From the Institute for Occupational, Social and Environmental Medicine
at Heinrich Heine University Düsseldorf

Ambient Air Pollution and Diabetes Mellitus

Investigations into Pathways of Inflammation and Altered Metabolism

Dissertation

to obtain the academic title of Doctor of Philosophy (PhD) in Medical Sciences
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submitted by
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To Justin & June, my heart.

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Zusammenfassung

Eine steigende Anzahl von Studien zeigt einen Zusammenhang zwischen der Belastung durch Luftverschmutzung und einem erhöhten Risiko für Diabetes mellitus (DM). Unbekannt ist, ob Luftverschmutzung möglicherweise schon vor dem Eintritt einer manifesten Diabetes-Erkrankung mit Biomarkern für einen gestörten Glukosestoffwechsel assoziiert ist. Die primären Ziele dieser Dissertation waren, (1) die Zusammenhänge zwischen kurz-, mittel-, und langfristiger Luftverschmutzung und Biomarkern der Glukoseregulation und einer Entzündungsreaktion zu untersuchen, (2) die Assoziation zwischen allgemeinen und quellenspezifischen Expositionen und der 10-Jahre DM-Inzidenz zu schätzen sowie (3) die Rolle von Entzündungs- und Stoffwechselmarkern als potenzielle Mediatoren zwischen Luftverschmutzung und der DM-Inzidenz zu untersuchen.

In allen Analysen wurden Teilnehmerdaten aus den Untersuchungen (t_0: 2000-2003; t_1: 2006-2008; t_2: 2011-2015) der prospektiven Heinz Nixdorf Recall-Kohortenstudie verwendet. Für alle Teilnehmer wurde die stündliche Exposition von Feinstaub ($PM_{2.5}$, aerodynamischer Durchmesser ≤ 2.5 µm; PM_{10}, aerodynamischer Durchmesser ≤ 10 µm), Stickstoffdioxid (NO_2), und Partikelanzahlkonzentration (PN_{AM}, aerodynamischer Durchmesser zwischen 0.1 und 1.0 µm) an der Wohnadresse mithilfe des European Air Pollution Dispersion Chemie-Transport-Modells ermittelt. Mittelwerte für allgemeine und quellenspezifische (Verkehr, Industrie) Expositionen wurden als kurz- (1- bis 7-Tage), mittel- (14- bis 182-Tage), und langfristige (365-Tage) Expositionen vor der Blutabnahme berechnet. Wir analysierten wiederholte Messungen von Glukose-Biomarkern (Glukose, glykosilierte Hämoglobin [HbA1c]) und Entzündungsmarkern (Adiponectin, Interleukin-1 Rezeptorantagonist [IL-1RA], hochsensitives C-reaktives Protein [hsCRP], Fibrinogen) von Nichtdiabetikern bei t_0 und t_1 unter Verwendung von linearen gemischten Modellen mit zufälligem Achsenabschnitt pro Proband. Die relativen Risiken für den Zusammenhang zwischen der allgemeinen und quellenspezifischen Luftverschmutzung und der Inzidenz von DM zu t_2 wurden unter Verwendung von Poisson-Regressionsmodellen mit robusten Varianzschätzern berechnet. Mittels Mediationsanalyse wurden natürliche direkte und indirekte Effekte für Adiponectin, IL-1RA, und hsCRP geschätzt. Alle Modelle wurden um potenzielle Störvariablen bereinigt, die auf der Grundlage von Vorwissen und gerichteten azyklischen Graphen identifiziert wurden.

Mittelfristige PM_{10}, $PM_{2.5}$, und PN_{AM} Expositionen waren mit erhöhtem Blutzucker (z.B. 28-Tage $PM_{2.5}$: 0.91 mg/dL [95% Konfidenzintervall (CI): 0.38, 1.44] pro 5.7 µg/m^3) und HbA1c (z.B. 91-Tage $PM_{2.5}$: 0.07 Prozentpunkte [95% CI: 0.04, 0.10] pro 4.0 µg/m^3) assoziiert. Wir beobachteten negative Zusammenhänge zwischen mittelfristiger Luftverschmutzung und Adiponectin (z.B. 91-Tage PN_{AM}: -2.51% [95% CI: -3.40%, -1.53%] pro 1,349 Partikeln/mL); positive Zusammenhänge zwischen kurz-, mittel- und langfristiger Luftverschmutzung und IL-1RA; positive Zusammenhänge zwischen langfristiger Luftverschmutzung und hsCRP; und positive wie negative Zusammenhänge zwischen Luftverschmutzung und Fibrinogen. Langzeit-Exposition gegenüber allen Schadstoffen waren mit einem erhöhten DM-Risiko assoziiert, mit stärkerem Zusammenhang für PM_{10} und PN_{AM} (z.B. relatives Risiko: 1.29 [95% CI: 1.09, 1.52] pro 494 Partikeln/mL PN_{AM}). Alle verkehr- und industriespezifischen Schadstoffe waren mit einem erhöhten DM-Risiko assoziiert, jedoch waren die Zusammenhänge für industriespezifischen PM etwas schwächer. Mediationsanalysen von Luftverschmutzung und DM zeigten eine Mediation durch verringerte Adiponectin-Werte (vermittelter Anteil: 28.7% für PM_{10}).

Schädliche Auswirkungen der Luftverschmutzung auf die kardiometabolische Gesundheit können bereits Tage oder Wochen nach Exposition sichtbar werden, wobei Langzeitveränderungen der Biomarker eine potentielle Rolle für das zunehmende DM-Risiko spielen. Im Zusammenhang mit der Evidenz aus anderen Studien sprechen die Ergebnisse dieser Arbeit dafür dass eine Senkung der Luftverschmutzung durch strengere Richtlinien die DM-Inzidenz reduzieren könnte.

Abstract

Increasing evidence shows a potential link between ambient air pollution exposure and diabetes mellitus (DM), but few studies have investigated whether air pollution exposure alters diabetes-associated biological markers prior to DM development. Additionally, mediation analyses on the topic are rare. The main objectives of this dissertation were to investigate associations between short-, medium-, and long-term air pollution exposure and biomarkers of glucose metabolism and inflammation; to estimate the associations between total and source-specific air pollution exposure and 10-year incidence of DM; and to evaluate the role of inflammatory and metabolic biomarkers as potential mediators of the association between air pollution exposure and incident DM.

Participant data from the examinations (t_0: 2000-2003; t_1: 2006-2008; t_2: 2011-2015) of the prospective Heinz Nixdorf Recall cohort study was utilized in all analyses. Residential air pollution exposures were estimated for each participant at a resolution of 1 km^2 using the European Air Pollution Dispersion chemistry transport model which produces hourly estimates of particulate matter ($PM_{2.5}$, aerodynamic diameter ≤ 2.5 µm; PM_{10}, aerodynamic diameter ≤ 10 µm), nitrogen dioxide (NO_2), and accumulation mode particle number concentration (PN_{AM}, aerodynamic diameter between 0.1 and 1.0 µm). Short- (1- to 7-d), medium- (14- to 182-d), and long-term (365-d) mean total and source-specific (traffic, industry) air pollution exposures were calculated for time windows prior to examination. For the analyses on glucose metabolism biomarkers (fasting blood glucose, glycated hemoglobin A1c [HbA1c]) and inflammation (adiponectin, interleukin-1 receptor antagonist [IL-1RA], high sensitivity C-reactive protein [hsCRP], fibrinogen), we analyzed repeated measures data from non-diabetic patients at t_0 and t_1 using linear mixed models with random participant intercepts. Relative risks (RR) for the association between baseline total and source-specific air pollution exposures and incident DM at t_2 were estimated using Poisson regression models with robust variance estimators. Natural direct and indirect effects were estimated for the potential mediating biomarkers (adiponectin, IL-1RA, hsCRP) using mediation techniques. All models were adjusted for potential confounding variables, which were identified based on prior knowledge and directed acyclic graphs.

Medium-term exposure to PM_{10}, $PM_{2.5}$, and PN_{AM} was associated with increased blood glucose (e.g., 28-d $PM_{2.5}$: 0.91 mg/dL [95% Confidence Interval (CI): 0.38, 1.44] per 5.7 µg/m^3) and HbA1c levels (e.g., 91-d $PM_{2.5}$: 0.07 percentage points [95% CI: 0.04, 0.10] per 4.0 µg/m^3) in persons without diabetes. We observed negative associations between medium-term air pollution and adiponectin (e.g., 91-d PN_{AM}: -2.51% change [95% CI: -3.40%, -1.53%] per 1,349 particles/mL); positive associations between short-, medium-, and long-term air pollution and IL-1RA; positive associations between long-term air pollution and hsCRP; and a mix of positive and negative associations between air pollution and fibrinogen. Long-term AP exposures for all pollutants were associated with increased risk of incident DM, with strongest associations for PM_{10} and PN_{AM} (e.g., RR for PN_{AM}: 1.29 [95% CI: 1.09, 1.52] per 494 particles/mL). Traffic- and industry-specific air pollution was associated with increased DM risk for all air pollutants, though associations were weaker for industry-specific PM. Mediation analyses showed mediation through decreased adiponectin levels for the associations between PM_{10}, PN_{AM} and incident DM (proportion mediated: 28.7% for PM_{10}).

