Temperatur gingen als multiplikative lineare Terme sowie zweidimensionale glatte Funktionen in die Modelle ein. Weitere Endpunkte neben der täglichen Gesamtzahl aller Herzinfarktfälle waren nichttödliche und tödliche Fälle sowie Erst- und Reinfarkte.

Ein Anstieg der PM_{10} Konzentration um 24.6 $\mu g/m^3$ war mit einem erhöhten Risiko (relatives Risiko (RR): 1.02, 95%-Konfidenzintervall (CI): 1.00 bis 1.05) für das Auftreten von Infarkten am selben Tag assoziiert. Nichttödliche Infarkte und Erstinfarkte reagierten um einen Tag verzögert. Tödliche Ereignisse wiesen inverse Effektschätzer in den folgenden Tagen auf, die möglicherweise auf eine vorgezogene Sterblichkeit (Harvesting) hindeuten. $PM_{2.5}$ zeigte keinen signifikanten Einfluss auf die verschiedenen Untergruppen. Ein möglicher Grund für dieses Ergebnis könnte fehlende Power sein, da nur für die letzten sechs Jahre der Studienperiode $PM_{2.5}$-Werte vorlagen. Bei einer Beschränkung von PM_{10} auf diesen verkürzten Zeitraum waren ebenfalls keine statistisch signifikanten Assoziationen mehr erkennbar. Für PNC konnte eine um drei Tage verzögerte Risikoerhöhung bei den Reinfarkten beobachtet werden (RR: 1.08 (95%-CI: 1.02 bis 1.14) pro 6,702 Partikel/cm^3). Diese war auch im verkürzten Zeitraum sichtbar. Ozon war negativ mit nichttödlichen Infarkten, jedoch positiv mit tödlichen Ereignissen assoziiert. Die anderen Gruppen zeigten keinen Effekt. Ebenso konnte auch kein eindeutiger Einfluss weiterer gasförmiger Schadstoffe beobachtet werden. Die Untersuchung von Effektmodifikationen, die auf PM_{10} beschränkt wurde, ergab ein erhöhtes Risiko für Männer, die älteste Personengruppe (65-74 Jährige) sowie für Nicht-Hypertoniker.

Ein Abfall der mittleren Temperatur der letzten fünf Tage um 10°C war mit einem RR von 1.10 (95%-CI: 1.04 bis 1.15) für die Gesamtzahl der Ereignisse assoziiert. Während tödliche Ereignisse noch am selben Tag reagierten, zeigten nichttödliche Infarkte einen verzögerten Effekt. Kein Zusammenhang bestand zwischen einer Temperaturänderung und der täglichen Anzahl an Reinfakten. Hinsichtlich Effektmodifikationen konnten keine Unterschiede zwischen Frauen und Männern festgestellt werden. Im Gegensatz zu Personen im Alter von 55 bis 74 Jahren reagierten Jüngere nicht auf einen Temperaturabfall. Insgesamt waren die Temperatureinflüsse stärker ausgeprägt in Jahren mit einer hohen mittleren Jahrestemperatur und ebenfalls sichtbar bei einer Beschränkung der Studienzeit auf die Sommerhalbjahre. Diese beiden Punkte sprechen gegen einen reinen Kälteeffekt. Die erhöhten Herzinfarktanzahlen scheinen eher die Folge von uner-

warteten Temperaturabfällen und/oder eines individuellen Kälteempfindens zu sein.

Es wurden keine wechselseitigen Einflüsse von Luftschadstoffen und Lufttemperatur auf das Auftreten von täglichen Herzinfarktfällen beobachtet.

Die Ergebnisse der vorliegenden Arbeit zu erhöhten Herzinfarktfällen in Zusammenhang mit erhöhten Luftschadstoffkonzentrationen bestätigen frühere Studien, leiden aber unter der geringen Power aufgrund der Größe der Studienregion. Es konnte ein Risikoanstieg der täglichen Ereignisse mit einem Abfall der Temperatur in Beziehung gebracht werden. Dies spricht für eine Berücksichtigung von Luftschadstoffen und Temperatur als unabhängige akute Risikofaktoren für einen Herzinfarkt.

Summary

Acute myocardial infarctions (MI) have often an unexplained etiology in subjects with underlying medically recognized or unrecognized vulnerability. Several factors have been identified to be associated with the onset of acute MI, thereof heavy exercise or physical exertion, emotional stress, diet, coffee and alcohol consumption, sexual activity, and cocaine or marijuana abuse. Air pollution and extreme ambient air temperature levels have been hypothesized to be acute risk factors for cardiovascular disease and in particular MI. Various epidemiological studies reported an association between elevated ambient air pollution and cardiovascular morbidity and mortality. Less studies investigated the effects of temperature extremes, and either cold or heat effects or both have been described depending on the regional climate. Only a few studies considered interacting effects of air pollutants and temperature, but not all of them could see interrelations. In this study, the influence of air pollutants and temperature and their interaction on the daily numbers of MI and coronary deaths was examined over a ten-year period from 1995 to 2004.

The MONICA/KORA MI registry recorded 9801 events occurring in inhabitants of the region of Augsburg, Germany, aged 25-74 years. Over the same period, mass concentration of particles with aerodynamic diameter <10 µm (PM_{10}), ozone (O_3), carbon monoxide (CO), nitrogen monoxide (NO), nitrogen dioxide (NO_2), sulphur dioxide (SO_2) and meteorologic parameters were measured on several monitoring stations in the study region. Mass concentration of particles <2.5 µm ($PM_{2.5}$) and particle number concentration (PNC) as a proxy for ultrafine particles were additionally assessed from 1999 on. PNC values were imputed for previous years based on a prediction model. Poisson regression analyses adjusting for time trend, season, and calendar effects were used to estimate immediate, delayed and cumulative air pollutant and temperature effects on the occurrence of MIs. The air pollution models were additionally adjusted for temperature and the temperature models for relative humidity. Penalized regression splines were used to control for nonlinear influences. Interaction effects of temperature and air pollutants were modeled as multiplicative linear terms and two–dimensional smooth functions. In addition to the daily numbers of total MI, we analyzed nonfatal and fatal events as well as incident and recurrent events.

Elevated PM_{10} concentrations increased the risk for MI immediately in the whole

sample with a relative risk (RR) of 1.02 (95%-confidence interval (CI): 1.00 to 1.05) per 24.6 $\mu g/m^3$ increase in PM_{10}. The subgroups of nonfatal and incident MIs reacted with a delay of one day. The estimates on fatal events were inverse and might suggest harvesting. No significant influence of $PM_{2.5}$ on either of the subgroups could be seen. A possible cause for this results could be the loss of power as only six years of $PM_{2.5}$ measurements have been available. When reducing PM_{10} to this shorter time period, no statistically significant association with MIs could be observed anymore. PNC showed a three days delayed risk increase in recurrent events (RR: 1.08 (95%-CI: 1.02 to 1.14) per 6,702 particles/cm^3) but not for the other groups. This was also visible in the reduced time period. Ozone was negatively associated with nonfatal MIs and positively with fatal events, but did not affect the other groups. Other gaseous pollutants showed no considerable effects. Effect modification was only inspected for PM_{10}. Males, patients aged 65 to 74, and especially non-hypertensive individuals indicated an increased risk.

A 10°C decrease in 5 day average temperature was associated with a RR of 1.10 (95%-CI: 1.04 to 1.15) for the total of MI cases. The effect of temperature on the occurrence of nonfatal events showed a delayed pattern, whereas the association with fatal MI was more immediate. No association could be observed for recurrent events. Regarding effect modification, men and women showed no differences. Individuals in the age range of 55 to 74 seemed to be affected but not younger patients. The effects of temperature decreases on the total daily events of MI were more pronounced in years with higher average temperature and also visible in summer which argues against an effect of extreme temperature levels. Thus, our results suggest not a pure „cold effect“, but an influence of unusual temperature decreases or individually felt cold.

No interaction effects between air pollutants and air temperature on the occurrence of MI could be observed.

The present thesis confirms previous studies in its findings of increased numbers of MI in association with elevated air pollution concentration, but suffers from low power due to the size of the study region. A temperature decrease was shown to be associated with a risk increase in daily MI events. This argues for considering air pollutants, but also unusual temperature decreases as independent acute risk factors for MI.

Contents

List of Abbreviations

AT	Apparent temperature
LfU	Bavarian Environmental Protection Agency
CO	Carbon monoxide
CI	Confidence interval
KORA	Cooperative Health Research in the Region of Augsburg
DT	Dewpoint temperature
GCV	Generalized cross validation criteria
HR	Hazard ratio
HEAPSS	Health Effects of Air Pollution among Susecptible Sub-populations study
$MaxO_3$	Ozone, maximum 8 hour moving average
MONICA	Monitoring of Trends and Determinants in Cardiovascular Disease, WHO project
MI	Myocardial infarction
NO_2	Nitrogen dioxide
NO	Nitrogen monoxide
O_3	Ozone
PNC	Particle number concentration
PNC_{m+f}	Particle number concentration, measured and fitted values
PNC_f	Particle number concentration, fitted values
PNC_m	Particle number concentration, measured values
PM	Particulate matter
PM_{10}	Particles with aerodynamic diameter < 10 µm
$PM_{2.5}$	Particles with aerodynamic diameter < 2.5 µm
RE	Recurrent event
RH	Relative humidity
RR	Relative risk
SO_2	Sulfur dioxide
T	24 hour mean temperature
$T_{m1\text{-}3}$	mean of lag1-3 day temperature
T_{min}	24 hour minimum temperature
T_{max}	24 hour maximum temperature
T_{range}	24 hour temperature range
TSP	Total suspended particles
WHO	World Health Organisation

1 Introduction

1.1 Background

Cardiovascular disease is the leading cause of death worldwide (WHO, 2007). Cardiovascular diseases are a group of disorders of the heart and blood vessels and include coronary heart disease, cerebrovascular disease, peripheral artery disease, rheumatic heart disease, congenital heart disease, deep vein thrombosis, and pulmonary embolism (WHO, 2007). Coronary heart disease again refers to any diseases of the blood vessels supplying the heart muscle. Among cardiovascular diseases, it accounts for the main proportion of deaths. The world health organisation (WHO) estimated that about 17.5 million people died from cardiovascular diseases in 2005 representing 30% of all global deaths. Of these deaths, about 7.6 million were due to coronary heart disease. Over 80% of cardiovascular disease deaths took place in low- and middle-income countries and occured almost equally in women and men. In Germany, more than 367,000 people died from cardiovascular diseases in 2005. Of these, 61,000 persons suffered from acute myocardial infarction (MI). Thus, 6.4% of all deceased women and 8.5% of all deceased men died due to MI (Statistisches Bundesamt Deutschland, 2006).

1.1.1 Myocardial infarction - pathophysiology and risk factors

MI is grouped along with unstable angina and sudden coronary death under the umbrella term acute coronary syndromes. The term covers any group of clinical symptoms compatible with acute myocardial ischemia and are most frequently a manifestation of coronary heart disease. MI is defined by pathology as myocardial cell death due to prolonged ischemia (Thygesen et al., 2007). Most MIs result from acute complication of atherosclerosis caused by thrombotic stenosis (Libby, 2001). About 70% of fatal MIs and sudden coronary deaths are due to the rupture of an atherosclerotic plaque with subsequent platelet aggregation and thrombus formation followed by occlusion of a coronary artery (Naghavi et al., 2003a).

Atherosclerosis Atherosclerosis is a disease affecting the arterial walls and progresses gradually over life. Chronic inflammation plays a key role and is supposed to participate in all stages of the disease. Early fatty streak development starts

with an altered function of the endothelium due to dyslipidemia, hypertension, hyperglycaemia or other risk factors of atherosclerosis. Endothelial cells express adhesion molecules, and smooth muscle cells secrete chemokines and chemoattractants which together attract monocytes. These monocytes penetrate into the intima and mature into macrophages. The uptake of modified lipoproteins leads to the transformation into foam cells. Simultaneously, macrophages multiply and release several growth factors and cytokines which sustain the inflammation. The additional migration of T lymphocytes secreting cytokines amplifies inflammatory signals and promotes the migration and proliferation of intimal smooth muscle cells. Inflammation promotes the progression to fibrous plaque lesions which are caused by accumulation of extracellular lipid and necrosis of macrophages and smooth muscle cells. The evolving lipid-rich necrotic cores are enclosed by fibrous tissue. Further inflammatory processes enlarge the lesions, and the fibrous cap becomes thin and susceptible to rupture (Insull, 2009; Libby and Theroux, 2005; Libby, 2006a;b; Paoletti et al., 2004).

Vulnerable patient Plaque vulnerability varies between indivuals but also over the lifetime of a person and thus, has to be seen in the context of the vulnerable patient. This concept was first proposed by Naghavi et al. (2003a;b) and asks for assessing the total vulnerability of a person as an interrelation among vulnerable plaque/artery, vulnerable blood and vulnerable myocardium.

Plaque vulnerability includes not only plaques which are prone to rupture, but also eroded and calcified nodule plaques. The first group is characterized by a lipid-rich atheromatous core, a thin fibrous cap, active inflammatory processes, and expansive remodeling. The plaque cap tears most frequently at the shoulder region and exposes the lipid core to flowing blood. Plaques prone to erosion are rich in smooth muscle cells and proteoglycans. Thrombus formation is caused by loss or dysfunction of lumenal endothelial cells. The last group covers heavily calcified plaques sometimes protruding into the lumen associated with endothelial dysfunction (Libby, 2001; Davies, 2003; Schaar et al., 2004; Culic, 2007).

Blood vulnerability comprises factors influencing the thrombogenicity of the blood. Naghavi et al. (2003b) summarized a multiplicity of serological and blood markers reflecting metabolic and immune disorders and hypercoagulability. Vulnerable myocardium denotes myocardial susceptibility to develop a fatal arrhythmia.

Risk factors Risk factors for MI are generally risk factors for atherosclerosis. A complex interaction between chronic and transient risk factors determines patient vulnerability (Figure 1.1).

Chronic risk factors mainly affect the progression of atherosclerosis and can be divided into nonmodifiable and modifiable risk factors. The first group includes family history, male sex and advanced age. Modifiable factors are mostly lifestyle-dependent. The INTERHEART study could show that smoking and hyperlipidemia are the two most important risk factors worldwide and were estimated to account for about two-thirds of the population attributable risks of MIs (Yusuf et al., 2004). Furthermore, it comprises psychosocial factors, abdominal obesity, history of diabetes and/or hypertension, that may also accelerate the progression of atherosclerosis. Within the INTERHEART study, their relative effect varied in different regions of the world. Furthermore, physical inactivity, hyperhomocysteinemia, and markers of chronic inflammation, such as increased levels of C-reactive protein or fibrinogen contribute to an increased risk of coronary heart disease.

Transient risk factors have the potential to trigger plaque thrombosis that are followed by the onset of MI or other acute coronary syndromes. Heavy physical activity has been shown to be associated with the onset of MI and sudden cardiac death (Mittleman et al., 1993; Mittleman and Siscovick, 1996; Mittleman, 2007; von Klot et al., 2008). Emotional stress like anger or anxiety can also provoke cardiac events and especially MI. This also includes emotionally stressful events like natural or unnatural disasters (Kloner, 2006), war, but also sporting events (Witte et al., 2000; Wilbert-Lampen et al., 2008). Sexual intercourse, coffee or alcohol consumption, and cocaine or marijuana abuse are further external triggers (Tofler, 1997; Servoss et al., 2002; Tofler and Muller, 2006; Culic, 2007).

The link between air pollution and acute myocardial infarction is epidemiologically well established, but the biological plausibility is not yet fully understood. However, exposures to ambient particles, particularly from traffic, are now considered as an independent acute as well as chronic risk factor. Mills et al. (2007) conducted a double-blind randomized crossover study in 20 men with prior MI and reported promoted myocardial ischemia and inhibition of endogenous fibrinolytic capacity after brief exposure to dilute diesel exhaust. A similar study in 20 healthy volunteers showed that inhalation of diesel exhaust increased ex

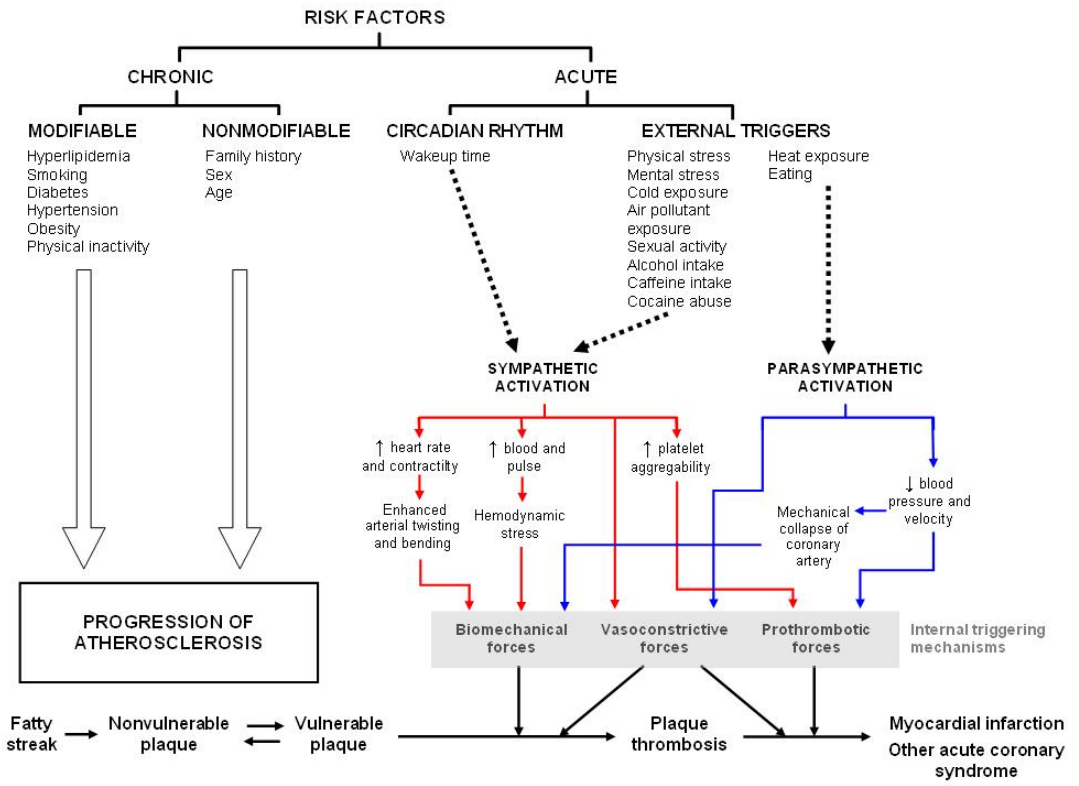

Figure 1.1: Chronic risk factors are fundamental for the progression of atherosclerosis. Acute risk factors interfere with the balance of the autonomic nervous system. Both sympathetic and parasympathetic activation induce biomechanical, vasoconstrictive and prothrombotic forces that may act as internal triggering mechanisms. These forces may trigger plaque thrombosis and cause the onset of myocardial infarction and other acute coronary syndromes. (Adapted from Culic, 2007.)

vivo thrombus formation and caused in vivo platelet activation (Lucking et al., 2008). An animal study showed that diesel exhaust particles enhance experimental thrombus formation within one hour of intratracheal instillation (Nemmar et al., 2002b). Transient exposure to traffic has been reported to increase the risk of MI (Peters et al., 2004). Furthermore, long term traffic exposure was related to increased rates in MI and coronary heart disease (Hoffmann et al., 2006; Rosenlund et al., 2006; Miller et al., 2007; Tonne et al., 2007; Rosenlund et al., 2008).

Recently, exposure to temperature extremes has been suggested as an indepen-

dent risk factor (Culic, 2007). The seasonality pattern of MI with winter peak and summer trough is generally known (Sarna et al., 1977; Spencer et al., 1998; Pell and Cobbe, 1999). Several studies investigated the effect of temperature on the onset of MI. While some described a U- or V-shaped association (Enquselassie et al., 1993; Liang et al., 2008), showing an increased risk on region-specific cold and hot days, others reported a linear relationship with increased risk only on colder days (Danet et al., 1999; Barnett et al., 2005).

Culic (2007) divided transient risk factors into external triggers and the circadian rhythm, thereof especially the morning hours. The author supposed that most external triggers lead to sympathetic activation, while extreme heat exposure leads to parasympathetic activation. Unhealthy diet may act over one of the two triggering pathways. Both pathways may activate biomechanical, vasoconstrictive, and prothrombotic forces potentially leading to plaque thrombosis and the onset of an acute coronary syndrome (Figure 1.1).

1.1.2 Characteristics of air pollution

The U.S. Environmental Protection Agency defined air pollutants as any substances in the air that can cause harm to humans or the environment. Their origin may be natural or man-made (U.S. EPA, 2009). Brook et al. (2004) described air pollution as a heterogeneous mixture of gases, liquids and particulate matter (PM). The latter again is a heterogeneous mixture consisting of solid and liquid particles suspended in the air and continually varies in size and chemically composition in space and time (Brook et al., 2004). Although the toxicity of PM most likely depends on its chemistry and surface area, the determination is difficult and remains to be better understood for a classification. Therefore, PM is categorized on the basis of its aerodynamic diameter which is also an indicator how far the particles infiltrate the pulmonary tree.

- Large particles with median aerodynamic diameter < 10 µm (PM_{10}) can be inhaled into the lungs. The coarse fraction ($PM_{10\text{-}2.5}$) is mostly derived from natural sources, thereof crustal material and grinding processes.
- Fine particles ($PM_{2.5}$, median aerodynamic diameter < 2.5 µm) can reach the smaller airways and alveoli and originate mainly from combustion sources.
- Ultrafine particles (median aerodynamic diameter < 0.1 µm) or nanopar-

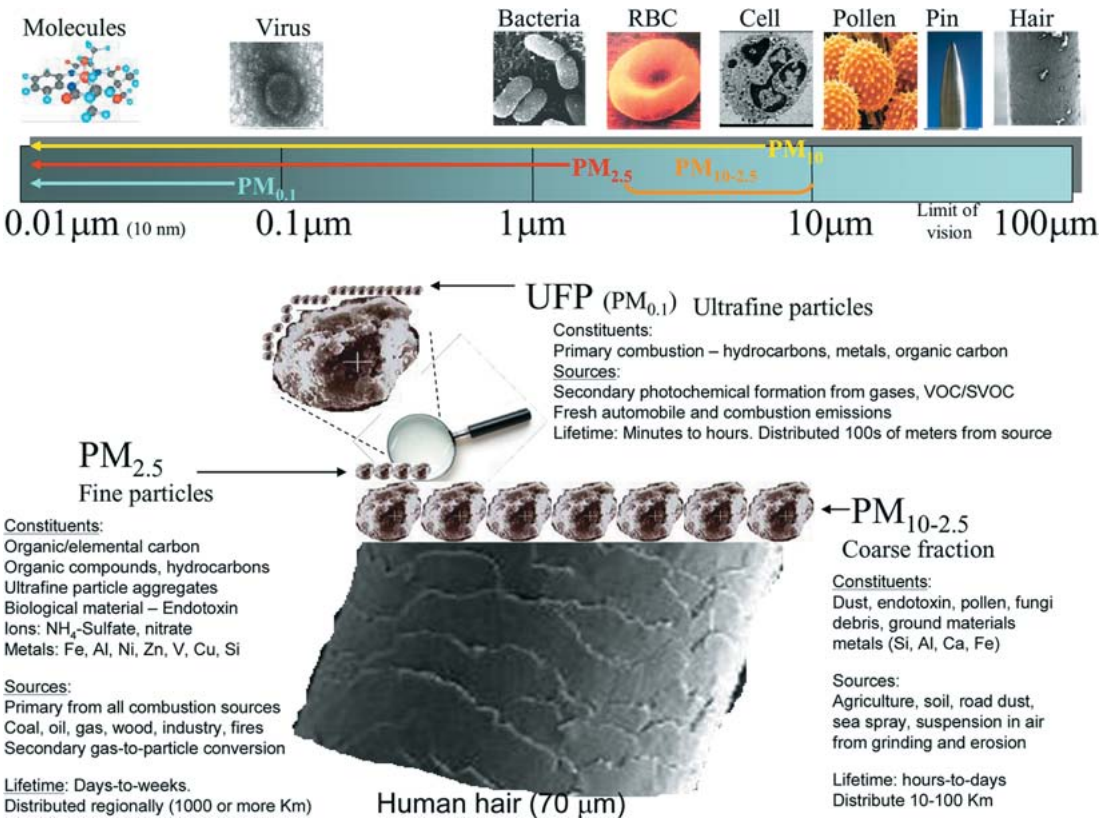

Figure 1.2: Size, sources and composition of PM air pollution (reprinted with permission from Brook, 2008). RBC, red blood cell; SVOC, semi-volatile organic carbons; UFP, ultra-fine particles; VOC, volatile organic carbons.

ticles can 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. Ultrafine particles have only little effect on PM mass, but contribute to the biggest part of the numbers of particles within PM. Therefore, particle number concentration (PNC) is often used as a proxy for ultrafine particles. As their surface area-to-mass ratio is much larger compared to the other size fractions, the potential of carrying diverse toxic materials on the surface is very high.

Figure 1.2 provides a general overview of PM characterstics.

Primary particles are directly emitted into the atmosphere, whereas secondary particles are formed through physiochemical transformation of gases. PM is con-

stantly interacting with gases and semi-volatile/volatile compounds forming secondary aerosol particles. Several gases have been discussed in association with adverse health effects, thereof nitric oxide (NO), nitrogen dioxide (NO_2), carbon monoxide (CO), sulfur dioxide (SO_2), and ozone (O_3). We refer to the literature for a more comprehensive description of sources and composition of particles and gases (Brook et al., 2004; Pope et al., 2004; Brook, 2008; Mills et al., 2009).

1.1.3 Biological mechanisms of particles and temperature

Particles and MI Although the complex combination and interaction of mechanisms are not yet fully understood, several putative pathways to explain the effects of particles on cardiovascular health have been suggested up to now (Brook 2004, Pope 2006, Mills 2008). However, a classification is quite difficult as the pathways are interdependent and might overlap. Brook (2008) summarized three main pathways (Figure 1.3):

1. Particles deposited in the pulmonary tree can alter systematic autonomic balance, either indirectly, by provoking oxidative stress and inflammation in the lung or directly, by stimulating pulmonary neural reflexes from receptors, or a combination of both. Alterations in autonomic tone might contribute to the instability of a vascular plaque or initiate cardiac arrhythmias (Brook et al., 2004). Exposure to air pollution has been linked to ventricular arrhythmias (Pope et al., 2004; Berger et al., 2006; Ljungman et al., 2008), alteration in heart rate and heart rate variability (Pope et al., 1999b; Gold et al., 2000; Park et al., 2005; Chuang et al., 2007), ECG repolarization abnormalities (Henneberger et al., 2005), ST-segment depression (Pekkanen et al., 2002; Gold et al., 2005; Mills et al., 2007; Chuang et al., 2008), and increased blood pressure (Ibald-Mulli et al., 2001; Zanobetti et al., 2004).

2. 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. Exposure to air pollutants

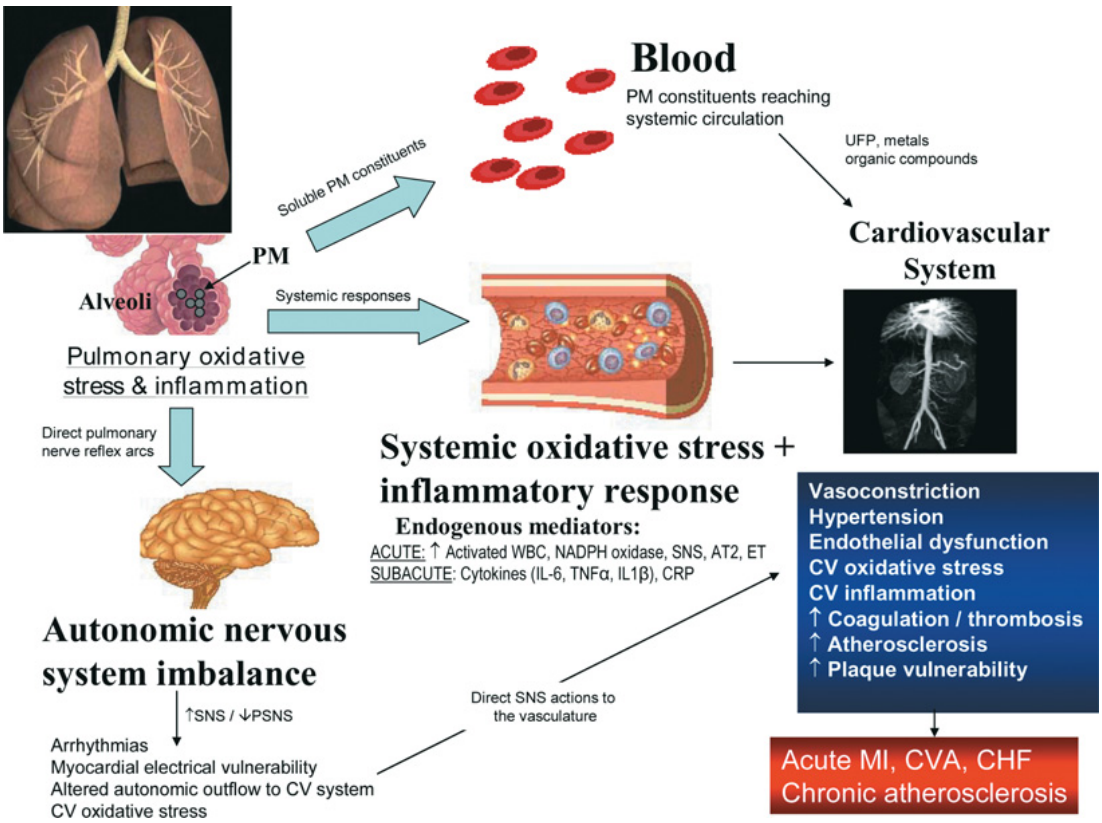

Figure 1.3: Broad biological pathways whereby PM may cause CV events (reprinted with permission from Brook 2008). AT2, angiotensin II; CVA, cerebrovascular accident; CHF, congestive heart failure; ET, endothelins; MI, myocardial infarction; ROS, reactive oxygen species; UFP, ultra-fine particles; WBC, white blood cells.

has been shown to be associated with increased inflammatory markers (Peters et al., 2001; Pope et al., 2004; Mills et al., 2007; Rückerl et al., 2007), endothelial dysfunction (Brook et al., 2002; O'Neill et al., 2005; Schneider et al., 2008a), altered blood coagulability (Peters et al., 1997; Baccarelli et al., 2007), and the progression of atherosclerosis (Künzli et al., 2005; Hoffmann et al., 2007). The latter is supposed to be induced by the generation of a chronic pro-inflammatory state.

3. Nanoparticles or soluble particle constituents may rapidly cross the pulmonary epithelium into the circulation and interact directly with the cardiovascular system. These small particles might not only affect vascular endothelium and atherosclerotic plaques, but also provoke local inflamma-

tion and oxidative stress. Several studies on animals (Nemmar et al., 2001; Oberdörster et al., 2002; Nemmar et al., 2004; Semmler et al., 2004) and humans (Nemmar et al., 2002a; Mills et al., 2006) could demonstrate extrapulmonary translocation of ultrafine particles. Once in the circulation, nanoparticles might have direct effects on the heart and other organs.

Direct pollutant effects are hypothesized to trigger acute cardiovascular events occurring within a few hours after the exposure. This includes direct effects on hemostasis and the cardiovascular system by particles translocated into the circulation (pathway 3) but also alterations in autonomic tone by activation of pulmonary neural reflexes (pathway 1). Indirect air pollutant effects are supposed to evoke rather delayed and chronic cardiovascular responses. Pulmonary oxidative stress and inflammation may contribute to systemic oxidative stress and inflammation (pathway 2) which, again, may activate hemostatic pathways, impair vascular function, and accelerate atherosclerosis.

Regarding MI, exposure to air pollutants may increase the acute risk by provoking plaque instability in the short term, but also the baseline risk by promoting atherosclerosis formation over the long term.

Temperature and MI Potential mechanisms to explain the increased risk for coronary events in association with decreasing temperature include the stimulation of cold receptors in the skin and, therefore, the sympathetic nervous system, leading to a rise in the catecholamine level. The consequences are vasoconstriction as well as increased heart rate and blood pressure (Elwood et al., 1993; Modesti et al., 2006; Barnett et al., 2007). An increased blood pressure decreases the ratio of myocardial oxygen supply to demand and may lead to myocardial ischemia, particularly in a vulnerable myocardium. Moreover, a drop in temperature could be related to an increase in fibrinogen (Woodhouse et al., 1994; Schneider et al., 2008b) and C-reactive protein (Horan et al., 2001; Schneider et al., 2008b). In cold conditions, the plasma concentrations of certain clotting factors, platelet count and their in vitro aggregation are all increased and promote clotting (Keatinge et al., 1984; Neild et al., 1994; Woodhouse et al., 1994). Furthermore, reduced plasma volume and increased blood viscosity during cold exposure also tend to promote thrombosis (Keatinge et al., 1984; Neild et al., 1994). Hence, well-known cardiovascular risk factors are elevated during colder

periods, and recurrent changes in markers of atherothrombosis may contribute to the risk of triggering acute coronary events.

