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Long-Term Exposure to Air Pollution and Prevalent and Incident Metabolic Syndrome – Results from the Heinz Nixdorf Recall Study.

Dissertation

zur Erlangung des Grades eines Doktors der Medizin der Medizinischen Fakultät der Heinrich-Heine-Universität Düsseldorf

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Zusammenfassung

Einleitung: In den letzten Jahren haben epidemiologische Studien einen Zusammenhang zwischen Luftschadstoffen und kardiopulmonaler Morbidität und Mortalität gezeigt. Jüngst haben epidemiologische Studien darüber hinaus Hinweise für einen möglichen Zusammenhang zwischen Luftschadstoffen und einzelnen Komponenten des Metabolischen Syndroms (MetS) gefunden, einem Symptomkomplex, der mit erhöhten Risiken für kardiovaskuläre Morbidität, Mortalität und einer Diabeteserkrankung verbunden ist. Bis jetzt haben jedoch wenige Studien einen möglichen Zusammenhang zwischen Luftschadstoffen und MetS erforscht, einem möglichen Wirkungspfad über den Luftschadstoffe das kardiovaskuläre und metabolische Erkrankungsrisiko beeinflussen könnten.

Zielsetzung: Ziel dieser Analyse ist es, die Auswirkungen von Langzeitexposition mit Luftschadstoffen auf die Prävalenz und Inzidenz von MetS zu untersuchen.

Methodisches Vorgehen: Daten der populationsbasierten Heinz Nixdorf Recall Studie (Basiserhebung 2000-2003) wurden verwendet um einen möglichen Zusammenhang zwischen Luftschadstoffen und MetS-Prävalenz bei der Basiserhebung (n=4,457) und MetS-Inzidenz (n=3,074; durchschnittliche Follow-up Zeit: 5,1 Jahre) zu untersuchen. Die Langzeitexposition mit größenfraktioniertem Feinstaub (Particulate Matter ($PM_{2.5}$, PM_{10}, PM_{coarse}, $PM_{2.5}$abs)) und Stickstoffdioxid (NO_2) wurde anhand von zwei verschiedenen Expositionsmodellen erfasst: einem Landnutzungsmodel (LUR), welches die Luftbelastung punktspezifisch an der Wohnadresse modelliert, und einem Dispersionsmodel (CTM), welches die urbane Hintergrundbelastung in einem Raster von 1 km^2 modelliert. MetS wurde wie folgt definiert: zentrale Fettleibigkeit plus zwei von vier weiteren Risikofaktoren (erhöhte Triglyceride, gesenktes High-Density-Lipoprotein-Cholesterin, erhöhten Blutdruck oder erhöhte Glukosewerte). Das Odds Ratio (OR) der MetS-Prävalenz und -Inzidenz wurde mit einer logistischen Regressionsanalyse pro Interquartilabstand (IQR) geschätzt und für soziodemographische und Lebensstilvariablen adjustiert.

Ergebnisse: Die MetS-Prävalenz bei der Basisuntersuchung lag bei 20.7% (n=922) und die kumulierte MetS-Inzidenz über einen mittleren Zeitraum von 5.1 Jahren bei 9.7% (n=299). Sowohl die punktspezifische Belastung mit NO_2 an der Wohnadresse als auch die urbane Hintergrundbelastung mit NO_2 waren positiv mit der MetS-Prävalenz assoziiert (OR pro IQR: 1.12 (95%-KI 1.02-1.24) für punktspezifische NO_2-Belastung). Die ORs pro IQR für PM_{10} und $PM_{2.5}$ und MetS-Inzidenz betrugen 1.14 (95%-KI 0.98-1.32) und 1.19 (95%-KI 0.98-1.44) für die punktspezifische Belastung.

Schlussfolgerung: Diese Studie liefert Hinweise, dass eine Langzeitexposition mit Luftschadstoffen möglicherweise das Risiko für MetS erhöht, wobei sowohl NO_2 als auch verschiedene Feinstaubfraktionen eine Rolle spielen könnten.

Abstract

Introduction: In the last few decades, epidemiological studies have observed an association between air pollution (AP) and cardiopulmonary morbidity and mortality. Recent epidemiological studies have further found a possible link between air pollution and individual components of the metabolic syndrome (MetS), a condition characterized by a combination of different symptoms that together increase the risk of cardiovascular morbidity, mortality, and type 2 diabetes mellitus. However, very few studies have explored whether an association between air pollution and MetS, a possible pathophysiological intermediate on the pathway between AP exposure and increased risk of cardiovascular and metabolic diseases, exists.

Objective: The aim of this analysis is to assess the effects of long-term exposure to AP on prevalence and incidence of MetS.

Methods: We used data from the population-based prospective Heinz Nixdorf Recall study to investigate the association between AP exposure and MetS prevalence at baseline examination (2000-2003; n=4,457) and MetS incidence at follow-up examination (n=3,074; average follow-up: 5.1 years). Mean annual exposure to size-fractioned particulate matter (PM_{10}, $PM_{2.5}$, PM_{coarse}, and $PM_{2.5}$abs) and nitrogen dioxide (NO_2) was assessed using two different exposure models: a Land Use Regression model (LUR), which captures point-specific AP exposure at each participant's residential address, and a chemistry transport dispersion model (CTM), which captures urban background AP exposure on a 1 km^2 grid cell corresponding to the participant's residential address. MetS was defined as central obesity plus two out of four additional risk factors (i.e., elevated triglycerides, reduced high-density lipoprotein cholesterol, elevated blood pressure, or elevated fasting plasma glucose). We estimated odds ratios (ORs) of MetS prevalence and incidence per interquartile range (IQR) of exposure using logistic regression, adjusting for demographic and lifestyle variables.

Results: We observed a MetS prevalence of 20.7% (n=922) at baseline and a cumulative 5.1-year incidence of 9.7% (n=299). Point-specific and urban background NO_2 exposures were positively associated with MetS prevalence (OR per IQR: 1.12 (95%-CI 1.02-1.24) for point-specific NO_2 exposure). ORs per IQR for PM_{10} and $PM_{2.5}$ with MetS incidence were 1.14 (95%-CI 0.98-1.32) and 1.19 (95%-CI 0.98-1.44), respectively for the point-specific model.

Conclusion: This study suggests that long-term exposure to NO_2 and size-fractionated particulate matter air pollution may be positively associated with prevalent and incident MetS.

Abbreviations

ANS	Autonomous Nervous System
AP	Air Pollution
ATC	Anatomical Therapeutic Chemical Classification System
ATP III	Adult Treatment Panel III
BMI	Body Mass Index
BP	Blood Pressure
BPLM	Blood Pressure Lowering Medication
COPD	Chronic Obstructive Pulmonary Disease
CTM	Chemistry Transport Model
CVD	Cardiovascular Disease
DAG	Directed Acyclic Graph
DALYs	Disability-Adjusted Life Years
ESCAPE	European Study of Cohorts for Air Pollution Effects
EMI	Dietary Pattern Index / ‚Ernährungsmusterindex‘
ETS	Environmental Tobacco Smoking
EU	European Uniona
EURAD	European Air Pollution Dispersion
FPG	Fasting Plasma Glucose
GBD	Global Burden of Disease
HDL	High-Density Lipoprotein
HNR	Heinz Nixdorf Recall
IDF	International Diabetes Federation
IFG	Impaired Fasting Glucose
IGT	Impaired Glucose Tolerance
IQR	Interquartile Range
LUR	Land Use Regression
MetS	Metabolic Syndrome
MSAS	Minimal Sufficient Adjustment Set
CH_4	Methane
NAS	Normative Aging Study
NCDs	Noncommunicable Diseases
NH_3	Ammonia
NO	Nitrogen Monoxide
NO_x	Nitrogen Oxides
NO_2	Nitrogen Dioxide
OR	Odds Ratio
O_3	Ozone
PAH	Polycyclic Aromatic Hydrocarbons
PM	Particulate Matter (size-fractioned PM_{10}, $PM_{2.5}$, $PM_{coarse,}$ $PM_{2.5}$abs)

RR	Relative Risk
SALIA	Study on the influence of Air pollution on Lung function, Inflammation, and Aging
SAPALDIA	Swiss study on Air Pollution and Lung Disease in Adults
SES	Socioeconomic Status
SO_2	Sulfur Dioxide
TG	Triglycerides
T/Wk	Times per Week
T2D	Type 2 Diabetes Mellitus
t_0	Baseline Examination
t_1	First Follow-up Examination
VOC	Volatile Organic Compounds
WC	Waist Circumference
WHO	World Health Organization
Yrs	Years

Content

1 Introduction

1.1 Background

The metabolic syndrome (MetS) is considered to be a major public health problem, as it increases the risk of many noncommunicable diseases (NCDs), such as atherosclerotic cardiovascular diseases (CVDs), type 2 diabetes mellitus (T2D), and all-cause mortality (Alberti et al. 2009; Kaur 2014). Overall, MetS is defined as a collection of concurrent abnormal body measurements and laboratory tests, including elevated fasting plasma glucose, central obesity, elevated total cholesterol, and elevated blood pressure (Alberti et al. 2009; IDF 2006). (Matthiessen et al. 2018)

Because MetS increases a person´s risk for many NCDs, prior studies have aimed at identifying modifiable risk factors for the syndrome (Grundy et al. 2006; IDF 2006). The major risk factors for MetS observed were insulin resistance and central obesity, with other risk factors including a proinflammatory state, genetics, physical inactivity, ageing, and hormonal changes (Grundy et al. 2006; IDF 2006), of which only a few are potentially modifiable. Environmental exposures, such as air pollution (AP), have rarely been investigated as potential modifiable risk factors to develop MetS, even though AP has been shown to have a wide range of acute and chronic health impacts related to MetS (Thurston et al. 2017) and can be influenced by a wide range of interventions and air quality regulations.

Most studies up to now have focused on the association between AP and cardiopulmonary morbidity and mortality (Brook et al. 2010; Pope III and Dockery 2006), with recent studies also suggesting that exposure to major air pollutants may increase the risk of T2D (Eze et al. 2014; Rao et al. 2015; Thiering and Heinrich 2015; Wang et al. 2014; Weinmayr et al. 2015; Yan and Wang 2014). Furthermore, epidemiological studies have observed associations between AP and specific components of MetS, such as obesity and insulin resistance (Li et al. 2016; Wolf et al. 2016; Robert D. Brook et al. 2015; Thiering et al. 2013). However, currently only two epidemiological studies exist that have looked at AP exposure and MetS as an outcome itself (Eze et al. 2015; Wallwork et al. 2016). „Both studies looked at long-term air pollution, one in a cross-sectional and one in a longitudinal design, and observed a positive association between AP exposure and MetS“ (Matthiessen et al. 2018).

The aim of this study was therefore to investigate whether exposure to AP is associated with prevalent and incident MetS, using data from the Heinz Nixdorf Recall (HNR) cohort study in Germany.

1.2 The Metabolic Syndrome (MetS)

1.2.1 MetS Definition

The constellation of risk factors related to MetS have been known for many decades, but were first described by Reaven in 1988 as "Syndrome X" (Alberti et al. 2005). Since then, various names have been proposed, with the most popular name being metabolic syndrome and the most recent being cardiometabolic syndrome (Alberti et al. 2005; Moebus et al. 2007).

Several different definitions of the metabolic syndrome have been proposed in the last two decades (Huang 2009; Kaur 2014; Parikh and Mohan 2012) (Table 1). The first was proposed in 1998 from the World Health Organization (WHO) (Alberti et al. 2009). This definition put forth insulin resistance as a major underlying risk factor for MetS and made insulin resistance a required criteria of its definition, plus two additional risk factors (obesity, hypertension, elevated triglycerides (TG), reduced high-density-lipoprotein (HDL), or microalbuminuria) (Alberti et al. 2009). In 2001, another major definition proposed by the National Cholesterol Education Program Adult Treatment Panel III (ATP III) was published. The ATP III definition weighted all MetS criteria equally, making insulin resistance no longer a requirement and instead requiring 3 out of 5 MetS risk factors to be fulfilled for the MetS diagnosis: obesity,

Table 1: Definition of the metabolic syndrome according to the WHO, ATP III, and IDF definition.

	MetS Criteria	WHO (1998): B + 2 out of A, C, D, E, F	ATP III (2005 Revision): 3 out of A, B, C, D, E	IDF (2006): A + 2 out of B, C, D, E
A	Central Obesity	Waist/hip ratio >0.90 ♂, >0.85 ♀ OR BMI > 30 kg/m^2	WC ≥ 102 cm ♂, WC ≥ 88 cm ♀	WC ≥ 94 cm ♂, WC ≥ 80 cm ♀
B	Hyperglycemia	Insulin resistance: IGT, IFG, or other evidence of insulin resistance[2]	FPG ≥ 100 mg/dL[2]	FPG ≥ 100 mg/dL[2]
C	Elevated TG	TG ≥ 150 mg/dL	TG ≥ 150 mg/dL[1]	TG ≥ 150 mg/dL[1]
D	Reduced HDL	HDL < 35 mg/dL ♂ < 39 mg/dL ♀	HDL < 40 mg/dL ♂[1] < 50 mg/dL ♀[1]	HDL < 40 mg/dL ♂[1] < 50 mg/dL ♀[1]
E	Elevated BP	Systolic BP ≥ 140 mmHg OR Diastolic BP ≥ 90 mmHg	Systolic BP ≥ 130 mmHg OR Diastolic BP ≥ 85 mmHg[1]	Systolic BP ≥ 130 mmHg OR Diastolic BP ≥ 85 mmHg[1]
F	Other Criteria	Microalbuminuria: Urinary albumin excretion of ≥ 20 µg/min OR Albumin-to-creatinine ratio of ≥ 30 mg/g		

[1]or pharmacological treatment; [2]or previously diagnosed diabetes mellitus;
WC, Waist Circumference; FPG, Fasting Plasma Glucose; TG, Triglycerides; HDL, High-Density-Lipoprotein; BP, Blood Pressure; IGT, Impaired Glucose Tolerance; IFG, Impaired Fasting Glucose

hypertension, elevated TG, reduced HDL, or elevated fasting glucose (Alberti et al. 2009). In 2005, a further revision of the ATP III definition was made, now also including individuals reporting a history of current antihypertensive drug or lipid lowering medication use, regardless of the measured values (Moebus et al. 2007). A third major definition was also published in 2005 by the International Diabetes Federation (IDF) (Huang 2009; IDF 2006). The IDF definition included the same criteria as the ATP III, but it required central obesity as an essential criteria to be present, suggesting it to be a major underlying risk factor in the pathomechanism of MetS development (Huang 2009) (Table 1).

1.2.2 Epidemiology of MetS

Overall, there is a wide variation in MetS prevalence depending on age, sex, ethnicity, as well as the criteria used for diagnosis (Rochlani et al. 2017). Large regional variation has also been seen, with estimates for MetS prevalence ranging from less than 10% to as much as 84% (Kaur 2014). Globally, the International Diabetes Federation (IDF) suggests that about 25% of the world´s adult population has MetS (IDF 2006). In Germany, MetS prevalence is estimated to be between 13% and 31%, depending on the used MetS definition, study population, and region (Boehm et al. 2009; Moebus et al. 2007, 2008). The studies from Germany, in agreement with international literature (Rochlani et al. 2017; Santilli et al. 2017), found that MetS prevalence was higher among older individuals, men, persons with lower education, individuals living in rural areas, and those living in the eastern part of Germany (Boehm et al. 2009; Moebus et al. 2007, 2008).

Further, among persons with MetS, variation in the MetS criteria most frequently fulfilled has been observed by sex and age (Ervin 2009; Kuk and Ardern 2010; Moebus et al. 2010; Santilli et al. 2017). Both Moebus et al. (2010) and Ervin (2009) found the MetS combination of central obesity, elevated blood pressure, and hyperglycemia to be most common, independent of sex and age. Central obesity and reduced HDL were more frequent in women than in men, whereas elevated triglycerides, elevated blood pressure, and hyperglycemia were more frequent in men than in women (Ervin 2009; Moebus et al. 2010). These studies also observed that reduced HDL is most commonly a part of the MetS combination among younger individuals, whereas elevated blood pressure and hyperglycemia are most common among older individuals (Ervin 2009; Kuk and Ardern 2010; Moebus et al. 2010).

1.2.3 Health Impacts of MetS

NCDs are responsible for approximately 70% of all deaths globally (WHO 2017). Cardiovascular diseases, cancers, respiratory diseases, and diabetes, which represent the four

main types of NCDs, account for over 80% of premature NCD deaths globally (WHO 2017). Along with behavioral risk factors, such as tobacco use, high salt intake, alcohol use, and insufficient physical activity, metabolic risk factors (e.g., elevated blood pressure, obesity, hyperglycemia, hyperlipidemia) contribute greatly to an increased risk of NCD development (WHO 2017). While each individual component of MetS increases the risk of different NCDs, the risk is even more pronounced when MetS itself is present (IDF 2003).

Overall, it is estimated that individuals with MetS are at twice the risk of developing CVD over the next 5 to 10 years compared to individuals without MetS (Alberti et al. 2009; Mottillo et al. 2010). Persons with MetS are also at 5-times increased risk of developing T2D, a 1.5 times increased risk for all-cause mortality, and a 2- to 4-times increased risk of stroke (Alberti et al. 2005; Kaur 2014). Increased cancer risk, most robustly for colorectal cancer, has also been shown for individuals with MetS (Esposito et al. 2012). Recent evidence suggests that persons with MetS or with MetS components may also be at a higher risk of non-alcoholic fatty liver disease, polycystic ovarian syndrome, and rheumatoid arthritis (Santilli et al. 2017). The value of MetS as a predictor of cardiometabolic risk, and whether this risk represents merely the sum of individual components or instead a synergistic effect related to the clustering of these components, is still under debate (Mottillo et al. 2010; Rochlani et al. 2017).

1.2.4 Pathophysiological Mechanism of MetS

The pathophysiological mechanisms of MetS are complex and remain to be fully elucidated (Grundy et al. 2004; Rochlani et al. 2017). Nevertheless, the majority of pathophysiological hypotheses mention three potential etiological categories: 1) obesity and disorder of adipose tissue; 2) insulin resistance; and 3) different independent factors (e.g. hepatic, vascular, and/or immunologic molecules) that mediate specific components of MetS (Figure 1) (Alberti et al. 2009; Grundy et al. 2004; Kaur 2014; Rochlani et al. 2017).

1) Obesity: The WHO defines obesity as an abnormal or excessive fat accumulation that causes health problems (Moreira et al. 2015). Adipose tissue is primarily composed of subcutaneous adipose tissue and visceral adipose tissue (Santilli et al. 2017). Central obesity, characterized by an increase in visceral adipose tissue, is more correlated with MetS and cardiovascular risk than an increase in subcutaneous adipose tissue (Santilli et al. 2017). Adipose tissue has been recognized as a key endocrine organ, as it secretes endocrine, paracrine, and autocrine substances in response to different stimuli (Schindler 2007). It is suggested that increasing obesity leads to hypertrophy of adipose tissue and to a reduction in blood supply to adipocytes that results in hypoxia (Francisqueti et al. 2017; Kaur 2014). The hypertrophy and hypoxia

of adipose tissue then leads to an overproduction of adipocytokines (e.g., tumor necrosis factor alpha, Leptin, Interleukin-6) and free fatty acids, which are responsible for mediating multiple processes, including insulin sensitivity, oxidant stress, energy metabolism, blood coagulation, and inflammatory responses (Francisqueti et al. 2017; Grundy et al. 2004; Kaur 2014) (Figure 1). Hypertrophy and hypoxia of adipose tissue, with consequent overproduction of adipocytokines, also results in localized inflammation that can become overall systemic inflammation, a condition which may eventually manifest itself as the abnormal measures that make up MetS (Kaur 2014; Schindler 2007).

2) Insulin Resistance: Insulin resistance occurs when the body cells become less sensitive and resistant to insulin, a hormone produced by beta cells of the pancreas and which facilitates glucose absorption (IDF 2006; Moreira et al. 2015). The primary targets for insulin are skeletal and cardiac muscle, adipose tissue, and the liver (Sesti 2006). Insulin-resistant individuals demonstrate an impaired glucose metabolism through an abnormal response to glucose (i.e., hyperglycemia) (Kaur 2014). In response, pancreatic beta cells secrete more insulin (i.e., hyperinsulinemia) than needed to compensate for the hyperglycemic state of insulin-resistant individuals (Kaur 2014). Insulin resistance leads to changes in the activity of multiple biological molecules (e.g., free fatty acids, autonomic nerves, adipocytokines) involved in several signaling pathways (Schindler 2007). Insulin signaling imbalance may eventually lead to the manifestation of MetS through endothelial dysfunction, decreased glucose uptake in skeletal muscle and adipose tissue, and/or dyslipidemia (Kaur 2014; Schindler 2007).

Because many of the same pathways and biomarkers are involved in the pathophysiologies of insulin resistance and obesity, it can be difficult to dissociate obesity and insulin resistance (Grundy et al. 2004). Indeed, in recent years the tradition of insulin resistance etiology being "glucocentric" has shifted to a more "lipocentric" perspective (Grundy et al. 2004; Sesti 2006). Nevertheless, it should be noted that insulin resistance can also be present in non-obese individuals (e.g., in South Asian populations) (Grundy et al. 2004).

3) Independent Risk Factors of MetS: Apart from obesity and insulin resistance, genetics and acquired risk factors also play a role in the expression of MetS components (Grundy et al. 2004). In addition to normal lifecourse factors, such as aging or hormonal changes (e.g., menopause), chronic inflammation or stress may also affect many levels of MetS pathogenesis (Grundy et al. 2004; Kaur 2014). More recently, air pollution and noise exposure have been raised as potential contextual risk factors for MetS (Münzel et al. 2016).

In summary, the interaction of many different genetic, behavioral and contextual risk factors, including obesity and insulin resistance, make the pathogenesis of MetS complex.