Harmful effects of air pollution exposure on cardiometabolic health may be apparent as early as days and weeks after exposure, with long-term changes in biological parameters playing a potential role in the increasing DM risk. These results add to a growing literature supporting that stricter regulations for decreasing air pollution levels could lower DM incidence.

List of Abbreviations

AAQD	Ambient air quality directive
ANS	Autonomic nervous system
AP	Air pollution
AQG	Air quality guideline
ATC	Anatomical Therapeutic Chemical classification system
BMI	Body mass index
CI	Confidence interval
CRP	C-reactive protein
CV	Coefficient of variation
CVD	Cardiovascular disease
d	Day
DAG	Directed acyclic graph
dB(A)	A-weighted decibels
DE	Direct effect
DFG	Deutsche Forschungsgemeinschaft
dL	Deciliter
DM	Diabetes mellitus
doy	Day of year
D_p	Particle diameter
DZD	German Center for Diabetes Research
EPA	Environmental Protection Agency
ETS	Environmental tobacco smoke
EU	European Union
EURAD	EURopean Air pollution Dispersion
GDM	Gestational diabetes mellitus
GLUT4	Glucose transporter type 4
h/hr	Hour
HbA1c	Glycated hemoglobin A1c
HNR	Heinz Nixdorf Recall
hsCRP	High sensitivity C-reactive protein
IE	Indirect effect
IKK	IκB kinase
IL-1	Interleukin-1
IL-1β	Interleukin-1 beta
IL-1RA	Interleukin-1 receptor antagonist
IL-6	Interleukin-6
IMIBE	Institute of Medical Informatics, Biometry and Epidemiology
IQR	Interquartile range
IRS	Insulin receptor substrate
iSES	Individual socioeconomic status
IUTA	Institute of Energy and Environmental Technology
JNK	c-Jun N-terminal kinase
kg	Kilogram
km	Kilometer
km^2	Square kilometer
L	Liter
L_{den}	24-hour weighted road noise
ln	Natural log
m	Meter
M1	Classically activated macrophages
M2	Alternatively activated macrophages
m^2	Square meter
m^3	Cubic meter
µg	Microgram
mg	Milligram
min	Minute
mL	Milliliter
µm	Micrometer
MN	Minnesota
MSAS	Minimal sufficient adjustment set
NDE	Natural direct effect

NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B-cells
NIE	Natural indirect effect
nm	Nanometer
NO	Nitric oxide
NO_2	Nitrogen dioxide
NO_x	Nitrogen oxides
nSES	Neighborhood socioeconomic status
O_3	Ozone
OR	Odds ratio
pg	Picogram
PM	Particulate matter
$PM_{0.5}$	Particulate matter with aerodynamic diameter ≤ 0.5 µm mass concentration
$PM_{2.5}$	Particulate matter with aerodynamic diameter ≤ 2.5 µm mass concentration
PM_{10}	Particulate matter with aerodynamic diameter ≤ 10 µm mass concentration
PN_{AM}	Accumulation mode particle number concentration
PNC	Particle number concentration
p.p.	Percentage points
ppb	Parts per billion
PY	Pack-years
ρ/r	Correlation coefficient
RIU	Rhenish Institute for Environmental Research
RR	Relative risk ratio
SD	Standard deviation
SES	Socioeconomic status
SO_2	Sulfur dioxide
t_0	Baseline examination
t_1	First (5-year) follow-up examination
t_2	Second (10-year) follow-up examination
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
Th1	T helper cell type 1
Th2	T helper cell type 2
TLR	Toll-like receptor
TNF-α	Tumor necrosis factor alpha
TRAP	Traffic-related air pollution
UFP	Ultrafine particles
UK	United Kingdom
US	United States of America
USD	United States Dollar
WHO	World Health Organization
wk	Week

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1 Introduction

1.1 Air Pollution

1.1.1 History of Air Pollution

Ambient air pollution (AP), a term which represents a range of gases, liquids, and particles of both anthropogenic and natural origin, is a topic that has garnered significant public, regulatory, and media attention in recent decades. Nevertheless, 'smoky' or 'bad' air has been a problem since Greek and Roman times, when residents of Rome and Athens complained about the poor urban air quality (Mosley 2014). In those days, household and workshop emissions as well as inefficient mining and smelting processes contributed to urban and regional pollution (Mosley 2014).

It was during the Middle Ages in Europe, particularly in the United Kingdom (UK), that coal-associated air pollution began to increase (Brimblecombe 1976). Rapid deforestation in the UK necessitated a shift from wood to coal as the main fuel source for industrial and domestic needs by the sixteenth century (Brimblecombe 1976; Mosley 2014). While the small-scale use of coal in household heating and workshop manufacturing certainly resulted in the worsening of air quality, widespread issues with AP in Europe and the United States of America (US) began during the Industrial Revolution from approximately 1760 to 1840 (Vallero 2008). The expansion of coal-burning industrial manufacturing and the development of new chemical processes quickly gave birth to high concentrations of smoke pollution and chemical byproducts, particularly in urban centers (Vallero 2008). Alongside coal, crude oil and natural gas were added as important fossil fuels used for energy generation (Smil 2000). These sudden increases in AP emissions, alongside mass migration of populations to city centers, heightened concern about AP as an important public health issue (Vallero 2008).

The worsening air quality that accompanied the rapid industrial advancements did not go unnoticed by governments (Heidorn 1978; Mosley 2014). Attempts at regulating AP arose in the UK in the early and mid-1800s, when commissions were organized to discuss potential regulation of furnaces and engines (Heidorn 1978). In Germany, the Prussian Industrial Statute of 1845 attempted to prevent industrial emissions that were noxious or damaging to health and property, with the Prussian Technical Instruction of 1895 marking the beginning of regulating industrial facilities (Weidner 2002). Unfortunately, these measures were largely unsuccessful at improving air quality. By the end of the nineteenth century, European and

North American cities were experiencing "smog events," in which extremely high concentrations of soot and sulfur dioxide (SO_2) resulted in excess deaths (Heidorn 1978). The most famous of these events was the "Great Smog" in London in December 1952, where approximately 12,000 excess deaths were attributed to high SO_2 (250-3,800 $\mu g/m^3$) and particulate concentrations (400-4500 $\mu g/m^3$; Bell and Davis 2001). In the Ruhr area of Germany, a deadly smog event in December 1962 saw extremely high levels of total suspended particle concentrations (2,400 $\mu g/m^3$) and SO_2 (5,000 $\mu g/m^3$), with researchers estimating the event increased local mortality by 30% (Bruckmann et al. 2014). Increased understanding of how SO_2 and nitrogen oxide (NO_x) emissions contribute to the formation of acid rain provided additional impetus for the need for regulation (Cowling 1982).

By the mid-1900s, governments in Europe and the USA began to organize large-scale monitoring networks and establish regulations to reduce AP emissions, with the US Air Pollution Control Act passed in 1955 (Smil 2000) and the UK Clean Air Act introduced in 1956 (Williams 2004). In Germany, relatively little attention was paid to environmental regulation during the decades following World War II, as economic recovery and growth were prioritized (Weidner 2002). Nevertheless, politicians from North Rhine Westphalia, the highly industrial German state where the Ruhr area is located, passed the Act on Air Pollution Control, Noise and Vibration Abatement in 1962 (Weidner 1995; Bruckmann et al. 2014). Similar environmental policies, which gave legal basis for systematic air pollution monitoring (Bruckmann et al. 2014), did not become a priority in federal politics in Germany until 1969 when the Social Democrat-Liberal coalition came into power and began to prioritize environmental protection (Weidner 2002).

The past several decades have seen increased regulation of AP across the world, in large part driven by an increasing number of studies demonstrating AP's negative health effects and ability to travel across international boundaries (Maynard 2004). The contribution of fossil fuel combustion, which produces both greenhouse gases and AP, to climate change and global warming has also increased public recognition of the problem (Kinney 2008). Significant progress in the US and Europe has been made towards decreasing AP levels, with total sulfur oxide levels estimated to have decreased 69% and particulate matter by 25% in Europe between 2000 and 2014 (Koolen and Rothenberg 2019). In the Ruhr area of Germany, it is estimated that annual SO_2 concentrations have decreased from approximately 200 $\mu g/m^3$ in 1964 to 5 $\mu g/m^3$ in 2012 (Bruckmann et al. 2014).