The mechanisms of heat exposure and its potential to trigger coronary events have been less frequently studied. Culic (2007) suggested a parasympathetic triggering pattern, where the overall balance of the autonomic nervous system is shifted toward parasympathetic activity. A decrease in blood pressure associated with parasympathetic predomination may reduce the volume and velocity of blood flow, favoring the thrombotic, embolic and ischemic incidents. Keatinge et al. (1986) reported increased platelet and red blood cell counts, blood viscosity, plasma cholesterol, and endothelial cell damage after exposure of volunteers to moving air at 41°C. Prolonged heat exposure has been associated with heat cramps, heat exhaustion, and heat stroke (McGeehin and Mirabelli, 2001). The latter has been described as a complex interplay among acute physiological alterations associated with hyperthermia, direct cytotoxic effects of heat, and inflammatory and coagulation responses (Bouchama and Knochel, 2002). This may result in injury to the vascular endothelium and thrombosis which again may promote acute coronary events.

1.2 Specific aims

Several studies have investigated the association between air pollution or temperature and MI, though most of them were limited by design to a certain group of events (MI survivors, first or recurrent MIs) or used hospital admission data which is limited to hospitalized cases. The existence of a myocardial infarction registry gave us the opportunity to examine almost all MIs and coronary deaths of persons aged 25 to 74 years living in the study area of Augsburg city and county. Moreover, it enables the seperate inspection of first and recurrent MIs because subjects at risk are hypothesized to differ in their susceptibility to air pollution and temperature. Individuals who already suffered a MI are perhaps more aware of the risk for a recurrent infarction and might show a different behaviour towards environmental exposure. Furthermore, they are supposed to have a higher and/or different medication intake. The subdivision in nonfatal and fatal events is of interest regarding the etiology. While the MI diagnosis is assured for the first group, this is not always the case for fatal events as most of them died prehospitally. In addition, fatal coronary events are more often precipitated by local

arrhythmia. Earlier analyses of air pollution and MI have been conducted based on Augsburg registry data, but only for a shorter period (Peters et al., 2005). Direct temperature effects on MI cases have not been investigated in this area so far. Continuous measurement of ambient air pollutants and meteorological parameters over the whole study period permitted the inspection of several specific research questions:

1. Is there an association between the variation of daily air pollutant concentrations and the daily numbers of MI?
   (a) Is the association similiar for fatal and nonfatal or incident and recurrent MIs?
   (b) Does the association differ by personal characteristics based on gender, age, history of diabetes and hypertension?
   (c) Is the association robust to different modeling approaches?
2. Is there an association between the variation of daily air temperature and the daily numbers of MI?
   (a) Is the association similiar for fatal and nonfatal or incident and recurrent MIs?
   (b) What is the shape of the exposure-response function?
   (c) Is the association robust for different temperature metrics?
   (d) Is the association similiar for warm and cold years?
   (e) Does the association differ by personal characteristics based on sex, age, history of diabetes and hypertension?
3. Are there interacting effects of daily air pollutant concentrations and daily temperature levels on the occurrence of MI?

2 Materials and methods

This chapter describes the data and models used to assess the impact of air pollution and air temperature on the number of daily cases of MI. The first section describes the MONICA/KORA MI registry and the air pollution and meteorology measurements. The second section presents the statistical approaches. The third section gives a detailed description of the model building.

2.1 Data description

2.1.1 MONICA/KORA MI Registry

In 1984, the Augsburg MI registry was founded within the framework of the WHO's Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) project which aimed on determining exact cardiovascular morbidity and mortality in several countries under a standardized protocol. Since the end of the MONICA project in 1996, the registry has been continued by the Cooperative Health Research in the Region of Augsburg (KORA).

Augsburg, situated in Southern Germany and administrative center of the south-western region of Bavaria, was chosen as representative city for Germany. The study region comprises the city of Augsburg with about 260,000 inhabitants and the adjacent predominantly rural districts Augsburg Land with 241,000 and Aichach-Friedberg with 127,000 inhabitants, hence in total 628,000 inhabitants in 2004. In 1995, the population amounted 605,000 (Bayerisches Landesamt für Statistik und Datenverarbeitung, 2009). The target study population of the MI registry therefore consisted of about 400,000 persons conforming to the age and regional constraints of the registry.

The registry records all nonfatal and fatal cases of MIs and coronary deaths of persons aged 25 to 74 with principal residence in the study area. Hospital admissions are continuously monitored, daily at the central hospital and weekly at six hospitals in the study region as well as at four hospitals next to the study region. The screening admission diagnoses are described elsewhere (Peters et al., 2005). MI patients, who survived at least 24 hours, are asked for an interview concerning the event, medication and family history. Coronary deaths are cases who died

outside the hospital or within the 24 hours 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. In 2000, the MI diagnosis was clinically redefined and patients with symptomatically angina and laboratory signs of ischemia (troponin positive) without persistent ST-segment elevations were also included (Löwel et al., 1991; 2005). However, we used the MI diagnosis established in 1985 over the whole period for consistency reasons. The diagnostic criteria included chest pain lasting more than 20 minutes that is not relieved by the administration of nitrates and either 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.

2.1.2 Air pollution data

During the study period, particulate and gaseous air pollutant concentrations were measured at seven monitoring stations in the city of Augsburg and its southern suburb Haunstetten (Figure 2.1). The sites Bourgesplatz, Karlstrasse, LfU (Bavarian Environmental Protection Agency), Königsplatz and Haunstetten belong to the Bavarian Air Monitoring Network, the Monastery site was established by GSF – National Research Center for Environment and Health (now Helmholtz Zentrum München) – during a project funded by the Health Effects Institute (Peters et al., 2005). The site at the technical college has been run by the GSF/Helmholtz Zentrum München from 2004 on.

A short description of the monitors with related measured variables and time periods can be found in Table 2.1. From 1995 to 1999, total suspended particles (TSP) were measured with a ß-absorption device (ESM-Andersen FH 62 I-N) at two fixed urban background sites (Bourgesplatz and Königsplatz) 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. $PM_{2.5}$ was measured with a TEOM model 1400A (Patashnick and Rupprecht, German distributor: MLU, Essen, Germany). Particle number concentrations (PNC), an indicator for ultrafine particles, were obtained from 1999-2004 by a condensation particle counter (CPC 3022A, TSI, Aachen, Germany) and predicted for previous years within a regularized linear prediction model based on the measurements

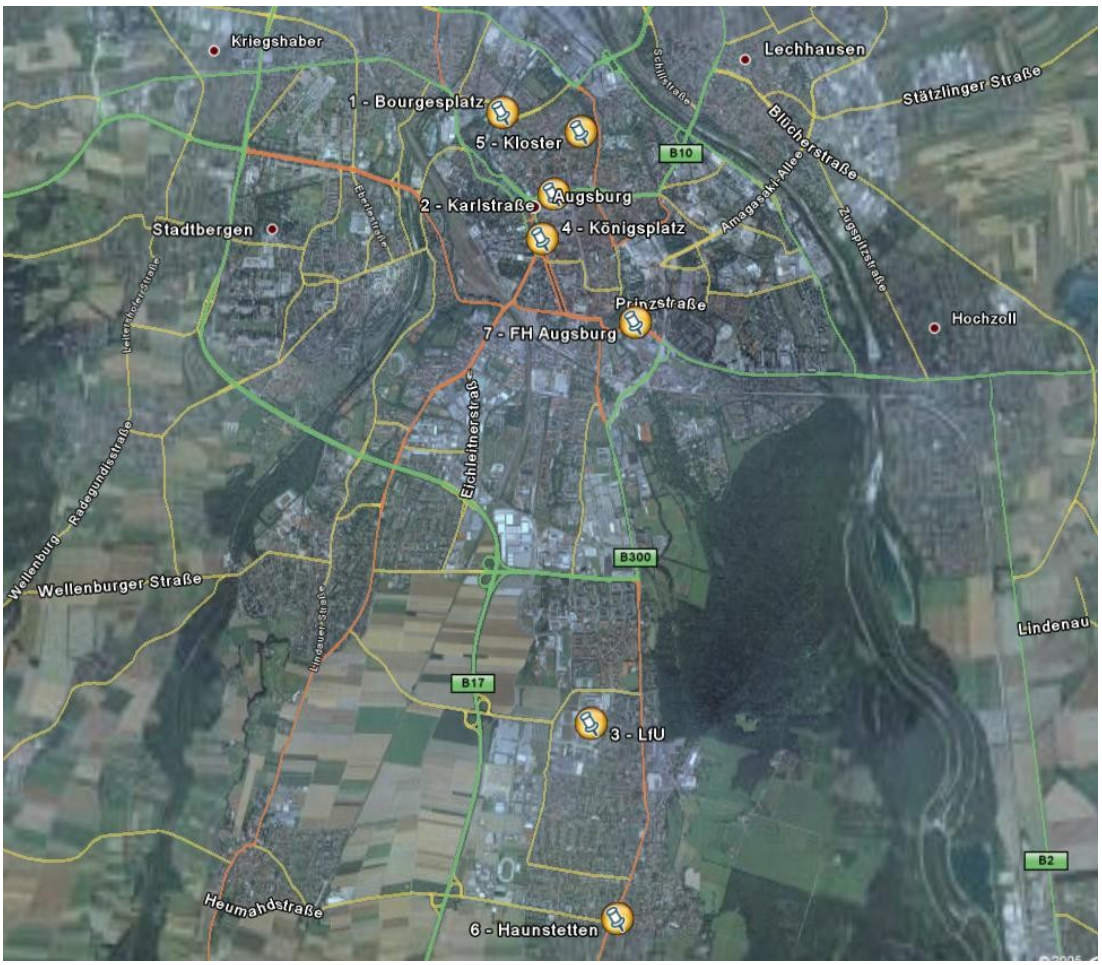

Figure 2.1: Monitoring stations in Augsburg.

for the year 2001 (Paatero et al., 2005). Measured values are indicated with PNC_m, fitted values with PNC_f and the combined time series with PNC_{m+f}. SO_2 was measured with UV fluorescence (Monitor labs, ML 8850 (M)), NO_2 and NO with chemiluminescence (Ecophysics CLD 700 AL), CO with gas filter correlation (API300A) and ozone with UV-absorption (Thermo instruments, TE 49).

TSP and PM_{10} were given as three-hour mean concentrations. All other variables were available on at least an hourly basis. Maximum 8-hour average of ozone and 24 hour mean values of the other air pollutants were calculated for each monitor if at least 75% of the hourly values were available.

Table 2.1: Description of monitoring stations.

Monitoring station Description	**Measured variables**	**Period of measurement**
Bourgesplatz	TSP†	01/1995 – 12/1999
urban background	PM_{10}†	02/2000 – 12/2004
	CO†	01/1995 – 02/2003
	NO_2†, NO†	01/1995 – 12/2004
	SO_2†	01/1995 – 08/2002
Karlstrasse	PM_{10}, CO, NO_2, NO	08/2003 – 12/2004
urban canyon		
LfU*	PM_{10}, CO, NO_2, NO, SO_2, O_3†	02/2001 – 12/2004
rural background	Meteorology	02/2001 – 12/2004
Königsplatz	TSP	01/1995 – 12/1999
urban street	PM_{10}	02/2000 – 12/2004
	CO, NO_2, NO, SO_2	01/1995 – 12/2004
Monastery	PNC†, $PM_{2.5}$†	02/1999 – 12/2004
urban background		
Haunstetten	SO_2, O_3	01/1995 – 03/2001
rural background	Meteorology	
Technical college	PNC	09/2003 – 12/2004
urban background		

* Bavarian Environmental Protection Agency;
† TSP: total suspended particles; PM_{10}: Particles with diameter < 10 µm; CO: Carbon monoxide; NO_2: Nitrogen dioxide; NO: Nitrogen monoxide; SO_2: Sulfur dioxide; O_3: Ozone; PNC: Particle number concentration; $PM_{2.5}$: Particles with diameter < 2.5 µm.

Aggregation of monitors Several monitoring stations collected data on PM_{10} and gases at the same time (Figure 2.2). In order to combine these data to one time series for each pollutant, a daily mean value was calculated from selected sites. Thereby, single missing values in the time series used for the mean series calculation were first imputed as proposed elsewhere (von Klot et al., 2005). For this purpose, a missing value of monitor m on day t is estimated with

$$\hat{x}_{tm} = \bar{x}_{.m} + \bar{z}_{t.} s_{.m} \ , \qquad \text{with} \quad \bar{z}_{t.} = \frac{\sum_{l=1}^{n} \left(\frac{x_{tl} - \bar{x}_{.l}}{s_{.l}} \right)}{n} \ .$$

where $\bar{x}_{.m}$ is the arithmetic mean of monitor m in the window of three months around x_{tm}, $s_{.m}$ denotes the standard deviation of monitor m in this window, and $\bar{z}_{t.}$ represents a standardized value of the other monitors on day i to take the

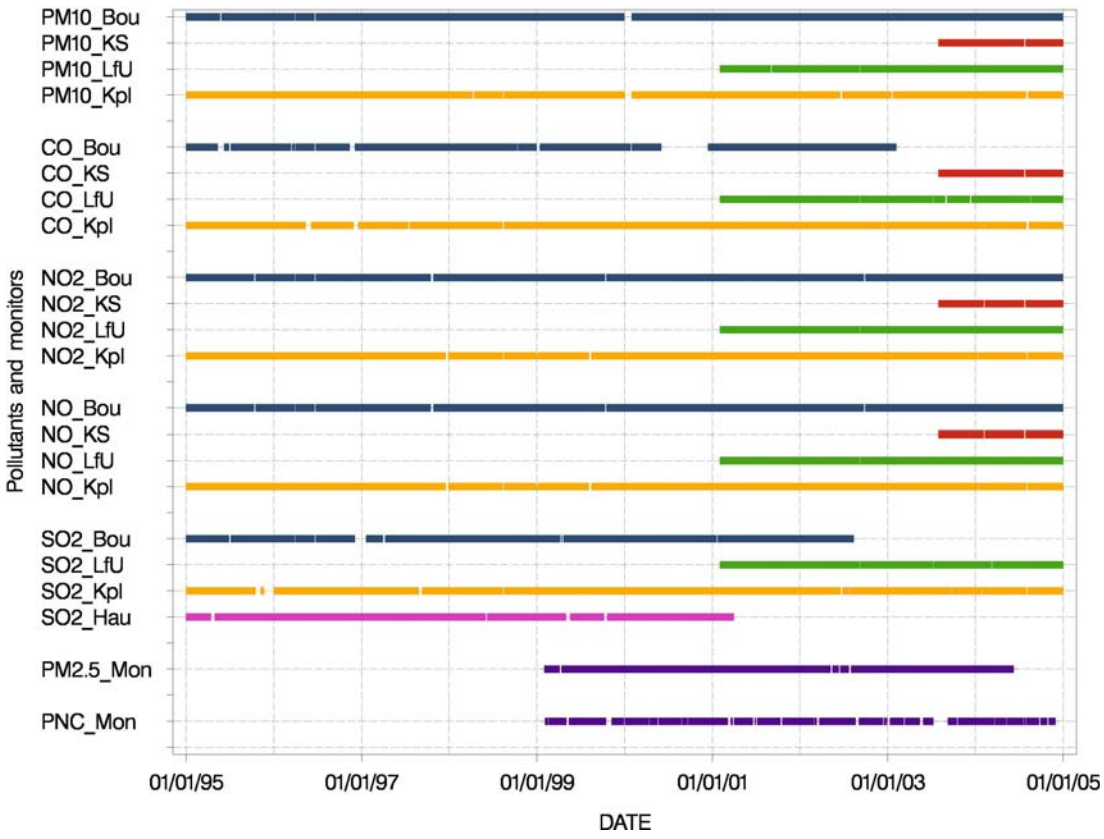

Figure 2.2: Monitors over time for PM_{10}, CO, NO_2, NO, SO_2, $PM_{2.5}$ and PNC_m: Bourgesplatz (blue), Karlstrasse (red), LfU (green), Königsplatz (orange), Haunstetten (pink) and Monastery (purple).

deviation of day t into account.

Secondly, we filled the remaining days of CO and SO_2 at Bourgesplatz where monitoring was stopped in 2003 and 2002, respectively, with values from the LfU monitor. This station was chosen as it showed strong correlation (Spearman's correlation coefficient between Bourgesplatz and LfU was 0.78 for CO and 0.76 for SO_2) and was not used as a whole for the aggregation because of only four years of measurement.

At last, we calculated a daily mean value from the sites Königsplatz and Bourgesplatz for PM_{10}, CO, NO_2, NO and SO_2, as both sites supplied data for the whole period for almost all pollutants. The Haunstetten site was additionally considered for the calculation of the SO_2 mean series as SO_2 data were collected there for more than six years. Karlstrasse was not used at all as only measurements

for 17 months of the ten year period were available. The filled and imputed time series for Bourgesplatz CO and SO_2 can be found in Figure 2.3.

In the final exposure data set, the variables are composed as follows (Spearman's rank correlation coefficient r_{Sp} relates to the correlation of the corresponding time series):

- Particles:
  - PM_{10}: Mean of monitors at Bourgesplatz and Königsplatz, $r_{Sp} = 0.80$.
  - $PM_{2.5}$: Measured values of monitor at Monastery (1999-2004).
  - PNC: Retrospectively fitted values (1995-1998), measured values of monitor at Monastery (1999-2004), $r_{Sp} = 0.81$ for 578 concurrent values in 1999 and 2000.
- Gases:
  - NO_2: Mean of monitors at Bourgesplatz and Königsplatz, $r_{Sp} = 0.66$.
  - NO: Mean of monitors at Bourgesplatz and Königsplatz, $r_{Sp} = 0.71$.
  - CO: Mean of monitors at Bourgesplatz (02/2003-12/2004: filled with LfU values) and Königsplatz, $r_{Sp} = 0.51$.
  - SO_2: Mean of monitors at Bourgesplatz (B) (09/2002-12/2004: filled with LfU values), Königsplatz (K) and Haunstetten (H), B and K: $r_{Sp} = 0.68$, B and H: $r_{Sp} = 0.70$ and K and H: $r_{Sp} = 0.51$.
  - O_3: Measured values of monitor at Haunstetten (01/1995–01/2001) and LfU (02/2001-12/2004).
- Meteorology: Measured values of monitor at Haunstetten (01/1995–01/2001) and LfU (02/2001-12/2004).

2.1.3 Meteorological data

Like ozone, air temperature, relative humidity, and barometric pressure were measured until January 2001 at the Haunstetten site and thereafter at the LfU station. Both sites are located in the southern suburban area of Augsburg (Figure 2.1). All weather variables were available on half-hourly basis. Hourly values were

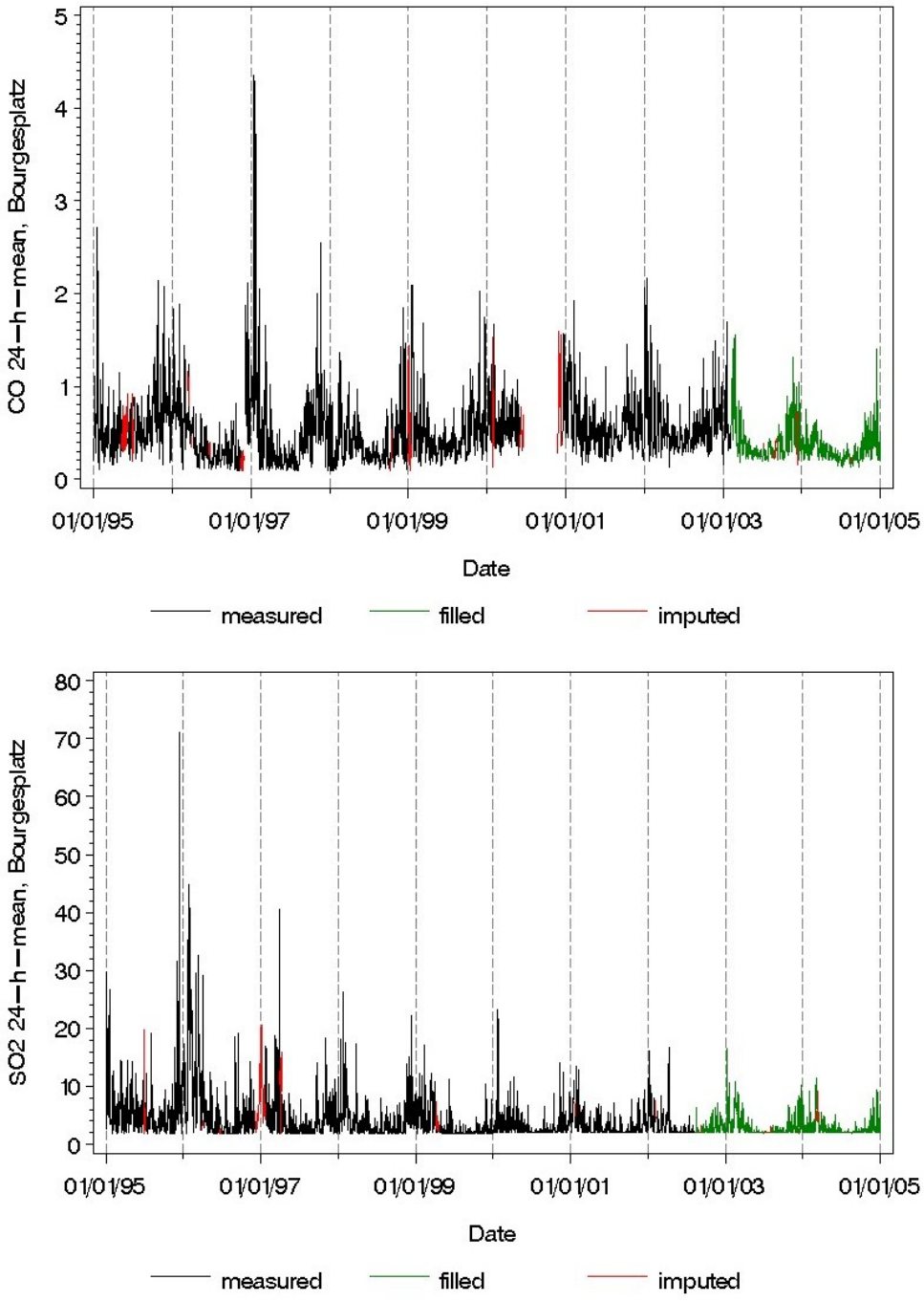

Figure 2.3: Time series of daily means for CO (top) and SO_2 (bottom) at Bourgesplatz, black: measured values, red: imputed values, and green: filled observations from LfU monitor.

also determined if one of the half-hourly values was missing. 24 hour mean values were calculated if at least 75% of the hourly values were available. Additionally, for temperature, we considered the 24 hour maximum and minimum as well as the daily temperature range (maximum minus minimum temperature). Dewpoint (DT) and apparent temperature (AT) were calculated based on the following formulas

$$DT = 1/(1/(T + 241.413) - (log10(RH \times 0.01)/1838.675)) - 241.413) \quad (2.1)$$

$$AT = -2.653 + (0.994 \times T) + (0.0153 \times DT^2), \quad (2.2)$$

where T denotes air temperature and RH relative humidity (O'Neill et al., 2003).

2.1.4 Influenza data

Data on influenza epidemics were obtained from the German Influenza Working Group (AGI, 2007). In the framework of an influenza surveillance system, the group supplies a weekly doctor′s practice index which measures the average relative deviation of the observed acute respiratory activity from a background level. The average deviation is calculated from all practices participating in the survey system. Since 1992, it has been determined for calendar weeks 40 through 15 of the next year. Values above 115 indicate an increased activity. For the remaining weeks, a value of 100 was assigned indicating background activity. As Augsburg is situated on the brink of Bavaria and next to Baden-Württemberg and data was partly quite sparse for both states, we used the doctor′s practice index for the whole of Germany.

2.2 Statistical approaches

2.2.1 Single exposure models

Due to the count nature of the outcome data, the number of MI cases per day, we choose loglinear Poisson regression as the base model. Poisson regression is an extension of the linear model and belongs to the group of generalized linear models (GLM) which have the basic form

$$g(\mu_t) = X_t\beta \ . \quad (2.3)$$

g is a smooth monotonic function and is called link function, μ_t corresponds to the expectation of Y_t which indicates the outcome of interest of unit t, X_t is the t^{th} row of the matrix of linearly independent covariates and β is the vector of parameters to estimate. The distributional assumption implies that the Y_t are independent and follow a distribution belonging to the exponential family. Furthermore, it could be shown that quasi-likelihood approaches also satisfy the requirements for GLM. A quasi-likelihood is used if only mean and variance function of Y_t can be specified, but not its distribution. A detailed description of GLMs is given in (McCullagh and Nelder, 1989).

The Poisson distribution (Po) and its probability function $P(Y_t)$ denote as follows

$$Y_t \sim \text{Po}(\mu_t) \tag{2.4}$$

$$P(Y_t) = \frac{e^{-\mu_t}{\mu_t}^{y_t}}{y_t!} = \exp\ \{y_t\ \ln(\mu_t) - \mu_t - \ln(y_t!)\}, \tag{2.5}$$

with

$$E(Y_t) = V(Y_t) = \mu_t. \tag{2.6}$$

The logarithmic function is the default link function for a Poisson distribution, as μ_t has to be positive and further restrictions on β are not necessary.

A further extension are generalized additive models (GAM) as they additionally allow for nonlinear functions of covariates in the linear predictor.

$$g(\mu_t) = X_{lin_t}\beta + \sum_j f_j(x_{jt})\ . \tag{2.7}$$

X_{lin_t} are the t^{th} observations of all linear covariates and β the corrensponding parameter vector. The smoothing functions f_j of the covariates x_j have to be continuous and differentiable. All other assumptions of the GLM remain valid. The response may follow any exponential family distribution, or has a known mean variance relationship which permits the use of a quasi-likelihood. Estimation and inference with GLM and GAM is based on maximum likelihood estimation and requires (penalized) iterative re-weighted least squares methods (Fahrmeir and Tutz, 2000; Wood, 2006).

Thus, the linear predictor of the model could have the following form:

$$\ln(\mu_t) = \ln(E(Y_t)) = \alpha + \beta_X\ X_{t-l} + \sum_j f_j(\text{conf}_{j_t}) + \sum_k \beta_k\ \text{conf}_{k_t}, \tag{2.8}$$

where Y_t denotes the number of events on day t, X the exposure of interest, which can be lagged with $l, l = 0, 1, \ldots$ days to examine not only immediate but also delayed effects of exposure, f_j are the smooth functions for nonlinear confounders, and β_k are the parameters for linear or categorial confounders. Thus, the exposure X is taken linearly in the model and the parameter of main interest β_X describes the additive change of the logarithmized expectation for one unit increase of exposure X. The rate ratio e^{β_X} is then the multiplicative change of the expectation itself if all other covariates are kept constant.

2.2.2 Polynomial distributed lag models

Distributed lag models relate the outcome variable jointly to the exposure of the current day and of several previous days. Since collinearity problems are likely to arise if the exposure is serially correlated, the coefficients can be restricted to follow a polynomial.

Thus, if we have the following model including the delayed exposure X_{t-i}, β_m the parameters to estimate, l the number of lags, and several possible linear and nonlinear covariates:

$$ln(E(Y_t)) = \beta_0 X_t + \beta_1 X_{t-1} + \cdots + \beta_l X_{t-l} + covariates, \tag{2.9}$$

the β's can be restricted to vary over the lags by following a polynomial of degree d:

$$\beta_m = \sum_{n=0}^{d} \zeta_n m^n, \qquad m = 0, \ldots, l. \tag{2.10}$$

Thus it follows

$$\begin{aligned}
&ln(E(Y_t)) \\
&= \zeta_0 X_t + (\zeta_0 + \zeta_1 + \cdots + \zeta_d) X_{t-1} + \cdots + (\zeta_0 + l\zeta_1 + \cdots + l^d \zeta_d) X_{t-l} + covariates \\
&= \zeta_0 (X_t + \cdots + X_{t-l}) + \zeta_1 (X_{t-1} + 2X_{t-2} + \cdots + lX_{t-l}) + \cdots \\
&\qquad + \zeta_d (X_{t-1} + 2^d X_{t-2} + \cdots + l^d X_{t-l}) + covariates \\
&= \zeta_0 Z_0 + \zeta_1 Z_1 + \cdots + \zeta_d Z_d + covariates.
\end{aligned} \tag{2.11}$$

The first step of the calculation includes the construction of the variables $Z_r, r =$

$0, \ldots, d$ as weighted sums of the $l+1$ exposure variables X_{t-l}

$$\begin{aligned} Z_0 &= X_t + X_{t-1} + \cdots + X_{t-l} \\ Z_1 &= X_{t-1} + 2X_{t-2} + \cdots + lX_{t-l} \\ &\vdots \\ Z_d &= X_{t-1} + 2^d X_{t-2} + \cdots + l^d X_{t-l}, \end{aligned} \tag{2.12}$$

or, in matrix notation

$$(Z_0 \cdots Z_d) = (X_t \cdots X_{t-l}) \begin{pmatrix} 1 & 0 & 0 & \cdots & 0 \\ & 1^1 & 1^2 & \cdots & 1^d \\ \vdots & 2^1 & 2^2 & \cdots & 2^d \\ & \vdots & \vdots & & \cdots \\ 1 & l^1 & l^2 & \vdots & l^d \end{pmatrix} \tag{2.13}$$

$$\Rightarrow \underset{T\times d+1}{Z} = \underset{T\times l+1}{X} \times \underset{l+1\times d+1}{A}, \tag{2.14}$$

where T denotes the total number of days.

In a second step, a GAM is estimated with the Z variables as regressors and additional covariates (equation (2.11)). The resulting $\hat{\zeta_0}, \hat{\zeta_1}, \cdots, \hat{\zeta_d}$ are then used to calculate the $\hat{\beta}_m$'s from equation (2.10) as well as the corresponding standard errors

$$\underset{l+1\times 1}{\hat{\beta}} = \underset{l+1\times d+1}{A} \times \underset{d+1\times 1}{\hat{\zeta}}, \tag{2.15}$$

$$cov(\hat{\beta}) = A \times cov(\hat{\zeta}) \times A^t, \tag{2.16}$$

$$se(\hat{\beta}) = \sqrt{diag(cov(\hat{\beta}))}. \tag{2.17}$$

Finally, the total effect $\hat{\beta}_{total}$ and its corresponding standard error can be determined with $v = \underset{l+1\times 1}{\mathbf{1}}$ as follows:

$$\hat{\beta}_{total} = \sum_{j=0}^{l} \hat{\beta}_j, \tag{2.18}$$

$$se(\hat{\beta}_{total}) = \sqrt{v^t \times cov(\hat{\beta}) \times v} = \sqrt{v^t \times A \times cov(\hat{\zeta}) \times A^t \times v} \quad . \tag{2.19}$$

2.2.3 Extended Cox model

The extended Cox model allows to estimate the effects of time-dependent covariates such as pollutants within a cohort setting. However, for our data, this

approach is limited to recurrent events as the incident MI serves as index event, hence, the entrance of the person in the cohort.

The classical Cox proportional hazards model relates a hazard rate to time-independent covariates X,

$$h(t, X) = h_0(t) \exp\left(\sum_{p=1}^{P} \beta_p X_p\right), \tag{2.20}$$

where $h_0(t)$ denotes the baseline hazard rate as a function of t, the time since the index event, and β_p contains the regression coefficients.

The stratified Cox model is an extension to account for different strata, but also for repeated measurements,

$$h_g(t, X) = h_{0g}(t) \exp\left(\sum_{p=1}^{P} \beta_p X_p\right). \tag{2.21}$$

Each stratum $g, g = 1, \ldots, G$ is assigned its own baseline hazard function, but values for the regression coefficients of the covariates are the same. This may result in different survival curves.

A further extension comprises the inclusion of time-varying covariates $X_q(t), q = 1, \ldots, Q$ such as air pollutants or temperature which can be implemented as

$$h_g(t, X(t)) = h_{0g}(t) \exp\left(\sum_{p=1}^{P} \beta_p X_p + \sum_{q=1}^{Q} \delta_q X_q(t)\right). \tag{2.22}$$

$X_p, p = 1, \ldots, P$ are time-invariant variables such as gender or age at cohort entry. The estimated coefficients δ_q of $X_q(t)$ are time-independent and thus, represent the overall effect (Therneau and Grambsch, 2001).

2.2.4 Interacting exposure models

To investigate possible interacting effects between two exposure variables, in this case air pollutants and air temperature, the single exposure model, presented in Section 2.2.1, was modified in four different ways:

A: Two exposures model: inclusion of linear terms for both air pollutant (ap) and temperature ($temp$)

$$ln(E(Y_t)) = \alpha + \beta_{ap} ap_{t-l} + \beta_{temp} temp_{t-l} + covariates. \tag{2.23}$$

B: Linear interaction model: like model A, plus a multiplicative interaction effect of temperature and air pollutant

$$ln(E(Y_t)) = \alpha + \beta_{ap} ap_{t-l} + \beta_{temp} temp_{t-l} + \beta_{int}(ap_{t-l} \times temp_{t-l}) + covariates. \tag{2.24}$$

C: Inclusion of air pollutant and temperature as a two-dimensional smooth function

$$ln(E(Y_t)) = \alpha + s(ap_{t-l}, temp_{t-l}) + covariates. \tag{2.25}$$

D: Like model C, but with explicit degrees of freedom specification

$$ln(E(Y_t)) = \alpha + s(ap_{t-l}, temp_{t-l}, df = 24) + covariates. \tag{2.26}$$

The two exposure variables were always included with the same lag l. Model A and B provide effect estimates β_{ap} and β_{temp} which can be compared with the effect estimates resulting from the single exposure models (2.8). The effect estimate β_{int} in Model B indicates a possible interaction effect and its direction and must be considered when comparing the main effects. Models C and D better fit the data by incorporating the joint effect of temperature and air pollutant as a continuous two-dimensional function of both variables. This means that the interaction can vary in its direction for portions of the data depending only on the specification and the degrees of freedom of the smooth function. Model C estimates the smoothness and hence, the degrees of freedom during the fitting routine by minimizing the generalized cross validation criteria (GCV). As this can also result in a linear function, we fixed the degrees of freedom in Model D to a relatively high number to increase the adaptation to the data.