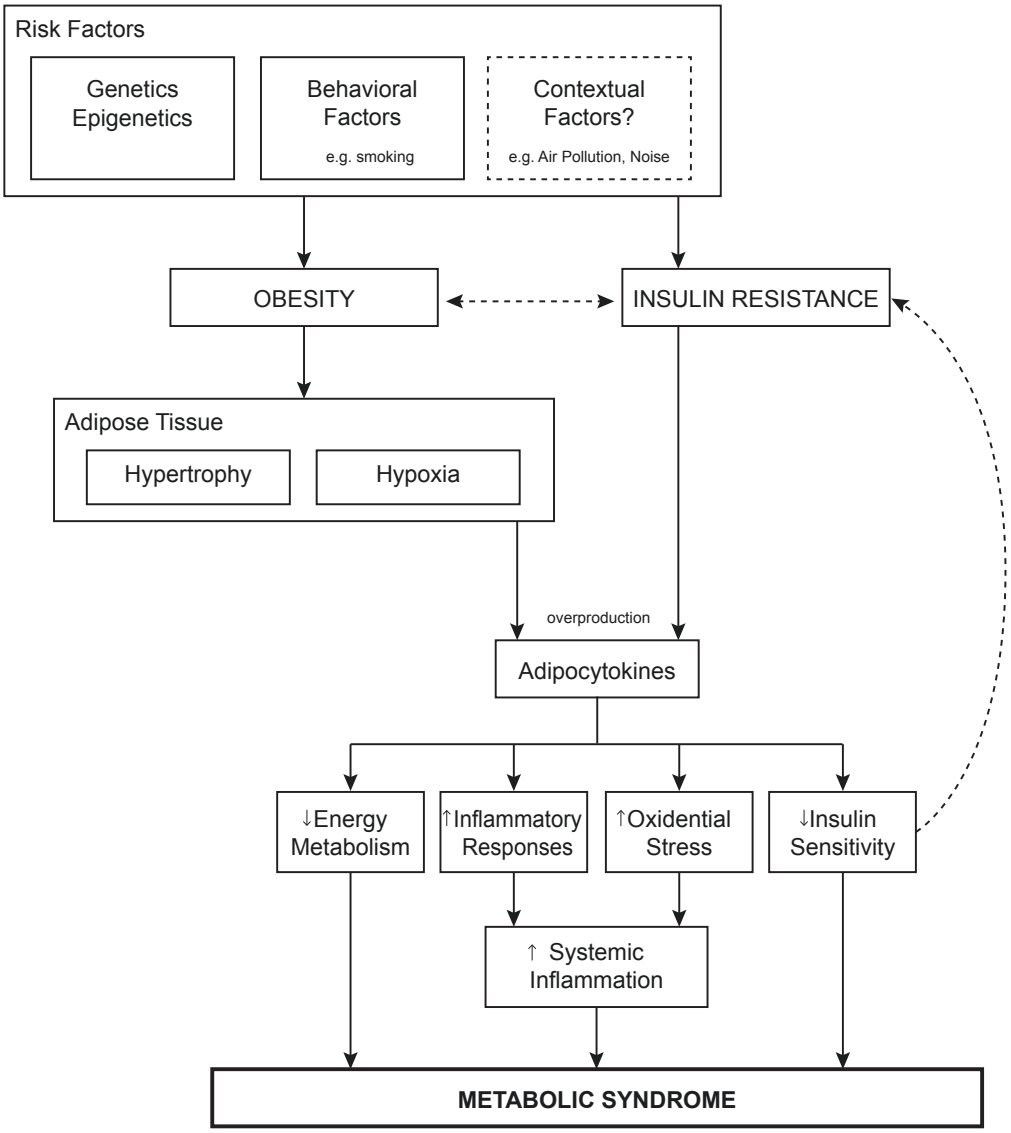

Figure 1. Pathophysiological mechanisms of the metabolic syndrome

1.3 Air Pollution (AP)

Air pollutants are emitted from anthropogenic (e.g., transport, agriculture, industry) and natural (e.g., ocean salt, earth crust, volcano eruption) sources and can differ widely by region (EEA 2016). Ambient AP is a complex mixture of particulate and gaseous components, including, but not limited to, particulate matter (PM), nitrogen oxides (NO_x), sulfur dioxide (SO_2), ozone (O_3), ammonia (NH_3), volatile organic compounds (VOCs), carbon monoxide (CO), and methane (CH_4) (EEA 2013). Particles are either directly emitted as primary pollutants or formed from precursor gases as secondary pollutants. In Europe, the main sources for anthropogenic AP emission are transport; commercial, institutional, and household electricity or heating; industry; energy; agriculture; and waste (EEA 2016). Overall, urban areas are more affected by air pollution exposure compared to rural areas, with road traffic being one of the most important within-city sources (Nieuwenhuijsen et al. 2017; WHO 2016).

1.3.1 Particulate Matter (PM) & Nitrogen Dioxide (NO_2)

PM and nitrogen dioxides (NO_2) are among the most intensively studied APs with negative impacts on human health (Brook et al. 2010; Faustini et al. 2014; WHO 2013). While PM emissions result primarily from commercial, institutional, and household electricity and heating, the transport sector makes up the largest contribution to NO_2 emissions (EEA 2016).

Particulate matter is a mixture of aerosol particles of a wide range of sizes and represents a broad mixture of solid and liquid particles of both organic and inorganic origin (EEA 2013). PM is both emitted directly to the atmosphere (primary pollutant) as well as formed in the atmosphere (secondary pollutant) through precursor gases such as SO_2, NO_x, or NH_3 (EEA 2016). By convention, airborne particles are often classified into groups by their size, irrespective of their sources or chemical composition, and measured as mass concentration, e.g., PM_{10} <10 µm, or $PM_{2.5}$ <2.5 µm (Figure 2). PM has a wide range of negative health impacts, with respiratory and cardiovascular disease being the best known (Brook et al. 2010; Cohen et al. 2015; Thurston et al. 2017).

NO_x is a group of gases consisting of nitrogen monoxide (NO) and NO_2 and contributes to the formation of ozone and PM (EEA 2013). Most atmospheric NO_2 is emitted as NO but is rapidly oxidized to NO_2 (WHO 2005). NO_2 can impact health via several different ways. In addition to being an irritant gas that can lead to local pulmonary and consecutive systemic inflammation, it is also a precursor gas for the formation of particulate matter (WHO

2013). Further, NO_2 has been used as a surrogate for traffic-related air pollution, which has been suggested to be particularly toxic due to its high fraction of ultrafine particles, diesel soot, and other components that may cause oxidative stress, including polycyclic aromatic hydrocarbons (PAH) (HEI 2009; WHO 2013).

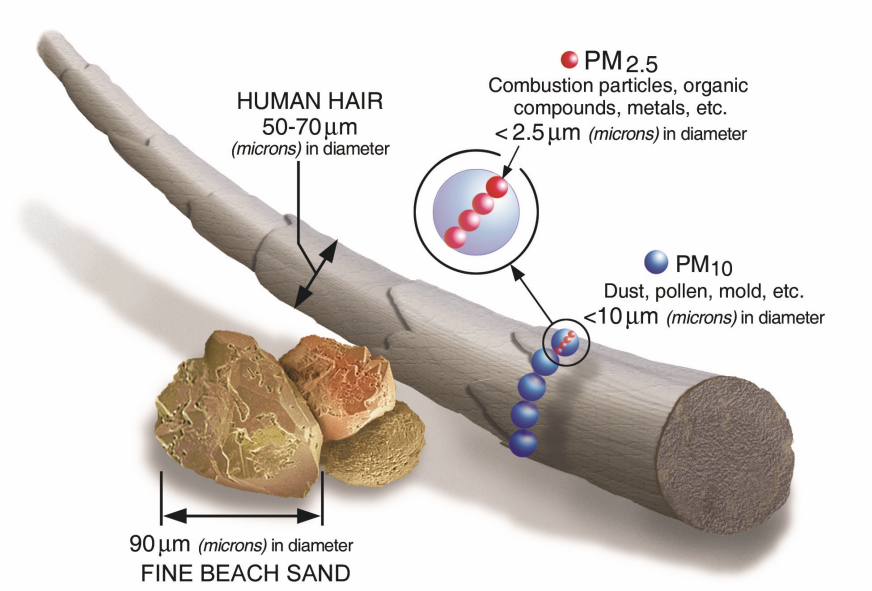

Figure 2: Size comparison for PM10 and PM2.5.
(Image courtesy by the United States Environmental Protection Agency (EPA))

1.3.2 Air Pollution Concentrations

Two different air pollution reference values are primarily being used in Europe (Table 2). First, legislation regarding maximal acceptable air pollution concentrations is issued by the European Union (EU) (EU 2008). These limit values are the result of negotiations between the member states. They are binding for the EU member states and will lead to lawsuits and fines if exceeded for a specific time period (EU 2008). Secondly, the WHO publishes recommendations in the form of air quality guidelines (WHO 2005) (Table 2).

Table 2: Annual mean of air-quality standards of the WHO and the EU for PM and NO_2.

Air Pollutant	WHO Guidelines	EU Legislation
PM_{10} ($\mu g/m^3$)	20	40
$PM_{2.5}$ ($\mu g/m^3$)	10	25
NO_2 ($\mu g/m^3$)	40	40

These guideline values are derived purely from epidemiological and other scientific studies and are designed to protect the public, including vulnerable populations, from adverse health effects due to air pollution (WHO 2005). For many air pollutants, the WHO guidelines are well below the current EU limit values. For PM, the WHO recommends an annual PM_{10} mean

of 20 μg/m^3 and an annual $PM_{2.5}$ mean of 10 μg/m^3 to protect the public from its negative health effects, while the EU legislations have limit values of 40 μg/m^3 and 25 μg/m^3 per year for PM_{10} and $PM_{2.5}$, respectively (EEA 2016). Current guidelines from the WHO as well as EU legislation set an annual NO_2 limit of 40 μg/m^3 (EEA 2016).

Worldwide, AP concentrations vary strongly by region, with highest concentrations found in mega-cities in India and Asia (WHO 2016). In Europe, a north-south gradient of air pollution can be found with higher concentrations found in Mediterranean cities (EEA 2016; Eeftens et al. 2012). While AP concentrations have increased in more than half of the cities during the last 5 years, especially in the Western Pacific, South-East Asia, and Eastern Mediterranean regions, a general trend towards decreased exposure of AP has been seen in Europe and North America (WHO 2016). While air pollution concentration in Germany have decreased during the last 25 years, EU air quality limit values and WHO guidelines are still being exceeded for PM and NO_2 (UBA 2017). In 2016, limits on NO_2 concentrations were exceeded at around 57% of the monitoring stations close to traffic, and WHO guidelines for PM_{10} were exceeded at around 24% of all monitoring stations (UBA 2017).

1.3.3 Health Impacts of Air Pollution

In the last two decades, the impact of outdoor AP on human health has increasingly been recognized as a global public health concern and is today considered the single largest environmental health risk in Europe (Cohen et al. 2015). Air pollution was ranked fourth as risk factor for premature mortality, only exceeded by hypertension, smoking, and dietary risks (EEA 2016; GBD 2016). A recent global burden of disease (GBD) report also mentioned air pollution as a leading cause of death and lost disability-adjusted life years (DALYs), as it is estimated to account for more than 4 million premature deaths and more than 100 million DALYs annually worldwide (GBD 2016). Around 80% of premature death attributable to AP are due to heart diseases and stroke, followed by lung diseases and cancer (EEA 2016). Negative health effects have also been observed between AP and the central nervous system and the reproductive system (EEA 2013) (Figure 3). Depending on the duration of AP exposure, the severity of health effects range from subclinical findings (e.g., elevated inflammatory markers), to clinical symptoms (e.g., respiratory complaints), to overt clinical diseases, with the most severe being myocardial infarction, stroke, and lung cancer (Thurston et al. 2017). As no 'safe' exposure threshold is known for air pollution, the whole population is exposed to the adverse effects of air pollution exposure. However, not every person is equally susceptible to the negative health effects of air pollution, with children, the elderly, and chronically ill people being especially vulnerable (Sacks et al. 2011).

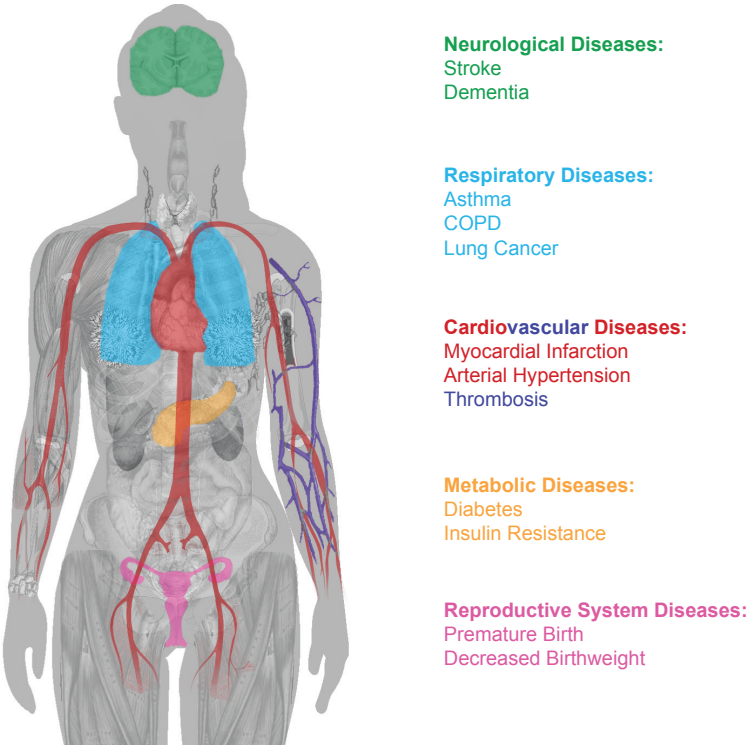

Figure 3: Examples of diseases affected by outdoor air pollution
(Background Images adapted from Wikimedia Commons)

Cardiovascular and cerebrovascular effects: Both short-term and long-term exposure to AP has been linked to an increased incidence of acute cardiovascular events (Brook et al. 2010; Cesaroni et al. 2014). Not only has short-term exposure to AP over the previous few days been associated with an increase in cardiovascular mortality and stroke, arrhythmia and increase in blood pressure have also been found to be associated with short-term AP exposure (Brook et al. 2010; Song et al. 2016; Thurston et al. 2017). The risk of cardiovascular mortality was even greater with long-term exposure to AP and reduced life expectancy by anywhere from a month to a few years (Brook et al. 2010). Further, coronary atherosclerosis, cerebrovascular events, and hypertension have been found to be associated with long-term exposure to AP (Beelen et al. 2014; Fuks et al. 2016a; Hoffmann et al. 2009a; Kaufman et al. 2016; Stafoggia et al. 2014).

Respiratory effects: The respiratory tract is the primary portal of entry for AP, which can result in short-term as well as long-term consequences for respiratory health (Thurston et al. 2017). Several studies have found an association between short-term exposure to AP and exacerbation of asthma or chronic obstructive pulmonary disease (COPD) (Bloemsma et al. 2016; McCreanor et al. 2007; Orellano et al. 2017). Further, short-term exposure to AP has been linked to an increase in hospital emission due to COPD or asthma (Lim et al. 2016; Zhang et al. 2016). Long-term exposure to AP has also been found to have negative

respiratory effects, including the development of asthma, decreased lung function, or the development of lung cancer over many years (Adam et al. 2015; Hamra et al. 2014; Jacquemin et al. 2015; Khreis et al. 2017; Raaschou-Nielsen et al. 2013). Indeed, the International Agency for Research on Cancer has classified outdoor air pollution as carcinogenic to humans in 2013, generating lung cancer (IARC 2013).

Air pollution exposure has also been linked to other health factors, including pneumonia, airway inflammation, increased blood coagulation, stroke, neurodegenerative diseases, congestive heart failure, premature birth, and decreased birthweight.

1.4 Potential Association between AP and MetS

„Previous reviews have described potential pathophysiological pathways that could explain the observed association between AP exposure and MetS“ (Matthiessen et al. 2018) and its downstream diseases (Brook et al. 2010; Franklin et al. 2015; Pope III and Dockery 2006). In order to provide a pathophysiological basis for the association of AP on health based on epidemiological studies, Brook et al. (2010) and Franklin et al. (2015) have described three potential mediating pathways after inhalation of particulate or gaseous air pollutants (Figure 4).

1) Release of Proinflammatory Mediators: Air pollution enters the body primarily through inhalation, in which components enter and interact with various regions of the respiratory tract (Brook et al. 2010; Franklin et al. 2015). In the first pathway, direct exposure to AP leads to oxidative stress and inflammation within the pulmonary tissue. Along with localized consequences for lung health, inflammatory mediators can “spill-over” into the systemic circulation (Franklin et al. 2015). Once there, several mediators have direct negative effects on the cardiovascular system (e.g., induce oxidative stress, blood coagulation) or on other organs (e.g., adipose tissue, liver). These systems and tissues subsequently release adipocytokines or acute phase proteins and instigate proinflammatory or oxidative stress mediators (Franklin et al. 2015). These same mediators are also involved in the pathophysiology of MetS development. (Matthiessen et al. 2018)

2) Perturbation of the Systemic Autonomous Nervous System: The second pathway is via the autonomous nervous system (ANS), with activation of several lung receptors after AP exposure resulting in an imbalance of the ANS favoring the sympathetic over the parasympathetic limb. This imbalance can cause short-term alterations in heart rate and blood pressure and,

with persistent sympathetic nervous system hyperactivity, possibly chronic diseases, such as hypertension and insulin resistance (Franklin et al. 2015).

3) Translocation of PM into the Systemic Circulation: The third "direct" pathway is via intrusion of particles into the blood stream and eventually into specific organs, with negative effects eventually reaching cardiovascular tissue (Brook et al. 2010; Franklin et al. 2015). This is

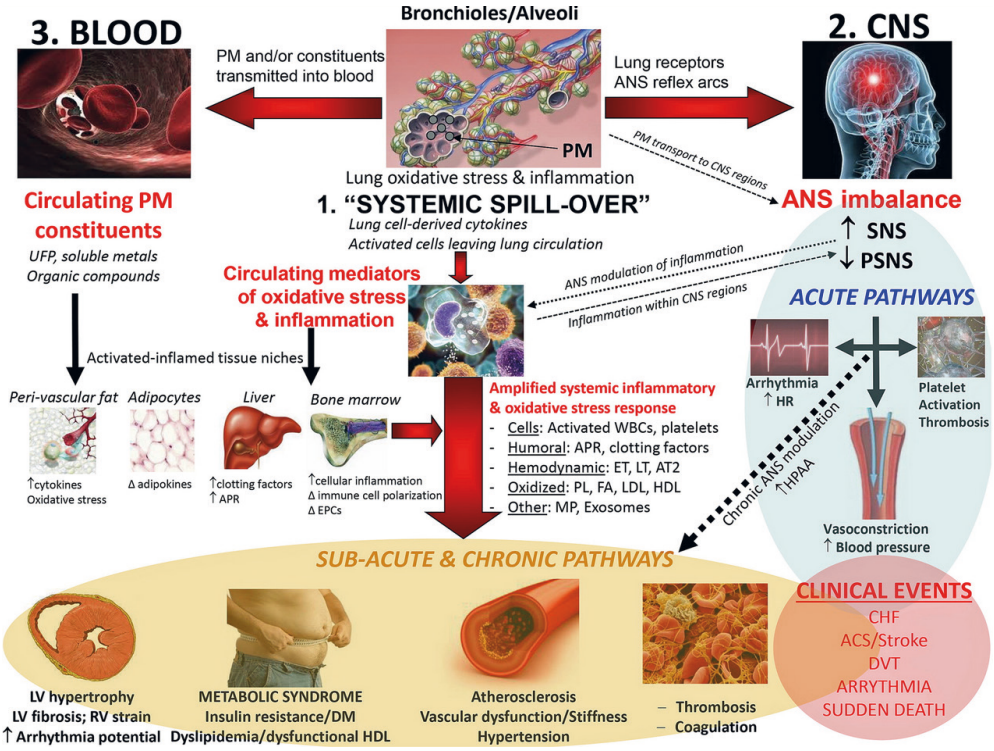

Figure 4: Potential biological mechanism linking AP with cardiovascular disease and its sequelae.
ANS, autonomic nervous system; APR, acute phase response; AT2, angiotensin-2; DM, diabetes mellitus; CHF, congestive heart failure; CNS, central nervous system; DVT, deep venous thrombosis; EPCs, endothelial progenitor cells; ET, endothelins; FA, fatty acids; HDL, high-density lipoproteins; HR, heart rate; LDL, low-density lipoproteins; LT, leukotrienes; LV, left ventricle; PL, phospholipids; PSNS, parasympathetic nervous system; RV, right ventricle; SNS, sympathetic nervous system; UFP, ultrafine particles < 100 nm; WBCs, white blood cells.
(Image courtesy by Franklin et al. 2015)

especially true for ultrafine particles and specific components attached to particle surfaces, for example, carcinogenic PAH attached to the carbon core of diesel soot (Brook et al. 2010; Franklin et al. 2015).

These three pathways are not mutually exclusive, and a large degree of overlap between pathways can be expected (Franklin et al. 2015). Further, the pathways may be activated at different time frames after AP inhalation, as it has been hypothesized that imbalance of

the ANS occurs mainly in the *acute* phase (minutes to hours) after AP inhalation, while the release of proinflammatory mediators plays a larger role in the *sub-acute* (hours to days) and *chronic* (weeks to years) development of NCDs (Franklin et al. 2015).

The first and second pathophysiological pathways of AP effects on human health are suggested to be those mainly involved in the development and progression of MetS.

The described pathophysiological mechanism of AP and MetS is supported by several toxicological studies. Sun et al. (2009) found an exaggeration of insulin resistance and visceral inflammation when mice were exposed to $PM_{2.5}$. Furthermore, Brocato et al. (2015) found an upregulation of genes involved in inflammation, cholesterol and lipid metabolism, and atherosclerosis in mice exposed to PM_{10}. Haberzettl et al. (2016) showed in mice exposed to $PM_{2.5}$ that vascular insulin resistance and inflammation can be triggered by pulmonary oxidative stress. A very recent study found weight gain and metabolic dysfunction, as well as histological evidence of inflammation in the lungs, increased tissue markers of systemic oxidative stress when rodents were exposed to Beijing's highly polluted air (Wei et al. 2017).