While progress has been made in decreasing AP, the World Health Organization (WHO) estimated that 92% of the world's population in 2016 remain exposed to annual

levels of particulate matter with aerodynamic diameter ≤ 2.5 μm ($PM_{2.5}$) higher than the WHO Air Quality Guideline of 10 μg/m^3 (World Health Organization 2016a). Additionally, research continues to show adverse health effects at AP exposure levels below those recommended in the WHO guidelines (World Health Organization, Regional Office for Europe 2013). Understanding air pollution's effects on health also remains important politically, as the European Green Deal policy initiatives aiming for zero net emissions by 2050 are currently in development (European Commission 2019b).

1.1.2 Types of Pollutants and Regulations

Air pollution has been defined as the presence of one or more substances with the potential to cause adverse effects at a level higher than what is natural, and it can result from naturally occurring events (e.g., particulate matter from volcanic eruptions) as well as anthropogenic activity (e.g., SO_2 from fossil fuel combustion; International Agency for Research on Cancer 2013). Because of the complicated variety of emission sources as well as the chemical reactions that occur in the atmosphere, it can be difficult to characterize AP in detail. In this work, only the main air pollutants that are important for this dissertation have been discussed here.

Particulate Matter (PM)

Particulate matter (PM) is a mix of suspended solid and/or liquid particles and is most frequently described by size-specific mass concentrations (Fig. 1.1; European Environment Agency 2013). PM_{10} denotes the PM mass concentration of particles with an aerodynamic diameter less than 10 μm while $PM_{2.5}$, which is also called fine PM, represents the mass concentration of particles with an aerodynamic diameter less than or equal to 2.5 μm (European Environment Agency 2013). The range between 2.5 μm and 10 μm is often labeled as coarse PM. While modern techniques allow relatively accurate measurements of mass concentrations down to very small aerodynamic diameters, the heterogeneity in PM composition by source, time, and space often makes generalizations difficult (International Agency for Research on Cancer 2013). It is further complicated by the fact that primary PM arises from anthropogenic (e.g., combustion processes) and natural sources (e.g., sea salt, dust) as well as being formed in secondary reactions in the atmosphere (European Environment Agency 2013).

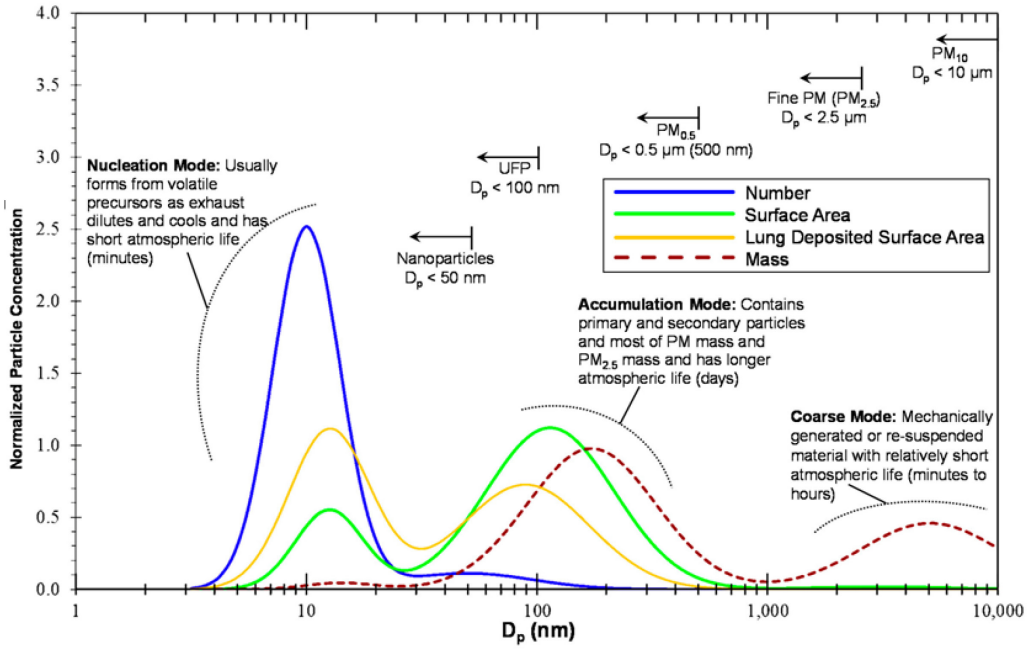

Fig. 1.1. Idealized illustration of the particle size distribution for various metrics (number, surface area, lung deposited surface area). Figure and caption adapted from Baldauf et al. (2016). Abbreviations: D_p, particle diameter; µm, micrometer; nm, nanometer; $PM_{0.5}$, particulate matter with diameter ≤0.5 µm; $PM_{2.5}$, particulate matter with diameter ≤2.5 µm; PM_{10}, particulate matter with diameter ≤10 µm; UFP, ultrafine particles.

Ultrafine Particles (UFP)

In recent years, interest has arisen concerning ultrafine particles (UFP; Fig. 1.1), which have aerodynamic diameters less than 100 nm (HEI Review Panel on Ultrafine Particles 2013). These particles, while contributing little to overall mass concentrations, are present in high number concentrations. For example, 10 µg/m^3 worth of airborne particles of 20 nm diameter would represent 2,400,000 particles, whereas the same mass would represent only 1,200 particles with 250 nm diameters (Oberdörster et al. 2005). The ratio of surface area to mass is also much greater for UFP than for larger particles (2005). UFP are known to be produced in large quantities by motor vehicles, particularly those with diesel-burning engines (HEI Review Panel on Ultrafine Particles 2013).

Nitrogen Oxides (NO_x)

The designation NO_x includes nitric oxide (NO) and nitrogen dioxide (NO_2; European Environment Agency 2013). These gases are emitted primarily during fuel combustion and contribute to the formation of ozone (O_3), PM, and acid rain (Vallero 2008). Because of its presence in combustion processes, NO_x levels are sometimes used as proxies for all road traffic-associated emissions (e.g., benzene, UFP; World Health Organization 2006).

Regulations and Guidelines

Varying regulations exist regarding the air pollutants described here (Table 1.1). Primary and secondary emissions are denoted as 1^o and 2^o, respectively. At present, there are no air quality guidelines regulating ambient levels of UFP.

Table 1.1. Major air pollutants and guidelines or limit values from the WHO Air Quality Guidelines (AQG), the EU, and the US Environmental Protection Agency (EPA). For $PM_{2.5}$, the US EPA distinguishes between primary (1^o) and secondary (2^o) emissions.

AP	Time Period	WHO AQG[1]	EU Ambient Air Quality Directive[2]	US EPA[3]
PM_{10}	24-hour mean	50 µg/m^3	50 µg/m^3	150 µg/m^3
	Annual mean	20 µg/m^3	40 µg/m^3	-
$PM_{2.5}$	24-hour mean	25 µg/m^3	-	35 µg/m^3
	Annual mean	10 µg/m^3	25 µg/m^3	1^o: 12 µg/m^3 2^o: 15.0 µg/m^3
NO_2	1-hour mean	200 µg/m^3	200 µg/m^3	100 ppb (188 µg/m^3)
	Annual mean	40 µg/m^3	40 µg/m^3	53 ppb (100 µg/m^3)

[1] World Health Organization 2006
[2] European Parliament, Council of the European Union 2008
[3] United States Environmental Protection Agency 2016
Abbreviations: AP, air pollution; EU, European Union; m^3, cubic meter; µg, microgram; NO_2, nitrogen dioxide; $PM_{2.5}$, particulate matter with diameter ≤2.5 µm; PM_{10}, particulate matter with diameter ≤10 µm; ppb, parts per billion; US, United States; WHO, World Health Organization.

1.1.3 Health Impacts of Air Pollution

While a detailed review of the health impacts of air pollution is beyond the scope of this introduction, air pollution's detrimental effects on health were first apparent for respiratory conditions, particularly after the deadly smog incidences of the early and mid-1900s (Kelly and Fussell 2015). Studies on AP and all-cause mortality in the early 1990s later revealed that AP was also a risk factor for cardiovascular disease (CVD; Schwartz and Dockery 1992; Dockery et al. 1993). This has been further confirmed in recent decades, with the WHO estimating that ambient $PM_{2.5}$ was the fifth most important risk factor in 2015 for mortality worldwide due to lung cancer, ischemic heart disease, cerebrovascular disease, chronic obstructive pulmonary disease, and lower respiratory infections (Cohen et al. 2017). Alongside well-established effects of AP on respiratory and cardiovascular diseases, studies in recent years have begun to examine a wider range of health outcomes. Of these, evidence supports that AP exposure is associated with worse cognitive outcomes (Clifford et al. 2016),

increased risk of cardiometabolic disease (Brook et al. 2017), worsening kidney function (Afsar et al. 2019), and increases in blood pressure (Cai et al. 2016).