2.3 Model building

This subsection describes how the above introduced statistical models were applied to investigate our specific aims (Section 1.2). The model building as well as outcome, exposure and confounder specification are explained corresponding to the order of the aims.

2.3.1 Influence of air pollutants as exposure of interest

Single exposure models To examine potential effects of air pollutants on daily numbers of MI (specific aim 1), we assumed a loglinear association. For each pollutant, a separate GAM was calculated for the exposure of the same day (lag0), the day before MI occurrence (lag1) and up to 4 days before the event (lag1 to lag4) as well as the average exposure over 5 days (mean of lag0 to lag4). Based on the literature on the triggering of MI, we included step by step the following potential confounders

1. Trend: a smooth function for the date to cover a global time trend,
2. Meteorology: smooth functions for
   - 24 hour mean temperature of the same day to adjust for immediate temperature effects (effect of hot days),
   - average temperature of the three previous days to adjust for delayed temperature effects (effect of cold days),
   - 24 hour mean relative humidity of the same day,
   - 24 hour mean barometric pressure of the same day,
3. Season: three indicator variables (Jun-Aug, Sep-Nov, Dec-Feb vs. Mar-May) or one indicator variable for winter (Oct-Mar) vs. summer (Apr-Sep),
4. Day of week: indicator variables for each day of the week or an indicator variable for weekend to filter periodicity.

We used penalized regression splines with the default smoothing parameter to model nonlinear confounder effects. Inclusion criteria were a reduction of GCV, minimization of the absolute value of the sum of the partial autocorrelation function and for the dummy variables, the statistical significance.

The last step of the confounder model building comprised a re-adjustment of the smooth function for the time trend (Touloumi et al., 2004). In this step, the smoothing parameter of the penalized spline was reduced to force an increase in the numbers of degrees of freedom. As the model fit did not improve while the absolute value of the sum of the partial autocorrelation function increased considerably, the default smoothing parameter was kept.

The final model included penalized regression splines of time trend, current day temperature and average temperature of the three previous days, season as a categorical variable (Mar-May, Jun-Aug, Sep-Nov and Dec-Feb) and an indicator variable for Mondays. As we assumed that changes of the underlying population at risk over the years could be modeled with a smooth trend function, we did not adjust the event rates for age or sex. Besides the daily rate of total MI, nonfatal (survived longer than 28 days) and fatal events as well as incident and recurrent events were separately inspected (specific aim 1a). To check whether the effects differ by personal characteristics (specific aim 1b), we assessed effect modification by gender, age groups (25-54, 55-64 and 65-74 years of age), and history of hypertension and diabetes using stratified analyses.

Sensitivity analysis To explore the robustness of the results, we used different values of smoothness for the function of time trend. Furthermore, as time trend, season and temperature partly compete for the same effects, the model was reduced by leaving out the seasonal categories. We also adjusted for influenza epidemics as described in Stölzel et al. (2007). To check the adjustment for weather variables, we reran the confounder selection and included hierarchically temperature, relative humidity and barometric pressure as penalized splines based on a reduction of GCV. For each variable, lag0 to lag4 and the 5 day average were compared and the term was chosen which minimized GCV most. As $PM_{2.5}$ was only measured from 1999 on, we recalculated the effects of PM_{10} and PNC for this shorter period to be comparable.

Alternative modeling approaches Specific aim 1c included the usage of different modeling approaches to evaluate the robustness of the models.

We used polynomial distributed lag models to assess how the exposures of same and previous days interact and jointly influence the daily numbers of MI. The same confounders were included as for the single exposure model to be comparable.

The extended Cox model was used as an alternative approach to estimate air pollutant effects on recurrent events. Only recurrent events of persons with incident MI during the study period could be included as the incident event served as index event. The starting time of observation was set to the date of the first

MI plus 28 days, as this was defined as the patient's first day at risk to suffer an independent secondary event (Tunstall-Pedoe et al., 1994). The counting process style of input was used to implement the extended Cox model (Peters et al., 2006). Therefore, we rearranged the data set and created for each person one observation for each day at risk. An example data set and its description are given in the appendix, Table A.1.

An advantage over the Poisson model is the possibility to adjust for personal characteristics. We additionally included linear terms of age and body mass index at entry, and indicator variables for diabetes, hypertension, hyperlipidemia, and wether a reperfusion therapy was performed. Instead of smooth terms, linear and quadratic functions were used for current day temperature and average temperature of the three previous days, respectively. Time trend was incorporated linearly in the model.

2.3.2 Influence of temperature as exposure of interest

Model building for the influence of temperature on MI (specific aim 2) was done similarly as for air pollutants. 24 hour mean temperature of the same day, lagged 1 to 4 days and the 5 day average were taken separately in the model as linear terms. As potential confounders, we considered a global trend over time, seasonal and weekday variations as well as relative humidity and barometric pressure. Model selection was carried out by minimizing the GCV criteria and the absolute value of the sum of the partial autocorrelation function (Touloumi et al., 2004). Time trend and relative humidity were forced into the model even if model fit was not improved.

The final model included a penalized regression spline of time trend, relative humidity as a linear term with the same lag as the temperature term, season as a categorical variable (Mar-May, Jun-Aug, Sep-Nov and Dec-Feb) and an indicator variable for Monday. Again, we inspected separately the daily rate of total MI, nonfatal (survived longer than 28 days) and fatal events as well as incident and recurrent events as outcome variables (specific aim 2a). Additionally, we assessed the shape of the exposure-response function by including air temperature as a penalized regression spline (specific aim 2b).

In addition to the 24 hour mean temperature, we estimated the influence of 5

day average, 24 hour maximum and minimum temperature, the daily temperature range (maximum minus minimum temperature), as well as apparent and dewpoint temperature on the daily count of MI to assess the robustness of the results for different temperature metrics (specific aim 2c). Furthermore, indicator variables for the 5% or, alternatively, for the 1% hottest and coldest days were added to the model to examine their particular influences.

To check whether the effects are similar for cold and warm years (specific aim 2d), we calculated the yearly mean temperature for each of the ten years and categorized them into cold, moderately tempered, and warm years to investigate wether short-term temperature effects differed in predominantly cold or warm years. The categories were defined on the 10 year distribution of the 24 hour average temperatures. We categorized the yearly averages within these tertiles and created three variables which contained the 5 day average temperature if the day derived from a cold, moderately tempered, or warm year, respectively, and zero else. The same procedure was carried out for winter (October to March) and summer (April to September). We thus calculated two separate models, one with the three temperature variables for cold, moderately tempered and warm years and one with the six winter and summer categories. Both were adjusted for time trend, an indicator variable for Mondays, 5 day average relative humidity and for the whole-years model, an additional adjustment for season was induced.

Again, potential differences based on personal characteristics were assessed by stratifying for gender, age groups (25-54, 55-64 and 65-74 years of age), and history of hypertension and diabetes (specific aim 2e).

Sensitivity analysis Corresponding to the sensitivity analysis of Section 2.3.1, we reduced the smoothness of the time trend function to increase the adaptation to the data. We also left out the seasonal categories because of potentially competing effects with time trend and temperature and additionally adjusted for influenza epidemics. Moreover, we included barometric pressure as well as air pollutants (PM_{10}, PNC_{m+f} and ozone) linearly with the same lag as the temperature term as additional adjustment. Air pollution marker and respective time lags were chosen on the basis of a significant influence on MI rates in at least one of the five main outcome groups. Alternatively, barometric pressure was also entered as a penalized regression spline. As urbanicity is known to affect

temperatures, we also stratified by region (city vs. counties of Augsburg).

2.3.3 Interactions between air pollutants and temperature

Specific aim 3 included the inspection of possible interacting effects between air pollutants and temperature on the occurrence of MI. We used the confounder model described in Section 2.3.2 for all four interaction models A to D. Thus, time trend was included as a penalized regression spline, and relative humidity as a linear term with the same lag as temperature and the air pollutant term. Season was included as a categorical variable (Mar-May, Jun-Aug, Sep-Nov and Dec-Feb) and day of the week was incorporated as an indicator variable for Mondays. Interactions between air pollutants and temperature were examined for the specific lag of one pollutant and the outcome groups which showed a significant association in the single exposure models. Models C and D incorporate the two exposures as bivariate smooth functions. We therefore standardized the air pollutant and temperature variables as the default thin plate regression splines approach does not fit optimally if the quantities are measured in different units (Wood, 2006).

3 Results

This chapter gives a detailed description of the study population in the first section. The second section describes the distribution of air pollutants and meteorologic parameters. The results of an association between air pollutants and MI (specific aim 1), temperature and MI (specific aim 2), and interacting effects of pollutants and temperature on MI rates (specific aim 3) are presented in Sections 3.3, 3.4 and 3.5.

3.1 Study population

A total of 9801 coronary events occurring in 9199 persons were recorded between 1995 and 2004. Baseline characteristics for all cases and MI subgroups are summarized in Table 3.1. Of all events, 4838 were nonfatal MIs and 4963 were coronary deaths and fatal MIs (MI's between the second and 28th day). The proportion of incident and recurrent MIs was 70% and 21%, respectively. The remaining 9% could not be categorized in either one of the two subgroups, because of missing information and originated almost exclusively from fatal cases. 56% of recurrent events but only 43% of incident MIs were fatal. The percentage of men was lower and mean age was higher within fatal cases than within nonfatal cases. Patients with recurrent MI were older and included more men than patients with incident MI.

Daily event numbers were quite stable over the ten-year period with approximately three cases per day (Figure 3.1). A locally weighted regression scatterplot smoother with a span of 0.1 visualizes the seasonality with higher rates in winter and lower rates in summer. The maximum number of ten occurred three times while 254 days showed no events. The yearly number of cases ranged from 937 to 1042 with a mean of 980.

Figure 3.2 shows the event numbers for nonfatal and fatal (left side) and incident and recurrent (right side) cases per day. The seasonality of events is still visible in these subgroups. Since the year 2000, rates for nonfatal events have been increasing while fatal cases have been decreasing. First or recurrent events did not show substantial changes over time.

Table 3.1: Study population in Augsburg, Germany, 1995-2004.

	Missings N (%)	Total MI	Nonfatal MI	Fatal MI	p-value	Incident MI	Recurrent MI	Insufficient data*	p-value
No. of cases	-	9801	4838	4963		6902	2030	869	
Mean age (SD) [years]	-	62.8 (9.2)	60.6 (9.6)	64.9 (8.3)	<0.001†	62 (9.5)	64.9 (7.7)	63.9 (8.8)	<0.001§
Men [%]	-	73	77	70	<0.001‡	72	79	68	<0.001‡
City of Augsburg [%]	-	50	49	51	<0.045‡	48	54	60	<0.001‡
History of									
Hypertension [%]	832 (8.5)	68	70	66	<0.001‡	66	77	72	<0.001‡
Diabetes mellitus [%]	835 (8.5)	34	29	39	<0.001‡	30	43	51	<0.001‡
25-54 years									
No. of cases	-	1828	1244	584		1462	230	136	
Men [%]	-	84	85	82	0.067‡	84	88	79	0.068‡
City of Augsburg [%]	-	50	49	52	0.161‡	49	51	61	0.021‡
History of									
Hypertension [%]	148 (8.1)	53	55	49	0.049‡	51	67	63	<0.001‡
Diabetes mellitus [%]	152 (8.3)	18	18	18	0.853‡	17	27	24	<0.001‡
55-64 years									
No. of cases	-	2937	1631	1306		2126	583	228	
Men [%]	-	79	79	80	0.813‡	78	84	81	0.010‡
City of Augsburg [%]	-	49	48	50	0.472‡	47	54	60	<0.001‡
History of									
Hypertension [%]	231 (7.9)	63	71	53	<0.001‡	64	74	22	<0.001‡
Diabetes mellitus [%]	226 (7.7)	33	30	38	<0.001‡	30	44	55	<0.001‡
65-74 years									
No. of cases	-	5036	1963	3073		3314	1217	505	
Men [%]	-	66	69	64	<0.001‡	66	80	70	<0.001‡
City of Augsburg [%]	-	52	51	52	0.364 ‡	49	54	59	<0.001‡
History of									
Hypertension [%]	453 (9.0)	69	72	64	<0.001‡	72	78	74	<0.001‡
Diabetes mellitus [%]	457 (9.1)	39	35	43	<0.001‡	37	45	54	<0.001‡

* for classifying incident or recurrent event

† Wilcoxon rank sum test; ‡ Pearson's chi-squared test; § Kruskal-Wallis rank sum test

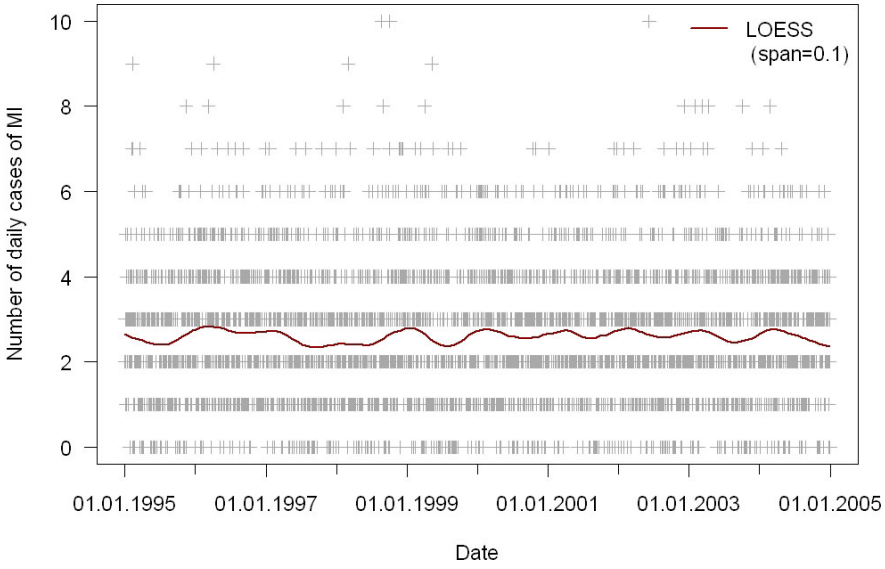

Figure 3.1: Daily numbers of MI between 01.01.1995 and 31.12.2004.

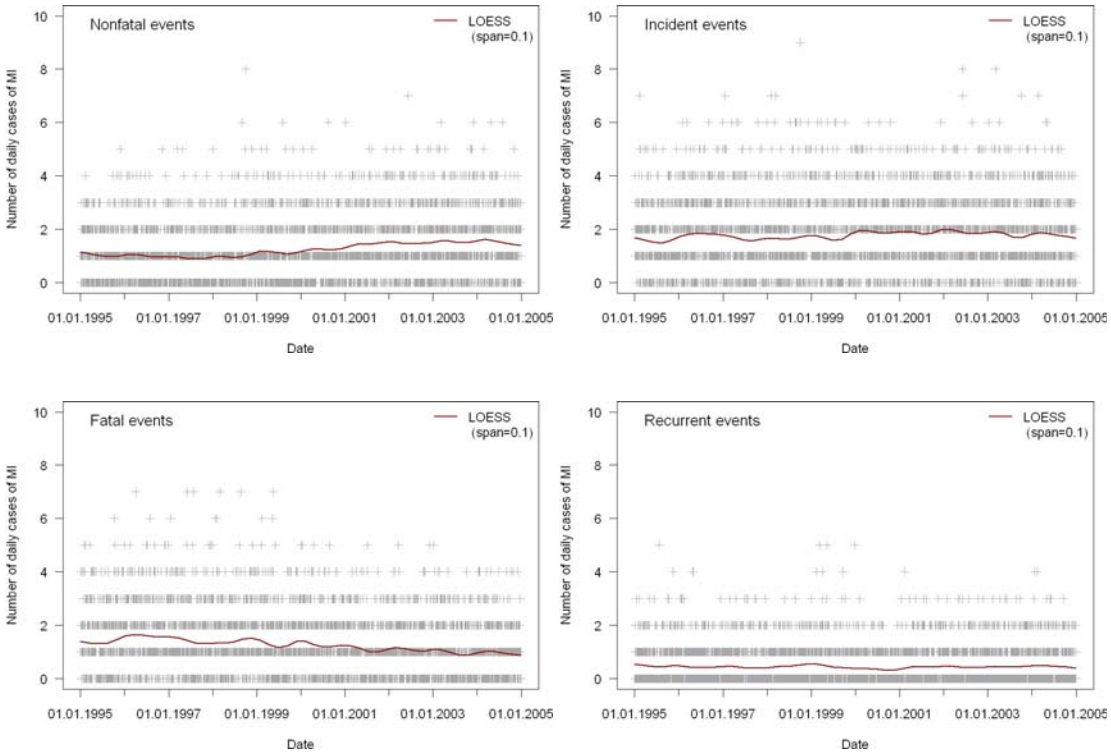

Figure 3.2: Daily numbers of nonfatal (top left), fatal (bottom left), incident (top right) and recurrent (bottom right) MIs between 01.01.1995 and 31.12.2004.

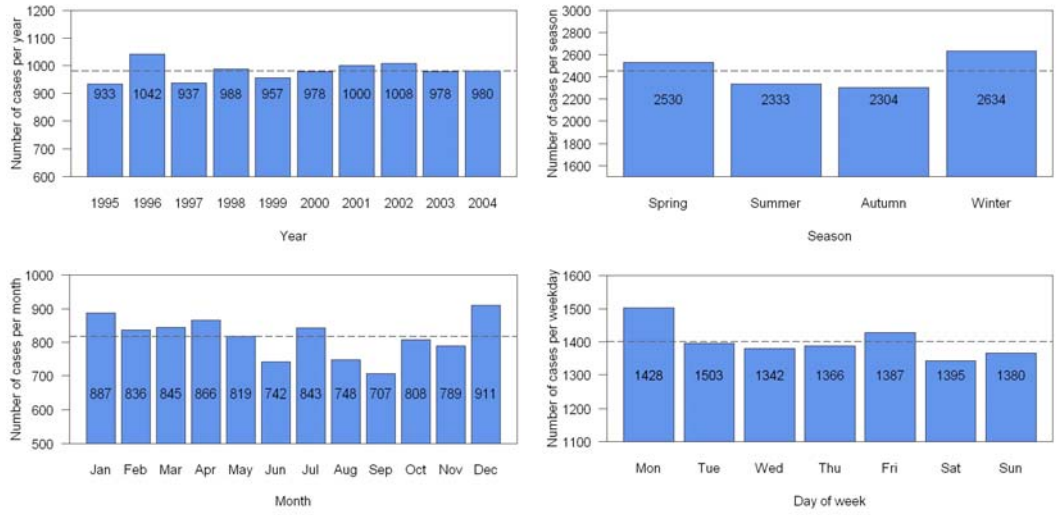

Figure 3.3: Numbers of MI cases per year (top left), season (top right), month (bottom left) and day of week (bottom right). The horizontal lines correspond to the number of cases if uniformly distributed.

Figure 3.3 specifies the frequencies per year, season, month and day of week, respectively, compared to the expected numbers if cases are uniformly distributed. These numbers were calculated by dividing all 9801 events by 10 years, 4 seasons, 12 months, and 7 days, respectively. Hence, expected mean numbers were 980 per year, 2450 per season, 817 per month, and 1400 per day. The distribution over the ten years was quite constant, only the year 1996 showed relatively high numbers with 1042 cases. Regarding season, event numbers were higher in winter and slightly elevated in spring. With the exception of Julys, event numbers in the colder months from December to April slightly exceeded the mean whereas the warmer months partly fell far below the average. Most of the MIs occured during the week and especially on Mondays, which is noticeable high with 1503 cases, and on Fridays. Saturdays showed the lowest frequency.

3944 persons suffered an incident nonfatal MI between 1995 and 2004. According to the guidelines of the MI registry, they could be followed for recurrent events as long as they were inhabitants of the study region. Of these 3944 persons, 458 persons developed at least one recurrent event. Follow–up time started 28 days after the incident event to be able to differentiate two successive events correctly and ended at the latest in December 2005. The frequencies of recurrent events are given in Table 3.2.

Table 3.2: Frequencies of recurrent events in persons with nonfatal incident event during the study period.

	Incident nonfatal MI	Recurrent event (RE)				
Obs. time	01.01.95 – 31.12.04	29.01.95 – 31.12.05				
Event	1. MI	1. RE	2. RE	3. RE	4. RE	5. RE
N	3944	458	52	10	2	1

The dates of occurrence and time between events for persons with at least two recurrent events are visualized in Figure 3.4.

3.2 Air pollution and meteorology measurements

Time series of PM_{10}, PNC_{m+f} and $MaxO_3$ are shown in Figure 3.5, time series of $PM_{2.5}$, and gaseous air pollutants can be found in the appendix, Figure A.1, and time series of meteorologic parameters in Figure 3.6. Seasonality is visible for all variables. Pollution concentrations are usually higher in winter, only ozone shows higher concentrations in summer months.

The distribution of the 24–hour average pollutant concentrations and meteorologic measures can be found in Table 3.3. As measured PNC values (PNC_m) have only been available since February 1999, we imputed missing days before with corresponding fitted values to complete the time series for the whole period (PNC_{m+f}).

Table 3.4 shows the Spearman correlation coefficients for particulate and gaseous air pollutants and meteorology. The particle mass concentrations PM_{10} and $PM_{2.5}$ were moderately correlated with PNC and gaseous pollutants but indicated no correlation with meteorologic parameters. PNC_{m+f} showed only moderate association with most other variables and was somewhat higher correlated with gases than PNC_m, especially for SO_2.

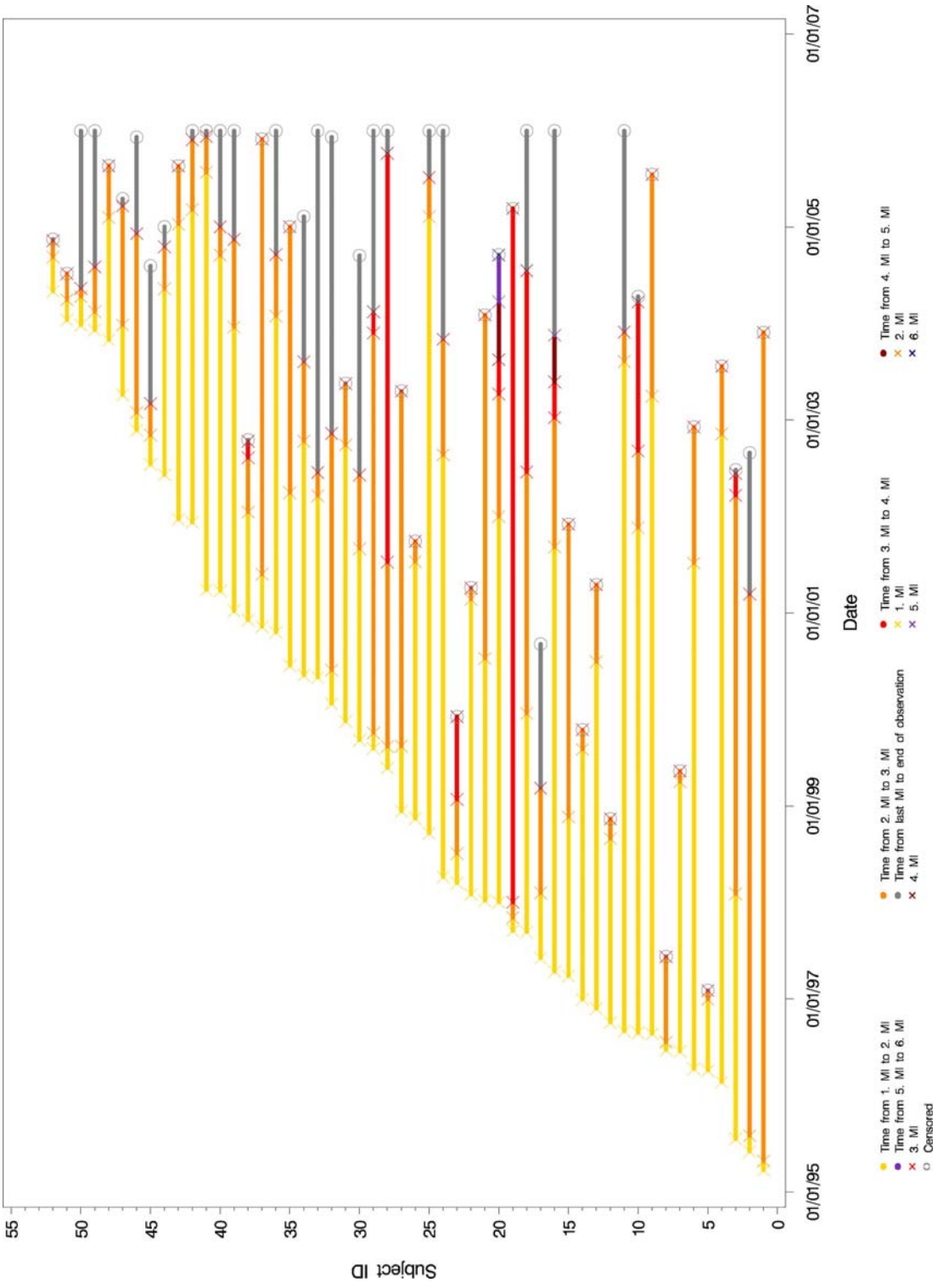

Figure 3.4: First and recurrent events over time for persons with at least three events. Censoring included end of follow-up (31.12.2005), death, removal or reaching the age limit of the registry (75 years). End of study period: 31.12.2004.

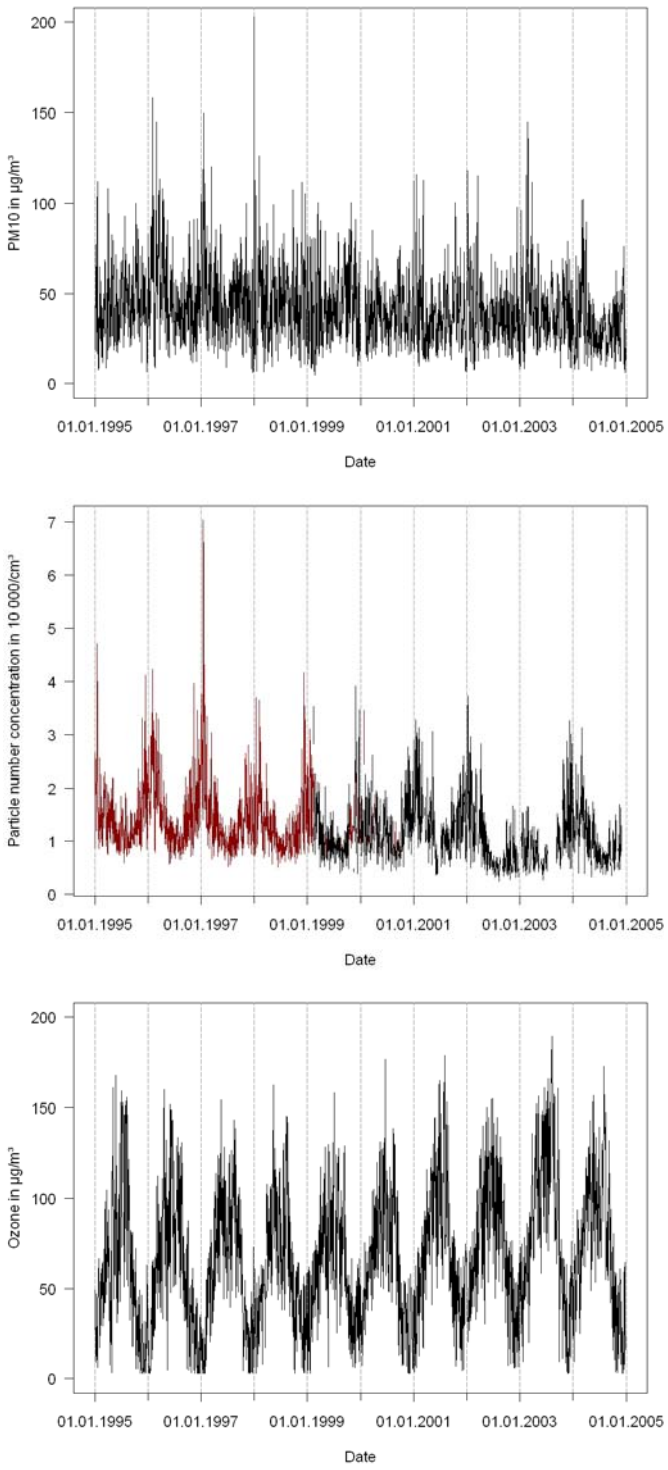

Figure 3.5: Time series of PM_{10}, PNC_{m+f} and $MaxO_3$. Imputed PNC_{m+f} values are marked red.

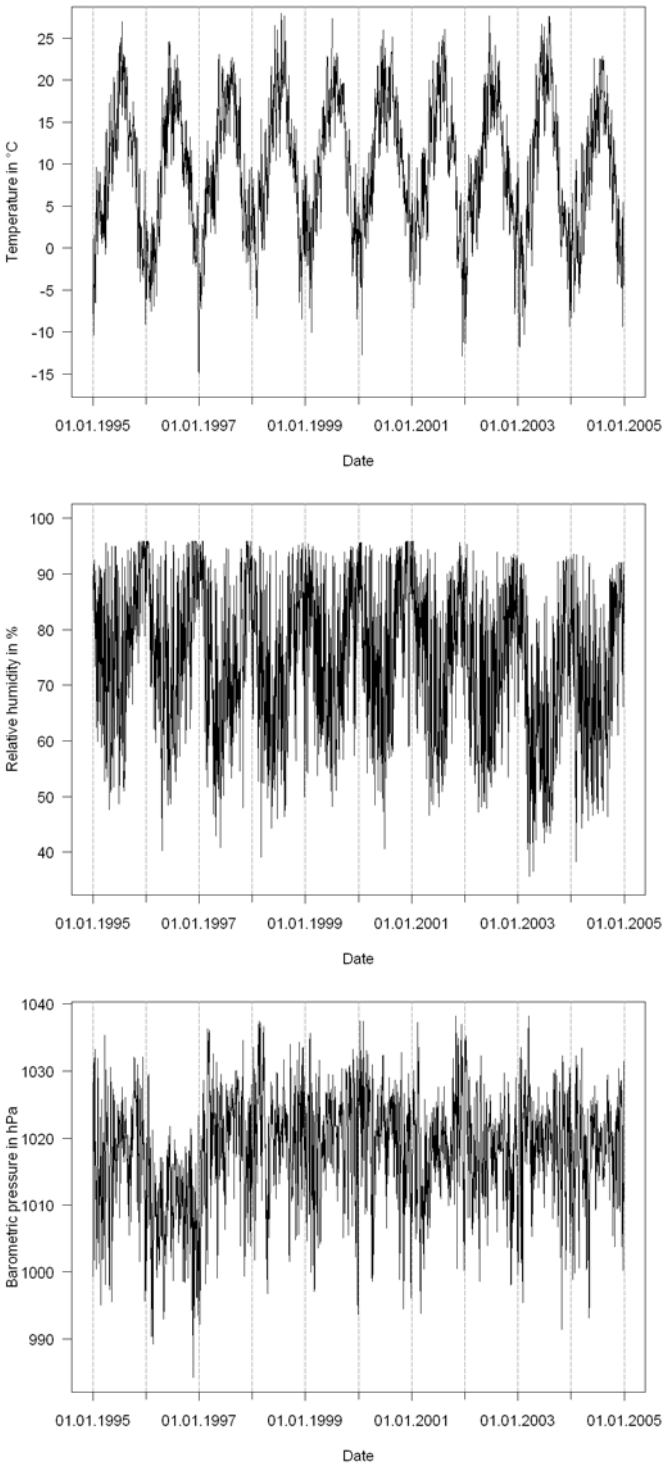

Figure 3.6: Time series of air temperature, relative humidity and barometric pressure.

Table 3.3: Summary statistics for meteorology and air pollutants (data on 3653 consecutive days).

Variable	N in %	Mean (SD)	Min	25%	50%	75%	Max	IQR*
Particles								
PM_{10}† ($\mu g/m^3$)	99.0	41.8 (19.9)	4.6	27.8	39.0	52.4	203.0	24.6
$PM_{2.5}$† ($\mu g/m^3$)	51.8	16.9 (7.1)	5.6	11.8	15.4	20.2	58.5	8.4
PNC_m‡ (10 000/cm^3)	48.0	1.1 (0.5)	0.2	0.7	1.0	1.4	3.9	0.6
PNC_{m+f}‡ (10 000/cm^3)	92.2	1.3 (0.6)	0.2	0.8	1.1	1.5	7.0	0.7
Gases								
CO (mg/m^3)	95.5	0.8 (0.4)	0.2	0.5	0.7	0.9	3.9	0.4
NO ($\mu g/m^3$)	99.8	50.0 (30.2)	9.7	30.9	42.9	60.4	282.3	29.5
NO_2 ($\mu g/m^3$)	99.8	46.0 (13.3)	14.7	37.1	44.7	53.2	160.1	16.1
SO_2 ($\mu g/m^3$)	99.9	4.5 (3.9)	1.9	2.4	3.3	5.2	54.7	2.8
$MaxO_3$ ($\mu g/m^3$)	99.3	66.6 (36.7)	3.0	40.8	62.9	90.8	189.7	50.1
Temperature measures								
T (°C)	99.6	9.5 (8.0)	-14.9	3.2	9.8	16.0	27.9	12.8
T_{min} (°C)	99.6	5.0 (7.1)	-20.1	-0.1	5.3	10.8	19.8	11.0
T_{max} (°C)	99.6	14.4 (9.7)	-11.8	6.8	14.2	22.1	39.2	15.4
T_{range} (°C)	99.6	9.4 (5.1)	0.5	5.3	8.6	13.2	25.1	7.9
AT§ (°C)	99.6	7.7 (8.7)	-13.0	0.6	7.5	14.7	28.9	14.1
DP§ (°C)	99.6	4.4 (6.5)	-17.0	-0.4	4.7	9.8	17.7	10.3
Other meteorological variables								
RH§ (%)	99.8	74.5 (13.2)	35.8	64.2	75.7	85.7	96.0	21.5
BP§ (hPa)	99.6	1018 (8)	984	1013	1019	1024	1038	10

* IQR: interquartile range;
† PM_{10}: particles with diameter <10µm; $PM_{2.5}$: particles with diameter <2.5µm;
‡ PNC_m: particle number concentration, only measured values (1999-2004); PNC_{m+f}: PNC_m and retrospectively fitted values (1995-1998);
§ AT: apparent temperature; DP: dewpoint temperature; RH: relative humidity; BP: barometric pressure.