These findings are further supported by epidemiological studies. A study by Wu et al. (2015) found an association between AP and biomarkers of oxidative stress. These findings were supported by a recent study from Kim et al. (2016), who found that an association between AP with blood pressure (BP) was mediated by genes related to oxidative stress. Further, an association between PM and markers of systemic inflammation has previously been observed in different cohorts (Huels et al. 2017; Li et al. 2017; Pope et al. 2016; Wolf et al. 2016), and also found within the HNR study (Hoffmann et al. 2009; Hennig et al. 2014; Viehmann et al. 2015). The associations between AP, insulin resistance, and/or obesity have also been observed in epidemiological studies (Brook et al. 2015b; Jerrett et al. 2014; Li et al. 2016; Thiering et al. 2013; Wolf et al. 2016). Furthermore, two studies have observed that persons with MetS may be particularly vulnerable to the effects of air pollution, as one study found stronger associations between long-term particulate matter exposure and markers of inflammation among participants with MetS (Chen and Schwartz 2008), while the other study found stronger associations between PM exposure and cardiovascular risk among participants with MetS (Park et al. 2010). Finally, two studies have observed an association between long-term exposure to AP and MetS as an outcome itself (Eze et al. 2015; Wallwork et al. 2016). Eze et al. (2015) found an association between PM_{10} and MetS prevalence as well as between NO_2 and MetS prevalence. This study was conducted among 3,769 middle-aged to elderly participants of the Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults (SAPALDIA). Wallwork et al. (2016), in a study conducted among 271 elderly men of the Normative Aging Study (NAS), observed an association between $PM_{2.5}$ and MetS incidence. (Matthiessen et al. 2018)

In prior analyses, associations between AP and several diseases downstream of MetS, such as hypertension, T2D, and coronary atherosclerosis, have been observed in many cohort studies (Balti et al. 2014; Brook et al. 2008, 2010, 2015a; Tamayo et al. 2014), as well as within the HNR study (Fuks et al. 2016b; Hoffmann et al. 2006, 2007; Weinmayr et al. 2015). The associations between AP exposure and MetS' downstream diseases suggest that MetS may be an intermediate on the pathophysiological pathway from AP exposure to other health conditions. (Matthiessen et al. 2018)

1.5 Role of Noise as an Environmental Risk Factor

„[...] It is hypothesized that noise, through annoyance and sleep disturbance, may induce activation of similar pathways as AP, including oxidative stress, vascular dysfunction, and autonomic imbalance (Babisch 2003; Münzel et al. 2016)" (Matthiessen et al. 2018). Chronic noise exposure may affect health by activating the sympathetic-adrenal medullar axis and/or the hypothalamic-pituitary-adrenocortical axis, generating an unspecific stress response and an overproduction of glucocorticoids such as cortisol (Babisch 2002; Münzel et al. 2016). It has therefore been suggested that chronic noise exposure may represent another environmental risk factor for developing NCDs (Münzel et al. 2016). Prior studies have found a positive association between noise and MetS components or MetS' downstream diseases such as hypertension, obesity, and T2D (Eriksson et al. 2014; Oftedal et al. 2015; Soerensen et al. 2013; van Kempen and Babisch 2012). In a meta-analysis, van Kempen & Babisch (2012) found a positive association between road traffic noise and hypertension. In addition, three studies have looked at either long-term aircraft or road traffic noise and a potential association to metabolic diseases in population-based cohort studies from Sweden, Norway, and Denmark. They found positive associations between noise and waist circumference (Eriksson et al. 2014), T2D (Soerensen et al. 2013), and markers of obesity in highly noise sensitive women and men with street-facing bedrooms (Oftedal et al. 2015). Since urban noise and air pollution have a common source, namely traffic, they may confound each other in their relationship to cardiometabolic outcomes. (Matthiessen et al. 2018)

2 Study Aim and Hypotheses

2.1 Aim of the Study

The aim of this study was to investigate whether long-term exposure to residential AP (PM and NO_2) is associated with increased prevalence and incidence of MetS. For this analysis, data from the baseline (t_0) and first follow-up (t_1) examinations of the Heinz Nixdorf Recall (HNR) cohort study in Germany were used. PM_{10}, $PM_{2.5}$, and NO_2 were the primary air pollution exposures of interest. In addition, coarse (PM_{coarse}) and $PM_{2.5}$ absorbance ($PM_{2.5}$abs), which is a marker for soot and black carbon, were analyzed as well. The associations of air pollutants with MetS were also estimated after taking potential confounding by ambient noise into account.

2.2 Hypotheses

I. Long-term exposure to residential PM and NO_2 is associated with an increase in MetS prevalence and incidence in the general population.

II. The association in I. is independent of sociodemographic and lifestyle factors as well as of ambient noise exposure.

2.3 Specific Objectives

I. To study the current knowledge base about air pollution and the metabolic syndrome.

a. To conduct a literature search about the current knowledge on MetS regarding its burden of disease, health impacts, and pathophysiology.

b. To conduct a literature search about the current knowledge on AP regarding its burden of disease, health impacts, and pathophysiology.

c. To review the current knowledge on the association between AP and MetS and its components.

II. To describe the HNR health and exposure data, including its strength and limitations.

a. To perform a descriptive analysis of the study population.

b. To perform a descriptive analysis of the exposure data.

c. To assess differences between excluded participants and those included in the cross-sectional analysis and/or the longitudinal analysis.

III. To analyze the associations between residential long-term exposure to PM_{10}, $PM_{2.5}$, PM_{coarse}, $PM_{2.5}$abs, and NO_2 with MetS.

a. To perform a cross-sectional as well as a longitudinal analysis controlling for relevant confounders.

b. To assess noise as a potential environmental confounder.

c. To assess the robustness of the results through the application of two different exposure models.

d. To assess the robustness of the results through in-depth sensitivity analyses, including analysis of potential exposure and outcome misclassification.

e. To assess the robustness of the results using an alternative regression model.

IV. To integrate and interpret the results, to discuss them, and to draw conclusions from them.

3 Materials and Methods

3.1 Study Area and Study Design

This study was conducted using data from the baseline (t_0: 2000-2003) and first follow-up (t_1: 2006-2008) examinations of the Heinz Nixdorf Recall (Risk factors, Evaluation of Coronary Calcium and Lifestyle) study, an ongoing prospective population-based cohort study located in three adjacent cities (Bochum, Essen, and Mülheim) within the highly urbanized German Ruhr-Area with a tight traffic and industrial network (Schmermund et al. 2002). The study region, with an area of approximately 600 km^2, covers a population of 1.15 million inhabitants with almost one fifth of the working population being occupied in the industrial sector (Hennig et al. 2016; Stang et al. 2005). Further, the majority of the german steel and coal industry is located in Duisburg, a city in the western part of the Ruhr-Area, including Europe's biggest steelwork and largest inland harbor with intensive shipping on the Rhine (Hennig et al. 2016).

The HNR study was originally initiated to evaluate the value of new tests in the detection of peripheral and coronary atherosclerosis for the prediction of myocardial infarction and cardiac death (Schmermund et al. 2002). Because a large amount of individual data, including health characteristics, biomarkers, socioeconomic indicators, and environmental exposures, was collected, data from the HNR study have been used in broad fields of research across several public health areas, among others the field of environmental risk factors and its impact on human health. The rationale and design of the cohort study have been described in detail in another paper (Schmermund et al. 2002). „In short, a sample of individuals aged 45-75 years were identified through a random selection process using local residency registries. In total, 4,814 participants were enrolled into the HNR study between December 2000 and August 2003 (recruitment efficacy proportion: 55.8%), and 4,157 participants returned for a follow-up examination between 2006 and 2008" (Matthiessen et al. 2018). Recruitment efficacy was highest among individuals between the age of 55-64 years (Stang et al. 2005). Participants were excluded from the study if they were institutionalized (e.g., nursing homes, prisons), had moved or died, had a wrong or nonexistent address, had insufficient command of German language, were severely ill (e.g., deafness, dumbness), were pregnant, or were relatives of the study personnel (Stang et al. 2005). During the follow-up period, self-reported questionnaires were sent to each participant annually via mail. „Assessment at both examinations included a self-administered questionnaire, face-to-face interviews for personal risk factor assessment, clinical examinations, and comprehensive laboratory tests" (Matthiessen et al. 2018). Examinations were conducted in accordance to the recommendations for research on human subjects by the 18th World Medical Assembly's revised Declaration of Helsinki (WMA 2013)

were approved by the institutional ethics committees of the University of Duisburg-Essen and the University Hospital of Essen (Number: 13-5412-BO, Date: 18.04.2013, Applicant: Dr. Lewin Eisele), and adhered to strict internal and external quality assurance protocols. All participants gave their written informed consent.

3.2 Environmental Exposures

An exposure includes the factors to which a person can be exposed to, such as smoking, alcohol, and environmental exposures such as air pollution.

3.2.1 Point-Specific Exposure Assessment (ESCAPE-LUR)

Exposure to PM_{10}, $PM_{2.5}$, NO_2, PM_{coarse}, and $PM_{2.5}$ abs was estimated with a Land Use Regression (LUR) model according to the European Study of Cohorts for Air Pollution Effects (ESCAPE) standardized procedure (ESCAPE-LUR) (Beelen et al. 2013; Eeftens et al. 2012; Hennig et al. 2016; Hoogh et al. 2013). The ESCAPE project was designed to study the effects of long-term air pollution exposure on health using health data from existing cohort studies throughout Europe, of which the HNR cohort study is one (Eeftens et al. 2012). LUR models were developed as part of the ESCAPE study for 36 study areas to estimate temporally-stable, spatially-variable concentrations of long-term exposure (Hennig et al. 2016). Within North-Rhine-Westphalia (the federal state where the HNR study population resides), three cohort studies in addition to the HNR study were included in the ESCAPE project, and the ESCAPE-LUR measurement campaign was designed to cover a range of environmental situations, ranging from the urban Ruhr-Area to the more rural city of Borken (Eeftens et al. 2012; Hennig et al. 2016).

Air pollution measurements were performed over one year between October 2008 and October 2009. Particulate matter of varying aerodynamic diameter was measured at 20 sites, and concentration of NO_2 was measured at 40 sites in three separate two-week periods in order to cover different seasons (Beelen et al. 2013; Eeftens et al. 2012). One additional background reference site was chosen to measure PM and NO_2 continuously during a complete year (starting in October 2008) in order to be able to adjust for discontinuous site-specific measurements and derive a long-term annual average (Hennig et al. 2016). Particulate matter was divided into different sizes as followed: PM_{10} (aerodynamic diameter<10 μm), $PM_{2.5}$ (aerodynamic diameter <2.5 μm), and PM_{coarse} (2.5< aerodynamic diameter <10 μm) (Eeftens et al. 2012). Further, a measurement of the blackness of $PM_{2.5}$ filters ($PM_{2.5}$abs) was carried out as a proxy for soot and black carbon, which is the dominant light absorbing substance

(Eeftens et al. 2012). Annual averages of measured pollutant concentrations at the monitoring sites and predictor variables, derived from European-wide and local geographic information system databases, were used to develop the study-specific LUR model. These models were then used to predict annual exposure concentrations at each participant's baseline address during the baseline year of the HNR study. An example of the estimated exposures is shown for $PM_{2.5}$ in Figure 5 (Hennig et al. 2016). In the Ruhr-Area, the models explained 69% of the variability in the annual concentrations of PM_{10}, 88% of that for $PM_{2.5}$, 66% of that for PM_{coarse}, 97% of that for $PM_{2.5}$ abs, and 89% of that for NO_2 (Beelen et al. 2013; Eeftens et al. 2012; Hennig et al. 2016).

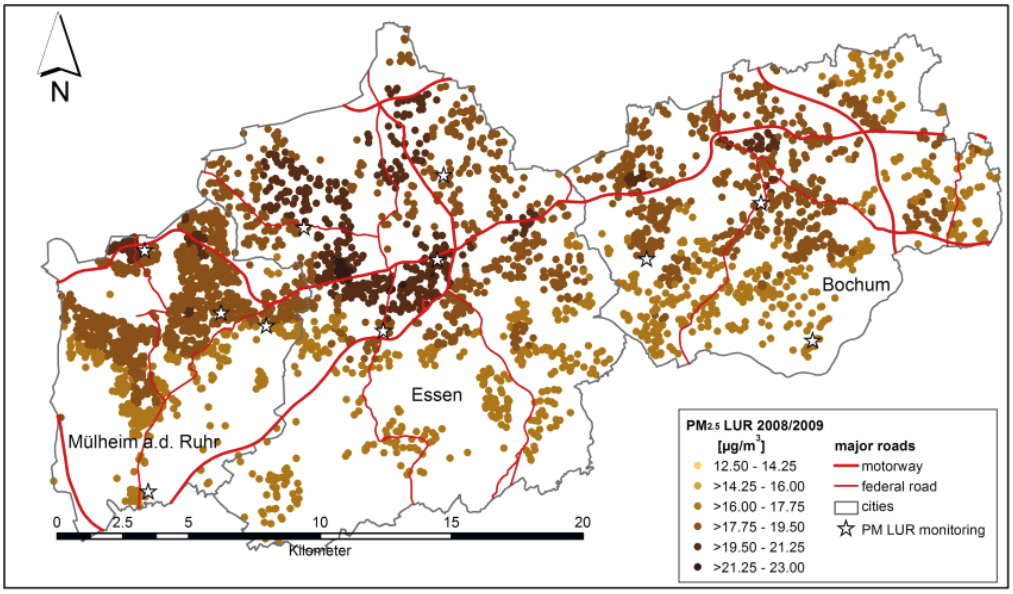

Figure 5: Visualization of point-specific $PM_{2.5}$ exposure for the participants of the Heinz Nixdorf Recall Study, modeled with ESCAPE-LUR in the HNR study area (2008-2009 annual mean). Ruhr Area, Germany.

3.2.2 Urban Background Exposure Assessment (EURAD-CTM)

We also used the European Air Pollution Dispersion and Chemistry Transport Model (EURAD-CTM), an urban background exposure model with a spatial resolution of 1 km^2 grid cells, to assess individual AP exposure at participants´ home addresses (Memmesheimer et al. 2004). The particulate matter sizes were defined by aerodynamic diameter as in the ESCAPE-LUR model. EURAD-CTM is a validated, time-dependent, three-dimensional model that uses input data from official emission inventories from different sources (e.g., industrial sources, household heating, traffic and agriculture) and data on hourly meteorology and regional topography to estimate PM_{10}, $PM_{2.5}$, and NO_2 concentrations on a scale of 1

km². The EURAD-CTM is a multilayer, multigrid model system that simulates the transport, chemical transformation, and deposition of tropospheric constituents (Büns et al. 2012). The EURAD-CTM model uses a sequential nesting method, starting with the large Europe-wide scale then narrowing down to the Ruhr-Area, with 4 nests with grid sizes of 125 km, 25 km, 5 km, and 1 km (Hennig et al. 2016; Memmesheimer et al. 2004; Nonnemacher et al. 2014) (Figure 6). This nesting method also includes the long-range transport and formation of secondary particles in the atmosphere (Hennig et al. 2016). Each participant of HNR was assigned daily mean PM and NO_2 concentrations of the 1 km² grid cell corresponding to his/her given residential address (Hennig et al. 2016; Nonnemacher et al. 2014). From these daily values, concentrations for longer exposure periods were calculated. For this analysis, mean exposure concentrations for the years 2001-2003 were used to reflect the pattern of long-term residential exposure prior to baseline examination. An example of the $PM_{2.5}$ exposures generated using this model are shown in Figure 7.

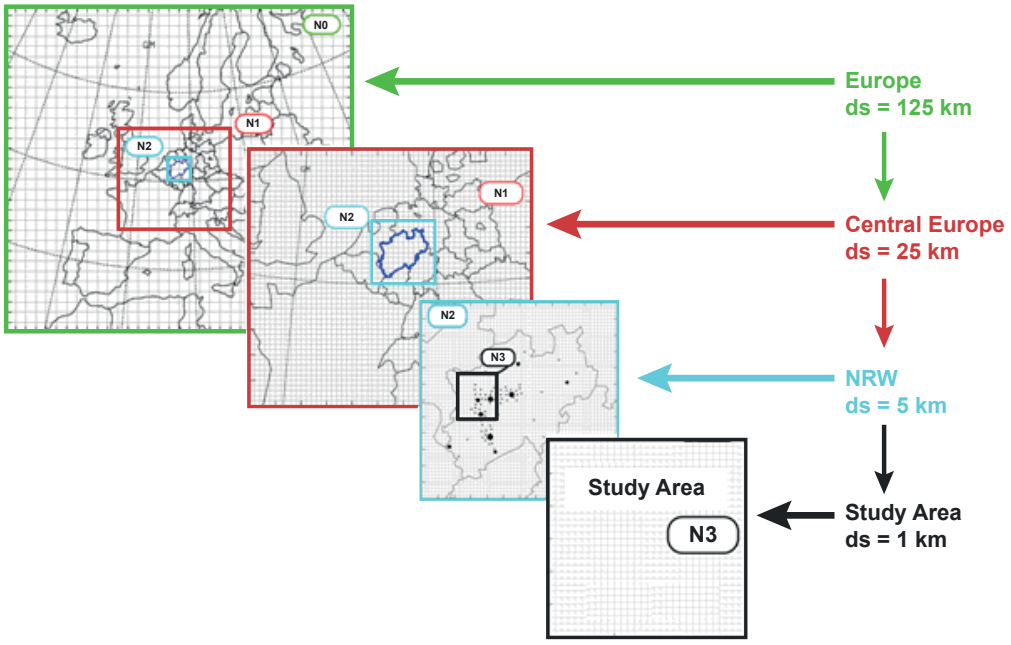

Figure 6: Study area via the method of sequential nesting used for EURAD-CTM. Ruhr Area, 2017, Heinz Nixdorf Recall Study.
NRW, North-Rhine Westphalia; ds, nesting domains

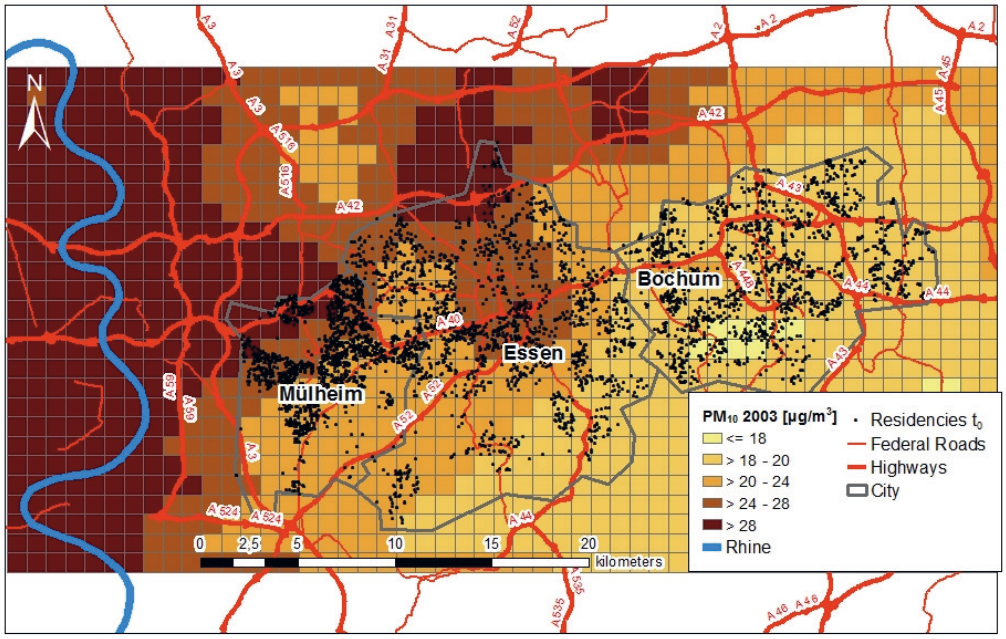

Figure 7: Visualization of urban background $PM_{2.5}$ exposure for the participants of the Heinz Nixdorf Recall Study, modeled with EURAD-CTM in the HNR study area (2003 annual mean). Ruhr Area, Germany.

3.2.3 Traffic Exposure Indicator

An additional traffic exposure variable was used for the EURAD-CTM model to capture small-scale intraurban variations resulting from traffic, as the model is, unlike the ESCAPE-LUR exposure model, not point-specific. We calculated distances (in meter (m)) between each participant´s residence and the next major road using official digitalized maps with a precision of at least ±0.5 m and daily traffic counts provided by the North Rhine Westphalia State Agency for Nature, Environment and Consumer Protection. A major road was defined as a federal or state highway with traffic density in the upper quintile of the daily traffic count (>26.000 vehicles/day). Distances were categorized as ≤50, 50 to 100, 100 to 200, and >200 m (reference category) (Hoffmann et al. 2006).

3.2.4 Noise Exposure

Long-term road noise was modeled for the year 2007 in the study area at the most exposed façade points according to the European Union Directive 2002/49/EC (Handbook on the Implementation of EU Environmental Legislation). The noise level at each façade point was calculated as weighted 24–hour (L_{den}) and night-time (22-6 h) (L_{night}) means (Tzivian et al. 2016). Residential exposures were then assigned for participants using the maximum noise value at the most exposed façade point for the building of residence or, if lacking building-

specific information, the maximum value in a 10-m buffer around each participant´s address (Tzivian et al. 2016). In this analysis, night noise (L_{night}) was included as a continuous variable. (Matthiessen et al. 2018)

3.3 Outcome

An outcome is defined as the disease or injury under investigation. In this study, the outcomes are prevalent and incident MetS.

3.3.1 Definition

Based on the data available for this study population, two common definitions of MetS can be applied - the IDF and the ATP III definition. We chose to use a slightly adapted version from the IDF definition for the main analyses (Table 3), using body mass index (BMI) as a surrogate for waist circumference (WC) since the IDF states that central obesity can be assumed if BMI ≥ 30 kg/m^2 (IDF 2006). BMI was used as a surrogate for waist circumference because there is still no consensus about the adequate waist circumference threshold for central obesity (Alberti et al. 2009). Data is lacking connecting WC thresholds confidently to NCDs, and sufficient research on WC differences between sexes and ethnic groups make the definition of the adequate WC threshold challenging (Alberti et al. 2009). The original, unmodified IDF definition and the revised ATP III definition of the year 2005 were used as part of the sensitivity analyses. (Matthiessen et al. 2018)

Table 3: Definition of the metabolic syndrome adapted from the IDF definition. Participants were defined as having MetS when they fulfilled A + 2 out of B, C, D, E criteria.