A broad literature exists describing the mechanistic pathways by which AP exposure may affect human health. AP first interacts with the respiratory system, which is broadly divided into the nasopharyngeal, the tracheobronchial, and the alveolar regions (Fig. 1.2; Oberdörster et al. 2005). Several defenses exist within the respiratory system to minimize the entrance of foreign particles into the alveolar region where gas exchange happens (Steiner et al. 2016). Sneezing and coughing constitute the first main defenses in the nasopharyngeal and upper tracheobronchial regions (Steiner et al. 2016). Should particles reach the lower tracheobronchial region, some will become stuck in mucus produced by epithelial cells and cleared. These clearing processes have varying efficacy based on particle size and, along with the decreasing size of the respiratory system from bronchi to alveoli, this results in uneven deposition of particles throughout the respiratory tract (Fig. 1.2; Oberdörster et al. 2005; Patton and Byron 2007).

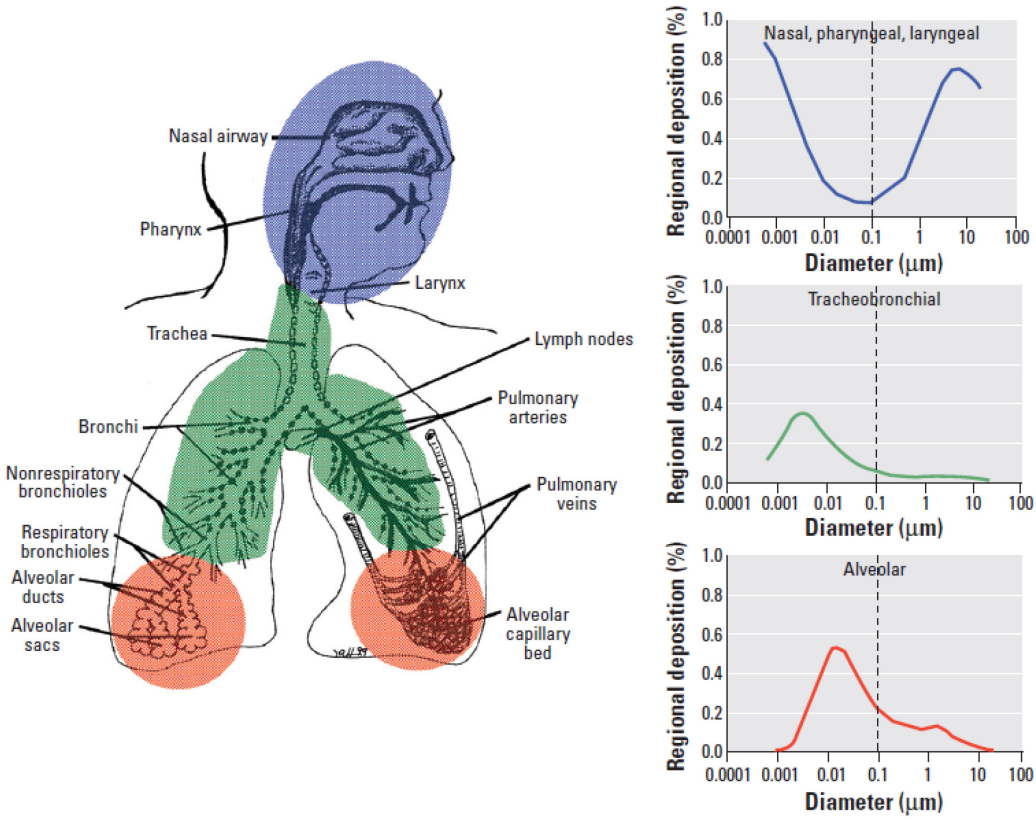

Fig. 1.2. Predicted fractional deposition of inhaled particles in the nasopharyngeal, tracheobronchial, and alveolar region of the human respiratory tract during nose breathing. Based on data from the International Commission on Radiological Protection (1994). Drawing courtesy of J. Harkema. Figure and caption used with permission from Oberdörster et al. (2005). Abbreviations: µm, micrometer.

Once deposited, experimental and epidemiologic evidence suggests that AP affects the body through a spillover of inflammatory mediators produced as a result of localized lung

inflammation, direct transfer of particles or particle components into the circulation, and alterations in the autonomic nervous system (Rajagopalan and Brook 2012; Liu et al. 2013). These pathways are not mutually exclusive, with pollutants potentially contributing to several pathways simultaneously or on varying time scales (Franklin et al. 2015). Deposited PM can contain redox-active components like metals or organic compounds that cause oxidative stress and an inflammatory reaction of alveolar macrophages (Franklin et al. 2015), leading to the release of reactive oxygen species as well as cytokines (e.g., tumor necrosis factor alpha [TNF-α], interleukin-1 beta [IL-1β]; Rajagopalan and Brook 2012). These localized inflammatory and oxidative stress species then enter systemic circulation, leading to a systemic inflammatory response, including the production of acute phase proteins such as high sensitivity C-reactive protein (hsCRP) in the liver (Rajagopalan and Brook 2012). Alternatively, fine and ultrafine PM are small enough to directly enter the circulation, and the transport of these particles to distant organ systems is hypothesized to produce systemic inflammation and oxidative stress as well as direct organ or tissue involvement (Rajagopalan and Brook 2012). Finally, AP is hypothesized to affect the autonomic nervous system (ANS) via activation of pulmonary nerve receptors (Rajagopalan and Brook 2012). Upon 'sensing' the AP, these nerves may set off a host of afferent nerve responses within the ANS, with evidence supporting a stimulation of the sympathetic over the parasympathetic nervous systems that results in an imbalance with sympathetic preponderance (Franklin et al. 2015).

1.2 Diabetes Mellitus

1.2.1 Definition of Diabetes

Diabetes mellitus (DM) is a chronic condition in which blood glucose levels are elevated because the body can either no longer use insulin efficiently, no longer produces enough insulin, or no longer produces any insulin (International Diabetes Federation 2017). Insulin is an important hormone that facilitates the transfer of glucose out of the blood stream and into cells, where it can be used and stored. When this process fails to function properly, chronically high levels of blood glucose (hyperglycemia) can result in organ damage, with persons with diabetes commonly suffering from CVD, lowered kidney function, eye disease, and neuropathy (International Diabetes Federation 2017).

Diabetes is typically classified into three main types: type 1 diabetes (T1DM), type 2 diabetes (T2DM), and gestational diabetes (GDM; International Diabetes Federation 2017). In T2DM, which is the most common type of DM worldwide, hyperglycemia occurs because of an inability to produce sufficient insulin in combination with a lowered ability to respond

to the insulin that is produced (insulin resistance; International Diabetes Federation 2017). Insulin resistance typically develops over time, with the lack of response initially leading to increases in insulin production, but the body is eventually unable to produce sufficient insulin to lower blood glucose levels (International Diabetes Federation 2017). Persons with T2DM may not have clear symptoms at the beginning of disease development, oftentimes delaying diagnosis and increasing the severity of disease by the time it is recognized (International Diabetes Federation 2017). While all contributing factors to T2DM are not known, there are several clear risk factors: overweight and obesity, family history, older age, and ethnicity. Lifestyle interventions provide potential medication-free treatment options for T2DM, as poor diet, physical inactivity, and smoking also increase a person's risk of T2DM (International Diabetes Federation 2017). If lifestyle changes are not enough to properly manage T2DM, oral medications can be prescribed, with insulin being the last management option (International Diabetes Federation 2017).

T1DM is an auto-immune condition, in which the immune cells of a person's body incorrectly attack the beta cells in the pancreas. These beta cells are responsible for insulin production and their loss results in a total or large deficiency in the amount of insulin able to be produced by the body (International Diabetes Federation 2017). As a result, persons with T1DM require daily insulin injections in order to maintain their blood glucose at appropriate levels. While there is no complete explanation for why this auto-immune condition develops in some people, it is believed to be a result of a combination of factors, including environmental exposures and genetic predisposition (International Diabetes Federation 2017).

Gestational diabetes (GDM) is a condition that develops during pregnancy, usually during the second and third trimesters, where blood glucose levels are slightly elevated because placental hormone production increases insulin resistance (International Diabetes Federation 2017). Because GDM often does not have overt symptoms, recommendations exist in many countries promoting that all pregnant women should be tested between the 24th and 28th weeks of pregnancy (American Diabetes Association 2016; International Diabetes Federation 2017). If left untreated, GDM increases the risk of fetal macrosomia, polyhydramnios, premature birth, and preeclampsia along with an increased risk for developing T2DM later in life (Coustan 2013). Most cases of GDM resolve after the birth.

While T1DM and GDM are important public health problems with extensive overlap with T2DM, T2DM is the focus of this dissertation and any subsequent allusions to "diabetes" or DM denote T2DM unless otherwise explicitly stated.