3.3 Association of air pollutants and MI

3.3.1 Single exposure models

Results of the single pollutant Poisson models for different lags of particulate and gaseous air pollutants are presented in Tables 3.5 and in the appendix, Table A.2. Relative risk (RR) estimates and corresponding 95% confidence intervals (CI) for the effects on daily number of MI are expressed for an interquartile range (IQR) increase in air pollutants.

Overall, most point estimates were positive, but not statistically significant. An IQR increase of PM_{10} was borderline associated with an increased RR for the total numbers of daily MIs on the same day. Nonfatal events showed a risk increase in association with lag1 PM_{10} and the 5–day average concentration. For incident events, results also pointed to an association for a lag of one day. $PM_{2.5}$ showed

Table 3.4: Spearman correlation coefficients for particulate and gaseous air pollutants and meteorology.

	$PM_{2.5}$	PNC_m	PNC_{m+f}	CO	NO	NO_2	SO_2	$MaxO_3$	T	$T_{m1\text{-}3}$	T_{min}	T_{max}	T_{range}	AT	DP	RH	BP*
PM_{10}*	0.87	0.38	0.48	0.59	0.50	0.51	0.57	−0.04	0.02	−0.05	−0.06	0.10	0.29	0.02	−0.03	−0.12	0.22
$PM_{2.5}$*		0.33	0.35	0.48	0.30	0.46	0.57	0.01	−0.01	−0.09	−0.12	0.08	0.37	−0.02	−0.10	−0.18	0.30
PNC_m*			1.00	0.60	0.54	0.38	0.66	−0.24	−0.37	−0.42	−0.47	−0.27	0.16	−0.38	−0.43	0.01	0.12
PNC_{m+f}*				0.63	0.63	0.42	0.78	−0.33	−0.46	−0.51	−0.55	−0.36	0.06	−0.47	−0.52	0.07	0.05
CO					0.74	0.41	0.68	−0.39	−0.25	−0.29	−0.27	−0.20	0.00	−0.24	−0.18	0.27	0.18
NO						0.33	0.60	−0.55	−0.30	−0.32	−0.30	−0.26	−0.09	−0.29	−0.2	0.36	0.07
NO_2							0.59	0.12	0.06	−0.03	−0.07	0.15	0.42	0.05	−0.05	−0.22	0.14
SO_2								−0.30	−0.40	−0.46	−0.48	−0.32	0.06	−0.41	−0.45	0.08	0.10
$MaxO_3$									0.70	0.63	0.56	0.74	0.66	0.68	0.46	−0.79	0.07
T										0.93	0.95	0.97	0.56	1.00	0.92	−0.56	0.08
$T_{m1\text{-}3}$											0.92	0.89	0.44	0.94	0.89	−0.46	0.07
T_{min}												0.87	0.30	0.96	0.96	−0.36	0.03
T_{max}													0.72	0.97	0.84	−0.65	0.10
T_{range}														0.54	0.30	−0.77	0.17
AT*															**0**.93	−0.53	0.07
DP*																−0.21	0.01
RH*																	−0.18

* PM_{10}: particles with diameter <10µm; $PM_{2.5}$: particles with diameter <2.5µm;
PNC_m: particle number concentration, only measured values (1999-2004); PNC_{m+f}: PNC_m and retrospectively fitted values (1995-1998);
AT: apparent temperature; DP: dewpoint temperature; RH: relative humidity; BP: barometric pressure.

Table 3.5: Relative risk (RR) estimates and 95% confidence intervals (CI) for daily cases of MI per interquartile range increase in air pollutants adjusted for time trend, season, current day temperature, mean of lag1-3 day temperature and Mondays.

		Total		Nonfatal		Fatal		Incident MI		Recurrent MI	
Pollutant		RR	(95% CI)	RR	(95% CI)	RR	(95% CI)	RR	(95% CI)	RR	(95% CI)
PM_{10}*	Lag0	1.02	(1.00;1.05)†	1.01	(0.97;1.06)	1.03	(0.99;1.07)	1.03	(0.99;1.06)	1.05	(0.99;1.11)
	Lag1	1.02	(0.99;1.05)	1.05	(1.01;1.10)‡	0.99	(0.95;1.03)	1.03	(1.00;1.07)†	1.02	(0.97;1.08)
	Lag2	1.00	(0.97;1.03)	1.02	(0.98;1.06)	0.98	(0.94;1.02)	1.01	(0.97;1.04)	1.03	(0.97;1.09)
	Lag3	1.01	(0.98;1.03)	1.03	(0.99;1.07)	0.99	(0.96;1.03)	1.01	(0.98;1.05)	1.03	(0.98;1.09)
	Lag4	0.99	(0.97;1.02)	1.02	(0.98;1.06)	0.97	(0.93;1.01)	1.00	(0.97;1.04)	0.99	(0.94;1.05)
	5d ave.	1.01	(0.99;1.04)	1.04	(1.00;1.08)†	0.99	(0.95;1.03)	1.02	(0.99;1.06)	1.03	(0.98;1.09)
$PM_{2.5}$*	Lag0	1.00	(0.96;1.04)	1.00	(0.95;1.05)	0.99	(0.94;1.05)	1.00	(0.96;1.05)	1.01	(0.94;1.09)
	Lag1	1.00	(0.97;1.04)	1.01	(0.96;1.06)	0.99	(0.94;1.05)	1.01	(0.97;1.06)	0.97	(0.90;1.05)
	Lag2	1.00	(0.96;1.03)	1.03	(0.98;1.08)	0.96	(0.91;1.02)	1.00	(0.96;1.05)	0.99	(0.92;1.06)
	Lag3	0.99	(0.96;1.03)	1.01	(0.96;1.06)	0.97	(0.92;1.02)	0.98	(0.94;1.02)	1.03	(0.96;1.11)
	Lag4	0.99	(0.96;1.03)	1.01	(0.96;1.05)	0.98	(0.93;1.03)	0.99	(0.95;1.03)	1.01	(0.94;1.08)
	5d ave.	0.99	(0.96;1.03)	1.01	(0.97;1.06)	0.97	(0.92;1.03)	0.99	(0.95;1.03)	1.01	(0.93;1.09)
PNC_{m+f}*	Lag0	1.01	(0.99;1.04)	1.01	(0.96;1.05)	1.02	(0.98;1.06)	1.01	(0.98;1.05)	1.05	(0.99;1.12)
	Lag1	1.00	(0.97;1.03)	0.99	(0.95;1.04)	1.00	(0.96;1.05)	1.01	(0.97;1.05)	1.01	(0.95;1.07)
	Lag2	1.00	(0.97;1.03)	1.02	(0.98;1.07)	0.98	(0.94;1.02)	1.01	(0.98;1.05)	1.02	(0.95;1.08)
	Lag3	1.00	(0.98;1.03)	1.03	(0.99;1.08)	0.98	(0.94;1.02)	0.99	(0.96;1.03)	1.08	(1.02;1.14)‡
	Lag4	1.00	(0.97;1.03)	1.02	(0.98;1.07)	0.97	(0.94;1.01)	0.99	(0.96;1.02)	1.06	(1.00;1.12)†
	5d ave.	1.01	(0.97;1.04)	1.03	(0.98;1.09)	0.98	(0.93;1.03)	1.00	(0.96;1.05)	1.08	(1.01;1.16)‡
$MaxO_3$*	Lag0	1.01	(0.96;1.06)	0.98	(0.91;1.05)	1.04	(0.97;1.11)	1.01	(0.96;1.08)	1.00	(0.90;1.11)
	Lag1	1.01	(0.97;1.06)	0.98	(0.92;1.05)	1.04	(0.98;1.12)	1.01	(0.95;1.07)	1.03	(0.93;1.14)
	Lag2	0.99	(0.95;1.04)	0.95	(0.89;1.02)	1.03	(0.96;1.10)	0.96	(0.90;1.02)	1.06	(0.96;1.17)
	Lag3	1.00	(0.96;1.05)	0.93	(0.87;1.00)†	1.07	(1.00;1.15)‡	0.97	(0.92;1.03)	1.03	(0.93;1.14)
	Lag4	1.01	(0.97;1.06)	1.01	(0.95;1.08)	1.01	(0.95;1.08)	1.01	(0.95;1.06)	1.07	(0.97;1.18)
	5d ave.	1.01	(0.95;1.07)	0.95	(0.87;1.04)	1.07	(0.98;1.17)	0.98	(0.91;1.06)	1.08	(0.94;1.24)

* PM_{10}: particles with diameter < 10μm; $PM_{2.5}$: particles with diameter < 2.5μm;
PNC_{m+f}: particle number concentration, retrospectively fitted (1995-1998) and measured values (1999-2004); $MaxO_3$: ozone, maximum 8 hour moving average;
† borderline significant; ‡ significant (p<0.05).

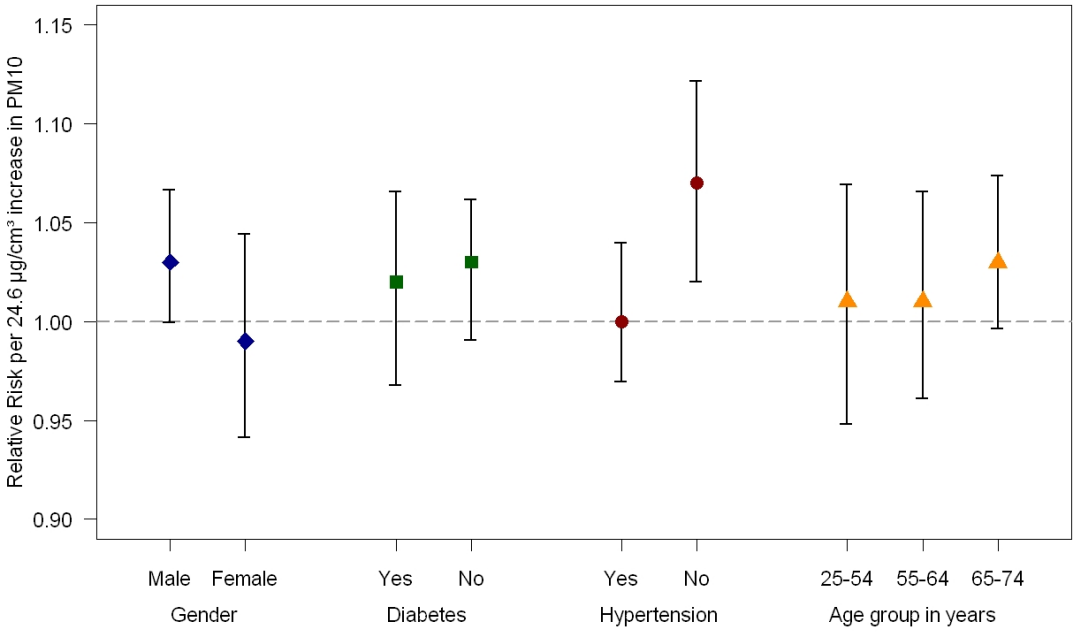

Figure 3.7: Relative risks for total numbers of daily MI cases per interquartile range increase in same-day PM_{10} adjusted for time trend, current day and previous 3–day average temperature, season, and Mondays stratified by subgroups.

no influence on the daily event numbers. A higher exposure of PNC_{m+f} affected the risk for recurrent events several days later. The estimates for ozone showed protective, but not statistically significant effects for nonfatal events. The risk for fatal cases was increased. Other gaseous pollutants were not associated with daily numbers of MI in any subgroup.

The inspection of potential effect modification by personal characteristics was limited to PM_{10} concentrations as the other pollutants did not show any effects on the total numbers of daily MIs. Figure 3.7 visualizes the RR estimates for an IQR increase in PM_{10} stratified by gender, history of diabetes and hypertension as well as three age groups. The risks were increased for men and hypertensive people, while women and people without hypertension were not influenced by a higher exposure to PM_{10}. No effect modification was found for diabetes. Persons aged 65 to 74 showed a somewhat higher risk compared to younger patients.

Sensitivity analysis RR estimates calculated by main and sensitivity models are compared for selected groups, pollutants and lags which showed significant

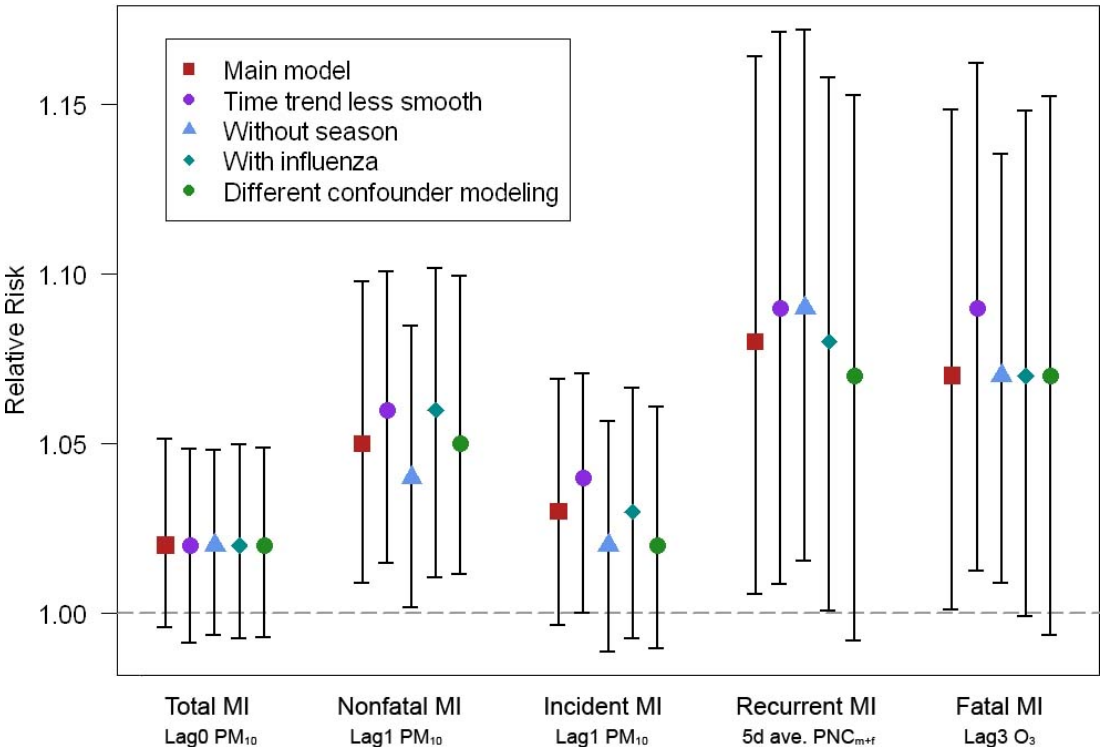

Figure 3.8: Sensitivity analysis: Relative risk estimates for total, nonfatal, incident, recurrent, and fatal MIs per interquartile range increase in lag0 PM_{10}, lag1 PM_{10}, 5 day average PNC_{m+f} and Lag3 $MaxO_3$. The main model (red squares) was adjusted for time trend, season, current day temperature, mean of lag1-3 day temperature and Mondays. Sensitivity models were altered according to the legend.

or borderline significant effects, in Figure 3.8. The comprehensive table can be found in the appendix, Table A.3. A less smooth function for time trend to allow more variability in the seasonal adjustment led to similar results. The RR estimates for an IQR increase in 5 day average PM_{10} in association with nonfatal events as well as previous day PM_{10} and incident events were now significant. The exclusion of season did not alter the results considerably for PM_{10} or PNC_{m+f}. Effects for ozone were slightly higher. An additional adjustment for influenza epidemics resulted in similar RR estimates. Moreover, the alternative confounder selection of meteorologic parameters based on a minimization of GCV produced more conservative estimates. PM_{10} effects were not consistent and indicated no statistically significant association with MIs when reducing the study period to the last six years. Like for the whole period, PNC_m showed a risk increase in

recurrent events for lag3 and additionally for same day concentrations.

3.3.2 Polynomial distributed lag models

Polynomial distributed lag models were used for a better understanding of the combined influence of same-day and lagged exposures on the daily numbers of MI. We finally chose a polynomial of 4 degrees and 12 lags as an influence appeared mainly in the shorter lags and flattened with longer lags.

For the total number of events, only an association with same-day PM_{10} concentrations could be observed which subsided for the other lags (Figure 3.9). This immediate association was also visible for fatal and incident events, whereas nonfatal MIs showed a more delayed pattern. The effects on fatal events showed kind of a harvesting pattern. The estimates became significantly negative for lag2 to lag4 and then, turned positiv again. The term harvesting implies increased events on the first day after exposure which reduce the risk pool of susceptible individuals. This results in a decrease of cases on the following days until the pool of susceptible people is filled up again. Incident MIs reacted more moderately. The delayed protective effects followed by a high positive effect of lag12 for recurrent events point to an overfitting which is caused by the polynomial assumption and the few event numbers. The overall association were all positive, but not significant.

Distributed lag estimates for PNC_{m+f} were quite similar to PM_{10} for all outcome groups (Figure 3.10). However, the overall effects were negative for total, fatal and incident events, but neither was significant.

The opposite shapes of ozone estimates in association with nonfatal and fatal as well as incident and recurrent events summed up to no influence on the total number of daily MIs in any lag (Figure 3.11). All four subgroups showed no effects for current day ozone. While risk estimates for nonfatal and incident MIs turned negative and switched to positive after lag5, estimates on fatal and recurrent events ran contrarily. The overall effects showed no association.

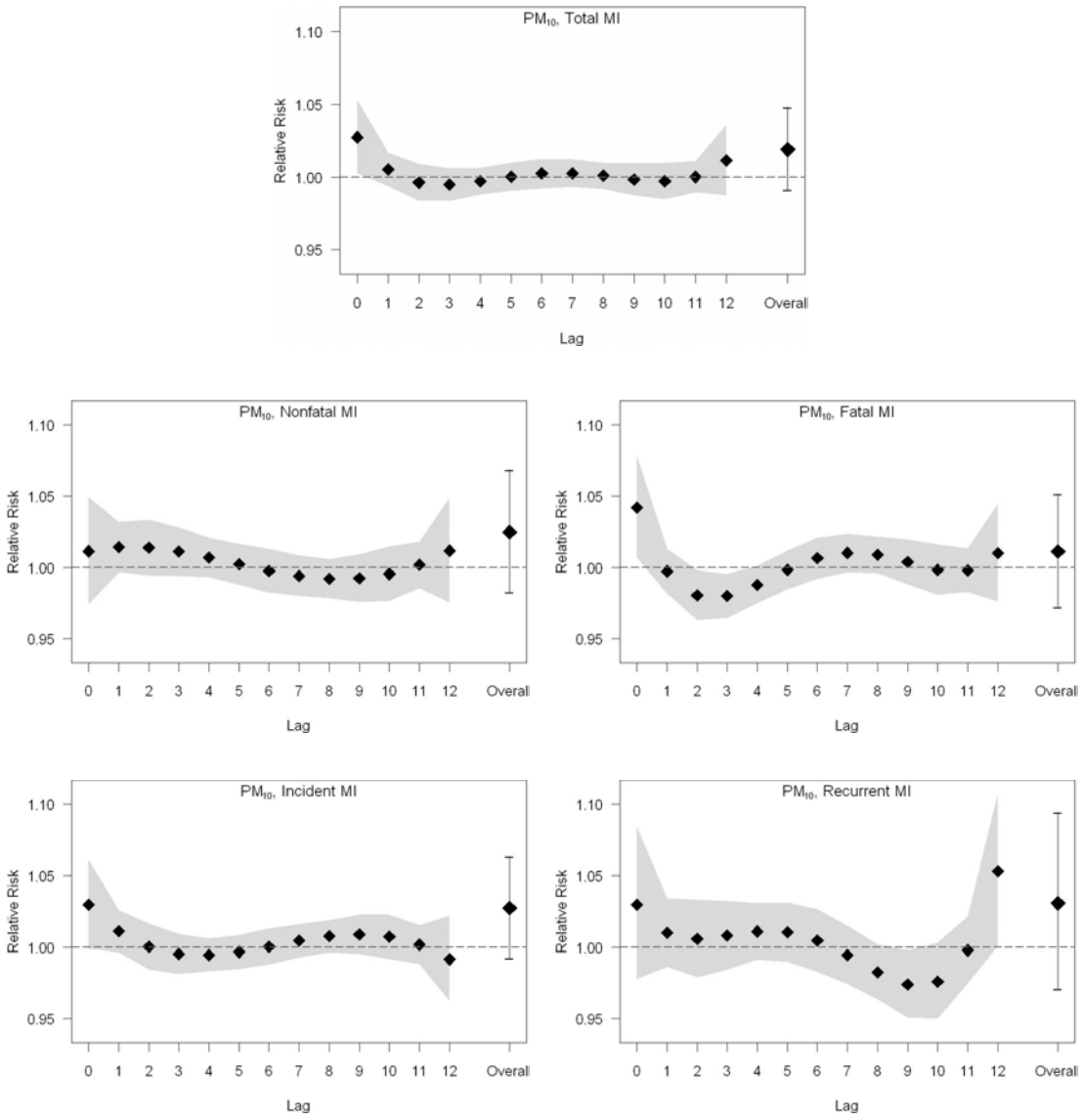

Figure 3.9: Distributed lag estimates of relative risk for an interquartile range increase in PM_{10} in association with daily total, nonfatal, fatal, incident or recurrent events. Distributed lags were calculated with a fourth-degree polynomial. Also shown is the cumulative 13 day relative risk. The shaded area corresponds to the 95% confidence intervals.

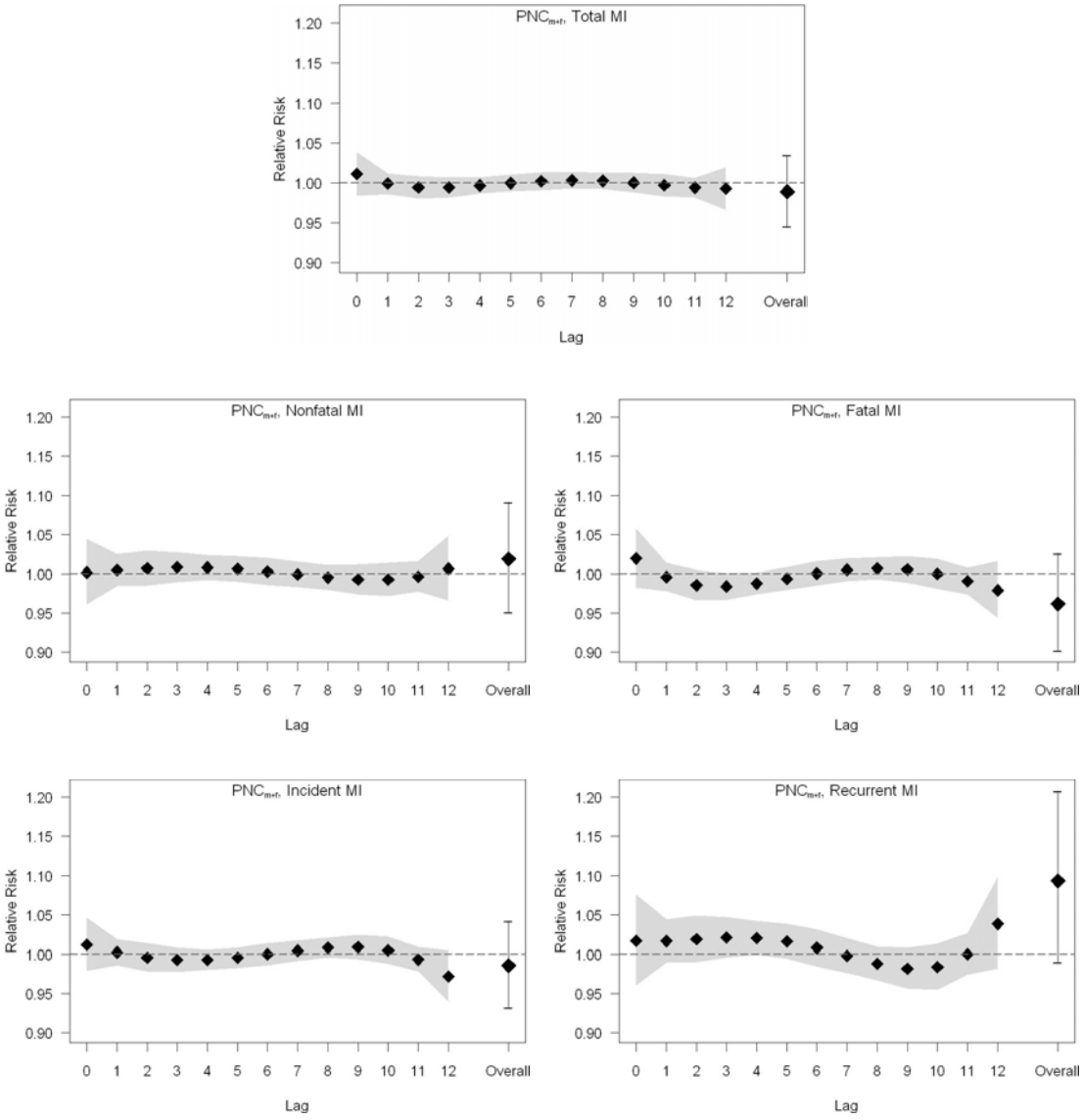

Figure 3.10: Distributed lag estimates of relative risk for an interquartile range increase in PNC_{m+f} in association with daily total, nonfatal, fatal, incident or recurrent events. Distributed lags were calculated with a fourth-degree polynomial. Also shown is the cumulative 13 day relative risk. The shaded area corresponds to the 95% confidence intervals.

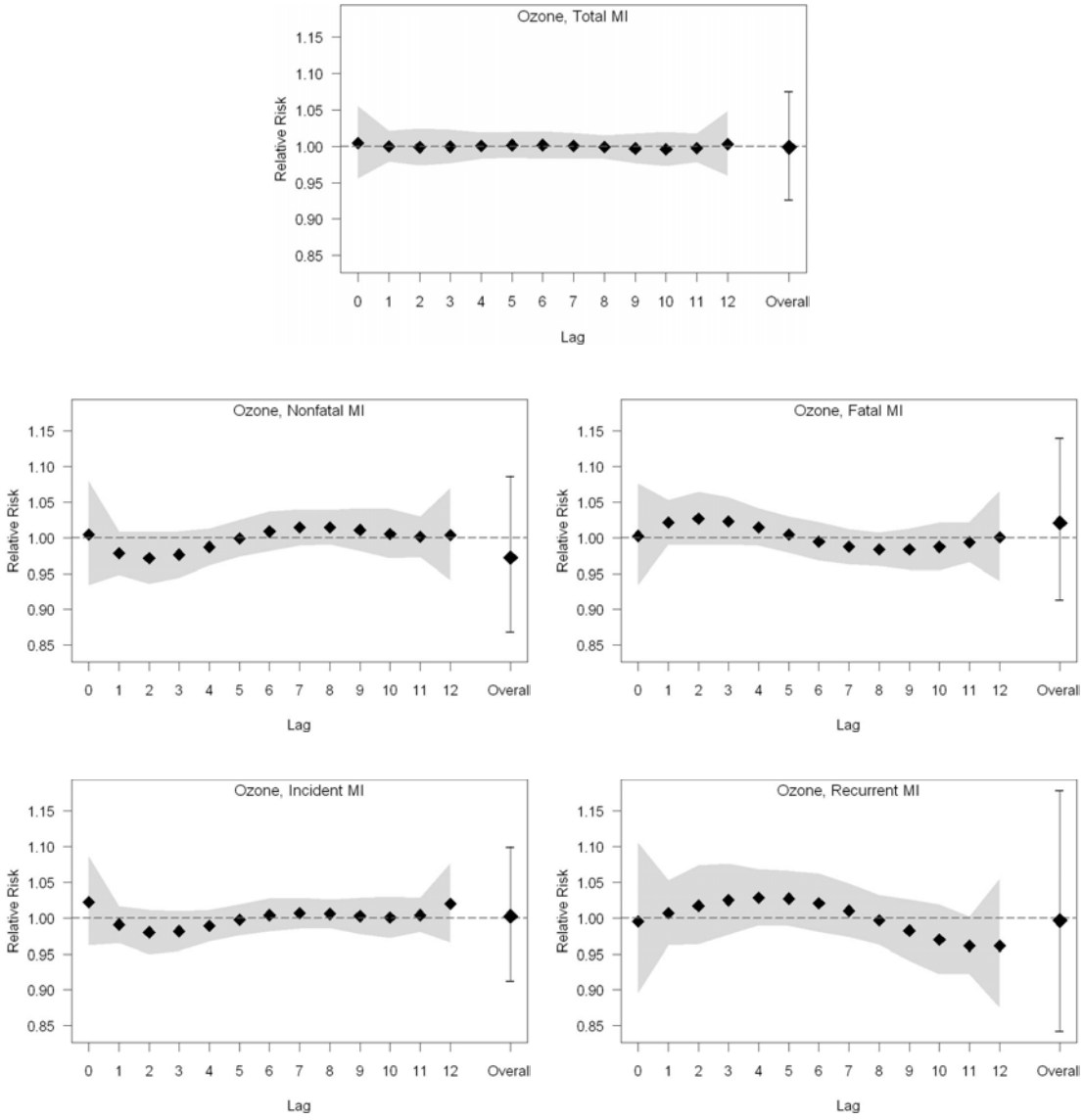

Figure 3.11: Distributed lag estimates of relative risk for an interquartile range increase in $MaxO_3$ in association with daily total, nonfatal, fatal, incident or recurrent events. Distributed lags were calculated with a fourth-degree polynomial. Also shown is the cumulative 13 day relative risk. The shaded area corresponds to the 95% confidence intervals.

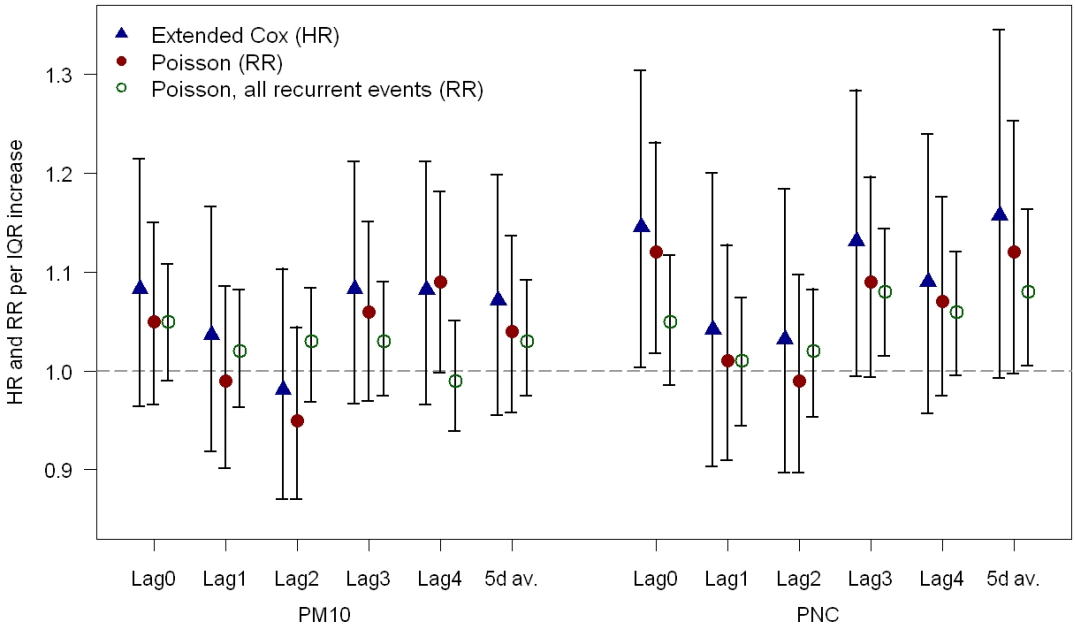

Figure 3.12: Hazard ratios (HR) and relative risks (RR) for recurrent events of persons with first MI during the study period per IQR increase in PM_{10} and PNC_{m+f} calculated with an extended Cox model (blue triangles) and a Poisson regression (red dots). Green circles correspond to Poisson RR estimates for all recurrent events (see Table 3.5).

3.3.3 Extended Cox model

Additional to the inspection of all recurrent events, we investigated recurrent events of persons who suffered their incident MI during the study period in an alternative approach. This constraint limited the number of observations to 3944 patients with first MI and 523 recurrent events. Figure 3.12 compares hazard ratios (HR) and RR estimates for PM_{10} and PNC_{m+f} calculated for this group by extended Cox and Poisson regression. Effects of the Cox model were slightly higher compared to those of the Poisson regression. The estimates were also quite similar to the results for all recurrent events, though the 95% confidence intervals were wider because of the smaller event numbers.