	MetS Criteria	Clinical Measure
A	Central Obesity	BMI ≥ 30 Kg/m^2
B	Elevated Triglycerides	Fasting TG ≥ 150 mg/dL (1.7 mmol/L)[1] or Random TG ≥ 175 mg/dL (2.0 mmol/L)[1]
C	Reduced High- Density Lipoprotein	HDL < 40 mg/dL (1.29 mmol/L) ♂[1] HDL < 50 mg/dL (1.29 mmol/L) ♀[1]
D	Elevated Blood Pressure	Systolic BP ≥ 130 mmHg or Diastolic BP ≥85 mmHg[1]
E	Elevated Glucose	Fasting Plasma Glucose ≥ 100 mg/dL (5.6 mmol/L)[2] or Random Plasma Glucose ≥ 200 mg/dL (11.1 mmol/L)[2]

[1]or pharmacological treatment; [2]or previously diagnosed diabetes mellitus

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3.3.2 Assessment

Anthropometric measurements (height, weight, WC) were taken at both examinations according to standard protocols, and BMI was calculated as kilograms per meter squared (kg/m^2). TG, HDL, and blood glucose levels (mg/dL) were measured at each examination with participants being advised to fast prior to examination visit. Information on the time since the last meal was also collected at time of blood drawn in order to facilitate classification of each test as random/non-fasting or fasting (non-fasting defined as last meal less than 8 hours before blood draw). All analyses were performed in the central laboratory of the University Hospital of Essen following a standard procedure.

BP was measured at each visit on the right arm three times (with a 3-minute interval in between) after at least 5 minutes of rest. The BP values used in this study were calculated as the mean of the 2^{nd} and 3^{rd} measurements (Stang et al. 2006). (Matthiessen et al. 2018)

Participants were asked to bring all packages of medication they had taken during the 7 days prior to each examination. Medication was then assigned to different classes via the WHO Anatomical Therapeutic Chemical Classification System (ATC) (Fuks et al. 2016). Statin medication use (Yes/No) was based on ATC code. Hypertensive medication use (Yes/No) was based on ATC code (blood pressure lowering medication (BPLM)) or on self-report (Fuks et al. 2016).

Diabetes mellitus status (Yes/No) was classified as positive if the participant reported a physician diagnosis, reported taking an anti-hyperglycemic drug, had a fasting blood glucose >125 mg/dL, or had a non-fasting blood glucose ≥200 mg/dL (Weinmayr et al. 2015). (Matthiessen et al. 2018).

3.3.3 Outcome Allocation

There were several challenges with the correct classification of the outcome (MetS; Yes/No). The main challenges were *participants with a non-fasting blood sample* and/or *missing information on individual components required for the MetS diagnosis*.

Non-fasting participants: Plasma triglycerides and glucose fluctuate depending on the individual's fasting state (IDF 2015; Nordestgaard et al. 2016; Ridker 2008; Sundvall et al. 2011). As a large percentage of the participants did not fast prior to blood draw (40% at t_0 and 24% at t_1), we modified the MetS criteria by adding non-fasting cutpoints for the blood glucose and triglyceride criteria. The following cutpoints were created for non-fasting samples: a) plasma glucose level ≥200 mg/dL and b) plasma triglycerides ≥175 mg/dL (Nordestgaard et al. 2016) (Matthiessen et al. 2018).

Missing information on individual components required for the MetS diagnosis: For some participants with missing information on MetS variables, MetS allocation was still possible. For example, if a participant was missing a measure for blood pressure but had a BMI and three other MetS criteria in accordance with having MetS, the participant was assigned as having MetS. However, in the following cases, it was not possible to determine MetS status:

- Participants with missing information on BMI
- Participants with missing information on ≥ 3 MetS components (e.g., HDL, TG and BP)
- Participants who fulfilled the BMI criteria for MetS (BMI ≥30 Kg/m^2), one other MetS criteria and
    - had a random glucose between 100 – 200 mg/dL.
    - had a random triglyceride between 150 – 175 mg/dL.

3.4 Covariates

3.4.1 Individual-Level Covariates

Individual-level characteristics, including age, sex, smoking status, exposure to environmental tobacco smoke (ETS), nutrition, and participation in regular physical activity, were assessed in standardized interviews and self-administered questionnaires. *Smoking status* was defined as current, former (>1 year since quitting), or never smoker. *Cumulative smoking* was assessed using pack-years for current and former smokers. Exposure to *environmental tobacco smoke* (*ETS*; Yes/ No) reflected any passive exposure to smoke at home, work, or other location. *A nutrition index* was calculated using a qualitative food frequency questionnaire with information on the consumption frequency of 13 food items (Winkler and Döring 1998). Frequency of the consumption was categorized into "hardly ever/never", "1-3 times/month", "1-3 times/week", "4-6 times/week", and "daily", and then given points between 1-5. By summing up the points for the different food items, a score (Dietary Pattern Index (Ernährungsmusterindex – EMI)) was calculated with a range from 0 to 26, with a higher score indicating better accordance to the recommendations of the German Society of Nutrition (Winkler et al. 1995). Two *physical activity* measures were used, one according to self-reported activity (sport; Yes/No) and one using self-reported times of physical activity in a typical week (T/wk). (Matthiessen et al. 2018)

3.4.2 Socioeconomic Status

Individual socioeconomic status (SES) was defined as years of formal education. Education was classified according to the International Standard Classification of Education as total years of formal education (UNESCO 1997) and divided into four categories for the analysis (≤10, 11-13, 14-17, ≥18 years).

The study area was divided into 106 neighborhoods with a median size of 11,263 inhabitants (Dragano et al. 2009). *Neighborhood SES* was assessed as neighborhood unemployment rate (%), which was obtained from local census authorities for each residential neighborhood according to administrative bounds (Dragano et al. 2009). The unemployment rate was calculated by dividing the number of unemployed by the economically active population (Dragano et al. 2009). (Matthiessen et al. 2018)

3.5 Statistical Analysis

3.5.1 Descriptive Analysis

We conducted a complete case analysis, excluding participants with missing exposure, outcome, or covariate data. For the cross-sectional analysis of prevalent MetS at baseline examination as well as the longitudinal analysis of incident MetS, we conducted descriptive statistics on the study population. Additionally, we divided the study population of the cross-sectional and the longitudinal analyses into subgroups of high and low air pollution exposure (defined as $PM_{2.5}$ exposure from ESCAPE-LUR equal to or above the mean versus below the mean, respectively). Subsequently, we compared subgroups using unpaired t-tests for variables that followed normal distribution (e.g., age, nutrition), Wilcoxon tests for variables that differed from normal distribution (e.g., neighborhood SES, cumulative smoking), and chi-squared tests for categorical variables (e.g., sex, individual SES), with an α of 0.05. (Matthiessen et al. 2018)

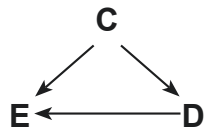
We calculated Spearman correlation coefficients (r) to examine the correlations between the air pollutant estimates from the different air pollution exposure models (i.e., ESCAPE-LUR and EURAD-CTM) (Matthiessen et al. 2018). A strong positive correlation was defined as $r \geq 0.7$, a moderate positive correlation was defined as $0.4 \leq r < 0.7$, and a weak positive correlation was defined as $r < 0.4$.

3.5.2 Selection Bias

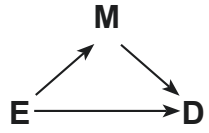
Study validity can be comprised if a proportion of participants cannot be traced to determine the disease outcome or other important data for the analysis (Rothman 2012). The concern is that if data is missing selectively, a response or selection bias can occur (Rothman 2012). The more missing data there is, the greater the potential for selection bias (Rothman 2012). Since we excluded participants with incomplete data for the cross-sectional analysis and even more participants for the longitudinal analysis, an increasing risk of selection bias is present for our study populations. Due to this risk, population characteristics, comparing participants with complete versus incomplete data were assessed for both the cross-sectional and the longitudinal analyses. Comparison of participants with complete vs. incomplete data was carried out using same tests as described in the above section 3.5.2 (unpaired t-test, Wilcoxon test, and chi-squared test).

3.5.3 Confounder Identification & Regression Models

Confounding is a major issue in observational studies, and there are many different definitions of confounding and confounder (Bonita et al. 2006; Greenland et al. 1999). Confounding can be considered as a type of systematic bias due to another factor in the study population that is associated both with the disease and the exposure being studied (Bonita et al. 2006; Rothman 2012). In our case, a confounder would be a third factor that is associated with the air pollutant as well as MetS. Three conditions must exist for a variable to be defined as a confounder (C): 1) a confounder must be associated with the disease (D) (e.g., MetS), 2) a confounder must be associated with the exposure (E) (e.g., air pollutant) (Rothman 2012).



The third condition states that if a factor is an intermediate (M) step between the exposure and the disease (i.e., on the causal pathway), then it is not a confounder (Rothman 2012).



Several different methods exist to *control for confounding* and to *identify confounding factors. Control for confounding* can either be carried out through the *study design* (e.g., randomization, matching, stratification) or during the *analysis of data* (e.g., adjustment) (Bonita et al. 2006; Rothman 2012). In this analysis, we controlled for confounding during the analysis of the results (Bonita et al. 2006).

The approach to *identify confounding factors* for the analytical phase can be either carried out *based on data and statistical criteria* or *based on prior knowledge*. The identification of confounding factors based on *statistical criteria (data-based)* can be accomplished via a stepwise construction of regression models by an algorithm that automatically selects which factors to include in the final model (e.g., change-in-point estimate of exposure, significance-testing) (Rothman 2012). The identification of confounding factors based on *prior knowledge* can be approached through the concept of causality or based on knowledge from similar studies.

For this analysis, we identified confounding factors based on *prior knowledg*e. We used two different approaches to select regression models and their adjustment sets: a) based on the concept of causality via a Directed Acyclic Graph (DAG) and b) based on knowledge from similar studies.

a) Based on the concept of causality via a Directed Acyclic Graph

Causality tries to understand the cause of a disease in order to prevent the disease and for correct diagnosis and treatment (Bonita et al. 2006). A cause of a disease must precede the disease/outcome (Bonita et al. 2006).

A DAG is a useful tool for visualizing the causal relationship between exposure and outcome and for identifying potential confounders (Greenland et al. 1999). The graph is called directed because all variables in the graph are connected by arrows representing direct causal effects (Suttorp et al. 2015). The graph is acyclic because causal paths cannot be cyclic, e.g., the outcome cannot cause the exposure (Suttorp et al. 2015). Based on prior biological and epidemiological knowledge, a DAG was constructed using DAGitty (Figure 8) (Textor et al. 2011).

According to the developers, 'DAGitty is a web-based software for analyzing causal diagrams […], (and) it contains some of the fastest algorithms available for this purpose.' (Textor 2013). With the help of these algorithms, Minimal Sufficient Adjustment Sets (MSAS) were identified to estimate the direct (causal) effect of air pollution on MetS (Textor 2013). MSASs try to identify the minimal set of factors one needs to adjust for in order to estimate an unbiased effect between exposure and outcome. Two MSASs were identified and included the following variables: MSAS 1) Age, sex, neighborhood SES, nutrition, physical activity, proximity to major road, smoking status, and ETS; MSAS 2) Individual SES and proximity to major road.

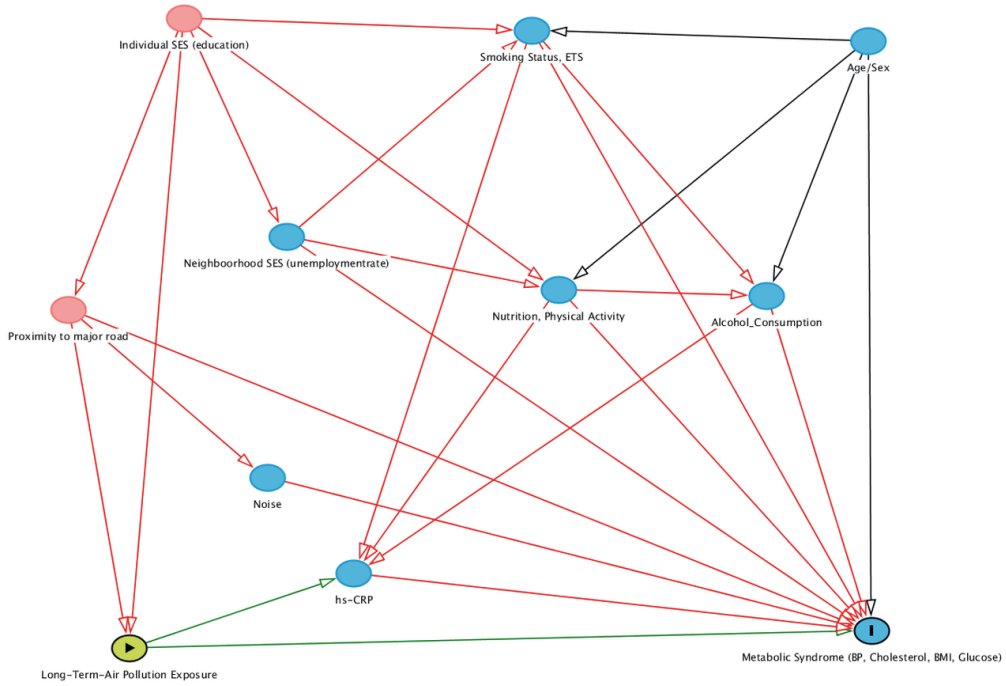


Figure 8: Directed acyclic graph with potential covariates between air pollution and the metabolic syndrome.
Suggested minimal sufficient adjustment sets: 1) Age, Sex, Neighborhood SES, Nutrition, Physical Activity, Proximity to Major Road, Smoking Status, ETS; 2) Individual SES, Proximity to Major Road.

b) Based on knowledge from similar studies

In many epidemiological studies with the same or related research questions, similar adjustment sets based on prior biological and epidemiological knowledge are used. Known or assumed confounding factors in environmental epidemiology include demographic variables and SES as well as lifestyle variables. In order to ensure easier comparability of study results, we chose models with similar adjustment sets as those previously used in other epidemiological cohorts and within the HNR study. Two models (*model 1* & *model 2*) of increasing covariate adjustment were conducted for each air pollutant exposure. In *model 1*, we adjusted for age, sex, individual SES, and neighborhood SES. In *model 2* (main adjustment set), we additionally adjusted for lifestyle variables such as smoking status, cumulative smoking, ETS, and physical activity. For the EURAD-CTM exposures, we additionally added a small scale indicator for traffic to the model (*model 3*). Furthermore, a model adjusting for chronic night noise exposure (ESCAPE-LUR: *model 2 + noise*; EURAD-CTM: *model 3 + noise*) was conducted for each air pollutant (Table 4). (Matthiessen et al. 2018)

Table 4: Regression Models with different adjustment sets for ESCAPE-LUR and EURAD-CTM exposure models. Ruhr Area, 2017, Heinz Nixdorf Recall Study.

Regression Model	Variable
Crude	Air Pollutant
Model 1	Crude + Sex, Age, Individual SES, Neighborhood SES
Model 2[A]	Model 1 + Lifestyle Variables (Smoking Status, Cumulative Smoking, ETS, Nutrition, Physical Activity)
Model 2 + Noise	Model 2 + Noise
Model 3	Model 2 + Traffic Indicator
Model 3 + Noise	Model 3 + Noise

[A]main adjustment set

Since there were no major differences in effect estimates between the two approaches to identify confounding factors (DAG-based vs. based on knowledge from similar studies), we used the models based on *knowledge from similar studies* for the analysis. Comparison of the models based on DAG versus knowledge from similar studies, can be found in the appendix (Figure A1-A4).

During the covariate selection process, different likelihood ratio tests were carried out *a priori* in order to test for the best model fit of the main adjustment set because several variables were available to reflect similar confounding factors. For *individual SES*, an income variable was added to the model with the education variable in order to evaluate if both variables together would better account for *individual SES* than education only. No influence on the model was found, and education was kept solely as a marker for *individual SES*. Further, it was evaluated if a binary *sport* variable (Yes/No) was sufficient to reflect physical activity as a confounding factor. The model fit was significantly improved when both the binary *sport* variable (Yes/No) and a continuous physical activity variable (times of physical activity per week) were included. Finally, *alcohol* consumption and *season* were tested for inclusion in the main adjustment set. As no change of the model was seen, alcohol consumption and season were omitted.

For this analysis, all covariates used were from the baseline examination. Age, neighborhood SES, cumulative smoking, physical activity, nutrition, and noise were introduced as continuous variables. Individual SES, and smoking status were introduced as categorical or ordinal variables, while sex, ETS, and sport were introduced as dichotomous variables.

3.5.4 Logistic Regression

We evaluated the association between air pollution exposures (PM_{10}, $PM_{2.5}$, PM_{coarse}, $PM_{2.5}$abs, NO_2) and prevalent as well as incident MetS using logistic regression for all models. We used 95% confidence intervals (CIs) to help assess significant differences. Logistic regression is a multiplicative model and the method most commonly used for the analysis of binary outcome variables, which is the case for this analysis (Kirkwood and Sterne 2003). Logistic regression models the association between exposure and outcome in terms of odds ratios (ORs) (Kirkwood and Sterne 2003). The general form of the logistic regression is as followed:

$$\text{Log of odds of outcome} = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \ldots + \beta_k x_k \beta_1 + \varepsilon$$

On the left-hand side of the equation, the dependent variable is inserted (e.g., MetS). On the right hand side, the βs represent the regression coefficients, with β_0 being the intercept (the value of the y-axis when all x=0) and β_i being the coefficients for the independent variables x_i (Bonita et al. 2006; Kirkwood and Sterne 2003). The term $\beta_i x_i$ represents the proportion of the dependent variable (MetS) attributed to the independent variable (e.g., the air pollutant $PM_{2.5}$) (Bonita et al. 2006). The error term, denoted as ε, represents what is left over after the other variables have been taken into account (Bonita et al. 2006).

Effect estimates of air pollution exposures were expressed per interquartile range (IQR) (Matthiessen et al. 2018). A distribution of continuous variables can be divided into four equal-sized groups called quartiles. The difference between the lower and upper quartile is known as the interquartile range.

$$\text{IQR} = \text{upper quartile} - \text{lower quartile}$$

The IQR indicates the spread of the middle 50% of the distribution of the variable (e.g., the air pollutant) and tends to be more stable for variables with extreme values (Kirkwood and Sterne 2003). Using the IQR also prevents extrapolation beyond the measured exposure range and allows distribution-based comparison of the different air pollutants.

3.6 Sensitivity analyses

To evaluate the robustness of our results, several sensitivity analyses were performed. The main focus areas for the sensitivity analyses were potential *exposure* and *outcome misclassification*, which were performed for both the cross-sectional and the longitudinal analyses. Further, we evaluated the association between AP and incident MetS among participants free of MetS at baseline by estimating the relative risk (RR), instead of the OR, using Poisson regression for a binary outcome (Zou 2004).

Sensitivity analyses were performed for the pollutants PM_{10}, $PM_{2.5}$, and NO_2 with the point-specific exposure model ESCAPE-LUR. Sensitivity analyses with the urban background exposure model (EURAD-CTM) can be found in the appendix (Table A1-A5 & Figure A5).

3.6.1 Exposure Misclassification

Because environmental exposure was assessed at the participants´ home addresses without information on the actual hours spend in their residence, sensitivity analyses taking into account variables with information on relocation and working hours were carried out. First, all analyses were repeated only among participants who did not relocate between baseline and 1st follow-up examination and additionally among participants who did not relocate during the 5 years before baseline examination. Further, we included only participants who reported working less than half-time, as these participants had a greater likelihood of spending the majority of their time in their residence. (Matthiessen et al. 2018)

3.6.2 Outcome Misclassification

Because there is no universally agreed upon MetS definition and the current definitions rely heavily on specific cutpoints, we conducted several sensitivity analyses using different cutpoints to evaluate the robustness of our results to changes in our outcome definition. We conducted one analysis using the IDF definition and one using the revised ATP III definition (Table 1) (Grundy et al. 2006; Huang 2009; IDF 2006). Further, we conducted two analyses where we varied the criteria for "elevated BP." Depending on the MetS definitions (Table 1), different cut points for hypertension are given: ≥140/90 mmHg or ≥130/85 mmHg. In addition, a prior study from our own group suggests that measured hypertension varies more than self-reported hypertension or intake of BPLM and may lead to fewer false positive cases (Fuks et al. 2016a). We therefore conducted two separate analyses: one using the cutpoint

to BP ≥140/90 mmHg and the other considering only participants with self-reported hypertension or taking BPLM as fulfilling the criteria for "elevated BP".

For the analysis of MetS prevalence, only participants with fasting blood draw were included. For analysis of the MetS incidence, similar as for the main analysis, participants with both fasting and non-fasting blood draw were included (Table 3). (Matthiessen et al. 2018)

3.6.3 AP and Incident MetS by Estimating Relative Risk

Kirkwood and Sterne (2003) mention that '(a) common mistake in the literature is to interpret an odds ratio as if it were a risk ratio.' When the outcome is rare (less than 10%), the numerical value of the OR approaches the value of the RR. However, when the outcome is common, RRs are constrained but ORs are not (Kirkwood and Sterne 2003). Our outcome was not a rare disease in the analysis of prevalence of MetS (20.7%). The incidence of MetS was close to 10%, leading to a potential overestimation of the risk for MetS incidence. Therefore, we conducted sensitivity analyses estimating RRs using a modified Poisson regression with a robust variance estimator in the longitudinal analysis (Lindquist; Zou 2004).

All statistical analyses and processing of the data were conducted in R version 3.3.1. (R Core Team 2016).