1.2.2 Epidemiology of Diabetes

T2DM is most commonly diagnosed in older adults (International Diabetes Federation 2017). It is estimated that around 425 million persons between 20-79 years worldwide suffer from DM at present (most with T2DM), with an increase to 629 million expected by 2045 (International Diabetes Federation 2017). The International Diabetes Federation also estimates that around 727 billion USD are spent yearly by persons with diabetes on healthcare (International Diabetes Federation 2017). Along with increased healthcare costs, diabetes is estimated to have caused 1.5 million deaths in 2012, with an additional 2.2 million deaths linked to higher-than-recommended glucose levels (World Health Organization 2016b). Globally, the percentage of deaths linked to diabetes and high blood glucose levels is higher in low- and middle-income countries compared to high-income countries (World Health Organization 2016b). In Germany, it was estimated that between 7.2% and 8.9% of adults had diabetes in 2017 (Heidemann and Scheidt-Nave 2017). This translates into high healthcare costs, with German healthcare expenditure in 2010 being on average 1.7 times greater for persons with diabetes compared to those without (Jacobs et al. 2017).

Diabetes is associated with high healthcare expenses because chronic elevations in blood glucose levels cause damage to vasculature across the body, affecting the heart, kidneys, nerves, and eyes (International Diabetes Federation 2017). This damage is linked to increased risk of many diseases, including CVD and kidney failure. As there is no cure for diabetes, prevention by managing modifiable risk factors (e.g., body mass index [BMI], blood pressure) is important for decreasing the burden worldwide. Early detection and regular disease management (e.g., regular screening for vasculature damage) are also key for improving outcomes and reducing diabetes-related healthcare expenditure (World Health Organization 2016b).

1.3 Air Pollution and Diabetes

An increasing number of studies have been published in the last two decades exploring whether AP exposure is associated with an increased risk of cardiometabolic disease (e.g., DM, metabolic syndrome, insulin resistance; Brook et al. 2017). For DM, the first studies were published in the late 2000s and early 2010s, and they were predominantly cross-sectional analyses of AP and prevalent DM (Lockwood 2002; Brook et al. 2008; Pearson et al. 2010; Dijkema et al. 2011). In the last decade, an increasing number of longitudinal studies investigating long-term AP exposures and incident DM have been published (e.g., Andersen et al. 2012; Chen et al. 2013; Coogan et al. 2016a; Eze et al. 2017; Bai et al. 2018; Qiu et al. 2018).

1.3.1 Epidemiology of Air Pollution and Diabetes

In response to the growing literature on the topic, a number of reviews and meta-analyses have summarized the current evidence on the association between AP and DM (e.g., He et al. 2017; Alderete et al. 2018; Dendup et al. 2018; Puett et al. 2019; Yang et al. 2020b; Yang et al. 2020a). In general, these reviews conclude that AP exposure is positively associated with DM prevalence and incidence, but the level of evidence varies by air pollutant and vulnerable sub-population.

For PM, both prevalent and incident DM studies have generally shown positive associations between AP and diabetes (Puett et al. 2019; Yang et al. 2020a). A meta-analysis by He et al. (2017) observed an overall relative risk ratio (RR) of 1.25 (95% CI: 1.10, 1.43) per 10 $\mu g/m^3$ increase in $PM_{2.5}$. For PM_{10}, Yang et al. (2020b) saw an overall hazard rate ratio of 1.12 (95% CI: 1.01, 1.23) per 10 $\mu g/m^3$ increase. Nevertheless, there have been several individual studies that have shown very weak or no association between PM exposure and DM (e.g., Puett et al. 2011; Coogan et al. 2016b; Renzi et al. 2018). Additionally, the vast majority of studies have been conducted in European and North American countries, with several studies in Asia only recently being published (e.g., Lao et al. 2019; Liang et al. 2019).

The evidence concerning NO_2 exposure and prevalent and incident DM is more mixed than that for PM (Puett et al. 2019). In a meta-analysis, Yang et al. (2020a) observed an association between NO_2 exposure and prevalent DM (Odds ratio [OR] of 1.07 [95% CI: 1.04-1.11] per 10 $\mu g/m^3$ increase) but not for incident DM (HR: 1.01 [95% CI: 0.99, 1.02] per 10 $\mu g/m^3$ increase). As pointed out in several meta-analyses, one reason for this uncertainty may be the significant heterogeneity across studies in relation to air pollution assessment measures, covariate adjustment, and method of ascertaining diabetes status.

At present, only two studies have been published on the topic of UFP and DM, with one investigating prevalent DM (Li et al. 2017) and one investigating incident DM (Bai et al. 2018). Li et al. (2017) employed a spatiotemporal model to estimate long-term particle number concentration (PNC) exposures and observed no association between PNC exposure and prevalent DM (e.g., OR: 0.71 [95% CI: 0.46, 1.10] per unit increase in ln[PNC]). Conversely, Bai et al. (2018) observed a positive association between annual UFP exposure and incident DM (HR: 1.06 [95% CI: 1.05-1.08] per 9,948.4 particles/mL). With only these two for comparison, there remains a need for more studies analyzing UFP exposures and DM before any conclusions can be made.

As PM represents a heterogeneous mixture, some studies have investigated source-specific exposures (e.g., traffic, industry) in order to try and tease apart which PM components are particularly important for explaining the association between AP and DM. Of these, most have focused on traffic-specific exposures, with many using NO_2 as a proxy (Brook et al. 2008; Coogan et al. 2016a; Eze et al. 2017) or measures of traffic load and proximity to major roads (e.g., Dijkema et al. 2011; Puett et al. 2011; Andersen et al. 2012). A few studies on DM have also modeled the traffic-specific components (e.g., traffic-specific $PM_{2.5}$) of AP exposures using emission inventories (Krämer et al. 2010) and chemistry transport models (Weinmayr et al. 2015). For industry-associated sources, analyses have only crudely compared DM prevalence in industrial areas versus non-industrial areas (Eom et al. 2018; Orru et al. 2018). Overall, results are mixed and more studies with source-specific exposure data are needed to understand whether increased DM risk is linked to specific sources.

Alongside studies investigating the association between AP and DM, there have been several epidemiologic studies looking at AP and diabetes-related intermediates in order to evaluate whether alterations in these biomarkers can be seen before disease onset. Of particular interest for this dissertation is the literature on AP and glucose homeostasis measures. Most commonly, studies have looked at AP's effect on fasting blood glucose and/or glycated hemoglobin A1c (HbA1c), a specific type of hemoglobin whose glycation level reflects circulating glucose concentrations over the previous weeks to months (Goldstein et al. 2003). For blood glucose, a recent meta-analysis by Ma et al. (2020) found positive associations between long-term PM (PM_{10} and $PM_{2.5}$) and fasting blood glucose levels. Short-term $PM_{2.5}$ was also associated with glucose levels. For HbA1c, the studies conducted among non-diabetic participants have primarily looked at long-term AP exposures (e.g., Wolf et al. 2016; Honda et al. 2017) with only a few considering the biologically-relevant medium-term (weeks to months) exposures (Yitshak Sade et al. 2015; Yitshak Sade et al. 2016).

A large literature also exists on AP exposures and circulating markers of inflammation (Rajagopalan and Brook 2012). Of these, few have focused on whether AP induces inflammation among persons without diabetes, the subpopulation of interest for investigating whether AP increases DM risk (e.g., Prins et al. 2014; Li et al. 2018). Commonly studied markers include those of general inflammation, such as hsCRP or fibrinogen, but there have been few studies on biomarkers associated with both diabetes and inflammation, such as adiponectin (Brook et al. 2016; Li et al. 2018) and interleukin-1 receptor antagonist (IL-1RA;

(Calderón-Garcidueñas et al. 2013; Teichert et al. 2013). Adiponectin, an adipokine produced by adipocytes, is known to be inversely correlated with inflammation and fasting insulin levels (Lontchi-Yimagou et al. 2013). IL-1RA is associated with the inflammatory cytokine response as well as long-term diabetes-related outcomes (Herder et al. 2009; Luotola et al. 2011; Herder et al. 2015; Herder et al. 2017). It remains to be seen whether unfavorable alterations in these diabetes-related markers may help explain how AP exposure increases DM risk.