3.4 Association of temperature and MI

Results of the Poisson models for different lags of air temperature are summarized in Table 3.6.

RR estimates and corresponding 95% CI for the effect of MI events are expressed for a 10°C decrease in air temperature as this number describes a plausible change in temperature and lies close to the interquartile range of 12.8°C. A decrease of 10°C was significantly associated with an increase in the numbers of MI except for recurrent events. Regarding the total number of daily cases the strongest effects were seen for a lag of 3 days and the 5 day average. Nonfatal events showed a delayed pattern, whereas fatal events were associated with temperature of all time windows except for lag4. For the subgroup of incident MIs, the cumulative effect of the 5 day average temperature had the largest RR. Regarding the exposure-response functions for the whole period, but also separately for winters and summers, there was no evidence for a deviation of log-linearity of the relationship between temperature and daily MI counts (Figure 3.13).

The effect estimates for same-day and 5 day average minimum and maximum temperature, temperature range as well as apparent or dew point temperature did not substantially differ from the effect estimate for current and 5 day average mean temperature, respectively (Figure 3.14). Same-day and 5 day average temperature range were less associated with the total number of daily MIs. The inclusion of indicator variables for the 5% and 1% hottest and coldest days did not change the temperature estimates, the indicators itself were not significant.

Figure 3.15 shows the association between MI cases and 5 day average temperature for cold, moderately tempered, and warm years (A), and further divided into cold, moderately tempered, and warm winters (B1) and summers (B2), respectively. The estimates of Panel A were derived from a separate model, whereas the estimates of Panel B1 and B2 resulted from a joint model. The effects of temperature were consistently observed in moderately tempered and warm years, summers and winters. In cold winters, MI rates were less influenced by temperature decreases.

Regarding effect modification, men and women and indiviuals with and without diabetes showed no differences in RR for MI. Patients with history of hypertension showed slightly larger RR compared to patients with no history. The strongest

Table 3.6: Relative risk (RR) and 95% confidence intervals (CI) estimates for daily cases of MI per 10°C decrease in temperature adjusted for time trend, season, Mondays and relative humidity.

	Total	Nonfatal MI	Fatal MI	Incident MI	Recurrent MI
Temperature	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
Lag0	1.07 (1.02;1.12)*	1.04 (0.97;1.12)	1.09 (1.02;1.17)*	1.10 (1.04;1.16)*	0.96 (0.86;1.06)
Lag1	1.08 (1.03;1.13)*	1.07 (0.99;1.14)	1.09 (1.02;1.17)*	1.10 (1.04;1.17)*	0.97 (0.88;1.07)
Lag2	1.08 (1.03;1.13)*	1.09 (1.02;1.17)*	1.08 (1.01;1.15)*	1.10 (1.03;1.16)*	1.02 (0.92;1.12)
Lag3	1.10 (1.05;1.15)*	1.11 (1.04;1.19)*	1.08 (1.01;1.16)*	1.10 (1.04;1.16)*	1.07 (0.97;1.19)
Lag4	1.07 (1.02;1.12)*	1.11 (1.04;1.19)*	1.04 (0.97;1.11)	1.08 (1.02;1.14)*	1.03 (0.93;1.14)
5d ave.	1.10 (1.04;1.15)*	1.10 (1.01;1.18)*	1.10 (1.02;1.19)*	1.12 (1.05;1.19)*	1.02 (0.91;1.14)

* significant ($p<0.05$).

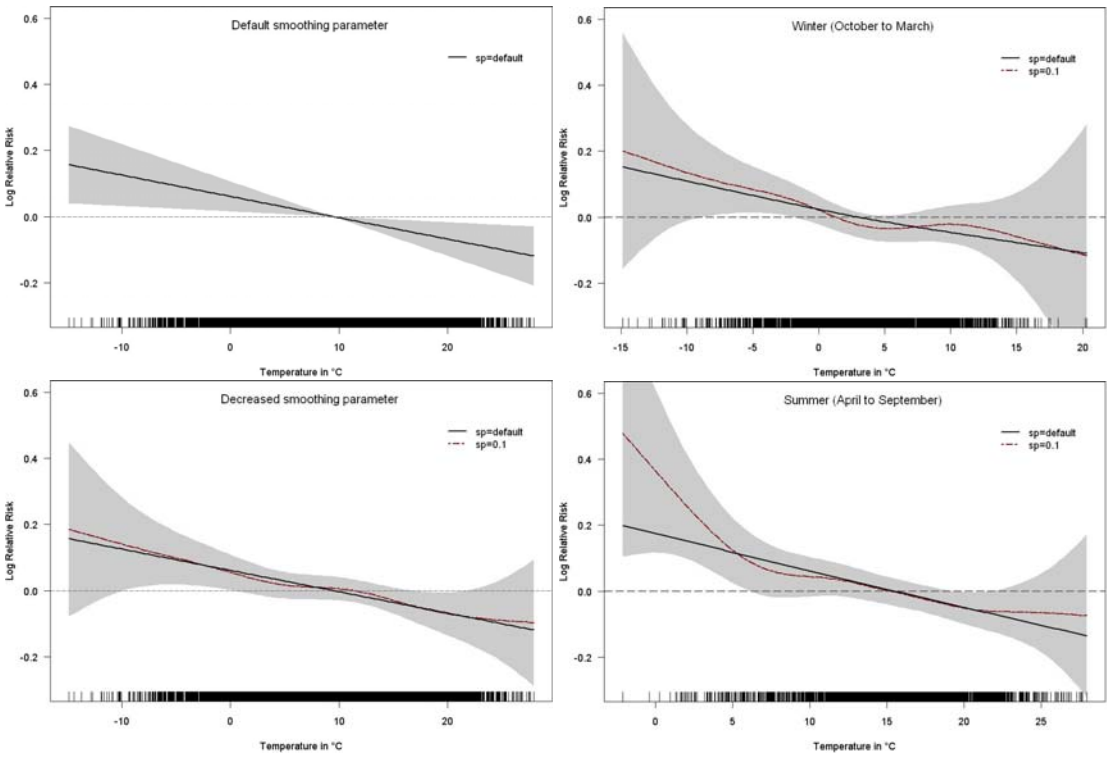

Figure 3.13: Penalized splines of air temperature with default smoothing parameter (black line) and decreased value for the smoothing parameter (red dashed line) for the whole period (left), winter months (top right) and summer months (bottom right).

association was found for patients aged 55-64, whereas for the younger group no effect was observed (Figure 3.16).

Sensitivity analysis

Allowing for more variability in the seasonal adjustment by reducing the smoothing parameter for the penalized spline of time trend did not alter the results considerably (Table 3.7). However, the examination of partial autocorrelation plots indicated some overfitting. The exclusion of season resulted in similar, but somewhat higher effect estimates with narrower confidence intervals. The additional adjustment for influenza epidemics did not affect the temperature estimates. Moreover, neither adjustment for air pollutants nor barometric pressure altered the temperature relationship with MI significantly (Table 3.7). Barometric pressure indicated a V-shaped, but not significant association with MI events (data not shown). Slightly higher RR estimates of 5 day average temperature

Table 3.7: Sensitivity analysis: Relative risk (RR) and 95% confidence intervals (CI) for the total number of daily cases of MI per 10°C decrease in air temperature and per IQR increase of potential confounding air pollutants adjusted for time trend, season, Mondays and relative humidity.

			Total		Nonfatal		Fatal		Incident MI		Recurrent MI	
Exposure			RR	(95% CI)	RR	(95% CI)	RR	(95% CI)	RR	(95% CI)	RR	(95% CI)
Main model												
	Lag0	Temperature	1.07	(1.02;1.12)†	1.04	(0.97;1.12)	1.09	(1.02;1.17)†	1.10	(1.04;1.16)†	0.96	(0.86;1.06)
	5d ave.	Temperature	1.10	(1.04;1.15)†	1.10	(1.01;1.18)†	1.10	(1.02;1.19)†	1.12	(1.05;1.19)†	1.02	(0.91;1.14)
Model with time trend less smooth												
	Lag0	Temperature	1.06	(1.02;1.11)†	1.04	(0.98;1.11)	1.09	(1.02;1.16)†	1.10	(1.04;1.16)†	0.96	(0.87;1.06)
	5d ave.	Temperature	1.10	(1.04;1.16)†	1.09	(1.02;1.18)†	1.10	(1.03;1.18)†	1.12	(1.05;1.19)†	1.02	(0.91;1.15)
Model without season												
	Lag0	Temperature	1.09	(1.06;1.12)†	1.05	(1.01;1.10)†	1.13	(1.08;1.18)†	1.10	(1.06;1.14)†	1.04	(0.97;1.11)
	5d ave.	Temperature	1.10	(1.07;1.14)†	1.08	(1.02;1.13)†	1.14	(1.08;1.19)†	1.11	(1.06;1.15)†	1.08	(1.01;1.17)†
Model additionally adjusted for influenza												
	Lag0	Temperature	1.05	(1.00;1.11)†	1.04	(0.97;1.11)	1.07	(1.00;1.15)†	1.08	(1.02;1.15)†	0.96	(0.86;1.06)
	5d ave.	Temperature	1.09	(1.03;1.15)†	1.10	(1.01;1.19)†	1.08	(1.00;1.17)†	1.10	(1.03;1.18)†	1.04	(0.92;1.16)
Model additionally adjusted for air pollutants												
PM_{10}*	Lag1	Temperature	1.07	(1.02;1.12)†	1.05	(0.98;1.12)	1.09	(1.02;1.17)†	1.09	(1.03;1.16)†	0.96	(0.87;1.06)
	Lag1	PM_{10}	1.02	(0.99;1.05)	1.06	(1.02;1.10)	0.98	(0.94;1.02)	1.02	(0.99;1.06)	1.03	(0.97;1.09)
PNC_{m+f}*	Lag0	Temperature	1.05	(1.00;1.10)†	1.02	(0.95;1.11)	1.08	(1.00;1.16)†	1.07	(1.01;1.14)†	0.93	(0.83;1.04)
	Lag0	PNC_{m+f}	1.02	(0.99;1.05)	1.03	(0.98;1.07)	1.01	(0.97;1.05)	1.01	(0.98;1.05)	1.07	(1.00;1.14)†
	5d ave.	Temperature	1.09	(1.03;1.16)†	1.06	(0.97;1.17)	1.15	(1.05;1.25)†	1.11	(1.03;1.20)†	0.97	(0.84;1.11)
	5d ave.	PNC_{m+f}	1.00	(0.97;1.04)	1.04	(0.99;1.09)	0.96	(0.91;1.01)	1.00	(0.95;1.04)	1.09	(1.01;1.17)
$MaxO_3$*	Lag0	Temperature	1.07	(1.01;1.12)†	1.04	(0.97;1.12)	1.09	(1.02;1.18)†	1.09	(1.03;1.16)†	0.97	(0.87;1.09)
	Lag0	$MaxO_3$	0.99	(0.93;1.05)	0.99	(0.91;1.08)	1.00	(0.91;1.09)	0.98	(0.91;1.05)	1.04	(0.91;1.18)
	5d ave.	Temperature	1.10	(1.04;1.17)†	1.09	(1.00;1.19)†	1.12	(1.03;1.22)†	1.11	(1.03;1.19)†	1.05	(0.92;1.19)
	5d ave.	$MaxO_3$	1.00	(0.92;1.09)	0.96	(0.85;1.09)	1.04	(0.92;1.17)	0.96	(0.86;1.06)	1.09	(0.91;1.32)

* PM_{10}: particles with diameter < 10µm; PNC_{m+f}: particle number concentration, retrospectively fitted (1995-1998) and measured values (1999-2004); $MaxO_3$: ozone, maximum 8 hour moving average;
† significant ($p<0.05$).

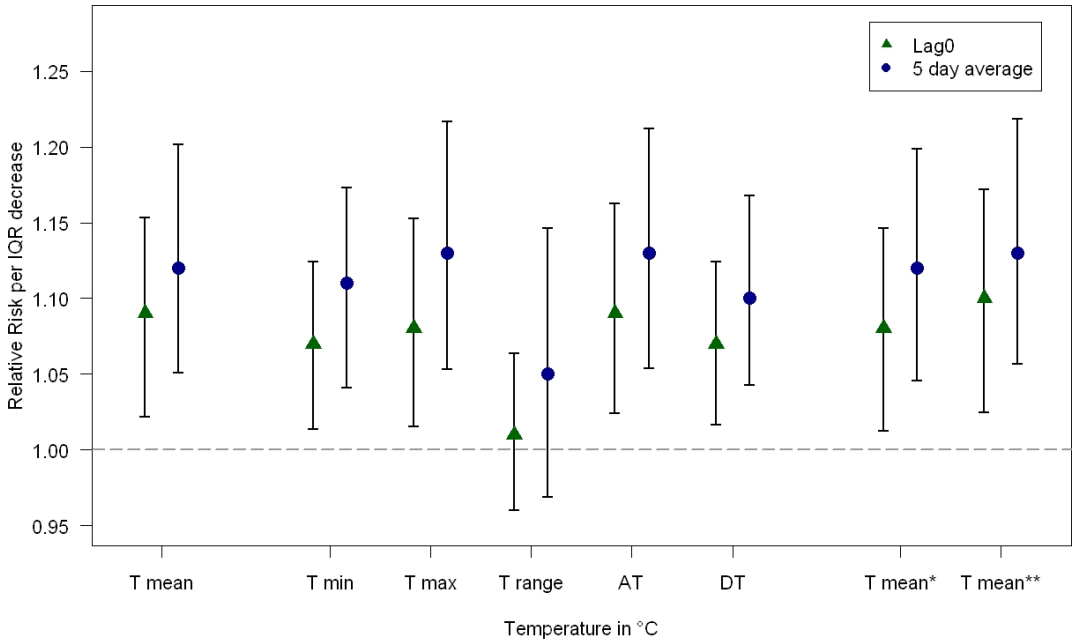

Figure 3.14: Relative risks for all daily cases of MI per IQR decrease in different measures of temperature (T) adjusted for time trend, season, Mondays and relative humidity. AT: apparent temperature; DT: dewpoint temperature; *,**: additional inclusion of indicators for 5% and 1% hottest and coldest days, respectively.

for the inhabitants of the city of Augsburg (RR: 1.12; 95% CI: 1.03 to 1.21) were observed compared to the county population, inhabitants of the county of Augsburg and Aichach-Friedberg (RR: 1.09; 95% CI: 1.01 to 1.17).

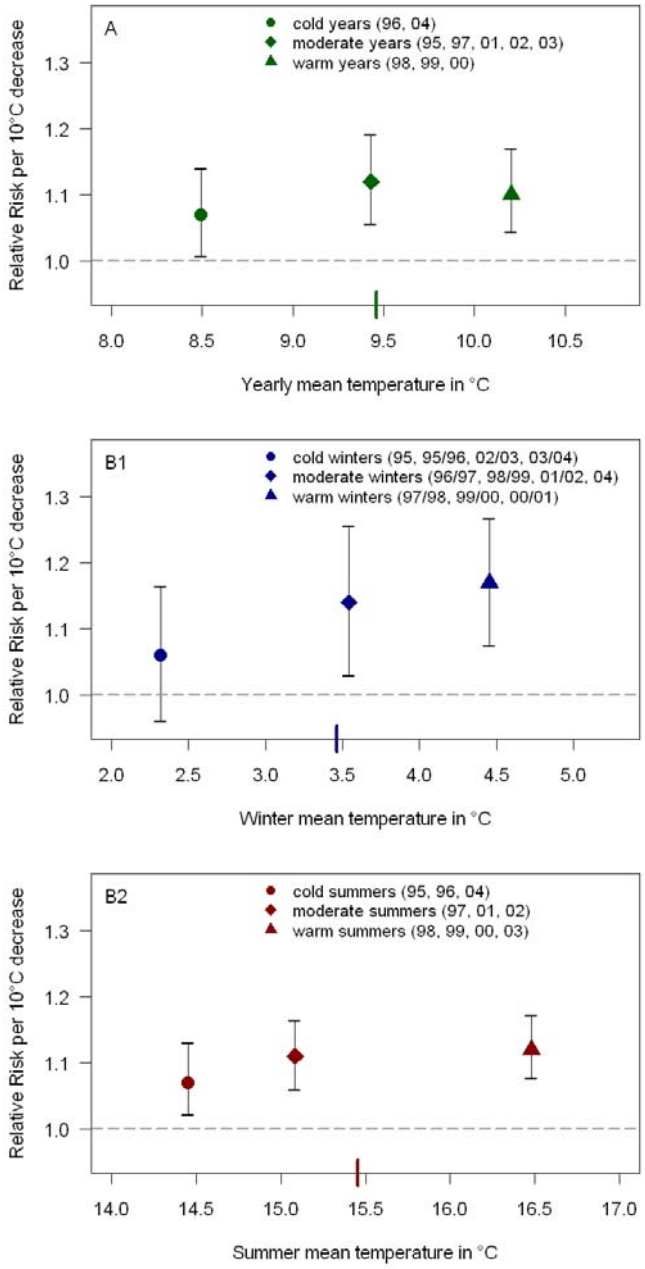

Figure 3.15: Relative risk estimates for daily cases of MI per 10°C decrease in 5 day average temperature. The estimates represent cold, moderately tempered and warm years (A), summers (B1) and winters (B2) and are placed on the x–axis corresponding to their mean temperature. The bold bars on the x-axis represent the corresponding 10-year mean temperature. Panel A was adjusted for time trend, season, Mondays and relative humidity; Panel B1 and B2 for time trend, Monday and relative humidity.

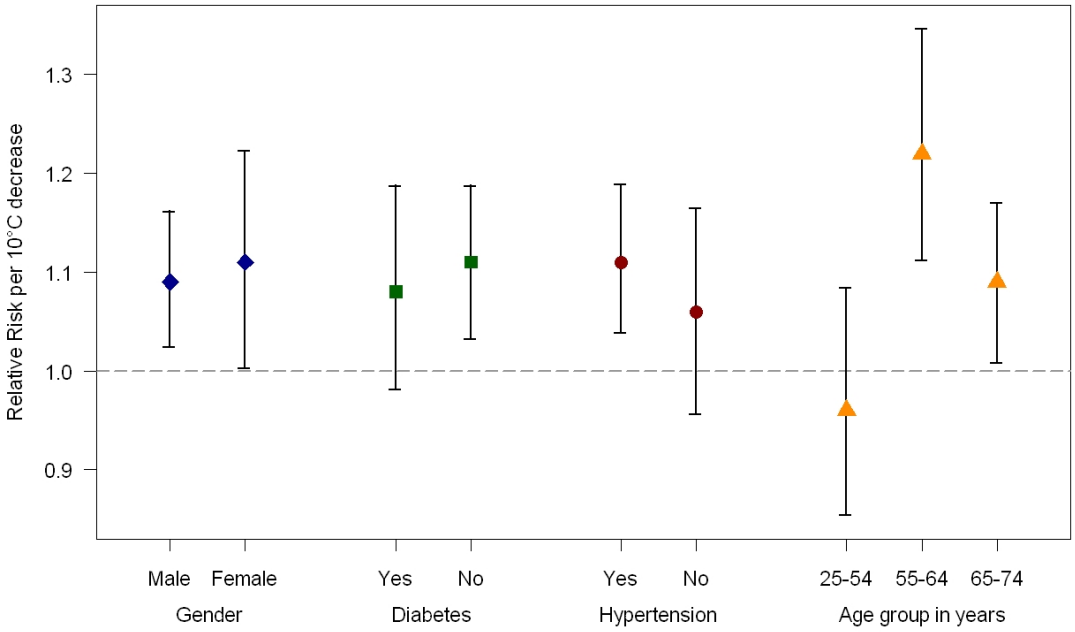

Figure 3.16: Relative risks for the total number of MIs per 10°C decrease in 5 day average temperature adjusted for time trend, season, Monday and relative humidity stratified by subgroups.

3.5 Interaction effects of air pollutants and temperature

Air pollution markers and respective time lags were chosen on the basis of a significant influence on MI rates in one of the five main outcome groups (results shown earlier). The coefficients for standardized temperature and air pollutant for single exposure models and additive two exposures model A (equation 2.23) as well as linear interaction model B with a multiplicative interaction term (equation 2.24) are presented in Table 3.8. Please note that temperature estimates are now expressed for a 10°C increase in temperature for reasons of consistency with the air pollutant estimates. As the temperature-MI-relationship was supposed to be log-linear, the estimates can easily be inversed. Thus, a negative coefficient estimate implies a risk decrease for a temperature increase, but also a risk increase for a temperature decrease. The main effect estimates of the two exposures model A and the interaction model B for same-day PM_{10} and temperature on total events, and previous day PM_{10} and temperature on nonfatal events showed no considerable changes compared to the corresponding estimates of the

single exposure models. However, the estimate of the main effect of same-day PM_{10} on total events was not significant anymore when a multiplicative interaction term was additionally included (Model B). Also, the main effect of $MaxO_3$ with a lag of three days showed no longer a significant influence on fatal events when entered together with temperature with a lag of three days, and the main effect standard error estimates were slightly higher. In exchange, the estimates of the temperature main effect were stronger pronounced. While neither of the mentioned models showed significant interaction terms for model B, the multiplicative effect of 5 day average PNC_{m+f} and temperature on recurrent events was significantly positively associated. The non-significant negative temperature estimate of the single exposure model switched to non-significant positive when PNC_{m+f} was additionally entered.

Furthermore, we estimated bivariate response surfaces of standardized temperature and air pollutants for the two exposures model A and the three interaction models B, C and D (equation (2.23) to (2.26)). Figures 3.17 to 3.20 show the four response surfaces of same-day PM_{10} and temperature on total MI events, previous day PM_{10} and temperature on nonfatal events, 5–day average PNC_{m+f} and temperature on recurrent events, and $MaxO_3$ and temperature lagged three days on fatal events, correspondingly. The colored areas of the plots mark concentrations which have been observed and data was available, whereas the grey–shaded areas are extrapolated.

Models A, B and C of Figure 3.17 show higher risks for total events if same-day PM_{10} concentrations were increased and temperature levels were decreased. The graph top right for model B included a multiplicative interaction term which modified the temperature slope dependent on the value of PM_{10} and vice versa. The lower the temperature level, the stronger the positive slope of PM_{10}, and the lower the PM_{10} concentration, the stronger the negative slope of temperature. If temperature levels were high, the plot showed no influence of same-day PM_{10} on event rates. However, only low PM_{10} concentrations were observed for warm temperatures. The surface of model C (panel bottom left), where the degree of smoothness of the two-dimensional thin plate regression spline was estimated during the fitting routine by minimizing GCV is similar to the linear approach of model A and does not show any interaction effects. If we overfitted the surface by increasing the degrees of freedom of the spline, the risk decreased for higher PM_{10} concentrations. As a risk decrease was mainly estimated for regions with-

Table 3.8: Estimated coefficients (beta) and standard errors (se) of standardized air pollutants and temperature for single exposure models, two exposures model (A) and interaction model (B) adjusted for time trend, season, relative humidity and Mondays together with p-values based on F-test.

Model		Air pollutant			Temperature			Interaction term		
		beta	se	p-value	beta	se	p-value	beta	se	p-value
Total daily events, exposure of same-day (Lag0)										
Single exposure	PM_{10}*	0.0188	0.0111	0.0902	-	-	-	-	-	-
	Temp	-	-	-	-0.0519	0.0194	0.0074	-	-	-
Two exposures	A	0.0223	0.0109	0.0409	-0.0446	0.0191	0.0200	-	-	-
Linear interaction	B	0.0187	0.0123	0.1281	-0.0406	0.0202	0.0449	-0.0067	0.0110	0.5412
Nonfatal events, exposure of previous day (Lag1)										
Single exposure	PM_{10}	0.0416	0.0173	0.0161	-	-	-	-	-	-
	Temp	-	-	-	-0.0508	0.0282	0.0719	-	-	-
Two exposures	A	0.0452	0.0162	0.0054	-0.0373	0.0285	0.1915	-	-	-
Linear interaction	B	0.0460	0.0184	0.0125	-0.0381	0.0300	0.2034	0.0015	0.0162	0.9266
Recurrent events, 5 day average exposure										
Single exposure	PNC_{m+f}*	0.0711	0.0334	0.0335	-	-	-	-	-	-
	Temp	-	-	-	-0.0133	0.0456	0.7702	-	-	-
Two exposures	A	0.0734	0.0351	0.0365	0.0236	0.0547	0.6663	-	-	-
Linear interaction	B	0.1474	0.0492	0.0028	0.0391	0.0555	0.4814	0.0631	0.0297	0.0334
Fatal events, exposure lagged 3 days (Lag3)										
Single exposure	$MaxO_3$*	0.0514	0.0256	0.0447	-	-	-	-	-	-
	Temp	-	-	-	-0.0649	0.0274	0.0178	-	-	-
Two exposures	A	0.0493	0.0324	0.1285	-0.0840	0.0295	0.0044	-	-	-
Linear interaction	B	0.0573	0.0333	0.0855	-0.0861	0.0296	0.0036	-0.0179	0.0173	0.3008

* PM_{10}: particles with diameter $< 10\mu m$; PNC_{m+f}: particle number concentration, retrospectively fitted (1995-1998) and measured values (1999-2004); $MaxO_3$: ozone, maximum 8 hour moving average.

out observed data, this part of the graph is implausible and was caused by the overfitting of the smooth function which weighted the outliers too much.

Figure 3.18 presents bivariate plots of previous day PM_{10} and temperature on nonfatal events. The surfaces of models A, B and C look almost equal with increased risks for increasing concentrations of previous day PM_{10} and a slight inverse association with previous day temperature. The overfitted smooth function of model D showed strongest effects for lower temperature levels, while higher PM_{10} concentrations decreased the risk with higher temperature levels. The estimate was zero for the lowest PM_{10} concentrations and highest temperature levels.

The estimated surface of model C of Figure 3.19 equals the surface estimated by model A and hence, does not identify any interaction effects of 5 day average PNC_{m+f} and temperature on recurrent events. On the other hand, model B points to a relative strong multiplicative interaction effect with highest risk for high PNC_{m+f} concentrations and high temperatures, and lowest risk for low PNC_{m+f} concentrations and high temperatures as well as high PNC_{m+f} concentrations and low temperatures. Model D visualizes that the risk increase for high temperatures and increasing PNC_{m+f} concentrations was quite strong, where data was observed, and almost null, where data was missing. The linear interaction approach of model B overestimated the risk when extrapolating the higher PNC_{m+f} concentrations.

For observed data, all four panels of Figure 3.20 showed highest risk for low temperature levels, and lowest risk for high temperature levels quite independent of the $MaxO_3$ concentrations. The extrapolation of missing concentrations by model B is again somewhat misleading.

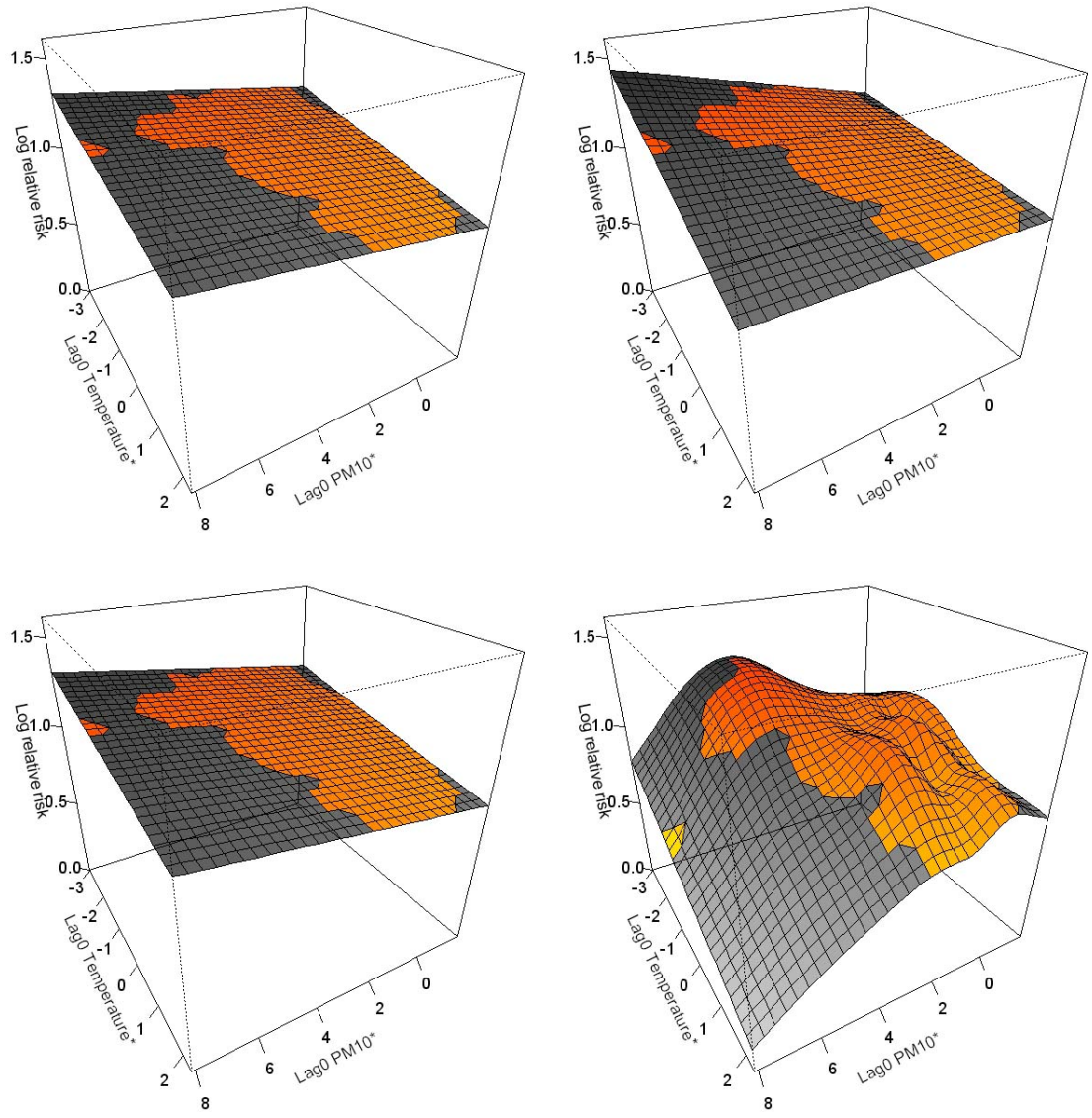

Figure 3.17: Bivariate response surfaces of standardized same-day PM_{10} and temperature on **total MI events**. The top panels are based on linear exposure modeling without interaction term (Model A, left), and with linear interaction term (Model B, right). The bottom panels correspond to two–dimensional thin plate regression splines, where degrees of freedom were estimated during the fitting routine (Model C, left) and were fixed to 24 degrees of freedom (Model D, right). Data was available for the colored area.

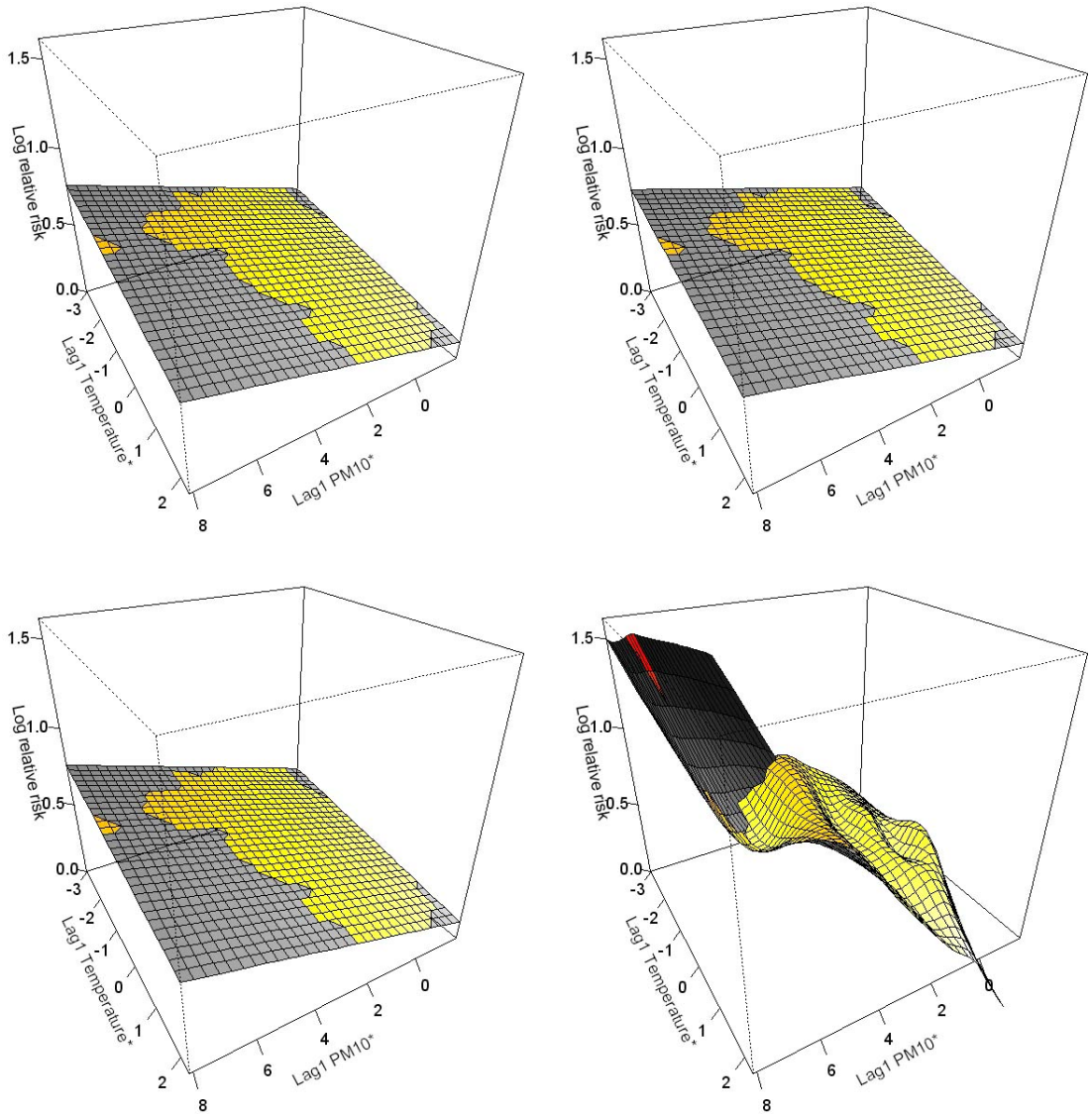

Figure 3.18: Bivariate response surfaces of standardized previous day PM_{10} and temperature on **nonfatal events**. The top panels are based on linear exposure modeling without interaction term (Model A, left), and with linear interaction term (Model B, right). The bottom panels correspond to two-dimensional thin plate regression splines, where degrees of freedom were estimated during the fitting routine (Model C, left) and were fixed to 24 degrees of freedom (Model D, right). Data was available for the colored area.