4 Results

4.1 Study Population

„In total, 4,457 participants were available for cross-sectional analyses with a MetS prevalence of 20.7% (n=922). Participants were excluded from the cross-sectional analyses if MetS (Yes/No) was not determinable at t_0 or if exposure or covariate data were missing (n=357; Figure 9).“ (Matthiessen et al. 2018)

For the longitudinal analysis, 3,074 participants were included with a cumulative MetS incidence of 9.7% (n=299) over a mean follow-up period of 5.1 years. Participants were excluded from the longitudinal analyses if they were lost to follow-up, if MetS (Yes/No) was not determinable at t_0 or t_1, if covariate or exposure data were missing, or if exposure data were not correctly assigned at t_1 due to participants relocation outside of the study area (n=1,013; Figure 9). Participants with MetS at baseline (n=727) were also excluded from the longitudinal analysis. (Matthiessen et al. 2018)

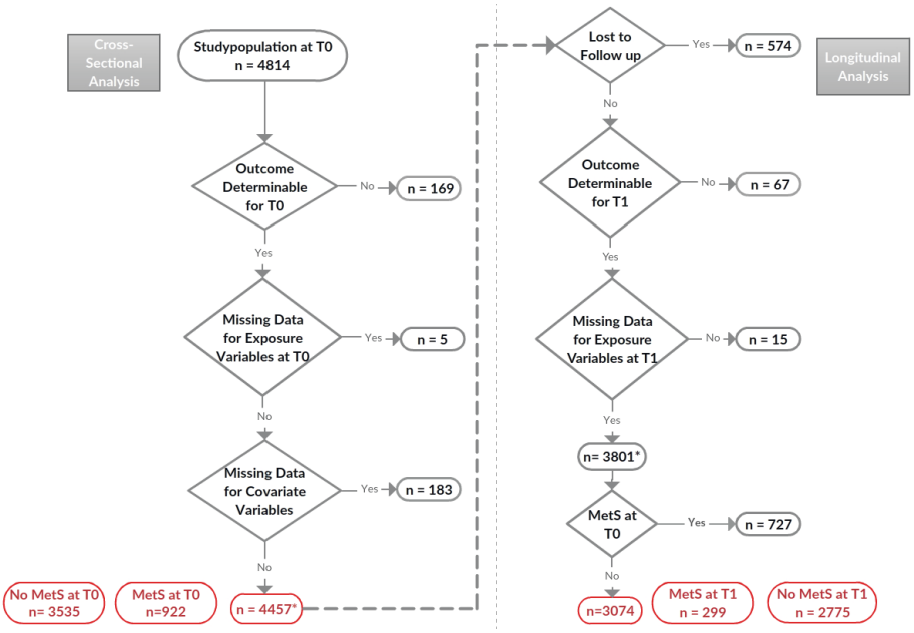


Figure 9: Flowchart on the selection of the study population for the cross-sectional and the longitudinal analyses. Ruhr Area, 2017, Heinz Nixdorf Recall Study.
*These numbers are used to check for selection bias T0 and T1, respectively

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4.2 Descriptive Results

4.2.1 Description of Study Population

„(The) mean (±SD) age of participants at baseline examination was 59.6 (±7.8) and 58.8 (±7.6) years for the cross-sectional and longitudinal analyses, respectively (Table 5 & 6). In both analyses, men and women were equally represented (women 50-51%), most participants (55-56%) had completed 11-13 years of education, and many were never-smokers (42-43%)." (Matthiessen et al. 2018)

When comparing participants with high versus low exposure, a significant difference in most sociodemographic characteristics and lifestyle behaviors was observed for both the cross-sectional and the longitudinal analyses (Table 5 & 6). Participants living in an area with higher AP exposure were more likely to have completed fewer years of education, to be more exposed to night-noise, and to be less physically active.

Table 5: Baseline characteristics of the study population in the *cross-sectional analysis* stratified by exposure level (high versus low). Ruhr Area, 2017, Heinz Nixdorf Recall Study.

Variable	Study Population, n = 4,457	$PM_{2.5}$ (µg/m³)		P-value[1]
		< 18.42 n = 2,448	≥ 18.42 n = 2,009	
Age [Yrs], mean ± SD	59.6 ± 7.8	59.5 ± 7.6	59.6 ± 8.0	0.6
Sex, Women, N (%)	2,238 (50.2)	1,184 (48.4)	1,054 (52.5)	<0.001
Neighborhood Unemployment [%], median (IQR)	12.0 (5.0)	10.4 (3.5)	13.6 (5.2)	<0.001
Education				
< 11 Yrs, N (%)	487 (10.9)	213 (8.7)	274 (13.6)	<0.001
11-13 Yrs, N (%)	2,487 (55.8)	1,298 (53.0)	1,189 (59.2)	
14-17 Yrs, N (%)	1,003 (22.5)	602 (24.6)	401 (20.0)	
> 17 Yrs, N (%)	480 (10.8)	335 (13.7)	145 (7.2)	
Pack-Years for former & current smokers, median (IQR)	21.4 (29.8)	19.8 (28.4)	23.5 (31.1)	<0.001
Smoking Status				
Never Smoker, N (%)	1,879 (42.2)	1,074 (43.9)	805 (40.1)	<0.001
Former Smoker, N (%)	1,524 (34.2)	855 (34.9)	669 (33.3)	
Current Smoker, N (%)	1,054 (23.6)	519 (21.2)	535 (26.6)	
Exposure to ETS, N (%)	1,628 (36.5)	832 (34)	796 (39.6)	
Physical Activity [T/wk], median (IQR)	0.8 (3.0)	1.0 (3.3)	0.3 (3.0)	<0.001
Sport, Yes, N (%)	2,411 (54.1)	1,396 (57.0)	1,015 (50.5)	<0.001
Nutrition Index [EMI], mean ± SD	12.7 ± 3.1	12.7 ± 3.1	12.6 ± 3.1	0.4
Night-Noise [dB], mean ± SD	45.1 ± 9.1	43.1 ± 8.9	47.7 ± 8.7	<0.001

[1]P-values of covariate difference between participants with low versus high AP exposure were calculated using t-tests for continuous variables that followed a normal distribution, Wilcoxon tests for continuous variables that differed from a normal distribution, and chi-squared tests for categorical or dichotomous variables

Table 6: Baseline characteristics of the study population in the *longitudinal analysis* stratified by exposure level (high versus low). Ruhr Area, 2017, Heinz Nixdorf Recall Study.

Variable	Study Population, n = 3,074	$PM_{2.5}$ (µg/m³)		P-value[1]
		< 18.38 n = 1,686	≥ 18.38 n= 1,388	
Age [Yrs], mean ± SD	58.8 ± 7.6	58.8 ± 7.4	58.8 ± 7.9	0.9
Sex, Women, N (%)	1576 (51.3)	837 (49.6)	739 (53.2)	0.1
Neighborhood Unemployment [%], median (IQR)	11.8 (4.3)	10.3(3.3)	13.6 (4.2)	<0.001
Education				
< 11 Yrs, N (%)	268 (8.7)	103 (6.1)	165 (11.9)	<0.001
11-13 Yrs, N (%)	1,704 (55.4)	885 (52.5)	819 (59.0)	
14-17 Yrs, N (%)	698 (22.7)	422 (25.0)	276 (19.9)	
> 17 Yrs, N (%)	404 (13.1)	276 (16.4)	128 (9.2)	
Pack-Years for former & current smokers, median (IQR)	19.5 (28.0)	17.9 (26.1)	22.0 (29.9)	<0.01
Smoking Status				
Never Smoker, N (%)	1,310 (42.6)	737 (43.7)	573 (41.3)	<0.001
Former Smoker, N (%)	1,033 (33.6)	595 (35.3)	438 (31.6)	
Current Smoker, N (%)	731 (23.8)	354 (21.0)	377 (27.2)	
Exposure to ETS, N (%)	1,114 (36.2)	569 (33.7)	545 (39.3)	<0.01
Physical Activity [T/wk], median (IQR)	1.0 (3.5)	1.0 (3.8)	0.8 (3.0)	<0.001
Sport, Yes, N (%)	1,807 (58.8)	1,043 (61.9)	764 (55)	<0.001
Nutrition Index [EMI], mean ± SD	12.7 ± 3.1	12.8 ± 3.1	12.6 ± 3.1	0.2
Night-Noise [dB], mean ± SD	44.9 ± 9.0	42.9 ± 8.7	47.5 ± 8.7	<0.001

[1]P-values of covariate difference between participants with low versus high AP exposure were calculated using t-tests for continuous variables that followed a normal distribution, Wilcoxon tests for continuous variables that differed from a normal distribution, and chi-squared tests for categorical or dichotomous variables

4.2.2 Selection Bias

„Participants who were excluded from *cross-sectional analyses* (n=357) due to incomplete data differed from participants with complete data (n=4,457) in several ways: they were more likely to be older, to live in a neighborhood with a higher unemployment rate, to have completed fewer years of education, and to be less physically active (Table 7)." (Matthiessen et al. 2018)

Table 7: Difference in baseline characteristics between participants with complete versus incomplete data for the *cross-sectional analysis*. Ruhr Area, 2017, Heinz Nixdorf Recall Study.

Variable	Participants with Complete Data n=4,457	Participants Excluded due to Incomplete Data n = 357[2]	P-value[1]
Age [Yrs], mean ± SD	59.6 ± 7.8	60.5 ± 8.2	<0.001
Sex, Women, N (%)	2,238 (50.2)	181 (50.7)	0.9
Neighborhood Unemployment [%], median (IQR)	12.0 (5.0)	12.5 (5.5)	<0.001
Education [Yrs], N (%)			
< 11 Yrs	487 (10.9)	60 (17.6)	<0.001
11-13 Yrs	2,487 (55.8)	189 (55.4)	
14-17 Yrs	1,003 (22.5)	65 (19.1)	
> 17 Yrs	480 (10.8)	27 (7.9)	
Pack-Years in former & current smokers, median (IQR)	21.4 (29.8)	29.9 (33.5)	0.3
Smoking Status			
Never Smoker, N (%)	1,879 (42.2)	135 (38.9)	0.1
Former Smoker, N (%)	1,524 (34.2)	138 (39.8)	
Current Smoker, N (%)	1,054 (23.6)	74 (21.3)	
Exposure to ETS, N (%)	1,628 (36.5)	117 (34.4)	0.5
Physical Activity [T/wk], median (IQR)	0.8 (3.0)	0.0 (2.4)	<0.001
Sport, Yes, N (%)	2,411 (54.1)	176 (49.4)	0.1
Nutrition Index [EMI], mean ± SD	12.7 ± 3.1	12.6 ± 3.1	0.8
Night-Noise [dB], mean ± SD	45.1 ± 9.1	46.1 ± 9.4	0.1
ESCAPE-LUR, mean ± SD			
PM_{10} [µg/m^3]	27.8 ± 1.9	27.8 ± 1.9	0.9
$PM_{2.5}$ [µg/m^3]	18.4 ± 1.1	18.5 ± 1.1	0.6
PM_{coarse} [µg/m^3]	10.0 ± 1.8	10.0 ± 2.0	0.6
$PM_{2.5}$abs [0.0001/m]	1.50 ± 0.4	1.60 ± 0.4	0.3
NO_2 [µg/m^3]	30.3 ± 4.9	30.2 ± 5.5	0.9

[1]P-values of covariate difference between participants with complete versus incomplete data were calculated using t-tests for continuous variables that followed a normal distribution, Wilcoxon tests for continuous variables that differed from a normal distribution, and chi-squared tests for categorical or dichotomous variables

[2]Number of missing values for variables were: Education (16), Pack-Years (49), Smoking Status (10), ETS (17), Phyiscal Activity (15), Sport (1), EMI (96), Night-Noise (41), ESCAPE-LUR pollutants (5)

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In the *longitudinal analysis*, the same covariates differed between participants with complete (n=3,801) versus incomplete (n=1,013) data (Table 8). In addition, participants with incomplete data for the *longitudinal analysis* were also more likely to have lifestyle variables associated with an unhealthy lifestyle (e.g., current smokers, exposure to ETS, low activity level) and higher exposure to $PM_{2.5}$, $PM_{2.5}$abs, and NO_2 (Table 8). (Matthiessen et al. 2018)

Table 8: Differences in baseline characteristics between participants with complete versus incomplete data for the *longitudinal analyses*. Ruhr Area, 2017, Heinz Nixdorf Recall Study.

Variable	Participants with Complete Data n=3,801	Participants Excluded due to Incomplete Data n = 1,013[2]	P-value[1]
Age [Yrs], mean ± SD	59.2 ± 7.6	61.4 ± 8.2	<0.001
Sex, Women, N (%)	1,925 (50.6)	494 (48.8)	0.3
Neighborhood Unemployment [%], median (IQR)	11.9 (4.3)	12.5 (5.2)	<0.001
Education [Yrs], N (%)			
< 11 Yrs	370 (9.7)	177 (17.8)	<0.001
11-13 Yrs	2,121 (55.8)	555 (55.7)	
14-17 Yrs	867 (22.8)	201 (20.2)	
> 17 Yrs	443 (11.7)	64 (6.4)	
Pack-Years in former & current smokers, median (IQR)	20.0 (28.5)	30.0 (34.3)	<0.001
Smoking Status			
Never Smoker, N (%)	1,625 (42.8)	389 (38.8)	<0.001
Former Smoker, N (%)	1,318 (34.7)	344 (34.3)	
Current Smoker, N (%)	858 (22.6)	270 (26.9)	
Exposure to ETS, N (%)	1358 (35.7)	387 (38.9)	0.1
Physical Activity [T/wk], median (IQR)	1.0 (3.0)	0.0 (2.0)	<0.001
Sport, Yes, N (%)	2,145 (56.4)	442 (43.7)	<0.001
Nutrition Index [EMI], mean ± SD	12.7 ± 3.1	12.6 ± 3.1	0.3
Night-Noise [dB], mean ± SD	45.1 ± 9.1	45.6 ± 9.3	0.1
ESCAPE-LUR, mean ± SD			
PM_{10} [µg/m^3]	27.8 ± 1.8	27.8 ± 1.9	0.3
$PM_{2.5}$ [µg/m^3]	18.4 ± 1.1	18.5 ± 1.1	<0.001
PM_{coarse} [µg/m^3]	10.0 ± 1.8	10.0 ± 2.0	0.7
$PM_{2.5}$abs [0.0001/m]	1.50 ± 0.4	1.60 ± 0.4	<0.001
NO_2 [µg/m^3]	30.2 ± 4.9	30.6 ± 5.0	<0.001

[1]P-values of covariate difference between participants with complete versus incomplete data were calculated using t-tests for continuous variables that followed a normal distribution, Wilcoxon tests for continuous variables that differed from a normal distribution, and chi-squared tests for categorical or dichotomous variables

[2]Number of missing values for variables were: Education (16), Pack-Years (49), Smoking Status (10), ETS (17), Phyiscal Activity (15), Sport (1), EMI (96), Night-Noise (41), ESCAPE-LUR pollutants (5)

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4.2.3 Description of Exposure Variables

For the *ESCAPE-LUR exposure model*, mean PM_{10} and $PM_{2.5}$ exposures in the cross-sectional analysis were 27.8 µg/m³ and 18.4 µg/m³, respectively (Table 9) (Matthiessen et al. 2018). For the E*URAD-CTM exposure model*, mean PM_{10} and $PM_{2.5}$ exposures in the cross-sectional analysis were 21.3 µg/m³ and 17.7 µg/m³, respectively (Table 10).

In addition, the interquartile ranges for the air pollution exposures in the two exposure models differed. While the IQR for PM was wider for the EURAD-CTM exposure model (e.g., PM_{10}: 2.1 µg/m³ for ESCAPE-LUR versus 4.2 µg/m³ for EURAD-CTM), the IQR for NO_2 was wider for the ESCAPE-LUR model (6.1 µg/m³ for ESCAPE-LUR versus 5.1 µg/m³ for EURAD-CTM) (Table 9 & 10).

Table 9: Description of air pollution exposures (2008-2009 annual mean) from the *ESCAPE-LUR* model in the *cross-sectional analysis*, n=4457. Ruhr Area, 2017, Heinz Nixdorf Recall Study.

	IQR	Min	Q1	Median	Q3	Max	Mean ± SD
PM_{10} [µg/m³]	2.1	23.9	26.6	27.5	28.7	34.7	27.8 ± 1.9
$PM_{2.5}$ [µg/m³]	1.5	16.0	17.6	18.3	19.1	21.5	18.4 ± 1.1
PM_{coarse} [µg/m³]	1.9	0.8	9.2	10.1	11.1	15.0	10.0 ± 1.8
$PM_{2.5}$abs [0.0001/m]	0.4	1.0	1.4	1.5	1.7	5.4	1.6 ± 0.4
NO_2 [µg/m³]	6.1	19.8	26.9	29.6	33.1	62.4	30.3 ± 4.9

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Table 10: Description of air pollution exposures (2001-2003, 3-year mean) from the *EURAD-CTM* model in the *cross-sectional analysis*, n=4,457. Ruhr Area, 2017, Heinz Nixdorf Recall Study.

	IQR	Min	Q1	Median	Q3	Max	Mean ± SD
PM_{10} [µg/m³]	4.2	17.3	18.8	21.4	23.0	29.5	21.3 ± 2.6
$PM_{2.5}$ [µg/m³]	2.1	15.4	16.7	17.7	18.7	22.1	17.7 ± 1.3
NO_2 [µg/m³]	5.1	28.6	38.7	41.5	43.8	53.8	41.4 ± 4.0

All exposure variables were positively correlated. Within the *ESCAPE-LUR exposure model*, $PM_{2.5}$ was strongly correlated with PM_{10}, and $PM_{2.5}$abs was strongly correlated with PM_{10}, $PM_{2.5}$, and PM_{coarse} (Spearman correlation coefficients (r), 0.70-0.90) (Table 11). Within the *EURAD-CTM exposure model*, a strong correlation between PM_{10} and $PM_{2.5}$ (r=0.88) was observed. Air pollutants showed a weak to moderate correlation between the two exposure models (ESCAPE-LUR and EURAD-CTM). Noise was weakly correlated with all air pollutants, except for $PM_{2.5}$abs where noise was moderately correlated (r=0.48). (Matthiessen et al. 2018)

Table 11: Spearman correlation coefficients for air pollution and noise exposures for both ESCAPE-LUR and EURAD-CTM exposure models, n=4,457. Ruhr Area, 2017, Heinz Nixdorf Recall Study.

		ESCAPE-LUR					EURAD-CTM			Noise
		PM_{10}	**$PM_{2.5}$**	**PM_{coarse}**	**$PM_{2.5}$ abs**	**NO_2**	**PM_{10}**	**$PM_{2.5}$**	**NO_2**	**L_{night}**
ESCAPE-LUR	**PM_{10}**	**1.00**	0.88	0.66	0.90	0.54	0.34	0.19	0.37	0.32
	$PM_{2.5}$		**1.00**	0.65	0.89	0.64	0.56	0.39	0.45	0,29
	PM_{coarse}			**1.00**	0.70	0.43	0.20	0.05	0.22	0.31
	$PM_{2.5}$ abs				**1.00**	0.62	0.33	0.14	0.35	0.48
	NO_2					**1.00**	0.49	0.39	0.37	0.36
EURAD -CTM	**PM_{10}**						**1.00**	0.88	0.49	0.22
	$PM_{2.5}$							**1.00**	0.62	0.14
	NO_2								**1.00**	0.17
Noise	**L_{night}**									**1.00**

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4.3 Main Regression Analyses

4.3.1 Point-Specific Exposure Assessment (ESCAPE-LUR) - Cross-Sectional Analyses

In general, AP exposure was positively associated with prevalent MetS, but these associations weakened towards the null upon increasing covariate adjustment (Table 12 & Figure 10). In the crude model, all air pollutants were significantly positively associated with MetS prevalence. Upon full adjustment (model 2), the estimate for NO_2 remained significantly elevated with an OR of 1.12 (95%-CI 1.02-1.24) per IQR, while the ORs for particulate air pollutants attenuated to the null. When noise was added to the models, point estimates decreased slightly for all air pollutants, e.g., for NO_2, the OR decreased to 1.09 (95%-CI 0.98-1.21). (Matthiessen et al. 2018)

Table 12: Main analysis of the associations between air pollutants and *prevalent MetS* at baseline per IQR using the *ESCAPE-LUR* exposure model, n=4,457. Ruhr Area, 2017, Heinz Nixdorf Recall Study.

	IQR	Crude[A] OR (95%-CI)	Model 1[B] OR (95%-CI)	Model 2[C] OR (95%-CI)	Model 2 + Noise OR (95%-CI)
PM_{10}	2.1	1.11 (1.03-1.21)	1.03 (0.94-1.13)	1.02 (0.93-1.11)	0.99 (0.90-1.09)
$PM_{2.5}$	1.5	1.21 (1.10-1.34)	1.08 (0.96-1.22)	1.07 (0.94-1.20)	1.04 (0.92-1.17)
PM_{coarse}	1.9	1.12 (1.03-1.21)	1.05 (0.96-1.14)	1.04 (0.96-1.13)	1.03 (0.94-1.12)
$PM_{2.5}$ abs	0.4	1.10 (1.03-1.17)	1.04 (0.97-1.12)	1.03 (0.96-1.11)	1.00 (0.92-1.08)
NO_2	6.1	1.23 (1.12-1.34)	1.14 (1.03-1.25)	1.12 (1.02-1.24)	1.09 (0.98-1.21)

[A]+ Air pollutant, [B]Crude + Age, sex, and individual and neighborhood SES, [C]Model 1 + Lifestyle variables (smoking status, cumulative smoking, environmental tobacco smoking, Nutrition, and physical activity)

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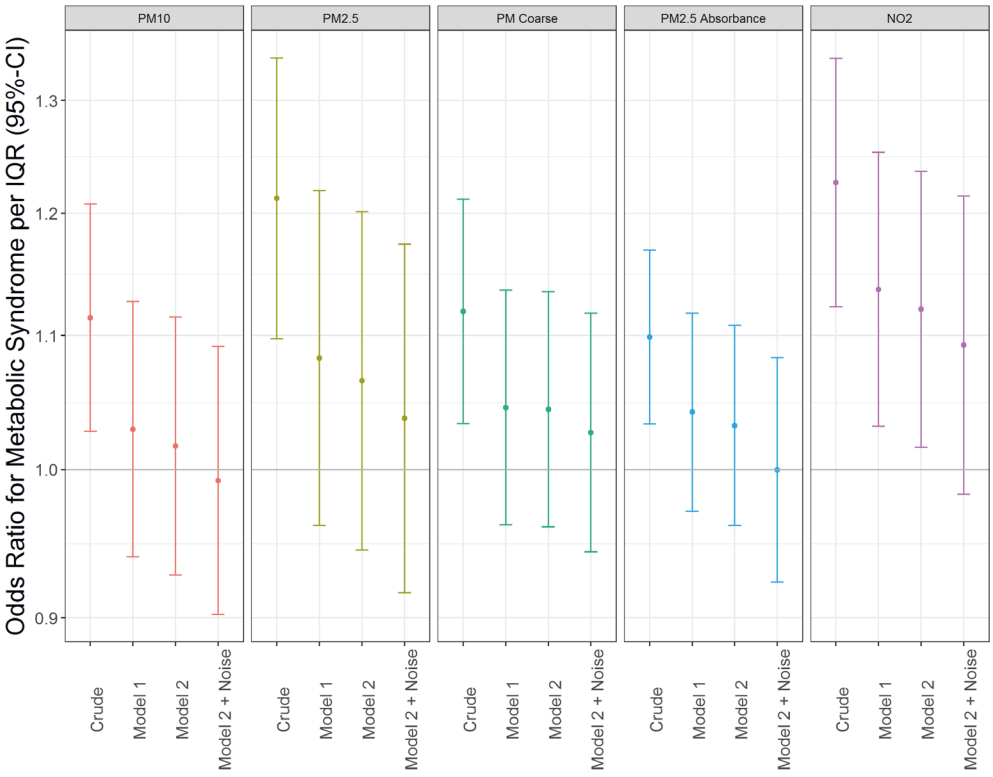

Figure 10: Effect estimates for the associations between air pollutants and prevalent MetS at baseline per IQR using the ESCAPE-LUR model. Ruhr Area, 2017, Heinz Nixdorf Recall Study, n=4,457.