1.3.2 Potential Mechanisms

As highlighted previously, AP is hypothesized to affect the human body through a variety of pathways, and these pathways are also implicated in how AP may increase DM risk (Fig. 1.3). Experimental studies have generally observed increases in biomarkers of systemic inflammation (e.g., hsCRP, leukocyte number, serum TNF-α) after short- and long-term AP exposure, though results from epidemiologic studies are more mixed (Teichert and Herder 2016). Experimental studies have also shown that AP exposure can cause increased macrophage infiltration into adipose tissue, a condition commonly seen in obese persons (Xu et al. 2010). Additionally, AP exposure has been shown to alter the balance of both the innate and adaptive immune responses, including increased pro-inflammatory helper T-cells (Th1) and greater polarization of macrophages into pro-inflammatory M1 types (Fig. 1.3; Rao et al. 2015). Changes in the balance of pro- and anti-inflammatory processes, such as what happens in the case of chronic low-grade inflammation, have been linked in experimental studies to insulin resistance, glucose intolerance, and an increased risk of T2DM (Teichert and Herder 2016). Decreases in adiponectin levels, which are inversely correlated with inflammation, have been observed even ten years before a diagnosis of diabetes (Tabák et al. 2012).

Animal studies have also shown that particles can translocate to the liver and cause elevated liver markers of endoplasmic reticulum stress (Rajagopalan and Brook 2012). As the liver regulates blood glucose levels through formation and breakdown of glycogen (International Diabetes Federation 2017), damage to this organ may increase diabetes risk. AP is also known to alter ANS signaling in the body, with increased stimulation of the sympathetic nervous system over the parasympathetic. Both the liver and pancreas, key organs in the regulation of insulin and glucagon, are innervated with nerves from the sympathetic and parasympathetic ANS (Nonogaki 2000), and chronic disruption of these systems may increase a person's risk of diabetes development (Carnagarin et al. 2018).

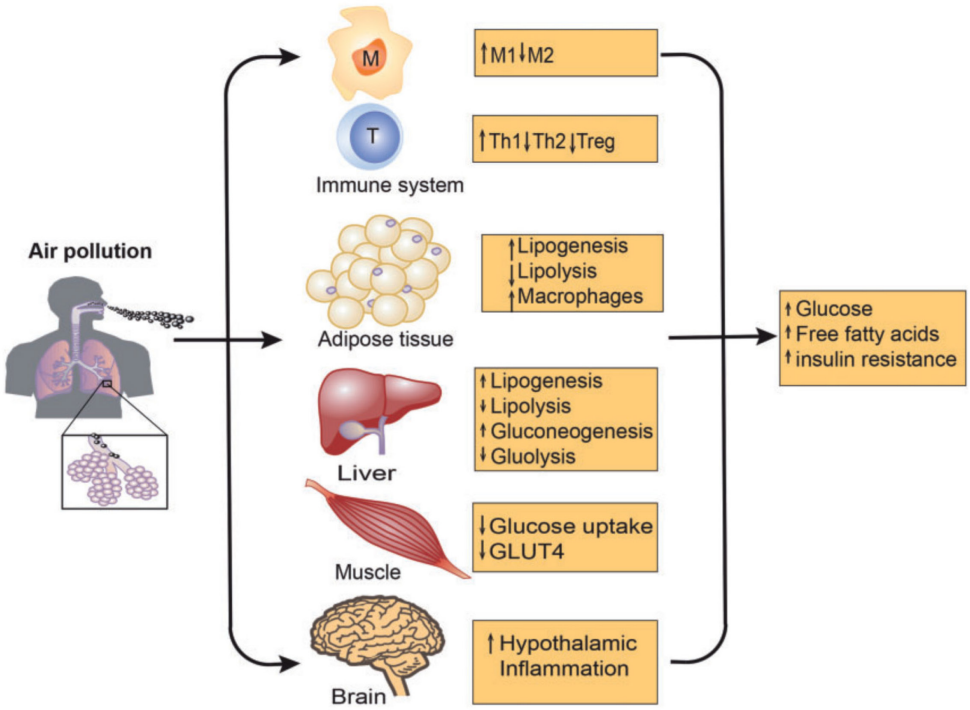

Fig. 1.3. Effect of air pollution on immune system, adipose tissue, muscle, liver, and brain. M1, classically activated macrophages; M2, alternatively activated macrophages; Th1, T helper type 1; Th2, T helper type 2; GLUT4, glucose transporter type 4. Figure and caption used with permission from Rao et al. (2015) and Oxford University Press.

1.4 Mediation Analysis

While estimating associations between exposures and outcomes is important, experimental and epidemiologic studies are oftentimes interested in also understanding the mechanisms and pathways that underlie these total effects. As such, the first statistical methods to assess potential intermediate variables (i.e., mediators) along a pathway were proposed in the social sciences using structural equation modeling (Judd and Kenny 1981; Baron and Kenny 1986). While these models came with limitations that were almost never met in practice (e.g., all covariates are continuous; Goldberger 1972; Pearl 2001), such methods continued to develop and became known as mediation analysis.

Interest in mediation analysis within the field of epidemiology has increased greatly in recent years, with methodological advancements keeping pace. Whereas earlier mediation methods were restricted to research questions with variables of certain types (e.g., dichotomous outcomes), recently developed methods using counterfactual-based inference methods have expanded the modeling capacities, an important factor for motivating the introduction of mediation analyses into common epidemiologic practice.

Mediation strategies traditionally aim to estimate two quantities: some form of direct effect (DE), which characterizes the part of the total effect which is not associated with

changes in the mediator, and some form of indirect effect (IE), which estimates the effect between the exposure and outcome that passes through the chosen mediator (Fig. 1.4). As methods have advanced, several ways for estimating these parameters have emerged.

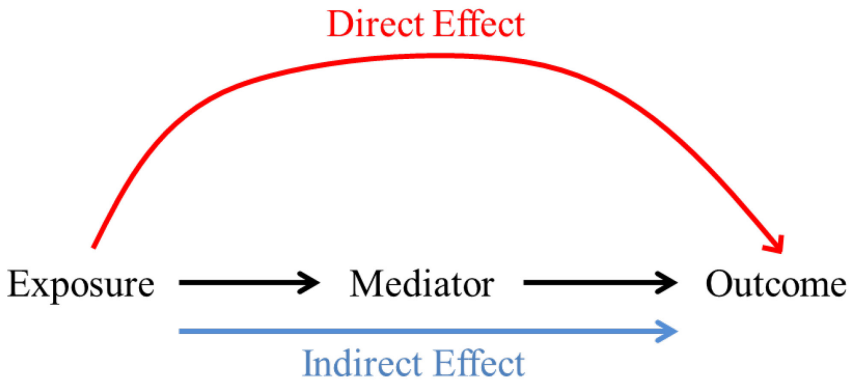

Fig. 1.4. Directed acyclic graph depicting the exposure, mediator, and outcome of an association along with the direct effect (red arrow) and the indirect effect (IE).

Controlled direct effects can be understood as the effect of exposure on the outcome when intervening to set the mediator to a specific level (Vanderweele 2016). While only the assumptions that there is no exposure-outcome and no mediator-outcome confounding need to be fulfilled for an unbiased estimate, controlled direct effects represent a somewhat artificial situation and have the downside that there is no comparable controlled IE (Vanderweele 2016). In 2001, Pearl first described natural direct and indirect effects by approaching the problem using counterfactual-based causal inference (Pearl 2001). These effects, rather than requiring one to set the mediator at a certain level, allow the mediator to take on the value it would normally assume. In this context, the natural direct effect (NDE) represents the effect of the exposure on the outcome when the mediator is set to what it would have been under conditions of no exposure (Vanderweele 2016). Conversely, the natural indirect effect (NIE) represents the effect when the exposure is set to some level and the mediator is set at the level it would have taken on under that exposure versus when the mediator is set at the level it would have taken under no exposure (Vanderweele 2016). The proportion of the effect mediated can be estimated by dividing the IE by the total effect.

Estimation of unbiased NDE and NIE requires several strong assumptions. These assumptions are as follows: 1) that one has controlled for exposure-outcome confounding, 2) that one has controlled for mediator-outcome confounding, 3) that one has controlled for exposure-mediator confounding, and 4) that there are no mediator-outcome confounders that

are themselves affected by the exposure (i.e., no intermediate confounding; Vanderweele 2016).

In the area of air pollution and DM, few studies have employed mediation analysis methods to investigate whether the association between AP and DM can be explained by changes in potential mediator variables. Peng et al. (2016) investigated whether epigenetic differences may explain the association between AP and fasting glucose levels, with some of the association being explained by changes in methylation of endothelial marker genes. In a study in China, Liu et al. (2019b) found that decreased diversity in gut microbiota partially mediated the association between PM and DM. Focusing on diabetes progression, Tong et al. (2019) evaluated whether decreased serum complement C3 levels mediated part of the association between AP and worsening DM disease. Overall, there remains a need for studies employing modern mediation techniques to examine whether AP-induced changes in hypothetical mechanistic intermediates (e.g., increases in glucose levels, systemic inflammation, and oxidative stress) in the AP-DM pathway can be verified in epidemiological data.