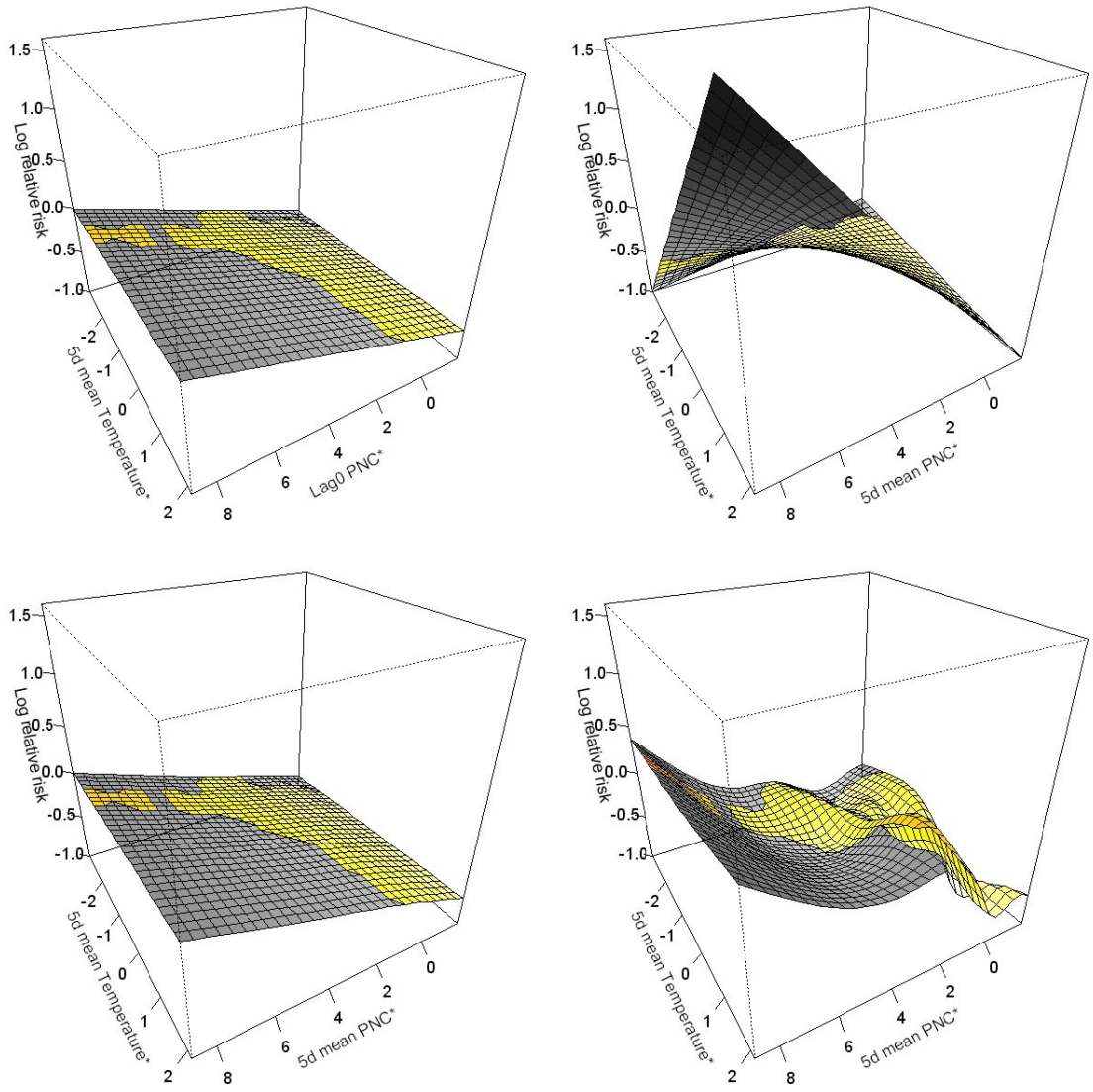

Figure 3.19: Bivariate response surfaces of standardized 5 day average $\mathrm{PNC}_{\mathrm{m+f}}$ and temperature on **recurrent events**. The top panels shows linear effect estimates without interaction term (Model A, left), and with linear interaction term (Model B, right). The bottom panels correspond to two-dimensional thin plate regression splines, where degrees of freedom were estimated during the fitting routine (Model C, left) and were fixed to 24 degrees of freedom (Model D, right). Data was available for the colored area.

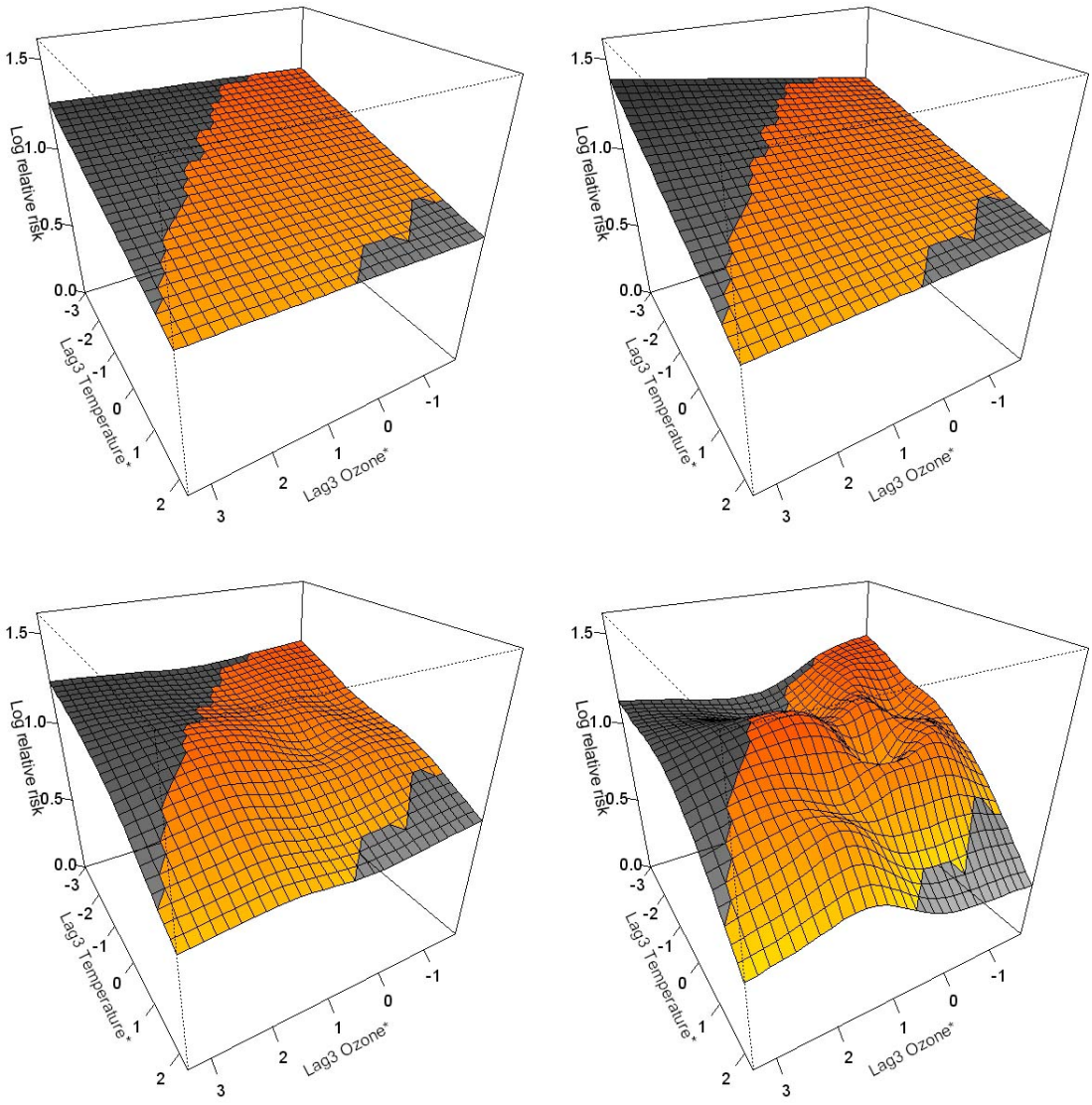

Figure 3.20: Bivariate response surfaces of standardized $MaxO_3$ and temperature lagged three days on **fatal events**. The top panels shows linear effect estimates without interaction term (Model A, left), and with linear interaction term (Model B, right). The bottom panels correspond to two-dimensional thin plate regression splines, where degrees of freedom were estimated during the fitting routine (Model C, left) and were fixed to 24 degrees of freedom (Model D, right). Data was available for the colored area.

4 Discussion

The first section of this chapter summarizes the results according to the specific research questions formulated in Section 1.2. Sections 4.2, 4.3 and 4.4 discuss the results regarding air pollutants, air temperature and their synergistic effects, respectively, in the context of the literature. Strengths and limitations of the underlying study are specified in Section 4.5. The final conclusion can be found in the last section.

4.1 Summary of results

4.1.1 Specific aim 1: Is there an association between variation of daily air pollutant concentrations and numbers of MI?

The present thesis suggested an association of PM_{10} with elevated numbers of MI and coronary death. With a 2% risk increase (95%-CI: 0% to 5%) per 24.6 $\mu g/m^3$ increase, only same-day PM_{10} exposure showed borderline significant effects. These effects are larger than previously observed for CVD mortality. In contrast, fine particles ($PM_{2.5}$), particle number concentrations (PNC_{m+f}) and ozone indicated no association with the total numbers of daily MIs. Also, other gaseous pollutants did not influence the rates.

(a) Is the association similar for fatal and nonfatal or incident and recurrent MIs?

Like the total numbers of daily MI cases, nonfatal events were positively associated with PM_{10}. The estimates were slightly higher compared to all events and statistically significant for previous day exposure (RR: 1.05, 95%-CI: 1.01 to 1.10). Elevated PNC_{m+f}, a marker for ultrafine particles, increased the risks for nonfatal MIs with a lag of two to four days as well as for the 5 day average. This indicates that particles are associated with MIs but not to the same extent with coronary deaths.

PM_{10} effects on fatal events were rather protective, except for same-day concentrations. Also $PM_{2.5}$ showed non-significant negative RR estimates for this group for all lags. For PNC_{m+f}, fatal MIs reacted opposite to nonfatal events with a risk decrease two to four days later as well as for the 5 day

average concentration. This indicates the potential for harvesting in coronary events. Ozone was positively associated with fatal events, especially with concentrations with a lag of three days. Except for SO_2, associations between gaseous pollutants and nonfatal and fatal events partly switched in opposite directions, like it was the case for some of the particles.

Like nonfatal MIs, incident events showed a risk increase after PM_{10} exposure, with borderline significance for lag1 (RR: 1.03, 95%-CI: 1.00 to 1.07). No associations could be seen for $PM_{2.5}$, PNC_{m+f} and ozone. Recurrent events indicated a significant risk increase for lag3 and the 5 day average of PNC_{m+f} concentration. This has been observed earlier and indicates that MI survivors may have acquired susceptibility on the basis of their diseases. Other pollutants did not affect this group.

(b) Does the association differ by personal characteristics based on gender, age, history of diabetes and hypertension?

Elevated same-day PM_{10} concentrations were associated with higher event numbers in men and in non-hypertensive individuals, while women and hypertensive people were not affected. No effect modification was found for diabetes. Individuals aged 65 to 74 showed a higher risk compared to younger patients.

(c) Is the association robust for different modeling approaches?

Polynomial distributed lag models relate the outcome variable jointly to same-day and several previous days exposure. The resulting estimates were used to get an idea of the shape of the concentrations up to a lag of twelve days but also to compare them with the estimates of the single pollutant models. The immediate association of same-day PM_{10} concentration with total daily MI, but also the delayed pattern for nonfatal MIs could be confirmed. Fatal events showed a slight harvesting effect which was also reflected in the negative effects in the single exposure models. The increased events on the first day reduced the risk pool of susceptible persons leading to a decrease of cases on the following days. Regarding the significant estimate for previous day PM_{10} on incident cases, the polynomial distributed lag model pointed rather to a joint effect of same- and previous day. The delayed increased risk for PNC_{m+f} on recurrent events and ozone on fatal

events could also be confirmed, but they were not significant. Overall, the two modeling approaches supplied quite similar results.

The extended Cox model was used to compare its hazard ratios with the Poisson RR estimates for recurrent events. Therefore, only recurrent events of persons who suffered their incident event during the study period could be used, as first MI served as index event for the Cox model. This constraint limited the number of observations to 3944 patients with first MI and 523 recurrent events. Effect estimates for PM_{10} and PNC_{m+f} were slightly higher if calculated with the extended Cox model compared to Poisson regression, but always in the range of its 95% confidence intervals. Estimates of both modeling approaches were also similar to results for all recurrent events, though the confidence intervals were wider because of the smaller event numbers.

Sensitivity analyses were conducted to check the robustness of the results. Neither the inclusion of different smooth functions for time trend, the exclusion of the seasonal categories, the additional adjustment for influenza, or an alternative confounder selection for meteorological parameters changed the results considerably. A reduction of the study period to the last six years resulted in somewhat different estimates. PM_{10} effects were not visible anymore and the influence of PNC_m was more immediate. This inconsistency might be caused by loss of power and has to be kept in mind when interpreting $PM_{2.5}$ effects.

4.1.2 Specific aim 2: Is there an association between variation of daily air temperature and numbers of MI?

The present study observed an inverse association between air temperature and daily MI cases and coronary deaths. A 10°C decrease in 5 day average temperature was associated with a 10% risk increase (95%-CI: 4% to 15%) for the total numbers of daily MI events. An effect of heat was not observed in this temperate climate.

(a) Is the association similar for fatal and nonfatal or incident and recurrent MIs?

Like for the total numbers of daily MIs, effects on fatal and incident events were immediate, whereas nonfatal cases showed a slightly delayed pattern.

The intensity was quite similar. No significant association was seen between temperature and recurrent events. In contrast to the results for air pollution, this result indicates a uniform response on MIs and coronary deaths, except for recurrent events.

(b) What is the shape of the exposure-response function?

We could identify an inverse log-linear relationship between temperature and MI occurrence. The shape was similar when analyzing only winter or summer half years. This means that there is no threshold.

(c) Is the association robust for different temperature metrics?

A comparison of different temperature metrics showed no appreciable differences except for the temperature range, which is rather a marker for the fluctuation within a day than for temperature itself. The additional inclusion of indicators for the 5% and 1% hottest and coldest days did not alter the estimates for mean temperature.

(d) Is the association similar for warm and cold years?

In warmer and moderately tempered years, the association of MI occurrence and decreasing temperature were more pronounced than in colder years. For cold winters, no significant risk increase for MI occurrence was observed.

(e) Does the association differ by personal characteristics based on gender, age, history of diabetes and hypertension?

No effect modification by gender or history of diabetes was observed while the effect of temperature on MI was somewhat stronger for patients with a history of hypertension. Patients aged 55 to 64 years were identified as most susceptible.

Sensitivity analyses included an increased data adaptation of the smooth functions for time trend, an exclusion of the seasonal categories, an additional adjustment for influenza, barometric pressure and air pollutants, as well as a stratification by region. Neither of these modifications changed the results considerably.

4.1.3 Specific aim 3: Are there interacting effects of daily air pollutant concentrations and temperature on the occurrence of MI?

The inspection of interacting effects was limited to air pollutants and lags which showed significant influence on one of the outcome groups. However, no interactions for those air pollutant concentrations and air temperature on the daily number of MI could be identified.

4.2 The role of air pollutants

Several studies have investigated the relationship between air pollutants and MI or coronary deaths, though the outcomes and sources of data were quite different. A study on more than 300,000 emergency admissions for MI in 21 U.S. cities reported a 0.65% (95% CI: 0.3 to 1.0 %) risk increase for a 10 $\mu g/m^3$ increase in same-day ambient PM_{10} concentration (Zanobetti and Schwartz, 2005). For the same increment, our study yielded with 0.9% to a slightly higher estimate for the total event rate. A considerably higher association was seen for MI survivors in the greater Boston area where elevated PM_{10} concentrations of 30 $\mu g/m^3$ 24 hours before the onset of symptoms revealed an odds ratio of 1.66 (95% CI: 1.11 to 2.49) (Peters et al., 2001). A study on 851 MI survivors in the Augsburg region pointed to PM_{10} effects which were delayed about two days when analyzed with the case-crossover method while time series analysis did not identify any association (Peters et al., 2005).

The Health Effects of Air Pollution among Susceptible Sub-populations (HEAPSS) study evaluated the effects of traffic related air pollutants on cardiovascular diseases in five European cities. Data based on hospital discharge registers (Helsinki, Rome, and Stockholm) and MI registers (Augsburg, and Barcelona). For Rome, non-hospitalized coronary deaths exhibited a somewhat higher risk increase than was seen in this thesis for fatal events with 4.8% (95% CI: 0.1 to 9.8%) for a 29.7 $\mu g/m^3$ rise in same-day PM_{10} (Forastiere et al., 2005). Pooled effect estimates over all cities did not point to an association between PM_{10} and hospitalization for first MI (Lanki et al., 2006). Cities with hospital discharge registers were also stratified by age (cut-off point 75 years) and fatality. For the younger group which covers the age range of the Augsburg MI registry, same-day PM_{10} estimates were slightly protective for nonfatal events and significantly positive for fatal MIs.

For Rome, D'Ippoliti et al. (2003) observed for the same outcome a significant association with total suspended particles averaged over concurrent and previous two days. Within the HEAPSS study, hospital readmissions for cardiac events (von Klot et al., 2005) and all-cause mortality (Berglind et al., 2009) among MI survivors were examined as well. Both studies reported increased event rates with 2.1% and 5.6%, respectively, for a 10 $\mu g/m^3$ increase in PM_{10} levels.

Peters et al. (2001) described an increased risk of MI onset in association with elevated levels of fine particulate matter which could not be replicated in a similar study from King County, Washington (Sullivan et al., 2005). Positive, but not significant effects of fine particles were identified for MI survivors for the years 1999 to 2001 (Peters et al., 2005), but were not visible within our analysis. This might be caused by loss of power due to the reduced time period of six years. Other studies provided evidence of $PM_{2.5}$ as a risk factor for cardiovascular disease thereof triggering of ischemic heart disease (Pope et al., 2006).

Only a few studies examined the influence of ultrafine particles on MI rates. While Peters et al. (2005) did not observe an effect of particle number concentration on nonfatal events in the Augburg region, Forastiere et al. (2005) reported a 7.6% increase of coronary deaths for an interquartile range increase of 27,790 particles/cm^3 for PNC. The HEAPSS study could also relate PNC to hospitalization for first MIs (Lanki et al., 2006), hospital readmissions for cardiac events (von Klot et al., 2005) and all-cause mortality (Berglind et al., 2009) with increases of about 0.5%, 2.6% and 5.6% per 10,000 particles/cm^3, respectively. This quite complies with the results of this analysis ranging from 1.2% for incident events, 1.9% for fatal events to 5.1% for recurrent events for an IQR increase of 6,702 particles/cm^3 for same-day PNC.

Regarding ozone, the literature is inconsistent. A registry based study from Toulouse, France, reported a 5% risk increase for a 5 $\mu g/m^3$ increase in same-day and previous day ozone concentrations, respectively (Ruidavets et al., 2005). When stratified by survival status and personal history of ischemic heart disease, the association was not significant anymore for fatal events and patients with previous ischemic heart disease. However, as our results pointed in the opposite directions, we could not confirm these findings. The HEAPSS study considered only the warmer months April to September and did not observe an association between ozone and hospitaliziation for first MIs (Lanki et al., 2006) or readmis-

sions for all-cause mortality (Berglind et al., 2009), but identified an increased risk for hospital readmissions for cardiac events (von Klot et al., 2005). However, the city-specific estimate for Augsburg was an outlier and showed a negative association, which was also seen in another study on nonfatal events in Augsburg (Peters et al., 2005). Two other studies on time of onset (Peters et al., 2001; Sullivan et al., 2005) did not find an association.

The literature evidence on CO and NO_2 is mixed. While all HEAPSS-based studies pointed to an immediate CO effect, the onset studies showed no associations (Peters et al., 2001; 2005; Sullivan et al., 2005). Increased risks related to elevated NO_2 concentrations were reported by D'Ippoliti et al. (2003); von Klot et al. (2005) and Berglind et al. (2009) (only for Augsburg and Barcelona, but not for the pooled data). Forastiere et al. (2005); Lanki et al. (2006) and the French registry study (Ruidavets et al., 2005) did not observe an association. Except for Berglind et al. (2009) and Peters et al. (2005) who described delayed associations of SO_2 with readmissions for all-cause mortality and nonfatal MIs, respectively, none of the other studies reported an association (Peters et al., 2001; D'Ippoliti et al., 2003; Forastiere et al., 2005; Ruidavets et al., 2005; Sullivan et al., 2005; Berglind et al., 2009).

The sparse literature about the influence of personal characteristics on the association between PM_{10} and MI and/or coronary deaths provides incoherent results and points in partly opposite directions compared to the results of this study. However, only the total number of daily events was stratified by personal characteristics because of power aspects and thus, the outcomes differ somewhat. Furthermore, the age ranges vary over these studies. A study on non-hospitalized coronary deaths (Forastiere et al., 2005) reported no gender differences, but increased risks for non-diabetic and hypertensive subjects and the elderly. Another study from Rome concerning TSP and hospitalizations for first MI (D'Ippoliti et al., 2003) observed slightly increased rates for females and the elderly, but no effect modification by diabetes or hypertension. Diabetic patients were also suggested to be at higher risk for cardiovascular admissions associated with PM_{10} in a study of four U.S. cities (Zanobetti and Schwartz, 2002).

4.3 The role of temperature

We observed an overall increase in the RR for all events of 7% per 10°C decrease in same-day temperature, while a French registry-based analysis (Danet et al., 1999) reported an increase of 13% for the same increment. The authors identified recurrent cases of MI as most susceptible, which could not be confirmed within our analysis. However, when analyzing seasonality and weather in relation to sudden cardiac deaths, Gerber et al. (2006) reported for temperatures below 0°C vs. 18°C to 30°C a 35% increased risk for subjects without prior coronary heart disease, whereas no effect for subjects with prior coronary heart disease was observed. A similar effect modification was described by Ruidavets et al. (2005) for the impact of air pollution on MI rates. A potential explanation for the lack of influence on recurrent events could be that, once people survive an event, they become more aggressively treated and may be protected from adverse effects of cold temperatures. Alternatively, the different finding could also be by chance as this subgroup was the smallest in our analysis.

As temperature influences on mortality have usually been described by U-, V- or J-shaped functions (Braga et al., 2001), we inspected the exposure-response curve by nonparametric smooth functions. An increased adaptation of the smooth function to the data confirmed the linear relationship identified by Danet et al. (1999) for this temperature range. One registry-based study from Australia (Enquselassie et al., 1993) and a study on emergency room admissions for acute coronary syndromes in Taiwan (Liang et al., 2008) reported U- and V-shaped exposure functions when using quantiles to model a non-linear relationship. Although the warmer categories showed higher effects compared to the corresponding reference categories, neither was significant.

Studies across U.S. cities (Curriero et al., 2002; Barnett et al., 2005) and European regions (The Eurowinter Group, 1997; Keatinge et al., 2000) have consistently reported stronger cold effects in warmer climates. The separate inspection of temperature for cold, moderately tempered and warm years as well as summers and winters in our study indicated similar results. Thus, it can be hypothesized that subjects do not adapt only to regional, but also to seasonal mean temperatures. We would assume that in a cold winter, people are more habituated to the cold, and therefore, the influence of decreasing air temperature has not the same extent than in a warm winter. Our analysis was able to show an increase of

MI rates for a previous drop of temperature in both winter and summer. Hence, our results point not only to a pure cold effect as described by Medina-Ramon et al. (2006) for extremely cold days and cardiovascular deaths, but rather to an influence of the unusualness of cold temperatures (Medina-Ramon and Schwartz, 2007). With regard to climate change and its speculated higher variation in temperature extremes (McMichael et al., 2006), rather an intensification than a reduction of this effect might be expected. Furthermore, the hypothesis of a compensation of higher heat-related rates by lower cold-related rates as suggested for mortality (Keatinge et al., 2000) seems not to apply to MI cases and coronary deaths. We identified a slightly protective effect of moderate temperature, but no effect of extreme heat. This could be due to the relatively tempered climate in Augsburg, which is not comparable to southern European countries or warmer U.S. states where heat effects in association with excess mortality have been frequently observed (Basu and Samet, 2002; Simon et al., 2005; Filleul et al., 2006; Fouillet et al., 2008). Moreover, heat possibly plays a minor role in the onset of MI. Medina-Ramon et al. (2006) reported a reduced risk for MI deaths compared to other mortality causes on days with extreme heat. On the other hand, when comparing the same 50 U.S. cities by their temperature means, Medina-Ramon and Schwartz (2007) saw greater heat effects in cities with lower mean temperatures, also for MI mortality.

Danet et al. (1999) reported strongest effects for the age group of 55-64 years, which could be confirmed within our study. However, subjects aged 65-74 years showed a still significant, but smaller effect which could be due to higher rates of medication intake as well as better susceptibility awareness of the older persons. Like Danet et al. (1999), we observed a V-shaped association for barometric pressure and MI cases, though it was not statistically significant within our data. Confounding or effect modification of the temperature effects due to gaseous or particulate air pollutants as suggested by several studies for mortality (O'Neill et al., 2003; Roberts, 2004; Ren et al., 2006) could not be detected and confirms recent results (Zanobetti and Schwartz, 2008).

4.4 Synergistic effects between air pollutants and temperature

Numerous studies have shown that air pollutants and temperature are both associated with cardiovascular morbidity and mortality (Brook et al., 2004; Pope et al., 2006; Brook, 2008). Temperature is usually included as a confounder variable in assessing air pollutant effects. However, only a few studies considered air pollutants in assessing temperature effects (O'Neill et al., 2003; Rainham and Smoyer-Tomic, 2003) or investigated effect modification or interacting effects of air pollutants and temperature or weather (Katsouyanni et al., 1996; Samet et al., 1998; Hales et al., 2000; Roberts, 2004; Ren et al., 2006; Ren and Tong, 2006; Ren et al., 2007; Carder et al., 2008; Qian et al., 2008). Most of theses studies were based on mortality end points. Although some of them confirmed the interaction assumption (Katsouyanni et al., 1996; Ren et al., 2007; Qian et al., 2008) or gave evidence in this direction (Roberts, 2004; Carder et al., 2008), others could not see any effect modification or interacting effects (Samet et al., 1998; Hales et al., 2000; Carder et al., 2008). This inconsistency potentially depends on differences in exposure variables and end points, but also in the various analytical methods used.

Two studies from Brisbane, Australia (Ren et al., 2006; Ren and Tong, 2006) reported synergistic effects of temperature and PM_{10} on respiratory and cardiovascular hospital admissions, respiratory and cardiovascular emergency visits, all nonexternal-cause mortality, and cardiovascular mortality. However, no clear evidence emerged when examining effect modification of each other. Maximum temperature did not modify PM_{10} effects on cardiovascular hospital admissions but on all other outcomes (Ren and Tong, 2006). Vice versa, PM_{10} did not modify minimum temperature effects on respiratory and cardiovascular emergency visits but the other outcomes (Ren et al., 2006). In this analysis, some pattern indicating slight synergistic effects within the bivariate response surface plots were seen, but this could not be confirmed with parametric analyses. Also, air pollutants did not alter the temperature-MI-relationship when included as additional confounders.

4.5 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 MONICA/KORA MI registry (Löwel et al., 1991; Tunstall-Pedoe et al., 1994; Löwel et al., 2005). Further strengths are the non-linear confounder adjustment and the information on patient characteristics to conduct subgroup analyses.

One of the limitations of our study is the different precision of time of onset for nonfatal and fatal events. For nonfatal events, time of symptom onset was used and validated against the information from the medical records. For fatal events, times of hospital arrival or death were used instead. The age range of the registry of 25 to 74 years has limitations especially for women who suffer from MIs more frequent at older ages. Moreover, effect modification by medication intake, individual smoking and exposure to second-hand smoke could not be considered, since these data were not available for most of the fatal cases.

Regarding air pollutants, the lack of $PM_{2.5}$ measurements for the first four years of our study period is a further limitation as the results are only partly comparable to estimates from the other pollutants. Maybe the loss of power due to the reduced numbers of observations impeded the detection of effects. When reducing the PM_{10} time series to the last six years, an association with MI was not visible anymore for either of the subgroups. Also, the retrospective PNC estimation for almost half of the days potentially biased the results. However, the correlation of fitted and measured PNC values was high (r=0.86) and a sensitivity analysis limited to only the observed values indicated similar but more immediate results. As the imputed values are less variable than the true values, the variance of the effect estimates may be affected. Thus, PNC effects are not directly comparable with the other pollutants measured over the whole period.

Only central site pollution 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. Cyrys 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.

The use of ecological ambient concentrations does not account for personal exposure which can greatly vary depending on the time spent outdoors, in traffic, and indoors. These micro-environments again depend on several factors. For the latter building characteristics like infiltration rate or ventilation, but also individual activities like cooking, smoking or window opening as well as a large number of other factors affect the exposure. Several studies compared indoor, outdoor and personal concentrations (Janssen et al., 1998; Ebelt et al., 2005) and could show high correlations. These findings support the use of ambient monitoring as an adequate alternative, especially for population-based studies where personal monitoring is often not feasible.

We cannot exclude that some effects might have occurred only by chance due to multi-comparisons of air pollutants and the small sample size. However, our results were consistent with earlier studies conducted in the study region (Peters et al., 2005; von Klot et al., 2005).

Regarding temperature effects, there is the potential for residual confounding. At cold temperatures behaviors such as smoking, physical activity, diet or stress reactions could change. A further limitation is that only outdoor temperature was measured while people usually spend a lot of time indoors at room-temperatures. Also, housing characteristics could play a role. However, we could identify similar effects of decreasing temperature in winters and summers where the impact of cold temperatures on behaviors is supposed to be very different in a temperate climate as well as the time periods spent outdoors are supposed to be very different. Moreover, only one measurement location was used. The stratification by region indicated slightly higher risks for inhabitants of the city and slightly lower risks for the county population. This deviation may originate from differences in microenvironmental temperatures, living conditions and behavioral factors of city and county inhabitants. Potential higher effects in winter which could be

partly attributed to greater exposure to second-hand smoke on cold days could not be seen.

4.6 Conclusion

The present thesis investigated the short term influence of air pollutants and temperature on the occurrence of MI in residents of Augsburg, Germany, aged 25 to 74 years over a period of ten years.

Regarding air pollutants, particles with diameter smaller than 10 µm (PM_{10}) were associated with an immediate risk increase for all events. Other particle fractions or gaseous pollutants did not affect the total daily event numbers. Subgroup analyses of nonfatal or fatal and incident or recurrent events indicated somewhat different patterns. While nonfatal and incident MIs were also increased, especially for previous day exposure, fatal events showed rather protective effects. Particles smaller than 2.5µm ($PM_{2.5}$) were only available for the second half of the study period; no significant influence on either of the subgroups could be seen. Particle number concentration (PNC_{m+f}) was imputed for the first four years. This proxy for ultrafine particles showed a delayed risk increase in recurrent events. Results for ozone were not distinct; it was negatively associated with nonfatal MIs and positively with fatal events, but did not affect the other groups. In particular, the effects of PM_{10} and PNC_{m+f} confirm results of previous studies. Effects of $PM_{2.5}$ on MI onset have also been reported, but cannot be confirmed within our data. This lack of association might be due to the reduced time period of only six years as well as the small sample size with a mean of one to three cases per day. However, this study reinforces the hypothesis that exposure to air pollutants is an acute risk factor for triggering MI events.