4.3.2 Point-Specific Exposure Assessment (ESCAPE-LUR) - Longitudinal Analyses

In general, exposure to AP was positively associated with incident MetS (Table 13 & Figure 11). „Effects were strongest for PM_{10} and $PM_{2.5}$ compared to the other air pollutants. In the fully adjusted model 2, the ORs for PM_{10} and $PM_{2.5}$ were 1.14 (95%-CI 0.99-1.32) per IQR and 1.19 (95%-CI 0.98-1.44) per IQR, respectively. No associations were seen for PM_{coarse}, $PM_{2.5}$abs, and NO_2 in model 2. When noise was added to the model, associations increased slightly for all pollutants (e.g., $PM_{2.5}$: 1.21 (95%-CI 0.99-1.48))“ (Matthiessen et al. 2018) (Table 13).

Table 13: Main analysis of the associations between air pollutants and *incident MetS* at first follow-up per IQR using the *ESCAPE-LUR* exposure model, n=3,074. Ruhr Area, 2017, Heinz Nixdorf Recall Study.

	IQR	Crude[A] OR (95%-CI)	Model 1[B] OR (95%-CI)	Model 2[C] OR (95%-CI)	Model 2 + Noise OR (95%-CI)
PM_{10}	2.1	1.19 (1.05-1.36)	1.15 (1.00-1.33)	1.14 (0.99-1.32)	1.16 (1.00-1-35)
$PM_{2.5}$	1.5	1.26 (1.07-1.48)	1.21 (1.00-1.46)	1.19 (0.98-1.44)	1.21 (0.99-1.48)
PM_{coarse}	1.9	1.13 (0.98-1.29)	1.08 (0.94-1.24)	1.08 (0.94-1.24)	1.09 (0.95-1.26)
$PM_{2.5}$abs	0.4	1.06 (0.96-1.17)	1.02 (0.91-1.14)	1.00 (0.90-1.12)	1.02 (0.90-1.16)
NO_2	6.1	1.13 (0.98-1.30)	1.06 (0.90-1.24)	1.03 (0.88-1.21)	1.06 (0.89-1.25)

[A]+ Air pollutant, [B]Crude + Age, sex, and individual and neighborhood SES, [C]Model 1 + Lifestyle variables (smoking status, cumulative smoking, environmental tobacco smoking, nutrition, and physical activity)

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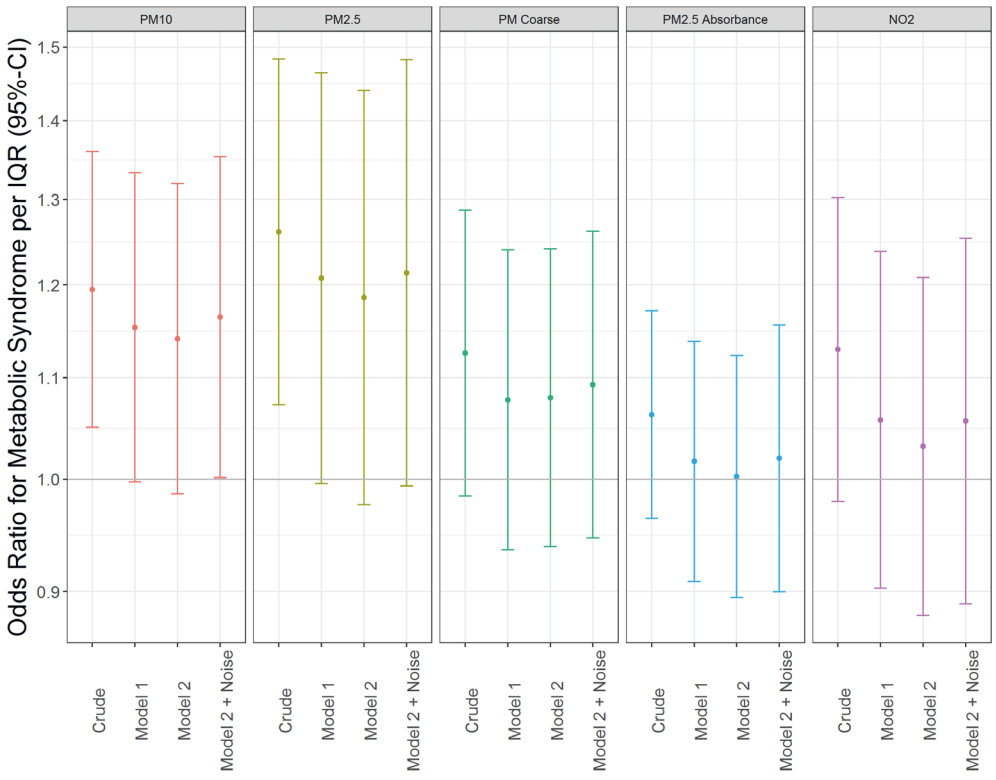

Figure 11: Effect estimates for the association between air pollutants and incident MetS at first follow-up per IQR using the ESCAPE-LUR exposure model. Ruhr Area, 2017, Heinz Nixdorf Recall Study, n=3,074.

4.3.3 Urban Background Exposure Assessment (EURAD-CTM) - Cross-Sectional Analyses

In general, exposure to AP was positively associated with prevalent MetS, but these associations weakened towards the null with increasing covariate adjustment (Table 14 & Figure 12). In the crude model, all air pollutants were significantly positively associated with MetS prevalence. In the fully adjusted model 3, the ORs for $PM_{2.5}$ and NO_2 continued to be significantly positive associated with MetS prevalence, with an OR of 1.16 (95%-CI 1.03-1.30) per IQR and 1.14 (95%-CI 1.03-1.26) per IQR, respectively. For PM_{10}, the association with prevalent MetS was of borderline significance in model 3, with an OR of 1.11 (95%-CI 0.99-1.25) per IQR. The positive associations for $PM_{2.5}$ and NO_2 were robust to adjustment for noise. (Matthiessen et al. 2018)

Table 14: Main analysis of the associations between air pollutants and *prevalent MetS* at baseline per IQR using the *EURAD-CTM* exposure model, n=4,457. Ruhr Area, 2017, Heinz Nixdorf Recall Study.

	IQR	Crude[A] OR (95% CI)	Model 1[B] OR (95% CI)	Model 2[C] OR (95% CI)	Model 3[D] OR (95% CI)	Model 3 + Noise OR (95% CI)
PM_{10}	4.2	1.17 (1.04-1.31)	1.12 (1.00-1.26)	1.11 (0.99-1.25)	1.11 (0.99-1.25)	1.09 (0.96-1.23)
$PM_{2.5}$	2.1	1.16 (1.04-1.30)	1.16 (1.03-1.30)	1.16 (1.03-1.30)	1.16 (1.03-1.30)	1.14 (1.01-1.28)
NO_2	5.1	1.19 (1.08-1.30)	1.15 (1.04-1.27)	1.14 (1.03-1.26)	1.14 (1.03-1.26)	1.12 (1.02-1.24)

[A]+ Air Pollutant, [B]Crude + Age, sex, and individual and neighborhood SES, [C]Model 1 + Lifestyle variables (smoking status, cumulative smoking, environmental tobacco smoking, nutrition, and physical activity), [D]Model 2 + Traffic indicator

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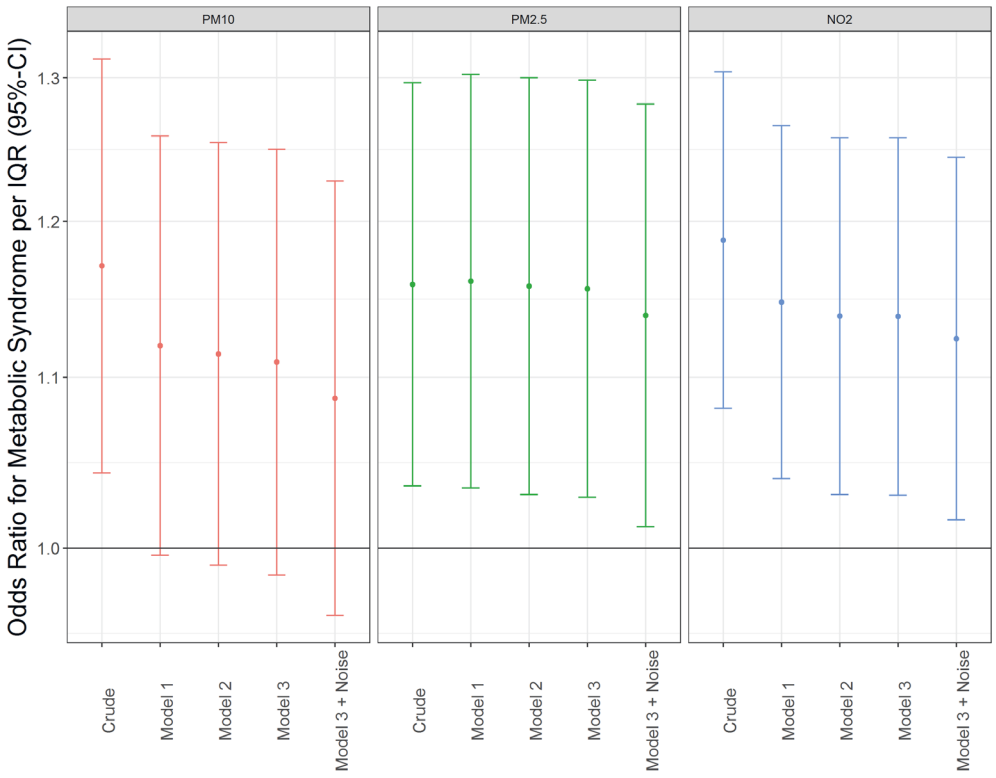

Figure 12: Effect estimates for the association between air pollutants and prevalent MetS at baseline per IQR using the EURAD-CTM exposure model. Ruhr Area, 2017, Heinz Nixdorf Recall Study, n=4,457.

4.3.4 Urban Background Exposure Assessment (EURAD-CTM) - Longitudinal Analyses

Overall, no clear association was found between AP and MetS incidence. Although all effect estimates for the association between AP and incident MetS were positive, confidence intervals included the null-value for all models and air pollutants (Table 15 & Figure 13). For example, the OR per IQR of PM_{10} was 1.10 (95%-CI 0.91-1.33) in model 3. When noise was added to the model, effects were similar to model 3. (Matthiessen et al. 2018)

Table 15: Main analysis of the associations between air pollutants and *incident MetS* at first follow-up per IQR using the *EURAD-CTM* exposure model, n=3,074. Ruhr Area, 2017, Heinz Nixdorf Recall Study.

	IQR	Crude[A] OR (95% CI)	Model 1[B] OR (95% CI)	Model 2[C] OR (95% CI)	Model 3[D] OR (95% CI)	Model 3 + Noise OR (95% CI)
PM_{10}	4.1	1.15 (0.95-1.39)	1.11 (0.92-1.34)	1.10 (0.91-1.32)	1.10 (0.91-1.33)	1.12 (0.92-1.36)
$PM_{2.5}$	2.2	1.11 (0.92-1.34)	1.10 (0.91-1.34)	1.09 (0.90-1.32)	1.11 (0.91-1.34)	1.12 (0.92-1.34)
NO_2	5.1	1.13 (0.97-1.31)	1.09 (0.93-1.28)	1.09 (0.93-1.27)	1.09 (0.93-1.27)	1.10 (0.93-1.29)

[A]+ Air Pollutant, [B]Crude + Age, sex, and individual and neighborhood SES, [C]Model 1 + Lifestyle variables (smoking status, cumulative smoking, environmental tobacco smoking, nutrition, and physical activity), [D]Model 2 + Traffic indicator

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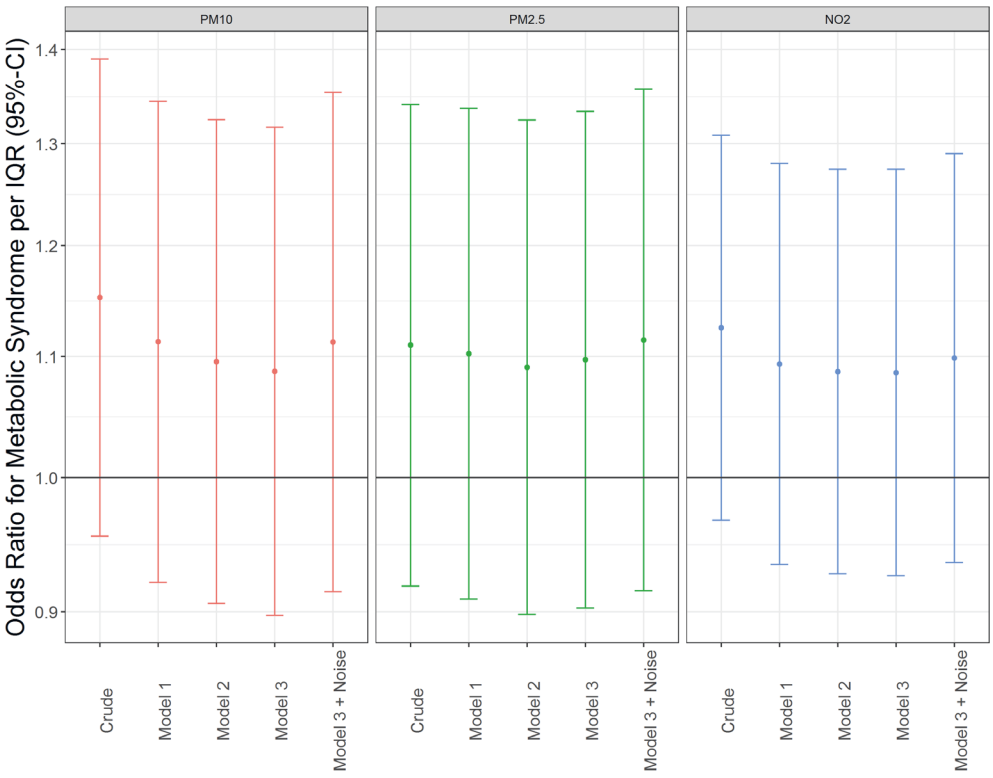

Figure 13: Effect estimates for the associations between air pollutants and incident MetS at first follow-up per IQR using the EURAD-CTM exposure model. Ruhr Area, 2017, Heinz Nixdorf Recall Study, n=3,074.

4.4 Sensitivity Analysis

4.4.1 Exposure Misclassification

MetS prevalence and incidence did not vary extensively when different sensitivity analysis were performed, MetS prevalence was between 20.4% to 23.5%, and MetS incidence was between 9.7% to 10.0% (Table 16 & 17). After restricting to participants who did not relocate between t_0 and t_1, results did not change substantially compared to the main analyses (Table 16 & 17). However, when restricting to those who did not relocate five years before t_0 or to participants who worked less than half-time, results were attenuated compared to the main analyses (Table 16 & 17). (Matthiessen et al. 2018)

Table 16: Sensitivity analyses of *exposure misclassification* for the association between AP and *prevalent MetS* at baseline per IQR, using the main adjustment set (model 2) and the *ESCAPE-LUR* exposure model. Ruhr Area, 2017, Heinz Nixdorf Recall Study.

Sensitivity Analysis	AP	Model 2[A] OR (95%-CI)
Main Analysis from Table 12. MetS prevalence: 20,7%, n=4,457	PM_{10}	1.02 (0.93-1.11)
	$PM_{2.5}$	1.07 (0.94-1.20)
	NO_2	1.12 (1.02-1.24)
Analysis restricted to participants who did not move between t_0 and t_1. MetS prevalence: 21%, n=3,739	PM_{10}	1.02 (0.93-1.13)
	$PM_{2.5}$	1.07 (0.94-1.21)
	NO_2	1.16 (1.04-1.29)
Analysis restricted to participants who did not move in the 5 years before t_0. MetS prevalence: 20.4%, n=2,715	PM_{10}	0.98 (0.87-1.10)
	$PM_{2.5}$	1.05 (0.89-1.25)
	NO_2	1.07 (0.94-1.23)
Analysis excluding participants working >15h/week. MetS prevalence: 23.5%, n=2,739	PM_{10}	1.00 (0.89-1.12)
	$PM_{2.5}$	1.04 (0.89-1.20)
	NO_2	1.09 (0.96-1.23)

[A]+ Air pollutant, age, sex, individual and neighborhood SES, and lifestyle variables (smoking status, cumulative smoking, environmental tobacco smoking, nutrition, and physical activity)

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Table 17: Sensitivity analyses of *exposure misclassification* for the association between AP and *incident MetS* at first follow-up per IQR, using the main adjustment set (model 2) and the *ESCAPE-LUR* exposure model. Ruhr Area, 2017, Heinz Nixdorf Recall Study.

Sensitivity Analysis	AP	Model 2[A] OR (95%-CI)
Main Analysis from Table 13. MetS prevalence: 9,7%, n=3,074	PM_{10}	1.14 (0.98-1.32)
	$PM_{2.5}$	1.19 (0.98-1.44)
	NO_2	1.03 (0.88-1.21)
Analysis restricted to participants who did not move between t_0 and t_1. MetS incidence: 9.8%, n=2,573	PM_{10}	1.10 (0.94-1.30)
	$PM_{2.5}$	1.17 (0.94-1.44)
	NO_2	1.01 (0.85-1.20)
Analysis restricted to participants who did not move in the 5 years before t_0. MetS incidence: 9.9%, n=1,892	PM_{10}	1.10 (0.91-1.33)
	$PM_{2.5}$	1.09 (0.83-1.44)
	NO_2	0.89 (0.72-1.10)
Analysis excluding participants working >15h/week. MetS incidence: 10.0%, n=1,754	PM_{10}	1.07 (0.87-1.30)
	$PM_{2.5}$	1.08 (0.83-1.41)
	NO_2	1.00 (0.81-1.24)

[A]+ Air pollutant, age, sex, individual and neighborhood SES, and lifestyle variables (smoking status, cumulative smoking, environmental tobacco smoking, nutrition, and physical activity)

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4.4.2 Outcome Misclassification

For MetS prevalence and incidence, the highest estimates were found for the IDF definition (MetS prevalence 54.2% and MetS incidence 29.8%), while the lowest MetS prevalence (21.4%) and incidence (9.0%) were observed when using self-reported hypertension or known pharmacological treatment as the criteria for "elevated BP" (Table 18 & 19).

Overall, sensitivity analyses for outcome misclassification supported the main analyses of a positive association between air pollutants and prevalent MetS (Table 18). For all analyses, exposure to NO_2 was positively associated with MetS prevalence, with the strongest effect seen when the criteria for "elevated BP" was changed. For the incident MetS analyses, effect estimates were not very robust to variation in the definition of MetS, as they were either attenuated or slightly negative (Table 19). (Matthiessen et al. 2018)

Table 18: Sensitivity analyses of *outcome misclassification* for the association between AP and *prevalent MetS* at baseline per IQR, using the main adjustment set (model 2) and the *ESCAPE-LUR* exposure model. Ruhr Area, 2017, Heinz Nixdorf Recall Study.

Sensitivity Analysis, n=2,629	AP	Model 2[A] OR (95%-CI)
Main outcome definition. MetS prevalence: 23.5%	PM_{10}	0.98 (0.88-1.10)
	$PM_{2.5}$	1.03 (0.90-1.20)
	NO_2	1.12 (0.99-1.27)
Outcome definition in accordance with the IDF definition. MetS prevalence: 54.2%	PM_{10}	1.04 (0.94-1.15)
	$PM_{2.5}$	1.10 (0.96-1.25)
	NO_2	1.04 (0.93-1.16)
Outcome definition in accordance with the ATP III definition. MetS prevalence: 36.5%	PM_{10}	1.06 (0.96-1.17)
	$PM_{2.5}$	1.10 (0.96-1.25)
	NO_2	1.12 (1.00-1.25)
"Elevated BP" cutpoint changed to ≥140/90 mmHg. MetS prevalence: 22.2%	PM_{10}	0.99 (0.88-1.11)
	$PM_{2.5}$	1.05 (0.90-1.22)
	NO_2	1.13 (0.99-1.28)
"Elevated BP" criteria changed to only self-reported hypertension or taking pharmacological treatment. MetS prevalence: 21.4%	PM_{10}	1.01 (0.90-1.13)
	$PM_{2.5}$	1.04 (0.89-1.21)
	NO_2	1.13 (1.00-1.29)

[A]+ Air pollutant, age, sex, individual and neighborhood SES, and lifestyle variables (smoking status, cumulative smoking, environmental tobacco smoking, nutrition, and physical activity)

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Table 19: Sensitivity analyses of *outcome misclassification* for the association between AP and *incident MetS* at first follow-up per IQR, using the main adjustment set (model 2) and the *ESCAPE-LUR* exposure model. Ruhr Area, 2017, Heinz Nixdorf Recall Study.