1.5 Aims of Thesis

1.5.1 General Aims

While an association between AP exposure and risk of DM has been confirmed by an increasing number of epidemiologic studies, the extent to which AP exposure affects diabetes-associated biomarkers before the manifestation of DM remains unclear. In particular, few studies have been able to investigate different exposure windows (short-, medium-, and long-term) due to a lack of spatiotemporal exposure information and therefore may have missed important associations. Using a well-characterized study population and a state-of-the-art spatiotemporal exposure model, this dissertation addresses these gaps by investigating the associations between short-, medium-, and long-term AP and various markers of metabolism (glucose, HbA1c, adiponectin) as well as inflammation (IL-1RA, hsCRP, fibrinogen) in a population without diabetes. This dissertation also evaluates the extent to which changes in these biomarkers mediate the association between long-term AP exposure and incident DM in an effort to provide mechanistic evidence for the air pollution-related development of DM. Finally, this dissertation expands the evidence on source-specific and UFP exposures and DM, an important step for identifying specifically harmful components within the complex air pollution mixture and informing effective policy development. All studies were conducted using data from the Heinz Nixdorf Recall (HNR)

cohort study (Schmermund et al. 2002) and approved by the Ethics Commission of the University Hospital Essen (ethics vote reference number: 13-5412-BO).

1.5.2 Specific Objectives and Hypotheses

Study I: **Air Pollution and Glucose Metabolism**

The aim of Study I was to investigate whether short- and medium-term exposures to residential AP (PM_{10}, $PM_{2.5}$, NO_2, and accumulation mode particle number concentration [PN_{AM}]) were associated with measures of serum glucose and HbA1c in adults without diabetes. Additionally, we explored whether varying patterns of association could be seen for glucose and HbA1c across a range of short- and medium-term exposure windows. We hypothesized that shorter exposure windows would be associated with blood glucose measures while medium-term exposure windows would be associated with HbA1c levels.

Study II: Air Pollution and Biomarkers of Inflammation and Altered Metabolism

The aim of Study II was to investigate whether short-, medium-, and long-term exposures to residential AP (PM_{10}, $PM_{2.5}$, NO_2, and PN_{AM}) were associated with biomarkers of inflammation and metabolism (IL-1RA, adiponectin, hsCRP, and fibrinogen) in adults without diabetes. We hypothesized that AP exposure would be associated with increased levels of IL-1RA, hsCRP and fibrinogen alongside decreased levels of adiponectin.

Study III: Air Pollution and Incident Diabetes Mellitus – A Mediation Analysis

The aim of Study III was to investigate whether long-term exposure to total and source-specific residential AP (PM_{10}, $PM_{2.5}$, NO_2, and PN_{AM}) was associated with incidence of diabetes mellitus at the 10-year follow-up examination of the HNR cohort study. Additionally, we aimed to investigate the potential role of various biomarkers of inflammation and metabolism (IL-1RA, adiponectin, hsCRP) as mediators of the association between AP and incident diabetes. We hypothesized that long-term AP exposure would be associated with an increased risk of incident DM and that this increased risk would be partially explained by changes in the biomarkers of inflammation and metabolism.

2 Study I - Air Pollution and Glucose Metabolism: An Analysis in Non-Diabetic Participants of the Heinz Nixdorf Recall Study

Lucht, S.A., Hennig, F., Matthiessen, C., Ohlwein, S., Icks, A., Moebus, S., Jöckel, K.-H., Hoffmann, B., (2018), Air pollution and glucose metabolism: An analysis in non-diabetic participants of the Heinz Nixdorf Recall study. *Environmental Health Perspectives*, 126(4): 47001.

3 Study II – Air Pollution and Diabetes-Related Biomarkers in Non-Diabetic Adults: A Pathway to Impaired Glucose Metabolism?

Lucht, S., Hennig, F., Moebus, S., Führer-Sakel, D., Herder, C., Jöckel, K.-H., Hoffmann, B., (2019), Air pollution and diabetes-related biomarkers in non-diabetic adults: A pathway to impaired glucose metabolism? *Environment International*, 124: 370–392.

4 Study III - All-Source and Source-Specific Air Pollution and 10-Year Diabetes Incidence: Total Effect and Mediation Analyses in the Heinz Nixdorf Recall Study

Lucht, S., Hennig, F., Moebus, S., Ohlwein, S., Herder, C., Kowall, B., Jöckel, K.-H., Hoffmann, B., (2020), All-source and source-specific air pollution and 10-year diabetes incidence: Total effect and mediation analyses in the Heinz Nixdorf Recall study. *Environment International*, 136: 105493.

5 Discussion

In the three studies presented in this dissertation, we observed evidence that higher exposure to air pollution adversely affects glucose metabolism, diabetes-associated inflammatory markers, and diabetes risk. Importantly, the associations with markers of glucose metabolism and diabetes-associated inflammatory markers were observed in participants without manifest DM, thereby pointing towards air pollution-related mechanisms that might play a role in the development of the disease. In support, mediation analyses in Study III suggested that decreases in adiponectin levels may be a mediating factor between AP exposure and increased risk of DM.

5.1 Comparison to Prior Literature

Glucose-Related Measures

In Study I, short- and medium-term PM and PN_{AM} exposures were associated with increases in blood glucose levels. A recent meta-analysis by Ma et al. (2020) compiled data from 17 studies on PM and fasting blood glucose and found that short-term $PM_{2.5}$ exposure was associated with fasting glucose (1.44 mg/dL [95% CI: 0.72, 1.98] per 10 $\mu g/m^3$). This association was weaker for PM_{10} (0.36 mg/dL [95% CI: -0.18, 0.72] per 10 $\mu g/m^3$). These results are largely consistent with those of Study I, where point estimates for $PM_{2.5}$ were slightly stronger than for PM_{10} (i.e. 1.59 vs. 0.80 mg/dL per 10 $\mu g/m^3$ increase in 28-day $PM_{2.5}$ and PM_{10}, respectively). For NO_2, we observed no association with blood glucose, in contrast to several other studies (Chuang et al. 2011; Kim and Hong 2012; Yitshak Sade et al. 2015; Chen et al. 2016; Wolf et al. 2016; Honda et al. 2017; Hwang et al. 2020). As NO_2 is produced by traffic but also industrial processes, it is possible that NO_2 effects are serving as proxies for other source-associated outputs. If study areas have different sources of NO_2, and therefore differing emissions accompanying it, this could serve as one explanation of why such varying results have been seen.

While many studies have been published on AP and blood glucose in the last ten years, results for short-term exposures remain heterogeneous, perhaps due to differences in air pollution exposure modeling (e.g., monitoring stations vs. land use regression model vs. satellite data) and exposure window used (e.g., 1-day lag vs. 7-day mean). Few have exploited the flexibility of chemistry transport models to investigate various exposure time windows as we have done in Study I (Peng et al. 2016; Yitshak Sade et al. 2016; Hwang et al. 2020). Peng et al. (2016) utilized a validated hybrid land use regression model to evaluate the

associations between 1-, 7-, and 28-day $PM_{2.5}$ exposure and fasting blood glucose. While we both observed positive associations for 28-day exposures, they also observed associations for 1- and 7-day exposure windows. Hwang et al. (2020) considered various short-term windows up to ten days prior to blood draw and saw no associations between PM and fasting blood glucose but a positive association for NO_2. As they did not look at exposure windows longer than 10 days, it is difficult to compare with our results and the effects we saw for 28- through 60-day means. Yitshak Sade et al. (2016) did not observe an association between 7-day PM and blood glucose but did see an effect for 3-month PM_{10}. As more temporally flexible AP models become available in areas where previously only monitoring data existed, we hope that other groups investigate whether the short- and medium-term pattern of associations we observed for AP and blood glucose are reproducible.

A second important result from Study I was the pattern of medium-term associations we observed for PM and PN_{AM} with HbA1c, with effects peaking for 75- to 105-day exposure means. This pattern is biologically plausible, as HbA1c reflects glucose levels over the previous weeks to months and the average red blood cell lives for 115 days (Franco 2012). Most prior studies on AP and HbA1c have either focused on long-term exposure windows (Chuang et al. 2011; Wolf et al. 2016; Honda et al. 2017; Li et al. 2018; Riant et al. 2018) and/or included persons with diabetes (Chuang et al. 2011; Yitshak Sade et al. 2016; Riant et al. 2018). In a recent study in South Korea, Hwang et al. (2020) also examined the association between 60-day AP exposure and HbA1c among non-diabetics and found positive associations for $PM_{2.5}$ (0.06 p.p. [95% CI: 0.03, 0.08] per 19.4 $\mu g/m^3$) and PM_{10} (0.04 p.p. [95% CI: 0.02, 0.06] per 23.5 $\mu g/m^3$). They also observed no association for NO_2, which is interesting as they did observe a positive association between short-term (10-day average) NO_2 and fasting blood glucose. The exposure contrast in the Korean study is much greater than in Study I while the effect sizes are similar. One explanation may be that the association between AP and glucose levels is non-linear, a finding which has been seen for other AP and health associations (e.g., for cause specific-mortality in Bowe et al. [2019]).