Regarding temperature effects, the present thesis observed an increased risk for the occurrence of MI in association with a decrease in air temperature. An effect of heat was not observed in this temperate climate. Fatal and non-fatal events, but not recurrent events were associated with cold temperatures. No difference was observed for men and women. Subjects aged 55 to 74 years seemed to be affected, but not younger patients. Risks associated with cold temperatures were more pronounced in years with higher average temperature and also occurred during summers which argues against an effect of extreme temperature levels

alone. Our results suggest that unusual temperature decreases or individually felt cold can increase the risk for an acute event and should also be considered as an acute risk factor for MI.

Earlier studies have shown that the pollutant-MI relationship is confounded by temperature and that it is necessary to adjust for it to capture the true pollutant effect. However, the additional adjustment for air pollutants when estimating temperature effects has not affected the results considerably in our study. Furthermore, the present thesis could not identify any interaction between air pollutants and temperature on the occurrence of MI. Therefore, we would suggest that air pollutants and temperature act as independent risk factors for MI.

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A Appendix

A.1 Figures

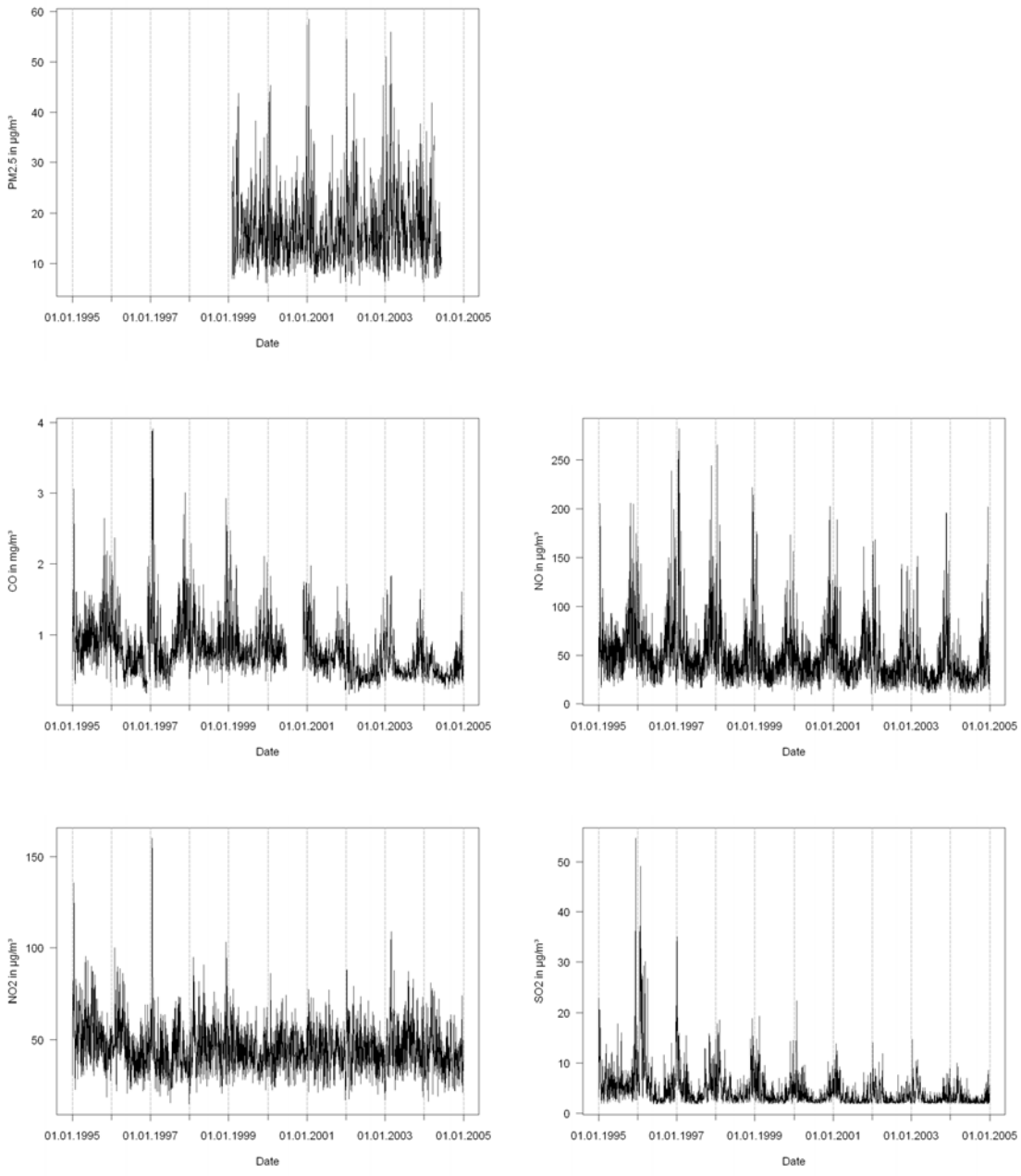

Figure A.1: Time series of particle mass concentrations and gaseous pollutants.

A.2 Tables

Extended Cox model data set description (Table A.1): The variable ID is the unique person identification number. TIME0 and TIME correspond to starting and ending time in days since last event. The difference indicates the time unit of the time-varying covariates, here one day. The variable EVENT is 1, if an event occurred and 0, else. DATE gives the actual date. SEX and L1PM10 are examples for a time-independent and a time-dependent variable. The variable STRATA indicates the number of the last event. After each recurrent event, TIME0 is reset to 0 again and STRATA is augmented about 1. DONSET, R1DONSET, R2DONSET, and so on, determine the date of onset of first, second (first recurrent) and third (second recurrent) MI, respectively. Persons without further event until censoring have always missing values for these variables and STRATA equals 1. Censoring included end of follow-up (31/12/2005), death, removal or reaching the age limit of the registry (75 years); the censoring date is given in ZENSDAT.

Table A.1: Example dataset for the Extended Cox model.

Obs	ID	TIME0	TIME	EVENT	DATE	SEX	L1PM10	STRATA	DONSET	R1DONSET	R2DONSET	...	ZENSDAT
111	1979	110	111	0	05/07/98	1	45.5981	1	16/03/98	06/07/98	26/01/99	...	06/12/99
112	1979	111	112	1	06/07/98	1	40.7910	1	16/03/98	06/07/98	26/01/99	...	06/12/99
113	1979	0	1	.	07/07/98	1	52.6704	.	16/03/98	06/07/98	26/01/99	...	06/12/99
114	1979	1	2	.	08/07/98	1	53.4485	.	16/03/98	06/07/98	26/01/99	...	06/12/99
...	...	...	...	...	...	...	...	...	...	...	...	...	...
114	1979	28	29	.	04/08/98	1	53.4485	.	16/03/98	06/07/98	26/01/99	...	06/12/99
114	1979	29	30	0	05/08/98	1	53.4485	2	16/03/98	06/07/98	26/01/99	...	06/12/99
114	1979	30	31	0	06/08/98	1	53.4485	2	16/03/98	06/07/98	26/01/99	...	06/12/99
...	...	...	...	...	...	...	...	...	...	...	...	...	...
315	1979	202	203	0	25/01/99	1	49.2813	2	16/03/98	06/07/98	26/01/99	...	06/12/99
316	1979	203	204	1	26/01/99	1	29.8800	2	16/03/98	06/07/98	26/01/99	...	06/12/99
317	1979	0	1	0	27/01/99	1	19.2975	.	16/03/98	06/07/98	26/01/99	...	06/12/99
318	1979	1	2	0	28/01/99	1	9.8563	.	16/03/98	06/07/98	26/01/99	...	06/12/99
...	...	...	...	...	...	...	...	...	...	...	...	...	...
317	1979	28	29	.	24/02/99	1	19.2975	.	16/03/98	06/07/98	26/01/99	...	06/12/99
318	1979	29	30	0	25/02/99	1	9.8563	3	16/03/98	06/07/98	26/01/99	...	06/12/99
...	...	...	...	...	...	...	...	...	...	...	...	...	...
781	1979	312	313	0	05/12/99	1	19.1938	3	16/03/98	06/07/98	26/01/99	...	06/12/99
783	1979	313	314	1	06/12/99	1	17.5338	3	16/03/98	06/07/98	26/01/99	...	06/12/99
1965	898	407	408	0	17/01/02	1	53.6250	1	05/12/00	18/01/02	12/08/02	...	18/10/02
1967	898	408	409	1	18/01/02	1	74.5000	1	05/12/00	18/01/02	12/08/02	...	18/10/02
1969	898	0	1	.	19/01/02	1	65.0000	.	05/12/00	18/01/02	12/08/02	...	18/10/02
1971	898	1	2	.	20/01/02	1	35.3125	.	05/12/00	18/01/02	12/08/02	...	18/10/02
...	...	...	...	...	...	...	...	...	...	...	...	...	...
1969	898	28	29	.	16/02/02	1	65.0000	2	05/12/00	18/01/02	12/08/02	...	18/10/02
1971	898	29	30	0	17/02/02	1	35.3125	2	05/12/00	18/01/02	12/08/02	...	18/10/02
...	...	...	...	...	...	...	...	...	...	...	...	...	...
2377	898	204	205	0	11/08/02	1	20.5208	2	05/12/00	18/01/02	12/08/02	...	18/10/02
2379	898	205	206	1	12/08/02	1	14.3125	2	05/12/00	18/01/02	12/08/02	...	18/10/02
2381	898	0	1	0	13/08/02	1	29.2917	3	05/12/00	18/01/02	12/08/02	...	18/10/02
2383	898	1	2	0	14/08/02	1	31.4167	3	05/12/00	18/01/02	12/08/02	...	18/10/02
...	...	...	...	...	...	...	...	...	...	...	...	...	...
2501	898	60	61	0	12/10/02	1	39.6667	3	05/12/00	18/01/02	12/08/02	...	18/10/02
2503	898	61	62	1	13/10/02	1	44.3958	3	05/12/00	18/01/02	12/08/02	...	18/10/02
4810	1323	2369	2370	0	30/12/05	1	34.7188	1	05/07/99	.	.	...	31/12/05
4812	1323	2370	2371	0	31/12/05	1	42.3021	1	05/07/99	.	.	...	31/12/05
4811	1545	1133	1134	0	30/12/05	0	34.7188	1	22/11/02	.	.	...	31/12/05
4813	1545	1134	1135	0	31/12/05	0	42.3021	1	22/11/02	.	.	...	31/12/05

Table A.2: Relative risk (RR) estimates and 95% confidence intervals (CI) for daily cases of MI per IQR increase in gasous air pollutants adjusted for time trend, season, same-day temperature, mean of lag1-3 temperature, and Mondays.

		Total		Nonfatal		Fatal		Incident MI		Recurrent MI	
Pollutant		RR	(95% CI)	RR	(95% CI)	RR	(95% CI)	RR	(95% CI)	RR	(95% CI)
CO*	Lag0	1.00	(0.96;1.04)	1.00	(0.95;1.05)	0.99	(0.94;1.05)	1.00	(0.96;1.05)	1.02	(0.94;1.10)
	Lag1	1.00	(0.97;1.04)	1.01	(0.96;1.06)	0.99	(0.94;1.05)	1.01	(0.97;1.06)	0.98	(0.90;1.06)
	Lag2	1.00	(0.96;1.03)	1.03	(0.98;1.08)	0.96	(0.92;1.02)	1.00	(0.96;1.05)	0.99	(0.92;1.07)
	Lag3	0.99	(0.96;1.02)	1.01	(0.96;1.06)	0.97	(0.92;1.02)	0.98	(0.94;1.02)	1.03	(0.96;1.10)
	Lag4	0.99	(0.96;1.03)	1.01	(0.96;1.05)	0.98	(0.93;1.03)	0.99	(0.95;1.03)	1.01	(0.94;1.09)
	5d av.	0.99	(0.96;1.03)	1.01	(0.97;1.06)	0.97	(0.92;1.03)	0.99	(0.95;1.03)	1.01	(0.93;1.09)
NO*	Lag0	1.01	(0.98;1.03)	1.00	(0.96;1.04)	1.02	(0.98;1.05)	1.01	(0.98;1.04)	1.02	(0.96;1.08)
	Lag1	0.99	(0.97;1.02)	1.00	(0.96;1.05)	0.99	(0.95;1.03)	1.00	(0.97;1.04)	1.01	(0.95;1.07)
	Lag2	0.99	(0.97;1.02)	1.03	(0.99;1.07)	0.97	(0.94;1.01)	1.01	(0.98;1.05)	0.99	(0.94;1.05)
	Lag3	1.00	(0.98;1.03)	1.02	(0.98;1.06)	1.00	(0.96;1.03)	1.00	(0.97;1.03)	1.04	(0.99;1.10)
	Lag4	1.00	(0.97;1.02)	1.02	(0.98;1.06)	0.98	(0.94;1.01)	1.00	(0.97;1.03)	1.03	(0.97;1.09)
	5d av.	1.00	(0.97;1.02)	1.02	(0.98;1.06)	0.99	(0.95;1.02)	1.01	(0.97;1.04)	1.03	(0.97;1.08)
NO_2*	Lag0	1.01	(0.98;1.04)	0.99	(0.95;1.03)	1.03	(0.99;1.07)	1.01	(0.98;1.05)	1.03	(0.97;1.09)
	Lag1	1.00	(0.97;1.03)	1.00	(0.96;1.05)	1.00	(0.96;1.04)	1.00	(0.97;1.04)	1.01	(0.96;1.08)
	Lag2	1.00	(0.97;1.02)	1.02	(0.98;1.06)	0.98	(0.95;1.02)	1.02	(0.98;1.05)	0.98	(0.93;1.04)
	Lag3	1.01	(0.98;1.04)	1.02	(0.98;1.06)	1.01	(0.97;1.05)	1.01	(0.98;1.04)	1.02	(0.97;1.08)
	Lag4	0.99	(0.97;1.02)	1.00	(0.96;1.05)	0.99	(0.95;1.03)	0.99	(0.96;1.03)	1.02	(0.97;1.08)
	5d av.	1.00	(0.97;1.03)	1.01	(0.97;1.06)	1.00	(0.96;1.04)	1.01	(0.98;1.05)	1.02	(0.96;1.09)
SO_2*	Lag0	1.01	(0.99;1.03)	1.02	(0.99;1.05)	1.01	(0.98;1.03)	1.01	(0.99;1.04)	1.01	(0.97;1.05)
	Lag1	1.01	(0.99;1.03)	1.02	(0.99;1.05)	1.01	(0.98;1.03)	1.02	(1.00;1.04)†	1.00	(0.96;1.04)
	Lag2	0.99	(0.98;1.01)	1.00	(0.97;1.03)	0.99	(0.96;1.01)	0.99	(0.97;1.02)	1.00	(0.96;1.04)
	Lag3	0.99	(0.97;1.01)	1.00	(0.97;1.02)	0.99	(0.96;1.01)	0.98	(0.96;1.00)	1.02	(0.99;1.06)
	Lag4	1.00	(0.98;1.01)	1.00	(0.97;1.03)	0.99	(0.97;1.02)	0.99	(0.97;1.01)	1.02	(0.98;1.05)
	5d av.	1.00	(0.98;1.02)	1.01	(0.98;1.05)	0.99	(0.97;1.02)	1.00	(0.97;1.03)	1.02	(0.97;1.06)

* CO: Carbon monoxide; NO: Nitrogen monoxide; NO_2: Nitrogen dioxide; SO_2: Sulfur dioxide;
† significant ($p<0.05$).

Table A.3: Sensitivity analysis: Relative risk (RR) estimates and 95% confidence intervals (CI) for daily cases of MI per IQR increase in air pollutants adjusted for time trend, season, same-day temperature, mean of lag1-3 day temperature, and Mondays.

		Total		Nonfatal		Fatal		Incident MI		Recurrent MI	
Pollutant		RR	(95% CI)	RR	(95% CI)	RR	(95% CI)	RR	(95% CI)	RR	(95% CI)
Model with time trend less smooth											
PM_{10}*	Lag0	1.02	(0.99;1.05)	1.01	(0.97;1.06)	1.03	(0.99;1.07)	1.03	(0.99;1.06)	1.04	(0.98;1.11)
	Lag1	1.02	(0.99;1.05)	1.06	(1.02;1.10)‡	0.99	(0.95;1.03)	1.04	(1.00;1.07)‡	1.01	(0.95;1.08)
	5d ave.	1.01	(0.99;1.04)	1.04	(1.00;1.09)‡	0.99	(0.95;1.02)	1.03	(0.99;1.06)	1.03	(0.97;1.09)
PNC_{m+f}*	Lag0	1.01	(0.98;1.04)	1.01	(0.96;1.05)	1.02	(0.98;1.06)	1.01	(0.97;1.05)	1.05	(0.98;1.12)
	5d ave.	1.01	(0.98;1.05)	1.05	(0.99;1.10)	0.98	(0.93;1.03)	1.01	(0.97;1.05)	1.09	(1.01;1.17)‡
$MaxO_3$*	Lag3	1.00	(0.96;1.06)	0.93	(0.87;1.00)	1.09	(1.01;1.16)‡	0.98	(0.92;1.04)	1.02	(0.91;1.13)
	5d ave.	1.01	(0.94;1.08)	0.94	(0.85;1.03)	1.09	(0.99;1.19)	0.99	(0.91;1.07)	1.07	(0.92;1.23)
Model without season											
PM_{10}	Lag0	1.02	(0.99;1.05)	1.01	(0.97;1.05)	1.03	(0.99;1.07)	1.02	(0.99;1.05)	1.05	(0.99;1.11)
	Lag1	1.02	(0.99;1.04)	1.04	(1.00;1.08)‡	0.99	(0.95;1.03)	1.02	(0.99;1.06)	1.02	(0.96;1.08)
	5d ave.	1.01	(0.98;1.04)	1.03	(0.99;1.07)	0.99	(0.95;1.03)	1.01	(0.98;1.05)	1.03	(0.98;1.09)
PNC_{m+f}	Lag0	1.02	(0.99;1.05)	1.01	(0.96;1.05)	1.02	(0.98;1.06)	1.01	(0.98;1.05)	1.05	(0.99;1.12)
	5d ave.	1.01	(0.98;1.04)	1.03	(0.98;1.08)	0.99	(0.94;1.04)	1.00	(0.96;1.05)	1.09	(1.02;1.17)‡
$MaxO_3$	Lag3	1.03	(0.99;1.07)	0.99	(0.93;1.05)	1.07	(1.01;1.14)‡	1.01	(0.96;1.06)	1.04	(0.95;1.14)
	5d ave.	1.05	(1.00;1.10)	1.03	(0.96;1.11)	1.07	(1.00;1.15)	1.04	(0.98;1.10)	1.08	(0.97;1.20)
Model additionally adjusted for influenza											
PM_{10}	Lag0	1.02	(0.99;1.05)	1.01	(0.97;1.06)	1.03	(0.99;1.07)	1.02	(0.99;1.06)	1.05	(0.99;1.11)
	Lag1	1.02	(0.99;1.05)	1.06	(1.01;1.10)‡	0.98	(0.95;1.02)	1.03	(0.99;1.07)	1.02	(0.97;1.09)
	5d ave.	1.01	(0.98;1.04)	1.04	(1.00;1.09)‡	0.98	(0.95;1.02)	1.02	(0.99;1.06)	1.04	(0.98;1.10)
	Lag0	1.01	(0.98;1.04)	1.00	(0.96;1.05)	1.03	(0.98;1.07)	1.01	(0.97;1.05)	1.04	(0.98;1.11)
	5d ave.	1.00	(0.97;1.03)	1.02	(0.98;1.06)	0.98	(0.94;1.02)	0.99	(0.95;1.02)	1.06	(0.99;1.12)
$MaxO_3$	Lag3	0.99	(0.95;1.04)	0.93	(0.87;1.00)	1.07	(1.00;1.15)‡	0.97	(0.92;1.04)	1.05	(0.95;1.16)
	5d ave.	1.01	(0.94;1.07)	0.94	(0.86;1.04)	1.07	(0.97;1.17)	0.99	(0.91;1.07)	1.10	(0.97;1.26)
Meteorolgy selection based on GCV†											
PM_{10}	Lag0	1.02	(0.99;1.05)	1.02	(0.98;1.06)	1.02	(0.98;1.06)	1.02	(0.99;1.06)	1.05	(0.99;1.11)
	Lag1	1.02	(0.99;1.05)	1.05	(1.01;1.10)‡	0.98	(0.94;1.01)	1.02	(0.99;1.06)	1.02	(0.96;1.08)
	5d ave.	1.01	(0.98;1.04)	1.04	(1.00;1.09)	0.98	(0.94;1.02)	1.02	(0.98;1.06)	1.03	(0.98;1.09)
PNC_{m+f}	Lag0	1.01	(0.98;1.04)	1.01	(0.96;1.05)	1.01	(0.97;1.05)	1.01	(0.97;1.05)	1.04	(0.97;1.10)
	5d ave.	1.00	(0.97;1.04)	1.04	(0.98;1.09)	0.97	(0.92;1.02)	1.00	(0.95;1.04)	1.07	(0.99;1.15)
$MaxO_3$	Lag3	1.01	(0.96;1.07)	0.95	(0.88;1.03)	1.07	(0.99;1.15)	0.98	(0.92;1.04)	0.98	(0.92;1.04)
	5d ave.	1.00	(0.93;1.08)	0.99	(0.89;1.11)	1.01	(0.91;1.12)	0.96	(0.88;1.05)	1.13	(0.97;1.32)

* PM_{10}: particles < 10µm; PNC_{m+f}: particle number concentration, retrospectively fitted (1995-1998) and measured values (1999-2004); $MaxO_3$: ozone, maximum 8 hour moving average;

† GCV: generalized cross validation;

‡ significant ($p<0.05$).

A.3 Article „Air temperature and the occurrence of myocardial infarction in Augsburg, Germany.“

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Air temperature and the occurrence of myocardial infarction in Augsburg, Germany.

WOLF: Temperature and myocardial infarction.

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ABSTRACT

Background: Air temperature changes have been associated with cardiovascular mortality and morbidity. The objective of this study was a detailed examination of registry-based myocardial infarction (MI) rates and coronary deaths in relation to air temperature in the area of Augsburg, Germany.

Methods and Results: Between 1995 and 2004, the MONICA/KORA registry recorded 9801 cases of MI and coronary deaths. Over the same period, meteorological parameters and air pollutant concentrations were measured in the study region. Poisson regression analyses adjusting for time trend, relative humidity, season, and calendar effects were used to estimate immediate, delayed and cumulative temperature effects on the occurrence of MIs. The daily rate of total MI, nonfatal and fatal events as well as incident and recurrent events were analyzed.

For the total of MI cases, a 10°C decrease in 5-day average temperature was associated with a relative risk of 1.10 (95%-CI: 1.04 to 1.15). The effect of temperature on the occurrence of nonfatal events showed a delayed pattern, whereas the association with fatal MI was more immediate. No association could be observed for recurrent events. The effects of temperature decreases on the total of MI cases were more pronounced in years with higher average temperature and also visible in summer.

Conclusions: We observed an inverse relationship between temperature and MI occurrence not only during winter, but also during summer. Thus, our results suggest not a pure “cold effect” but an influence of unusual temperature decreases.

Key words: air temperature, myocardial infarction, registry, epidemiology

(Word count: 241)

INTRODUCTION

Cold periods, but also extreme heat have been reported to be associated with cardiovascular mortality[1-5] and morbidity[6-8]. Most of these studies analyzed mortality data from national death statistics or hospital admission rates which might be subject to misclassification and/or referral biases[9]. There were several studies which examined the relationship between weather variables and the incidence of cardiovascular events and especially myocardial infarctions (MI) based on registry[10-15] or similar validated data[9]. Some of them considered only seasonal[15] or monthly[12] variations in MI rates, but the most part investigated the influence of meteorology on MI rates on a daily basis. Except for one study[9] which did not see any seasonal changes in incident MIs, the seasonality pattern for coronary heart disease with winter peak and summer trough[16] could be confirmed. Regarding air temperature, the results differed not only in their strength but also in their directions. While two studies[9;14] could not identify any effect, another study[13] described a V-shaped association, showing an increased risk on region-specific cold days and to a lesser extent on hot days. Furthermore, a linear relationship with increased risk on colder days was also described[10;11]. With regard to climate change, a proper specification of the exposure-response curve is needed to correctly assess the impact of global warming and higher variation in temperature extremes[17].

The objective of this analysis was the examination of MI rates and coronary deaths in relation to air temperature on the basis of the MONICA/KORA Augsburg myocardial infarction registry data between 1995 and 2004. Specific aims were to test whether effects on fatal and nonfatal or incident and recurrent MIs are similar, to assess the exposure-response function, to compare different temperature metrics, to study the influence of warm and cold years and to inspect potential effect modification by personal characteristics.

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 fatal and nonfatal myocardial infarction (MI) and of coronary deaths among persons aged 25 to 74 with principal residence in the city of Augsburg, Southern Germany, and the two adjacent rural districts of Augsburg and Aichach-Friedberg. Altogether, the study population consists of about 400,000 inhabitants aged 25 to 74 years. According to the MONICA protocol[18], hospital admissions are continuously monitored and MI patients, who survived at least 24 hours, are asked for an interview concerning the event, medication and family history. Coronary deaths are fatal cases outside the hospital or within the 24 hours 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[19;20]. The diagnostic criteria included chest pain lasting more than 20 minutes 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. We considered all recorded fatal and nonfatal events between 1995 and 2004.

Meteorological, air pollution and influenza data

Air temperature, relative humidity, barometric pressure and ozone were measured by the Bavarian Air Monitoring Network at background air monitoring sites located at Haunstetten, a suburb 7 km south of the Augsburg city center. From 1995-1999, total suspended particles

were measured with a ß-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 particulate matter with an aerodynamic diameter < 10µm (PM_{10})[21]. 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[21;22]. Particle number concentration (PNC), an indicator for ultrafine particles, was obtained from 1999-2004 by a condensation particle counter (CPC 3022A, TSI) and imputed retrospectively within a regularized linear prediction model[23]. All data except PM_{10} were available on an hourly basis and 24-hour mean values were calculated if at least 75% of the hourly values were available. Data on influenza epidemics were obtained from the German Influenza working group (AGI)[24].

Statistical analyses

We assessed the association between air temperature and daily cases of MI and coronary deaths using generalized additive Quasi-Poisson models to accommodate a Poisson distribution with constant overdispersion. As we assumed that changes of the underlying population at risk over the years could be modelled with a smooth trend function, we did not adjust the event rates for age or sex. 24-hour mean temperature of the same day (lag0), the day before MI occurrence (lag1) and up to 4 days before the event (lag1 to lag4) as well as the average temperature over 5 days (mean of lag0 to lag4) were taken separately in the model as linear terms. As potential confounders, we considered a global trend over time, seasonal and weekday variations as well as relative humidity and barometric pressure. Model selection was carried out by minimizing the generalized cross validation (GCV) criteria and the absolute value of the sum of the partial autocorrelation function[25]. Time trend and relative humidity were forced into the model even if model fit was not improved. The

final model included a penalized regression spline of time trend, relative humidity as a linear term with the same lag as the temperature term, season as a categorical variable (Mar-May, Jun-Aug, Sep-Nov, and Dec-Feb) and an indicator variable for Monday (for a detailed summary see Online Supplement, Table 1).

Besides the daily rate of total MI, nonfatal (survived longer than 28 days) and fatal events as well as incident and recurrent events were inspected separately. Additionally, we assessed the shape of the exposure-response function by including air temperature as a penalized regression spline.

In addition to the 24-hour mean temperature, we estimated the influence of 5-day average, 24-hour maximum and minimum temperature, the temperature range (maximum minus minimum temperature), apparent and dewpoint temperature on the daily count of MI. Apparent temperature (AT) was defined as $AT = -2.653 + (0.994 \times T) + (0.0153 \times DT^2)$, where DT denotes dew point temperature ($DT=1/(1/(T+241.413)-(\log10(RH*0.01)/1838.675))-241.413$), T air temperature and RH relative humidity[26]. Furthermore, indicator variables for the 5% or, alternatively, for the 1% hottest and coldest days were added to the model to examine their particular influences.

We calculated the yearly mean temperature for each of the ten years and categorized them into cold, moderately tempered and warm years to investigate if short-term temperature effects differed in predominantly warm or cold years. The categories were defined on the 10-year distribution of the 24-hour average temperatures. We categorized the yearly averages within these tertiles and created three variables which contained the 5-day average temperature if the day derived from a cold, moderately tempered or warm year, respectively, and zero else. The same was carried out for winter (October to March) and summer (April to September). We thus calculated two separate models, one with the three temperature variables for cold, moderately tempered and warm years and one with the winter and summer

categories. Both were adjusted for time trend, an indicator variable for Monday, 5-day average relative humidity and the whole-years model additionally for season.

Moreover, we assessed effect modification by gender, age groups (25-54, 55-64 and 65-74 years of age), and history of hypertension and diabetes. All statistical analyses were performed with R software[27], version 2.7.2, package "mgcv"[28].

Sensitivity analysis

To explore the robustness of the models, we used different values of smoothness for the function of time trend. Furthermore, as time trend, season and temperature partly compete for the same effects, the model was reduced by leaving out the seasonal categories. We also adjusted for influenza epidemics as described in Stölzel et al.[29]. Moreover, we included barometric pressure as well as air pollutants (PM_{10}, PNC and ozone) linearly with the same lag as the temperature term as additional adjustment. We also investigated interaction effects between barometric pressure or air pollutants and temperature by considering those variables as multiplicative linear terms. Air pollution marker and respective time lags were chosen on the basis of a significant influence on the RR for MI in at least one of the four main outcome subgroups. As urbanicity is known to affect temperatures, we also stratified by region (city vs. counties of Augsburg).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

RESULTS

Study population

A total of 9801 coronary events occurring in 9199 subjects were recorded between 1995 and 2004. Of these events, 4838 were nonfatal MIs and 4963 were coronary deaths and fatal MIs

(MI's between the second and 28th day). The proportion of incident and recurrent MIs constituted 70% and 21%, respectively. The remaining 9% could not be categorized in either of the subgroups, because of missing information and originated almost exclusively from fatal cases. 56% of recurrent events but only 43% of incident MIs were fatal. Baseline characteristics for all cases and MI subgroups are summarized in Table 1. The percentage of men was lower and mean age was higher within fatal cases than within nonfatal cases. Patients with recurrent MI were older and included more men than patients with incident MI.

Meteorology and air pollutants

Summary statistics for meteorology and air pollutants are presented in Table 2; for the Spearman correlation coefficients see the Online Supplement, Table 2. The different temperature measures were highly positively correlated apart from the temperature range, whereas only a moderate correlation could be observed for mean temperature and relative humidity, ozone or PNC. No correlation was present between mean temperature and barometric pressure or PM_{10}.

Association of temperature and MI

Daily air temperature and daily numbers of nonfatal and fatal MIs are presented in the Online Supplement, Figure 1. A smooth function for the observed numbers of daily events showed higher rates in winter and lower rates in summer.

Results of the Poisson models for same day and 5-day average temperature are summarized in Table 3. Results for temperature changes lagged 1 to 4 days are shown in the Online Supplement, Table 3. Relative Risk (RR) estimates and corresponding 95% confidence intervals (CI) for the effect of MI events are expressed for a 10°C decrease in air temperature as this number describes a plausible change in temperature and lies close to the interquartile

range of 12.8°C. A decrease of 10°C was significantly associated with an increase in the numbers of MI except for recurrent events. Regarding total cases the strongest effect was seen for lag of 3 days and a similar effect for the 5-day average. Nonfatal events showed a delayed pattern, whereas fatal events were associated with all time windows. For the subgroup of incident MIs, the cumulative effect of the 5-day average temperature had the largest RR. Regarding the exposure-response function, there was no evidence for a deviation of log-linearity of the relationship between temperature and daily MI counts (data not shown).

The effect estimates for 5-day average minimum, maximum, apparent or dew point temperature did not substantially differ from the effect estimate for 5-day average mean temperature (Online Supplement, Figure 2). 5-day average temperature range was less associated with the total number of MI. The inclusion of indicator variables for the 5% and 1% hottest and coldest days did not change the temperature estimates and the indicators itself were not significant (data not shown).

Figure 1 shows the association between MI cases and 5-day average temperature for cold, moderately tempered and warm years (A), and further divided into cold, moderately tempered and warm summers (B1) and winters (B2), respectively. The estimates of Panel A were derived from a separate model, whereas the estimates of Panel B1 and B2 resulted from a joint model. The effects of temperature were consistently observed in moderately tempered and warm years, summers and winters. In cold winters, MI rates were less influenced by temperature decreases.

Men and women, diabetics and non-diabetics showed no difference in the RR of MI for a 10°C change in temperature. Patients with history of hypertension showed slightly larger RR compared to patients with no history. Strongest influence was found for patients aged 55-64, whereas for the younger group no association was observed (Figure 2).

Sensitivity analysis

Allowing for more variability in the seasonal adjustment did not alter the results considerably (Online Supplement, Table 4). However, the examination of partial autocorrelation plots indicated some overfitting. The exclusion of season resulted in similar, but somewhat higher effect estimates with narrower confidence intervals. The additional adjustment for influenza epidemics did not affect the temperature estimates. Moreover, air pollutants did not alter the temperature relationship with MI significantly, when entered as additional confounders (Online Supplement, Table 4) or interaction terms (data not shown). Slightly higher RR estimates of 5-day average temperature for the inhabitants of the city (RR: 1.12; 95% CI: 1.03 to 1.21) were observed than for the county population (RR: 1.09; 95% CI: 1.01 to 1.17).

DISCUSSION

Summary

This registry-based time-series study over ten years observed an inverse association between air temperature and the total of MI cases and coronary deaths. The subgroup of recurrent events was not affected. A comparison of different temperature metrics showed no appreciable differences except for the temperature range, which is rather a marker for the fluctuation within a day than for temperature itself. In warmer and moderately tempered years, the association of MI occurrence and decreasing temperature were more pronounced than in colder years. For cold winters, no significant risk increase was observed. Patients aged 55 to 64 years were identified as most susceptible. No effect modification by gender or history of diabetes was observed while the effect of temperature on MI was somewhat stronger for patients with a history of hypertension. No interaction with air pollutants could be detected.