Sensitivity Analysis	AP	Model 2[A] OR (95%-CI)
Main outcome definition from Table 15. MetS incidence: 9.7%, n=3,074	PM_{10}	1.14 (0.98-1.32)
	$PM_{2.5}$	1.19 (0.98-1.44)
	NO_2	1.03 (0.88-1.21)
Outcome definition in accordance with the IDF definition. MetS incidence: 29,8%, n= 1,689	PM_{10}	0.98 (0.85-1.12)
	$PM_{2.5}$	1.01 (0.85-1.21)
	NO_2	0.96 (0.84-1.11)
Outcome definition in accordance with the ATP III definition. MetS incidence: 20.9%, n=2,249	PM_{10}	0.90 (0.79-1.04)
	$PM_{2.5}$	0.91 (0.77-1.08)
	NO_2	0.96 (0.84-1.10)
"Elevated BP" cutpoint changed to ≥140/90 mmHg. MetS incidence: 9.7%, n=3,114	PM_{10}	1.11 (0.96-1.29)
	$PM_{2.5}$	1.15 (0.94-1.39)
	NO_2	1.02 (0.87-1.20)
"Elevated BP" criteria changed to only self-reported hypertension or taking pharmacological treatment. MetS incidence: 9.0%, n=3,132	PM_{10}	1.07 (0.92-1.24)
	$PM_{2.5}$	1.10 (0.90-1.35)
	NO_2	1.03 (0.88-1.21)

[A]+ Air pollutant, age, sex, individual and neighborhood SES, and lifestyle variables (smoking status, cumulative smoking, environmental tobacco smoking, nutrition, and physical activity)

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4.4.3 AP and Relative Risk of Incident MetS

Similar to the main analyses with logistic regression, positive effect estimates were observed for the association between AP and incident MetS using Poisson regression, with weakening of the effects towards the null with increasing covariate adjustment (Table 20 & Figure 14). All effect estimates were slightly attenuated compared to the main analyses, e.g., for $PM_{2.5}$, the OR was 1.19 (95%-CI 0.98-1.44) and the RR was 1.16 (95%-CI 0.97-1.39) per IQR in model 2. Similar to the main analysis, associations increased slightly for all pollutants when noise was added to the model. Even though effect estimates were slightly attenuated when using Poisson regression compared to the main analyses, results did not fundamentally change.

Table 20: Sensitivity analyses of the associations between air pollutants and *incident MetS* at first follow-up per IQR, using a modified Poisson regression and the *ESCAPE-LUR* exposure model, n=3,074. Ruhr Area, 2017, Heinz Nixdorf Recall Study.

	IQR	Crude[1] RR (95%-CI)	Model 1[2] RR (95%-CI)	Model 2[3] RR (95%-CI)	Model 2 + Noise RR (95%-CI)
PM_{10}	2.1	1.17 (1.04-1.32)	1.13 (0.99-1.30)	1.12 (0.98-1.28)	1.14 (1.00-1-31)
$PM_{2.5}$	1.5	1.23 (1.06-1.42)	1.18 (0.99-1.42)	1.16 (0.97-1.39)	1.19 (0.99-1.43)
NO_2	6.1	1.12 (0.99-1.26)	1.05 (0.92-1.20)	1.03 (0.90-1.17)	1.05 (0.91-1.21)

[1]+ Air pollutant, [2]Crude + Age, sex, and individual and neighborhood SES, [3]Model 1 + Lifestyle variables (smoking status, cumulative smoking, environmental tobacco smoking, nutrition, and physical activity)

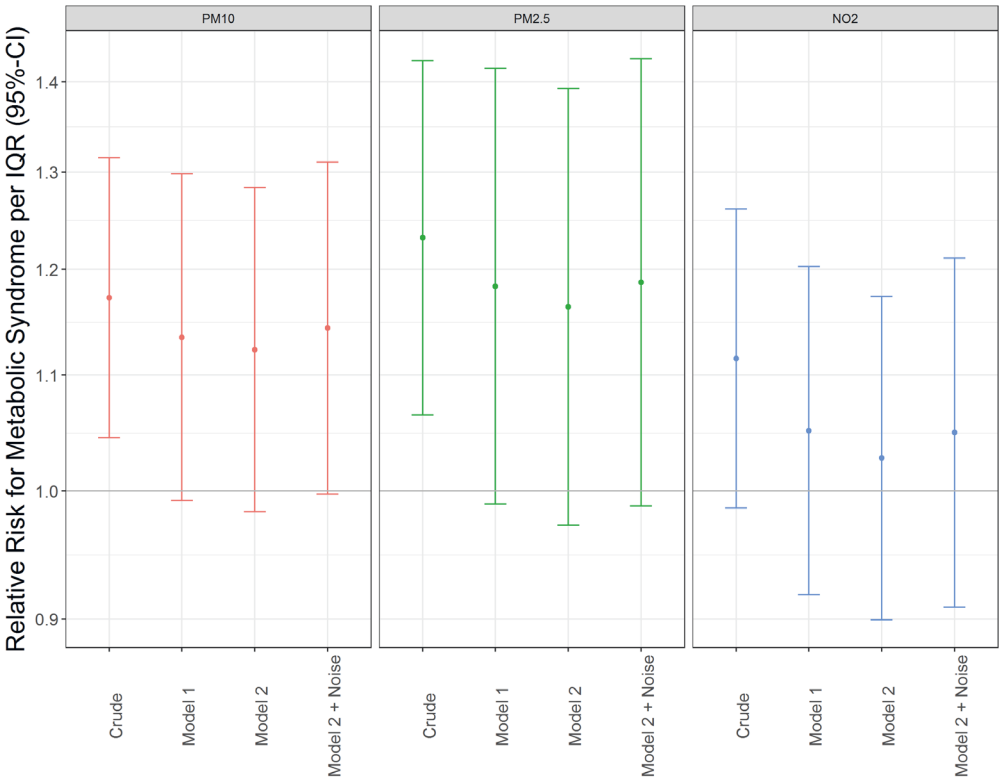

Figure 14: Effect estimates for the associations between air pollutants and incident MetS at first follow-up per IQR using the ESCAPE-LUR exposure model. Ruhr Area, 2017, Heinz Nixdorf Recall Study, n=3,074.

5 Discussion

„In general, our results suggest that a weak positive association may exist between long-term AP exposure and prevalent and incident MetS, with most consistent associations apparent between NO_2 and prevalent MetS. PM_{10} and $PM_{2.5}$ exposures were most strongly associated with incident MetS [...]“ (Matthiessen et al. 2018).

5.1 Comparison to Prior Literature

Little evidence is available so far about the relationship between air pollution exposure and MetS (prevalent or incident). Two prior studies have observed associations between at least one air pollutant and *prevalent MetS* (Eze et al. 2015) or *incident MetS* (Wallwork et al. 2016). Even though these two studies and our own work differ by study population, level of air pollution exposure, main air pollution sources and composition, and MetS definition, they all show associations between AP exposure and MetS.

Prevalent MetS: Eze et al. (2015) observed ORs of 1.21 (95%-CI 0.99-1.49) and 1.10 (95%-CI 0.97-1.24) per 10 µg/m³ for PM_{10} and NO_2, respectively, using the IDF definition for MetS. Similar to our results, the estimates in the Swiss study were sensitive to different outcome definitions with an attenuation of estimates when using the ATP III definition (ORs per 10 µg/m³: PM_{10} 1.10 (95% 0.98-1.24); NO_2 1.01 (95% CI 0.93-1.09)) (Eze et al. 2015). The size of our effect estimates for NO_2 are in line with the results from Eze et al. (2015), showing an increase in the odds of MetS prevalence of approximately 20% to 29% per 10 µg/m³. While our findings do not suggest an association between PM_{10} and MetS prevalence using the ESCAPE-LUR exposure model (OR for PM_{10}: 1.08 (95% CI 0.70-1.67) per 10 µg/m³), we did observe a positive association similar to Eze et al. (2015) using the urban background particle mass concentration as modeled with the EURAD-CTM (OR for PM_{10}: 1.29 (95% CI 0.98-1.71) per 10 µg/m³).

Incident MetS: Our results for incident MetS were slightly weaker than those observed by Wallwork et al. (2016) in a cohort of elderly men in a low-exposure setting between 2000-2011. The investigators conducted a time-to-event analysis with 517 observations and 140 incident MetS cases (Wallwork et al. 2016). They found a hazard ratio of 1.27 (95%-CI 1.06-1.52) per 1 µg/m³ for $PM_{2.5}$ using the ATP III definition, while our analysis showed an odds ratio of 1.12 (95% CI 0.98-1.28) per 1 µg/m³ for $PM_{2.5}$ modeled with the ESCAPE-LUR and an odds ratio of 1.04 (95% CI 0.95-1.14) for $PM_{2.5}$ modeled with the EURAD-CTM exposure model.

Overall, our study partially supports the findings of the above-mentioned studies and adds to the current knowledge by strengthening the evidence for an association between air pollution and MetS. Specifically, the associations of NO_2 and $PM_{2.5}$ with MetS point to the possibility that traffic-related air pollution might be an important fraction of the overall air pollution mixture. (Matthiessen et al. 2018)

5.2 Exposure Models

Our results revealed that health effect estimates differ by exposure modeling techniques. While we observed stronger observations between air pollutants modeled with *EURAD-CTM* and prevalent MetS, air pollutants modeled with the *ESCAPE-LUR model* showed stronger associations with incident MetS. One possible explanation may be the modeling differences. First, the EURAD-CTM models grid-based, urban background air pollution concentrations, while the ESCAPE-LUR model estimates are point-specific (Hennig et al. 2016). Urban background exposures averaged over a 1 km^2 grid cell represent different pollution mixtures than point-specific estimates, such as those modeled with a land use regression model. Second, the pattern of exposure misclassification is different, since even small differences in distances to a major road can lead to substantial changes in exposure estimates when using the land use regression model, while the grid-based estimates are the same for all subjects within one grid cell. Furthermore, the time of exposure assessment varies between the two exposure models. While the CTM models hourly exposures, which can then be averaged over the relevant exposure time (e.g., the years 2001-2003 during which the baseline examination was conducted), the land use regression model is based on measurements that were conducted from 2008 to 2009. While LUR-based exposure estimates are generally quite stable over time periods of up to 15 years, misclassification can occur if changes in the emissions occur (for example, restricted access zones). Due to these differences between exposure assessment models, different misclassification patterns may help explain the heterogeneity of the results.

5.3 Noise as a Potential Confounder

Among different environmental noise sources, road traffic presents the most dominant source of noise in Europe (EEA 2010). Since air pollution and noise exposure share some common sources, such as road transport, the role of noise as a potential confounder has become more important in recent years (Stansfeld 2015).

In this analysis, noise and air pollution exposure were only weakly to moderately correlated (r=0.14-0.48), with the highest correlation seen between noise and $PM_{2.5}$abs (a proxy for soot and black carbon) (Table 11). Noise did not act as a relevant confounder in our analysis. Both AP and noise exposure increase systemic inflammation, oxidative stress, and the activation of the sympathetic nervous system. On the other hand, noise perception as a psychological stressor is somewhat subjective (e.g., sleep disturbance, arousal), whereas AP acts unconsciously (Münzel et al. 2016). Noise is influenced strongly by noise barriers and buildings, whereas AP dispersion is highly dependent on meteorological conditions (Stansfeld 2015), which may explain the relatively low correlations we observed between noise and air pollution exposures. Therefore, exposure to AP and noise may have affected our participants differently. In addition, the noise exposure variable might not have been precise enough. Because noise was assessed only as outdoor noise in this study (see also 3.2.4.) and other factors such as noise annoyance and indoor noise might be important factors for the association between noise and metabolic health, the noise variable used may not reflect the true noise exposure of study participants.

5.4 Outcome

A common definition of MetS remains undecided, and discussions about inclusion criteria and cutpoints are ongoing (Alberti et al. 2009). „While Wallwork et al. (2016) used the ATP III definition, Eze et al. (2015) used both the ATP III and IDF definitions as well as the definition from the WHO. The uncertainty of the MetS definition led to our extensive sensitivity analyses with different outcome criteria (Table 18 & 19). Overall, the associations between AP and prevalent MetS were more robust to changes in MetS definition than those for incident MetS“ (Matthiessen et al. 2018).

When the IDF definition was used, estimated associations between air pollution exposure and MetS prevalence were attenuated compared to the main outcome definition, while use of the ATP III definition and stricter “elevated BP” criteria yielded similar or slightly higher effect estimates (Table 18) (Matthiessen et al. 2018). In addition, the IDF definition had highest MetS prevalence (54.2%) and incidence (29.8%) compared to the other outcome definitions used in sensitivity analyses. Further, the IDF definition has stricter waist circumference criteria compared to the ATP III definition, even when using ethnic- and sex-specific values. Compared to the known MetS prevalence estimates for Germany (see 1.2.2), MetS prevalence in our cohort using the IDF definition seems very high, potentially suggesting the inclusion of false positive MetS cases.

In summary, the effect estimates for prevalent and incident MetS were highly dependent on the exact definition of MetS in our analyses. This variability is supported by the findings of Eze et al. (2015), who also found differences in OR by MetS definition, with the WHO definition having the highest OR and the ATP III definition having the lowest OR. (Matthiessen et al. 2018)

5.5 Selection of the study population

Several mechanisms of selection of the study population took place in this study, which might have contributed to various forms of bias. (Matthiessen et al. 2018)

The *first* selection occurred during the initial recruitment process (Matthiessen et al. 2018). Stang et al. (2005) released a paper where nonresponders versus participants of the HNR study were compared. Nonresponders were asked to fill in a short questionnaire with basic information on sociodemographic factors and lifestyle indicators. Stang et al (2005) concluded that in comparison to known demographic characteristics within the Ruhr Area, a higher proportion of participants from a high social class and with good health status participated in the HNR cohort (Stang et al. 2005). This has also been found in other cohort studies, where nonresponders tended to be less educated and less healthy compared to responders (Barchielli and Balzi 2002; Brøgger et al. 2003; Korkeila et al. 2001).

The *second* selection occurred due to the exclusion of participants with incomplete data from the cross-sectional analysis. These excluded participants were less educated and older compared to those included in the cross-sectional analysis (Table 7). (Matthiessen et al. 2018)

The *third* selection occurred due to an even higher proportion of study participants excluded for the longitudinal analysis due to loss to follow-up, more participants with missing variables, and inability to assign MetS status (Yes/No) to more participants. While the study population in the cross-sectional analyses (n=4,457) only differed slightly from those excluded due to incomplete data (n=357) (Table 7), the study population included in the longitudinal analysis (n=3,801) was substantially younger, healthier, and less exposed compared to those excluded (n=1,013) (Table 8). (Matthiessen et al. 2018)

In summary, these three important selection processes resulted in a relatively healthy study population. Prior studies have found that vulnerable populations, such as older or multimorbid participants, are more susceptible to the adverse effects of air pollution (Goldberg et al. 2001;

Rückerl et al. 2011; Sacks et al. 2011; Simoni et al. 2015). It may therefore be possible that even the selection during the initial recruitment process, with the HNR participants being healthier and having higher socioeconomic status, may have contributed to weaker estimates in this study compared to the general population in the Ruhr Area for both the cross-sectional and the longitudinal analyses. Furthermore, exclusion processes in the statistical analysis due to incomplete data may also have attenuated estimates towards the null. It may be possible that the greater instability of the effect estimates observed in the longitudinal analysis compared to the cross-sectional analysis was driven by the younger and healthier study population, as selection towards a less vulnerable population was more likely to occur in the longitudinal analysis. This may be one explanation for the greater variability in results for incident MetS compared to prevalent MetS upon adjustment for covariates and in sensitivity analyses. (Matthiessen et al. 2018)

Another explanation for the inconsistencies in the analysis of incident MetS may be that the five year follow-up period was not long enough to develop a sufficient number of MetS cases in this selected group of more healthy participants that were free of disease at baseline. (Matthiessen et al. 2018)

5.6 Air Pollution and its Health Impact on the General Population

While the effect sizes found in this analysis are small compared to other MetS risk factors, such as behavioural risk factors, the fact that air pollution exposure is ubiquitous can lead to a high attributable risk. This phenomenon has been explained in detail by Geoffrey Rose (1985) using smoking as an example. If every individual were to smoke 20 cigarettes per day, most studies would conclude that lung cancer was a genetic disease, since everyone is exposed to smoking. This phenomenon led to the following conclusion: 'The hardest cause to identify is the one that is universally present, for then it has no influence on the distribution of disease.' (Rose 1985). This is also the case with environmental risk factors such as air pollution. If a large number of individuals, or the whole population in the case of air pollution, is exposed to a weak risk factor, it may give rise to more cases of disease than a small number of individuals who are exposed to a strong risk factor (Rose 1985). This theory leads to two prevention strategies: the "high-risk" strategy from clinical medicine that produces interventions appropriate for the particular individual at high risk and the "population" strategy from public health that attempts to lower the mean level of highly prevalent risk factors and thereby shift the entire distribution of exposure in a favorable direction (Rose

1985). The latter is the strategy commonly applied in air quality regulations. It attempts to reduce an unhealthy exposure and to protect the general population from future adverse health effects.

5.7 Future Research Needs

There are several research needs in relation to air pollution and its potential association with MetS. *First*, studies in potentially more susceptible subgroups (e.g., effect modification by sex, age, unhealthy lifestyle, prevalent cardiovascular disease risk factors, or SES) may be beneficial, because MetS prevalence not only varies between age and sex (see 1.2.2), but susceptibility to air pollution and its health impacts also increases in chronically ill individuals (see 1.3.3). *Second*, different combinations of MetS criteria might be interesting to study, since they vary depending on sex and age (see 1.2.2). Different types of MetS (i.e., different combinations of the individual constituents of the syndrome) could be studied in order to assess whether certain combinations are more strongly related to air pollution than others. This might help to explain the partially inconsistent results of this study and could clarify whether MetS should be considered as an outcome itself or different MetS combinations, having partially diverging etiologies, should be considered separately. *Third*, the individual MetS components should be studied in relation to air pollution exposure with the aim to understand more clearly which components are more strongly associated with AP. Within the HNR and other studies, T2D, insulin resistance, and BP have already been studied, and an association with AP has been found in the HNR as well as in several other studies. However, little evidence is currently available for central obesity and dyslipidemia. *Fourth*, source-specific air pollution and its association with MetS should be studied, since specific sources, such as AP from traffic, seem to be more toxic and have greater impact on human health (Hennig et al. 2014; Hoffmann et al. 2007; Weinmayr et al. 2015). *Fifth*, it would be desirable to investigate the long-term effect of AP on incident MetS with longer longitudinal follow-up. *Lastly*, noise as a potential confounder with a more detailed noise assessment of indoor noise and personal perception of noise annoyance may prove to be another interesting avenue to better elucidate the correlation between AP and noise and their mutual impact on NCDs.

5.8 Strengths and Limitations of the Study

The HNR study is a well-characterized, population-based cohort with extensive covariate data, allowing us to adjust for multiple potential confounders. „In addition, we conducted comprehensive sensitivity analyses including different MetS outcome definitions and model

specifications. Furthermore, a thorough investigation of potential differences in study population of participants with complete versus incomplete data was carried out“(Matthiessen et al. 2018). One strength is that we were able to evaluate the association of interest using two comprehensive and complementary exposure assessment models. „We were also able to evaluate whether our estimates were sensitive to adjustment for chronic noise exposure, a covariate that is frequently unavailable in other studies“(Matthiessen et al. 2018).

As mentioned previously, one limitation is the uncertainty of the MetS definition, with results being highly dependent on the exact definition of MetS. Another limitation is that differences between the study populations of the cross-sectional and longitudinal analyses, which may have resulted in the weaker effects observed in the younger and healthier participants of the longitudinal analysis. (Matthiessen et al. 2018)

6 Conclusion

In summary, our results suggest that long-term exposure to AP may be positively associated with MetS in the general population, with most consistent effects observed between NO_2 and prevalent MetS as well as between PM_{10} and $PM_{2.5}$ with incident MetS (Matthiessen et al. 2018). Noise did not substantially confound the estimated AP effects. The main reasons for inconsistencies in the association between AP and incident MetS may have been a stronger selection bias and a relatively short follow-up for this middle-aged to elderly population to develop a sufficient number of MetS cases. Future studies using source-specific AP exposures, identifying particularly susceptible groups, and examining different MetS combinations could help to improve our understanding of the hypothesized mechanisms between AP exposure and MetS as well as the health impacts in the general population.

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8 Appendix

Comparison of Regression Models: DAG-based vs. Based on Knowledge from Prior Studies.

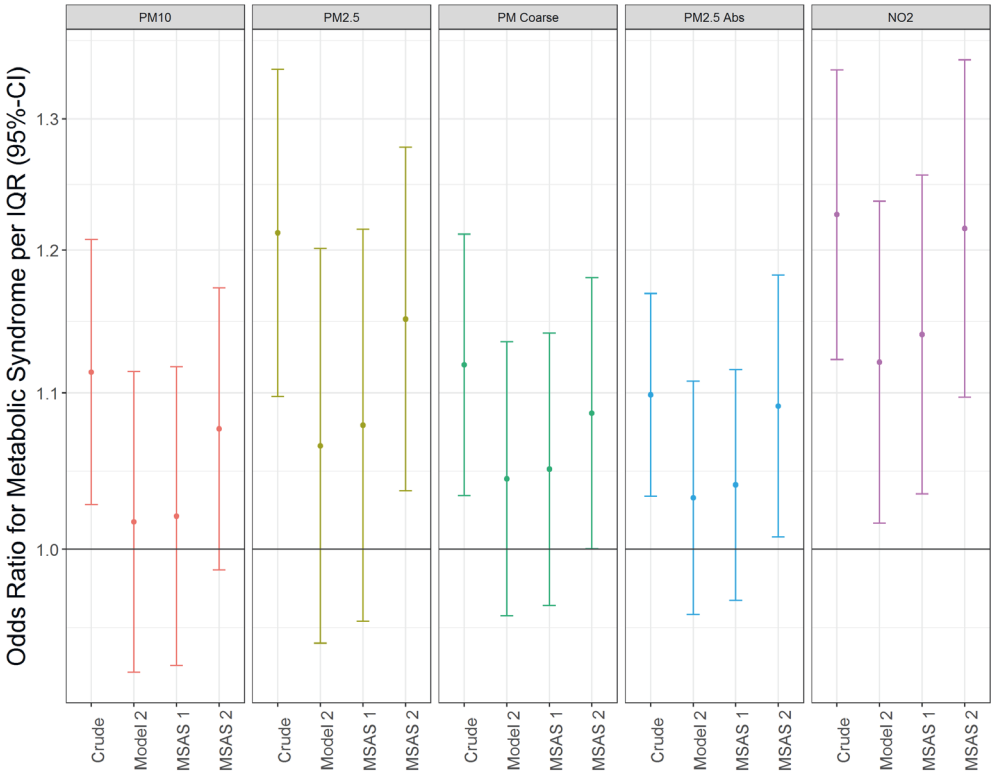

Figure A1 Effect estimates for the associations between air pollutants and prevalent MetS at baseline per IQR using the ESCAPE-LUR exposure model. Ruhr Area, 2017, Heinz Nixdorf Recall Study, n=4,457.
Crude, +Air Pollutant; Model 2, Crude + Age, Sex, Individual and Neighborhood SES, Lifestyle Variables (Smoking Status, Cumulative Smoking, Environmental Tobacco Smoking, and Physical Activity); MSAS 1, Crude + Age, Sex, Neighborhood SES, Nutrition, Physical Activity, Proximity to Major Road, Smoking Status, ETS; MSAS 2, Crude + Individual SES, Proximity to Major Road.

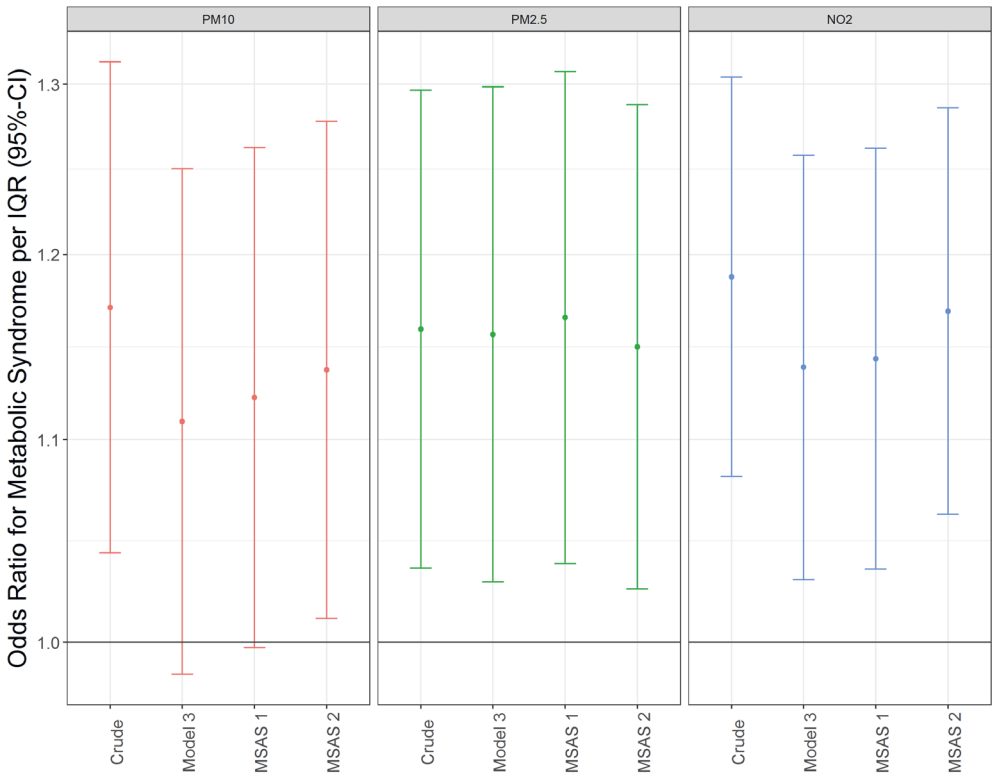

Figure A2: Effect estimates for the associations between air pollutants and prevalent MetS at baseline per IQR using the EURAD-CTM exposure model. Ruhr Area, 2017, Heinz Nixdorf Recall Study, n=4,457.
Crude, +Air Pollutant; Model 3, Crude + Age, Sex, Individual and Neighborhood SES, Lifestyle Variables (Smoking Status, Cumulative Smoking, Environmental Tobacco Smoking, and Physical Activity), Proximity to Major Road; MSAS 1, Crude + Age, Sex, Neighborhood SES, Nutrition, Physical Activity, Proximity to Major Road, Smoking Status, ETS; MSAS 2, Crude + Individual SES, Proximity to Major Road.

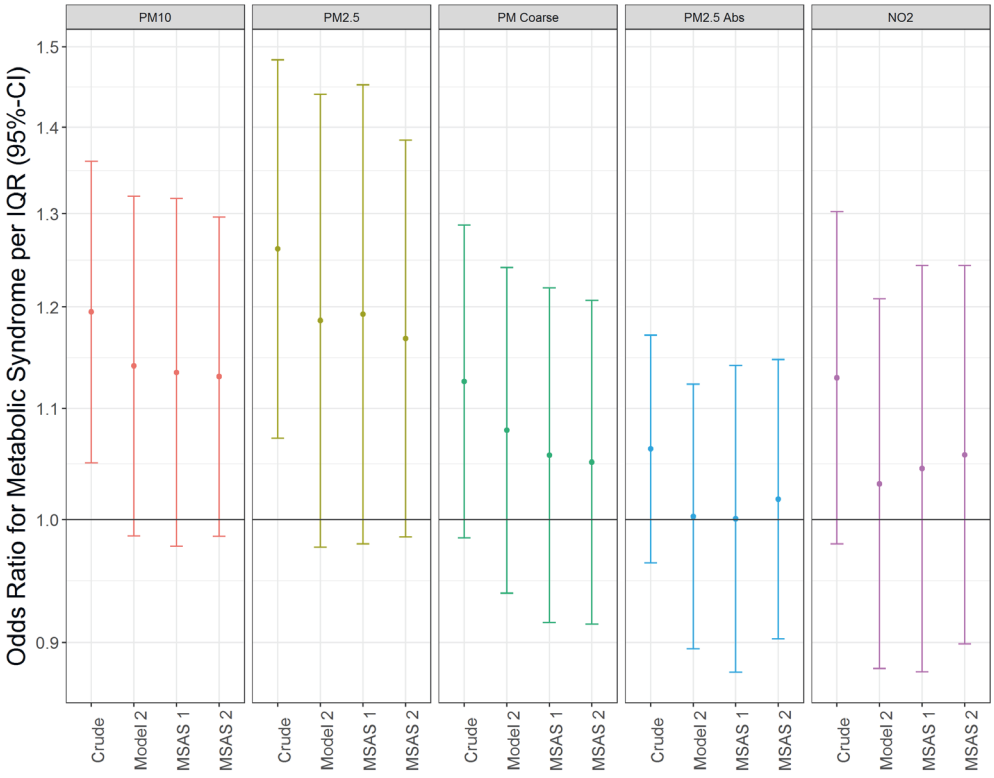

Figure A3: Effect estimates for the associations between air pollutants and incident MetS at first follow-up per IQR using the ESCAPE-LUR exposure model. Ruhr Area, 2017, Heinz Nixdorf Recall Study, n=4,457.
Crude, +Air Pollutant; Model 2, Crude + Age, Sex, Individual and Neighborhood SES, Lifestyle Variables (Smoking Status, Cumulative Smoking, Environmental Tobacco Smoking, and Physical Activity); MSAS 1, Crude + Age, Sex, Neighborhood SES, Nutrition, Physical Activity, Proximity to Major Road, Smoking Status, ETS; MSAS 2, Crude + Individual SES, Proximity to Major Road.

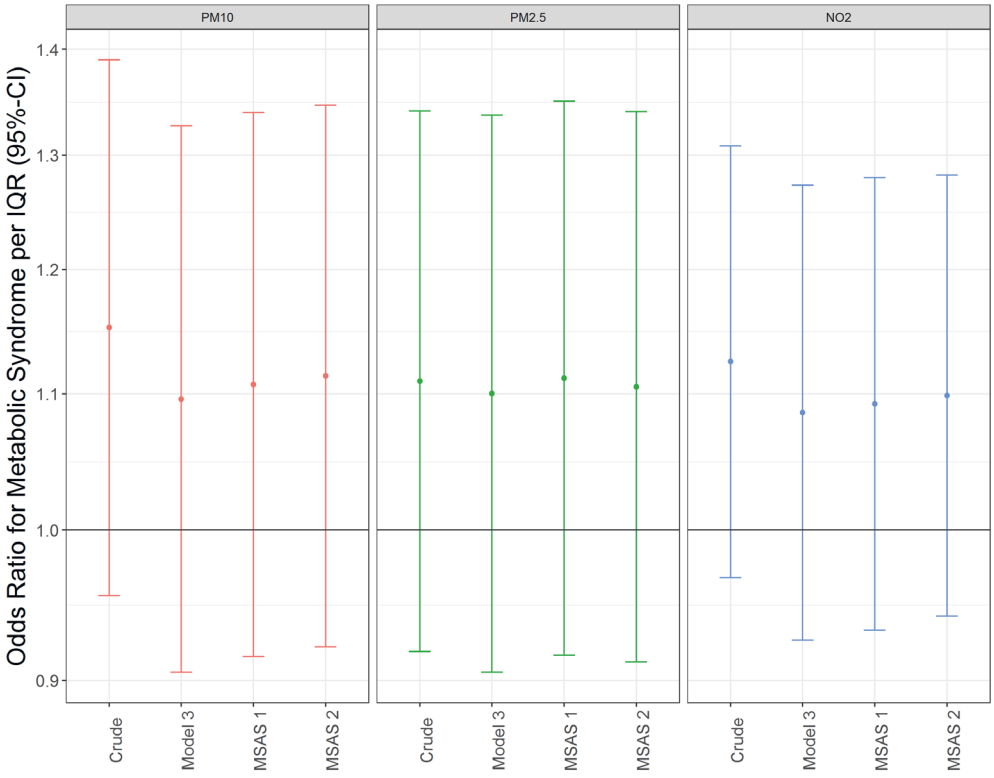

Figure A4: Effect estimates for the associations between air pollutants and incident MetS at first follow-up per IQR using the EURAD-CTM exposure model. Ruhr Area, 2017, Heinz Nixdorf Recall Study, n=4,457.
Crude, +Air Pollutant; Model 3, Crude + Age, Sex, Individual and Neighborhood SES, Lifestyle Variables (Smoking Status, Cumulative Smoking, Environmental Tobacco Smoking, and Physical Activity), Proximity to Major Road; MSAS 1, Crude + Age, Sex, Neighborhood SES, Nutrition, Physical Activity, Proximity to Major Road, Smoking Status, ETS; MSAS 2, Crude + Individual SES, Proximity to Major Road.

Sensitivity Analysis with the Exposure Model EURAD-CTM

Exposure Misclassification

Table A1: Sensitivity analyses concerning *exposure misclassification* for the associations between air pollutants and *prevalent MetS* at baseline per IQR, using the main adjustment set (model 2) and the *EURAD-CTM* exposure model. Ruhr Area, 2017, Heinz Nixdorf Recall Study.

Sensitivity Analysis	AP	Model 2[A] OR (95%-CI)
Main Analysis from Table 14. MetS prevalence: 20.7%, n=4,457	PM_{10}	1.11 (0.99-1.25)
	$PM_{2.5}$	1.16 (1.03-1.30)
	NO_2	1.14 (1.03-1.26)
Analysis restricted to participants who did not move between t_0 and t_1. MetS prevalence: 21%, n=3,739	PM_{10}	1.12 (0.99-1.27)
	$PM_{2.5}$	1.17 (1.02-1.33)
	NO_2	1.15 (1.03-1.28)
Analysis restricted to participants who did not move in the 5 years before t_0. MetS prevalence: 20.4%, n=2,715	PM_{10}	1.13 (0.99-1.27)
	$PM_{2.5}$	1.19 (1.04-1.36)
	NO_2	1.12 (0.98-1.29)
Analysis excluding participants working >15h/week. MetS prevalence: 23.5%, n=2,739	PM_{10}	1.13 (0.98-1.30)
	$PM_{2.5}$	1.14 (0.99-1.32)
	NO_2	1.10 (0.97-1.24)

[A]+ Air Pollutant, age, sex, individual and neighborhood SES, and lifestyle variables (smoking status, cumulative smoking, environmental tobacco smoking, nutrition, and physical activity)

Table A2: Sensitivity analyses concerning *exposure misclassification* for the associations between air pollutants and *incident MetS* at first follow-up per IQR, using the main adjustment set (model 2) and the *EURAD-CTM* exposure model. Ruhr Area, 2017, Heinz Nixdorf Recall Study.

Sensitivity Analysis	AP	Model 2[A] OR (95%-CI)
Main Analysis from Table 15. MetS prevalence: 9,7%, n=3,074	PM_{10}	1.10 (0.91-1.32)
	$PM_{2.5}$	1.09 (0.90-1.32)
	NO_2	1.09 (0.93-1.27)
Analysis restricted to participants who did not move between t_0 and t_1. MetS incidence: 9.8%, n=2,573	PM_{10}	1.08 (0.88-1.34)
	$PM_{2.5}$	1.06 (0.85-1.32)
	NO_2	1.09 (0.92-1.29)
Analysis restricted to participants who did not move in the 5 years before t_0. MetS incidence: 9.9%, n=1,892	PM_{10}	0.96 (0.79-1.17)
	$PM_{2.5}$	0.95 (0.76-1.19)
	NO_2	1.02 (0.81-1.27)
Analysis excluding participants working >15h/week. MetS incidence: 10.0%, n=1,754	PM_{10}	1.05 (0.81-1.35)
	$PM_{2.5}$	1.10 (0.86-1.41)
	NO_2	1.15 (0.93-1.42)

[A]+ Air Pollutant, age, sex, individual and neighborhood SES, and lifestyle variables (smoking status, cumulative smoking, environmental tobacco smoking, nutrition, and physical activity)

Outcome Misclassification

Table A3: Sensitivity analyses concerning *outcome misclassification* for the associations between air pollutants and *prevalent MetS* at baseline per IQR, using the main adjustment set (model 2) and the *EURAD-CTM* exposure model. Ruhr Area, 2017, Heinz Nixdorf Recall Study.

Sensitivity Analysis, n=2,629	AP	Model 2[A] OR (95%-CI)
Main outcome definition. MetS prevalence: 23.5%	PM_{10}	1.08 (0.93-1.25)
	$PM_{2.5}$	1.16 (1.00-1.35)
	NO_2	1.20 (1.05-1.36)
Outcome definition in accordance with the IDF definition. MetS prevalence: 54.2%	PM_{10}	1.06 (0.93-1.21)
	$PM_{2.5}$	1.09 (0.96-1.24)
	NO_2	1.13 (1.02-1.26)
Outcome definition in accordance with the ATP III definition. MetS prevalence: 36.5%	PM_{10}	1.06 (0.93-1.21)
	$PM_{2.5}$	1.11 (0.97-1.26)
	NO_2	1.13 (1.01-1.26)
"Elevated BP" cutpoint changed to ≥ 140/90 mmHg. MetS prevalence: 22.2%	PM_{10}	1.10 (0.95-1.28)
	$PM_{2.5}$	1.20 (1.03-1.39)
	NO_2	1.21 (1.07-1.38)
"Elevated BP" criteria changed to only self-reported hypertension or taking pharmacological treatment. MetS prevalence: 21.4%	PM_{10}	1.06 (0.91-1.24)
	$PM_{2.5}$	1.16 (1.00-1.36)
	NO_2	1.23 (1.08-1.41)

[A]+ Air Pollutant, age, sex, individual and neighborhood SES, and lifestyle variables (smoking status, cumulative smoking, environmental tobacco smoking, nutrition, and physical activity)

Table A4: Sensitivity analyses concerning *outcome misclassification* for the associations between air pollutants and *incident MetS* at first follow-up per IQR, using the main adjustment set (model 2) and the *EURAD-CTM* exposure model. Ruhr Area, 2017, Heinz Nixdorf Recall Study.

Sensitivity Analysis	AP	Model 2[A] OR (95%-CI)
Main outcome definition from Table 15. MetS incidence: 9.7%, n=3,074	PM_{10}	1.10 (0.91-1.32)
	$PM_{2.5}$	1.09 (0.90-1.32)
	NO_2	1.09 (0.93-1.27)
Outcome definition in accordance with the IDF definition. MetS incidence: 29,8%, n=1,689	PM_{10}	0.99 (0.83-1.18)
	$PM_{2.5}$	0.94 (0.80-1.12)
	NO_2	0.95 (0.82-1.08)
Outcome definition in accordance with the ATP III definition. MetS incidence: 20.9%, n=2,249	PM_{10}	0.98 (0.83-1.16)
	$PM_{2.5}$	0.99 (0.84-1.17)
	NO_2	0.98 (0.86-1.12)
"Elevated BP" cutpoint changed to ≥140/90 mmHg. MetS incidence: 9.7%, n=3,114	PM_{10}	1.07 (0.89-1.30)
	$PM_{2.5}$	1.08 (0.89-1.31)
	NO_2	1.06 (0.91-1.24)
"Elevated BP" criteria changed to only self-reported hypertension or taking pharmacological treatment. MetS incidence: 9.0%, n=3,132	PM_{10}	1.05 (0.86-1.27)
	$PM_{2.5}$	1.08 (0.88-1.31)
	NO_2	1.06 (0.90-1.25)

[A]+ Air Pollutant, age, sex, individual and neighborhood SES, and lifestyle variables (smoking status, cumulative smoking, environmental tobacco smoking, nutrition, and physical activity)

Estimating RR

Table A5: Sensitivity analyses of the associations between air pollutants and *incident MetS* at first follow-up per IQR, using a modified Poisson regression and the *EURAD-CTM* exposure model, n=3,074. Ruhr Area, 2017, Heinz Nixdorf Recall Study.

	IQR	Crude[1] RR (95%-CI)	Model 1[2] RR (95%-CI)	Model 2[3] RR (95%-CI)	Model 3[4] RR (95%-CI)	Model 3 + Noise RR (95%-CI)
PM_{10}	4.2	1.14 (0.96-1.35)	1.10 (0.93-1.30)	1.08 (0.91-1.29)	1.08 (0.91-1.29)	1.11 (0.93-1.32)
$PM_{2.5}$	2.1	1.10 (0.93-1.30)	1.09 (0.92-1.30)	1.08 (0.90-1.29)	1.09 (0.92-1.31)	1.11 (0.92-1.31)
NO_2	5.1	1.11 (0.97-1.27)	1.08 (0.94-1.25)	1.08 (0.93-1.24)	1.08 (0.93-1.24)	1.09 (0.94-1.26)

[1]+ Air pollutant, [2]Crude + Age, sex, and individual and neighborhood SES, [3]Model 1 + Lifestyle variables (smoking status, cumulative smoking, environmental tobacco smoking, nutrition, and physical activity), [4]Model 2 + Traffic Indicator

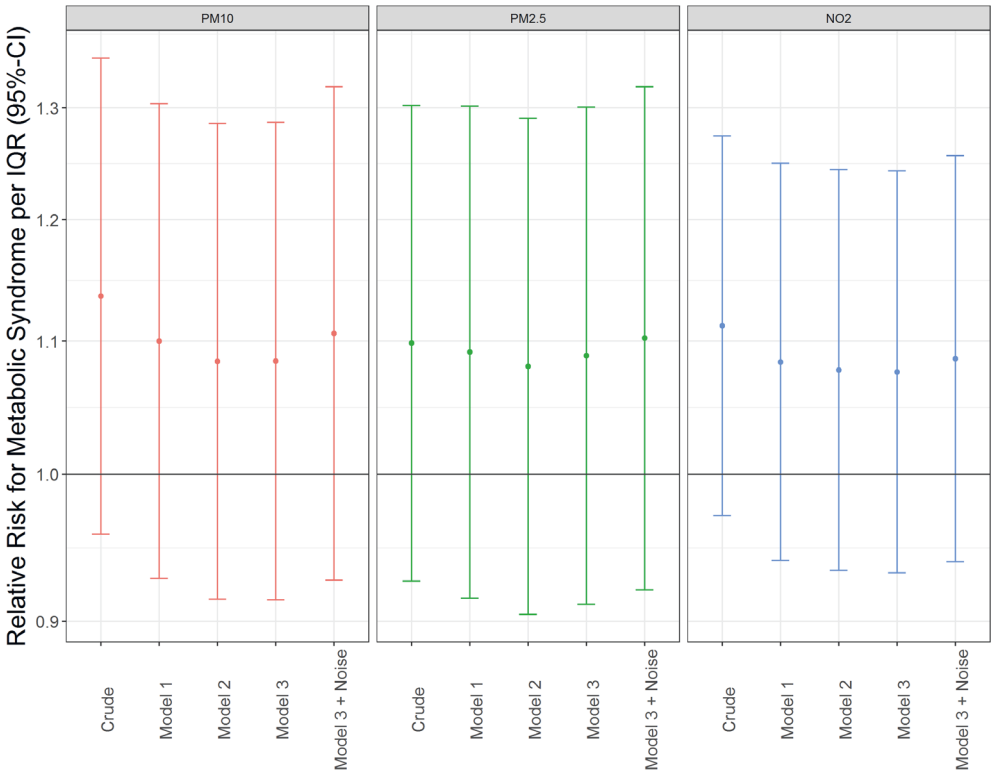

Figure A5: Effect estimates for the associations between different air pollutants and incident MetS at first-follow-up per IQR, using a modified Poisson regression and the EURAD-CTM model. Ruhr Area, 2017, Heinz Nixdorf Recall Study, n=3,074.
Crude, + Air pollutant; Model 1, Crude + Age, sex, and individual and neighborhood SES; Model 2, Model 2 + Lifestyle variables (smoking status, cumulative smoking, environmental tobacco smoking, and physical activity); Model 3 + Traffic Indicator

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