In this study, we observed an overall increase in the RR for all events of 7% per 10°C decrease in same day temperature, while a French registry-based analysis reported an increase of 13% for the same increment[10]. The authors identified recurrent cases of MI as most susceptible, which could not be confirmed within our analysis. However, when analyzing seasonality and weather in relation to sudden cardiac deaths, Gerber et al.[9] reported for temperatures below 0°C vs. 18°C to 30°C a 35% increased risk for subjects without prior coronary heart disease, whereas no effect for subjects with prior coronary heart disease was observed. A similar effect modification was described by Ruidavets et al.[30] for the impact of air pollution on MI rates. A possible explanation could be the improved medication, but also the increased consciousness of subjects with MI history to be susceptible.

As temperature influences on mortality have usually been described by U-, V- or J-shaped functions[4], we inspected the exposure-response curve by nonparametric smooth functions. An increased adaptation of the smooth function to the data confirmed the linear relationship identified by Danet et al.[10] for this temperature range. One registry-based study from Australia[13] and a study on emergency room admissions for acute coronary syndromes in Taiwan[7] reported U- and V-shaped exposure-response functions when using quantiles to model a non-linear relationship. Although the warmer categories showed higher effects compared to the corresponding reference categories, neither was significant.

Studies across US cities[11;31] and European regions[5;32] have consistently reported stronger cold effects in warmer climates. The separate inspection of temperature for cold, moderately tempered and warm years as well as summers and winters in our study indicated similar results. Thus, it can be hypothesized that subjects do not adapt only to regional, but also to seasonal mean temperatures. We would assume that in a cold winter, people are more habituated to the cold, and therefore, the influence of decreasing air temperature has not the same extent than in a warm winter. Our analysis was able to show an increase of MI rates for

a previous drop of temperature in both winter and summer. Thus, our results point not only to a pure cold effect as described by Medina-Ramon et al.[33] for extremely cold days and cardiovascular deaths, but rather to an influence of the unusualness of cold temperatures[1]. With regard to climate change and its speculated higher variation in temperature extremes[17], rather an intensification than a reduction of this effect might be expected. Furthermore, the hypothesis of a compensation of higher heat-related rates by lower cold-related rates as suggested for mortality[32] seems not to apply to MI cases and coronary deaths.

We identified a slightly protective effect of moderate temperature, but no effect of extreme heat. This could be due to the relatively tempered climate in Augsburg, which is not comparable to southern European countries or warmer US states where heat effects in association with excess mortality have been frequently observed[34-37]. Moreover, heat possibly plays a minor role in the onset of MI. Medina-Ramon et al.[33] reported a reduced risk for MI deaths compared to other mortality causes on days with extreme heat. On the other hand, when comparing the same 50 US cities by their temperature means, Medina-Ramon and Schwartz[1] saw greater heat effects in cities with lower temperature, also for MI mortality. Danet et al.[10] reported strongest effects for the age group of 55-64 years, which could be confirmed within our study. However, subjects aged 65-74 years showed a still significant, but smaller effect which could be due to higher rates of medication intake as well as better susceptibility awareness of the older persons.

Confounding or effect modification of the temperature effects due to gaseous or particulate air pollutants as suggested by several studies[26;38;39] for mortality could not be detected and confirms recent results[40].

Mechanisms

Potential mechanisms to explain the increased risk for incident coronary events in association with decreasing temperature include the stimulation of cold receptors in the skin and therefore the sympathetic nervous system, leading to a rise in the catecholamine level. The consequences are vasoconstriction, increased heart rate and blood pressure[41-43]. An increased blood pressure decreases the ratio of myocardial oxygen supply to demand and may lead to myocardial ischemia, particularly in a vulnerable myocardium. Moreover, a drop in temperature could be related to an increase in fibrinogen[44;45] and C-reactive protein[44;46]. In cold conditions the plasma concentrations of certain clotting factors, platelet count and their in vitro aggregation are all increased and promote clotting[45;47;48]. Furthermore, reduced plasma volume and increased blood viscosity during cold exposure also tend to promote thrombosis[47;48]. Hence, well-known cardiovascular risk factors are elevated during colder periods and recurrent changes in markers of atherothrombosis may contribute to the risk of triggering acute coronary events. A potential explanation for the lack of influence on recurrent events could be that once people survive an event, they become more aggressively treated and may be protected from adverse effects of cold temperatures. Alternatively, the difference could also be a chance finding as this subgroup was the smallest in our analysis.

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 MONICA/KORA MI registry[18-20]. Further strengths are the possible non-linear confounder adjustment, the consideration of other meteorological parameters, the information on patient characteristics to conduct subgroup analyses as well as the availability of air pollutant measurements to examine potential confounding and effect modifying influences.

However, there is the potential for residual confounding. At cold temperatures behaviours such as smoking, physical activity, diet or stress reactions could change. Though, we could identify similar effects of decreasing temperature in winters and summers where the impact of cold temperatures on behaviours is supposed to be very different in a temperate climate. One of the limitations of our study is the different precision of time of onset for nonfatal and fatal events. For nonfatal events, time of symptom onset was used and validated against the information from the medical records. For fatal events, time of hospital arrival or death were used instead. The age-range of the registry of 25-74 years has limitations especially for women who suffer from MIs more frequent at older ages. A further limitation is that only outdoor temperature was measured while people usually spend a lot of time indoors at room-temperatures. Also, housing characteristics could play a role. However, we could identify similar effects of decreasing temperature in winters and summers where the time periods spent outdoors are supposed to be very different. Only one measurement location was used which poses a source for exposure misclassification. The stratification by region indicated slightly higher risks for inhabitants of the city and slightly lower risks for the county population. This deviation may originate from differences in microenvironmental temperatures, living conditions and behavioural factors of city and county inhabitants. Moreover, effect modification by medication intake, individual smoking and exposure to second-hand smoke could not be considered since these data were not available for most of the fatal cases. Potential higher effects in winter which could be partly attributed to greater exposure to second-hand smoke on cold days could not be seen.

Conclusion

This registry-based study carried out over ten years in a region of tempered climate, observed an increased risk for the occurrence of MI in association with a decrease in air temperature.

The association was similar for winters and summers and was more pronounced in years with higher average temperature. Therefore, we suggest that the influence of unexpected temperature decreases is more relevant than the absolute temperature level itself.

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Conflict of Interest Disclosures:

The authors declare that they have no conflict of interests.

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Figure legends:

Figure 1. Relative risk estimates for daily cases of MI per 10°C decrease in 5-day average temperature*. The estimates represent cold, moderately tempered and warm years (A), summers (B1) and winters (B2) and are placed on the x-axis corresponding to their mean temperature†.

Subtitle Figure 1:
* Panel A: adjusted for time trend, season, Monday and relative humidity;
Panel B1 and B2: adjusted for time trend, Monday and relative humidity.
† The bold bars on the x-axis represent the corresponding 10-year mean temperature.

Figure 2. Relative risks for total cases of MI per 10°C decrease in 5-day average temperature adjusted for time trend, season, Monday and relative humidity stratified by subgroups.

TABLE 1. Study population in Augsburg, Germany, 1995-2004.

	Missings N (%)	Total MI	Nonfatal MI	Fatal MI	p-value	Incident MI	Recurrent MI	Insufficient data*	p-value
No. of cases	-	9801	4838	4963		6902	2030	869	
Mean age (SD) [years]	-	62.8 (9.2)	60.6 (9.6)	64.9 (8.3)	<0.001†	62 (9.5)	64.9 (7.7)	63.9 (8.8)	<0.001§
Men [%]	-	73	77	70	<0.001‡	72	79	68	<0.001‡
City of Augsburg [%]	-	50	49	51	0.045‡	48	54	60	<0.001‡
History of									
Hypertension [%]	832 (8.5)	62	70	55	<0.001‡	64	72	25	<0.001‡
Diabetes mellitus [%]	835 (8.5)	31	29	32	<0.001‡	30	40	18	<0.001‡

* for classifying incident or recurrent event

† Wilcoxon rank sum test

‡ Pearson's Chi-squared test

§ Kruskal-Wallis rank sum test

TABLE 2. Summary statistics for meteorology and air pollutants (data on 3653 consecutive days).

Parameter	N in %	Mean (SD)	Min	Q1	Median	Q3	Max	IQR*	IQR* of 5-day average
Temperature measures									
Mean temperature (°C)	99.6	9.5 (8.0)	-14.9	3.2	9.8	16.0	27.9	12.8	12.7
Min temperature (°C)	99.6	5 (7.1)	-20.1	-0.1	5.3	10.8	19.8	11.0	10.8
Max temperature (°C)	99.6	14.4 (9.7)	-11.8	6.8	14.2	22.1	39.2	15.4	15.0
Temperature range (°C)	99.6	9.4 (5.1)	0.5	5.3	8.6	13.2	25.1	7.9	5.8
Apparent temperature (°C)	99.6	7.7 (8.7)	-13.0	0.6	7.5	14.7	28.9	14.1	13.9
Dewpoint temperature (°C)	99.6	4.4 (6.5)	-17.0	-0.4	4.7	9.8	17.7	10.3	10.1
Other meteorological variables									
Relative humidity (%)	99.8	74.5 (13.2)	35.8	64.2	75.7	85.7	96.0	21.5	16.2
Barometric pressure (hPa)	99.6	1018.0 (8.0)	984.3	1013.0	1019.0	1024.0	1038.0	10.3	8.9
Air pollutants									
PNC[†] (number/cm³)	92.2	12630 (6120)	2434	8479	11400	15180	70300	6702	5607
PM_{10}[‡] (µg/m³)	99.0	41.8 (19.9)	4.6	27.8	39.0	52.4	203.0	24.6	18.3
Ozone (µg/m³)	99.3	66.6 (36.7)	3.0	40.8	62.9	90.8	189.7	50.1	50.0

* IQR: Interquartile range (Q3-Q1)

[†] PNC: Particle number concentration

[‡] PM_{10}: Particles with an aerodynamic diameter < 10µm

TABLE 3. Relative risk estimates for daily cases of MI per 10°C decrease in air temperature adjusted for time trend, season, Monday and relative humidity.

	Air temperature			
	Same day		5-day average*	
Group	RR	(95% CI) †	RR	(95% CI) †
Total MI	1.07	(1.02;1.12)	1.10	(1.04;1.15)
Nonfatal MI	1.04	(0.97;1.12)	1.10	(1.01;1.18)
Fatal MI	1.09	(1.02;1.17)	1.10	(1.02;1.19)
First MI	1.10	(1.04;1.16)	1.12	(1.05;1.19)
Recurrent MI	0.96	(0.86;1.06)	1.02	(0.91;1.14)

* 5-day average: Mean temperature of same and 4 previous days

† RR: Relative risk, CI: confidence interval

Figure 1.

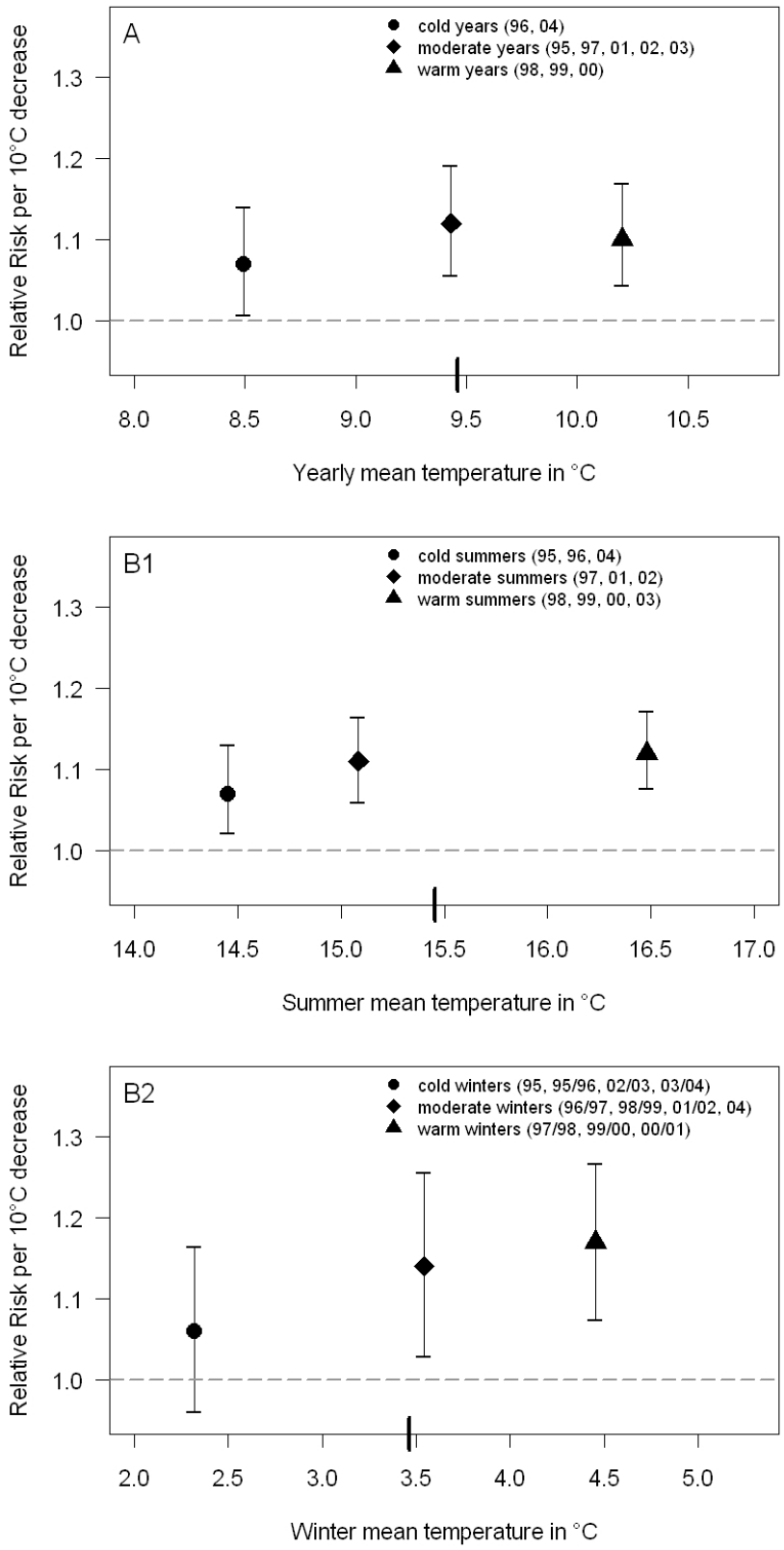
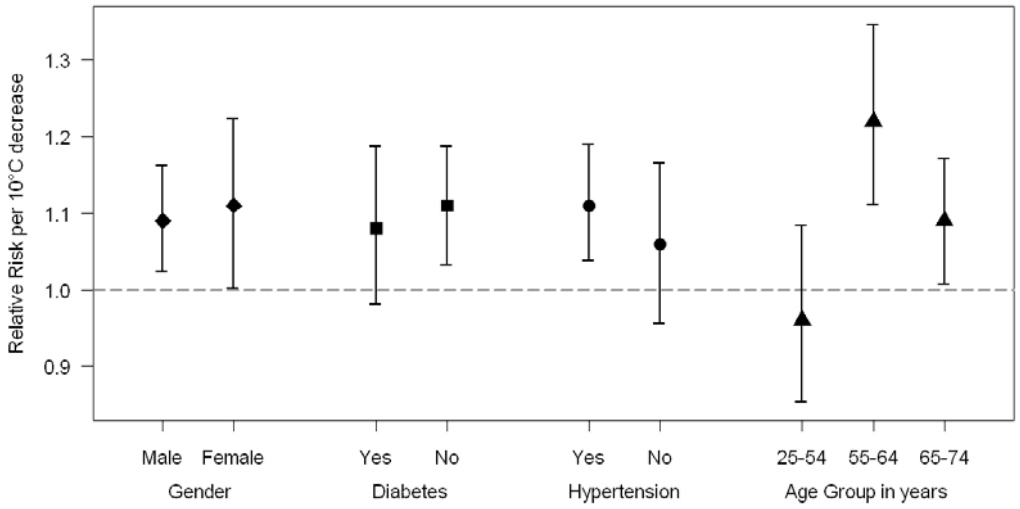

A
cold years (96, 04)
moderate years (95, 97, 01, 02, 03)
warm years (98, 99, 00)
Relative Risk per 10°C decrease
1.0
1.1
1.2
1.3
8.0
8.5
9.0
9.5
10.0
10.5
Yearly mean temperature in °C
B1
cold summers (95, 96, 04)
moderate summers (97, 01, 02)
warm summers (98, 99, 00, 03)
Relative Risk per 10°C decrease
1.0
1.1
1.2
1.3
14.0
14.5
15.0
15.5
16.0
16.5
17.0
Summer mean temperature in °C
B2
cold winters (95, 95/96, 02/03, 03/04)
moderate winters (96/97, 98/99, 01/02, 04)
warm winters (97/98, 99/00, 00/01)
Relative Risk per 10°C decrease
1.0
1.1
1.2
1.3
2.0
2.5
3.0
3.5
4.0
4.5
5.0
Winter mean temperature in °C

Figure 2.


Relative Risk per 10°C decrease
1.3
1.2
1.1
1.0
0.9
Male
Female
Gender
Yes
No
Diabetes
Yes
No
Hypertension
25-54
55-64
65-74
Age Group in years

SUPPLEMENTAL MATERIAL

Online Supplement: TABLE 1. Exposure and covariate term description for each model. If variables were included, the corresponding fields are marked with a x (functional form as described in the header) or a description of its type of inclusion.

Model		Exposure	Covariates					
	Variable	Temp*	Trend	Season	Monday	Relative humidity	Additional covariates	Functional form for add. covariates
	Definition			1=Mar-May; 2=Jun-Aug; 3=Sep-Nov; 4=Dec-Feb	1, if Monday; 0, else			
	Functional form	linear	prs†	categorical	indicator	linear		
Main Model		x	x	x	x	x		
Cold, medium and warm years model (Figure 1, A)		Temp×$\mathbf{I}_{\text{cold year}}$‡ Temp×$\mathbf{I}_{\text{medium year}}$‡ Temp×$\mathbf{I}_{\text{warm year}}$‡	x	x	x	x		
Cold, medium and warm winters and summers model (Figure 1, B1 and B2)		Temp×$\mathbf{I}_{\text{cold summer}}$‡ Temp×$\mathbf{I}_{\text{medium summer}}$‡ Temp×$\mathbf{I}_{\text{warm summer}}$‡ Temp×$\mathbf{I}_{\text{cold winter}}$‡ Temp×$\mathbf{I}_{\text{medium winter}}$‡ Temp×$\mathbf{I}_{\text{warm winter}}$‡	x		x	x		
Sensitivity analysis (Online supplement, Table 4)								
S1		x	prs† with higher degrees of freedom	x	x	x		
S2		x	x		x	x		
S3		x	x	x	x	x	influenza	prs† for each winter
S4		x	x	x	x	x	pollutant	linear

* Temp: mean temperature

† prs: Penalized regression spline

‡ **I**: Indicator variable, 1, if day corresponds to condition; 0, else

Online Supplement: TABLE 2. Spearman correlation coefficients for meteorology and air pollutants (data on 3653 consecutive days).

	Spearman correlation coefficient									
Parameter	Min temp	Max temp	Temp range	App temp	Dewp temp	Rel. humid.	Bar. press.	PNC*	PM_{10}†	Ozone
Temperature measures										
Mean temperature (°C)	0.95	0.97	0.56	1.00	0.92	-0.56	0.08	-0.46	0.02	0.70
Min temperature (°C)		0.87	0.30	0.96	0.96	-0.36	0.03	-0.55	-0.06	0.56
Max temperature (°C)			0.72	0.97	0.84	-0.65	0.10	-0.36	0.10	0.74
Temperature range (°C)				0.54	0.30	-0.77	0.17	0.06	0.29	0.66
Apparent temperature (°C)					0.93	-0.53	0.07	-0.47	0.02	0.68
Dewpoint temperature (°C)						-0.21	0.01	-0.52	-0.03	0.46
Other meteorological variables										
Relative humidity (%)							-0.18	0.07	-0.12	-0.79
Barometric pressure (hPa)								0.05	0.22	0.07
Air pollutants										
PNC* (number/cm³)									0.48	-0.33
PM_{10}† (µg/m³)										-0.04
Ozone (µg/m³)										

* PNC: Particle number concentration

† PM_{10}: Particles with an aerodynamic diameter < 10µm

Online Supplement: TABLE 3. Relative risk estimates for daily cases of MI per 10°C decrease in air temperature adjusted for time trend, season, Monday and relative humidity.

	Total MI		Nonfatal MI		Fatal MI		First MI		Recurrent MI	
Air temperature	RR	(95% CI)*	RR	(95% CI)	RR	(95% CI)	RR	(95% CI)	RR	(95% CI)
Lag0[†]	1.07	(1.02;1.12)	1.04	(0.97;1.12)	1.09	(1.02;1.17)	1.10	(1.04;1.16)	0.96	(0.86;1.06)
Lag1	1.08	(1.03;1.13)	1.07	(0.99;1.14)	1.09	(1.02;1.17)	1.10	(1.04;1.17)	0.97	(0.88;1.07)
Lag2	1.08	(1.03;1.13)	1.09	(1.02;1.17)	1.08	(1.01;1.15)	1.10	(1.03;1.16)	1.02	(0.92;1.12)
Lag3	1.10	(1.05;1.15)	1.11	(1.04;1.19)	1.08	(1.01;1.16)	1.10	(1.04;1.16)	1.07	(0.97;1.19)
Lag4	1.07	(1.02;1.12)	1.11	(1.04;1.19)	1.04	(0.97;1.11)	1.08	(1.02;1.14)	1.03	(0.93;1.14)
5-day average[‡]	1.10	(1.04;1.15)	1.10	(1.01;1.18)	1.10	(1.02;1.19)	1.12	(1.05;1.19)	1.02	(0.91;1.14)

* RR: Relative risk; CI: confidence interval

[†] Lag0: Temperature of the same day; Lag1: Temperature of the previous day; Lag2-4: Temperature 2 to 4 days ago

[‡] 5-day average: Mean temperature of same and 4 previous days

Online Supplement: TABLE 4. Sensitivity analysis: Relative risk estimates for daily cases of MI per 10°C decrease in air temperature and potential confounding air pollutants per IQR increase adjusted for time trend, season, Monday and relative humidity.

			Total MI		Nonfatal MI		Fatal MI		Incident MI		Recurrent MI	
			RR	(95% CI)*	RR	(95% CI)	RR	(95% CI)	RR	(95% CI)	RR	(95% CI)
S1: Model with time trend less smooth												
	Lag0[†]	Temperature	1.06	(1.02;1.11)	1.04	(0.98;1.11)	1.09	(1.02;1.16)	1.10	(1.04;1.16)	0.96	(0.87;1.06)
	5-day average[‡]	Temperature	1.10	(1.04;1.16)	1.09	(1.02;1.18)	1.10	(1.03;1.18)	1.12	(1.05;1.19)	1.02	(0.91;1.15)
S2: Model without season												
	Lag0	Temperature	1.09	(1.06;1.12)	1.05	(1.01;1.10)	1.13	(1.08;1.18)	1.10	(1.06;1.14)	1.04	(0.97;1.11)
	5-day average	Temperature	1.10	(1.07;1.14)	1.08	(1.02;1.13)	1.14	(1.08;1.19)	1.11	(1.06;1.15)	1.08	(1.01;1.17)
S3: Model additionally adjusted for influenza												
	Lag0	Temperature	1.05	(1.00;1.11)	1.04	(0.97;1.11)	1.07	(1.00;1.15)	1.08	(1.02;1.15)	0.96	(0.86;1.06)
	5-day average	Temperature	1.09	(1.03;1.15)	1.10	(1.01;1.19)	1.08	(1.00;1.17)	1.10	(1.03;1.18)	1.04	(0.92;1.16)
S4: Model additionally adjusted for air pollutants												
PM_{10}[§]	Lag1[†]	Temperature	1.07	(1.02;1.12)	1.05	(0.98;1.12)	1.09	(1.02;1.17)	1.09	(1.03;1.16)	0.96	(0.87;1.06)
	Lag1	PM_{10}	1.02	(0.99;1.05)	1.06	(1.02;1.10)	0.98	(0.94;1.02)	1.02	(0.99;1.06)	1.03	(0.97;1.09)
PNC[§]	Lag0	Temperature	1.05	(1.00;1.10)	1.02	(0.95;1.11)	1.08	(1.00;1.16)	1.07	(1.01;1.14)	0.93	(0.83;1.04)
	Lag0	PNC	1.02	(0.99;1.05)	1.03	(0.98;1.07)	1.01	(0.97;1.05)	1.01	(0.98;1.05)	1.07	(1.00;1.14)
	5-day average	Temperature	1.09	(1.03;1.16)	1.06	(0.97;1.17)	1.15	(1.05;1.25)	1.11	(1.03;1.2)	0.97	(0.84;1.11)
	5-day average	PNC	1.00	(0.97;1.04)	1.04	(0.99;1.09)	0.96	(0.91;1.01)	1.00	(0.95;1.04)	1.09	(1.01;1.17)
Ozone	Lag0	Temperature	1.07	(1.01;1.12)	1.04	(0.97;1.12)	1.09	(1.02;1.18)	1.09	(1.03;1.16)	0.97	(0.87;1.09)
	Lag0	Ozone	0.99	(0.93;1.05)	0.99	(0.91;1.08)	1.00	(0.91;1.09)	0.98	(0.91;1.05)	1.04	(0.91;1.18)
	5-day average	Temperature	1.10	(1.04;1.17)	1.09	(1.00;1.19)	1.12	(1.03;1.22)	1.11	(1.03;1.19)	1.05	(0.92;1.19)
	5-day average	Ozone	1.00	(0.92;1.09)	0.96	(0.85;1.09)	1.04	(0.92;1.17)	0.96	(0.86;1.06)	1.09	(0.91;1.32)

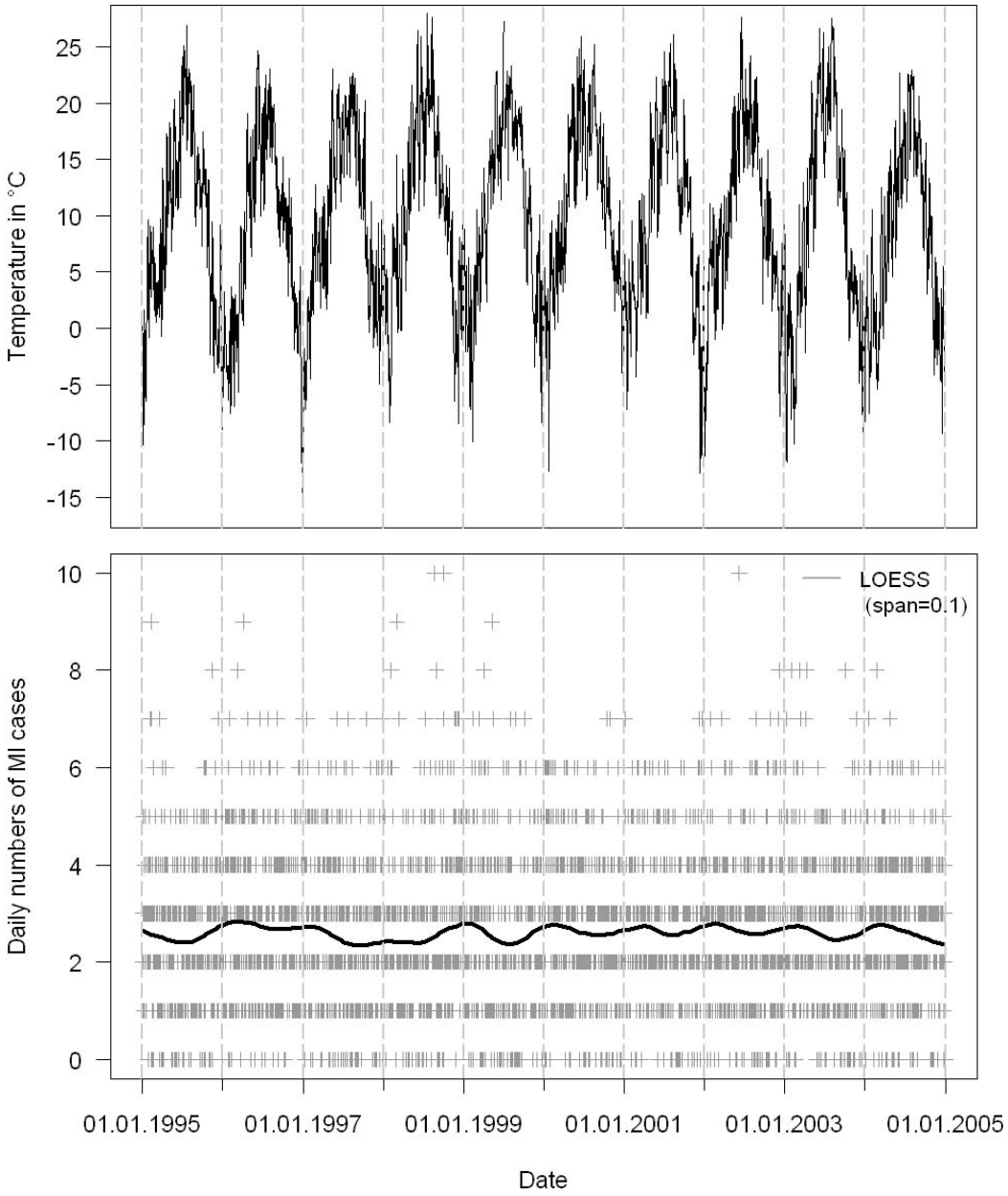
* RR: Relative risk; CI: confidence interval

[†] Lag0: Temperature of the same day; Lag1: Temperature of the previous day

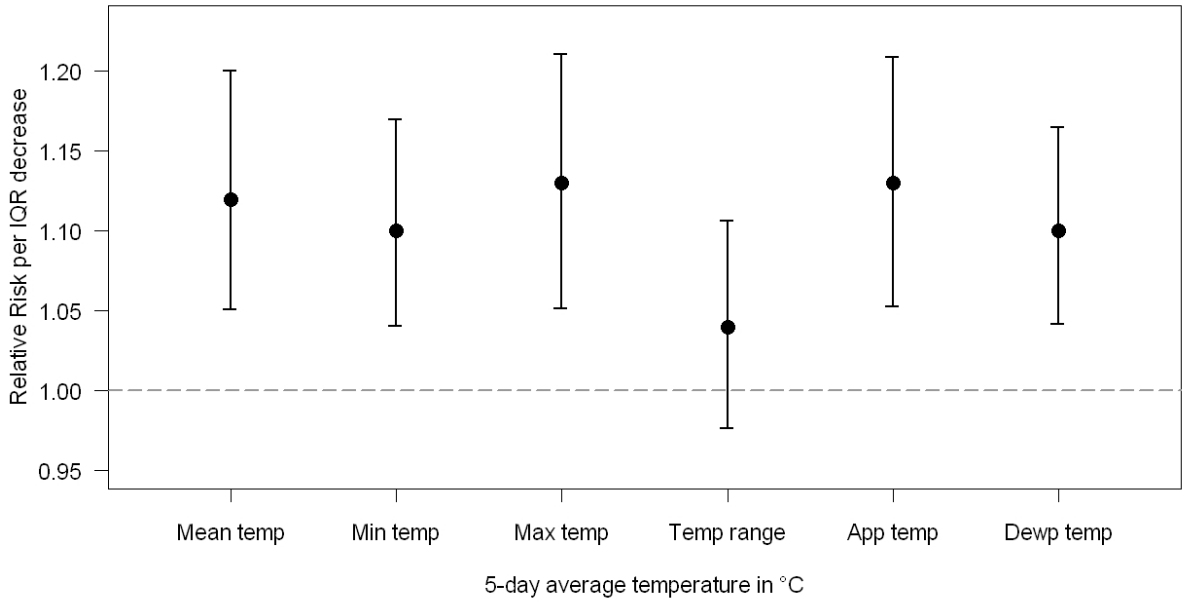
[‡] 5-day average: Mean temperature of same and 4 previous days

[§] PM_{10}: Particles with an aerodynamic diameter < 10µm; PNC: Particle number concentration

Online Supplement: Figure 1. 24-hour average temperature (top) and daily number of MI cases (bottom) in the Augsburg area, Germany, 1995 to 2004.



Online Supplement: Figure 2. Relative risk estimates for total cases of MI per interquartile range (IQR) decrease in different measures of temperature (5-day averages of 24-hour mean, minimum and maximum temperature, 24-hour temperature range, 24-hour mean apparent and dewpoint temperature) adjusted for time trend, season, Monday and relative humidity.



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Hiermit erkläre ich, Kathrin Wolf, dass ich die vorliegende Dissertation selbständig angefertigt habe. Ich habe mich außer der angegebenen keiner weiteren Hilfsmittel bedient und alle Erkenntnisse, die aus dem Schrifttum ganz oder annähernd übernommen sind als solche kenntlich gemacht und nach ihrer Herkuft unter Bezeichnung der Fundstelle einzeln nachgewiesen. Ich habe bisher noch keinen Promotionsversuch unternommen, und die vorliegende Dissertation wurde nicht in gleicher oder ähnlicher Form bei einer anderen Stelle zur Erlangung eines akademischen Grades eingereicht

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