Air Pollution and Diabetes-Associated Inflammatory Biomarkers

The literature surrounding AP exposures and inflammation is vast, and a detailed summary is beyond the scope of this dissertation, but studies have generally seen increases in local and systemic inflammatory markers with AP exposure (Rajagopalan and Brook 2012). Many of these studies have included hsCRP and fibrinogen as general markers of inflammation (e.g., Hampel et al. 2015; Bind et al. 2016; Zhang et al. 2017; Corlin et al.

2018; Fuller et al. 2018), but the heterogeneity of modeling strategies, exposure windows, and population demographics makes drawing marker-specific conclusions difficult (Li et al. 2012). Our results from Study II for hsCRP add to the existing literature and support the hypothesis that long-term AP exposure is tied to increased systemic inflammation.

In Study II, higher medium-term AP exposure was associated with decreases in adiponectin, a connection which has not been widely studied. Of the few studies on this topic, both Li et al. (2018) and Teichert et al. (2013) also observed weak negative associations between long-term AP and adiponectin levels. In a cohort of persons with metabolic syndrome, Brook et al. (2016) observed no association between short-term $PM_{2.5}$ lags and adiponectin levels. To our knowledge, no previous studies have investigated whether medium-term AP is associated with adiponectin levels. As we also observed mediation of the AP-DM association through decreased adiponectin levels in Study III, we hope future studies will be published further expanding the literature on this topic.

In Study II, we observed positive associations between short-, medium-, and long-term AP and IL-1RA levels. In the literature on AP and cytokines, few studies have included IL-1RA as an outcome (Calderón-Garcidueñas et al. 2013; Teichert et al. 2013). Of these, Calderón-Garcidueñas et al. (2013) observed higher IL-1RA levels among children with high urban AP exposures, while Teichert et al. (2013) saw no association with long-term NO_2 or NO_x exposure. Several studies have been conducted looking at IL-1 family members (e.g., IL-1β) and generally show positive associations with higher AP exposure (e.g., Calderón-Garcidueñas et al. 2008; Brugge et al. 2013; Prins et al. 2014; Chen et al. 2018). The short- and long-term effects we observed for IL-1RA may reflect both acute and chronic inflammatory responses, with short-term increases indicating a properly functioning feedback loop while long-term increases reflect an overloaded system. It should be noted that IL-1RA likely serves as a proxy for other inflammatory stimuli (i.e., IL-1 signaling pathways) that have known links to increases in diabetes risk (Herder et al. 2016).

AP & Incident DM

In general, the associations we observed between AP and incident DM in Study III align with estimates from recent meta-analyses on the topic (Yang et al. 2020a). The relative risks estimated in Study III were slightly stronger than in a previous study within the HNR cohort (e.g., RR per 3.8 $\mu g/m^3$ increase in PM_{10} of 1.25 [95% CI: 1.02, 1.53] in Study III vs. 1.05 [95% CI: 1.00, 1.10] in Weinmayr et al. 2015). This difference may be due to increased

follow-up period in Study III, with an average follow-up of 10.3 years in Study III and 5.1 years in Weinmayr et al. (2015).

While the majority of epidemiologic studies suggest that long-term AP exposure may increase diabetes risk, some lingering questions remain as to which pollutants and exposure levels are of particular importance. In meta-analyses, Liu et al. (2019a) found that only $PM_{2.5}$ was associated with incident DM, whereas Yang et al. (2020a) and Yang et al. (2020b) observed associations for both $PM_{2.5}$ and PM_{10}. All three saw no association between NO_2 and DM, which we also observed. In Study III, we observed the strongest associations with incident DM for PM_{10} and PN_{AM} exposures, whereas effects for total $PM_{2.5}$ and NO_2 were still positive but slightly weaker.

Prior to 2015, published studies on AP and DM had been conducted almost exclusively in North America and Europe, where AP levels are generally lower than in developing nations. It was hypothesized that similar, and perhaps stronger, effects would be apparent in countries with higher average exposure levels. Recent publications from China have shown positive associations between AP exposure and incident diabetes (Qiu et al. 2018; Lao et al. 2019; Liang et al. 2019), but it is not clear whether these effects are significantly stronger than those seen in Europe, despite the higher average AP exposure. Further studies in non-Western countries are needed in order to allow region-specific meta-analysis and better understanding of the exposure-response relationship between AP and DM.

In several of the first studies on AP and DM, there appeared to be some evidence that associations were stronger among females than among males (Brook et al. 2008; Dijkema et al. 2011; Andersen et al. 2012; Chen et al. 2013), a finding which was corroborated for $PM_{2.5}$ and NO_2 in the meta-analyses by Eze et al. (2015) and Wang et al. (2014). Liu et al. (2019a) observed a stronger association between NO_2 and incident DM among females but not for $PM_{2.5}$ or PM_{10}. In Study III, we observed no evidence of effect modification by sex with similar or slightly higher point estimates for males than for females. It is possible that prior reports of higher estimates among females compared to males may be due to better exposure estimation for women, who on average spend a greater percentage of their time in their place of residence.

5.2 Potential Pathways: Theoretical Concepts & Study Evidence

Experimental and epidemiologic studies have increasingly supported the hypothesis that inflammation is a key mechanism by which AP exposure adversely affects both short- and long-term health (Rajagopalan and Brook 2012; Franklin et al. 2015). With chronic

exposure, local inflammatory oxidative stress processes in the lungs are hypothesized to "spill over" into systemic inflammation (Franklin et al. 2015). Systemic inflammation has long been known to be associated with T2DM (Rajagopalan and Brook 2012), and experimental and epidemiologic studies have shown that the signaling pathways and molecules involved in systemic inflammation overlap with those that regulate metabolism (Donath and Shoelson 2011; Herder et al. 2015; Hotamisligil 2017). This cross-talk is particularly apparent in adipose tissue, where persons with diabetes often have an increased number of pro-inflammatory phenotype macrophages (Rajagopalan and Brook 2012; Hotamisligil 2017). Cross-talk also occurs within cell receptor signaling pathways, where activation of IL-1 and Toll-like receptors initiates important inflammatory signaling cascades, including the JNK/IKK NF-κB pathways, that are known to inhibit insulin action (Lontchi-Yimagou et al. 2013; Hotamisligil 2017).

While there is strong evidence connecting inflammation and diabetes development, the role AP plays remains unclear. The biomarkers in Study II were selected because they are known to be involved in both metabolic and inflammatory pathways. Adiponectin is a protein hormone produced by adipocytes, and its levels are known to be inversely associated with insulin resistance, HbA1c, fasting glucose, fasting insulin, and beta-cell function (Lontchi-Yimagou et al. 2013; Herder et al. 2016). It is also part of a feedback loop wherein pro-inflammatory cytokines downregulate adiponectin production and adiponectin levels promote increased anti-inflammatory cytokines and suppress macrophage activation (Lontchi-Yimagou et al. 2013). A person's IL-1RA is also associated with both inflammation and metabolism and generally represents the initial inflammatory macrophage response to foreign particles (Herder et al. 2013). Binding of the IL-1 receptor initiates several downstream inflammatory processes (e.g., JNK/IKK NF-κB) but also pathways that inhibit insulin action (Lontchi-Yimagou et al. 2013; Hotamisligil 2017). Elevated IL-1RA and decreased adiponectin levels are associated with increased risk of T2DM (Herder et al. 2013), but Herder et al. (2016) also observed that these markers were associated with glucose metabolism changes among persons without diabetes.

In Study II, hsCRP and fibrinogen were also included because of their roles in short- as well as long-term inflammatory processes (Pepys and Hirschfield 2003; Davalos and Akassoglou 2012). The epidemiologic literature surrounding both is extensive (e.g., Hampel et al. 2015; Corlin et al. 2018; Fuller et al. 2018; Pilz et al. 2018) and generally supports the idea that AP exposure may increase biomarker levels. Nevertheless, there remains uncertainty about which exposure windows are most associated and whether biomarker levels

are valid in all subpopulations (e.g., among persons with chronic inflammation; Li et al. 2012).

Direct translocation of particles, typically UFP or soluble metal constituents, into the blood stream and on to other organs may initiate local inflammatory processes across the body (Nemmar et al. 2002). The ability of very small particles to directly contribute to disease processes via translocation was supported in a recent controlled exposure study in humans, in which inhaled gold nanoparticles were tracked and identified to have translocated to the blood as well as the liver and sites of vascular inflammation (e.g., atherosclerotic plaques; Miller et al. 2017). AP exposures have also been linked to alterations in adipose tissue, where macrophages showed increased M1-phenotype activation, monocytes increased, and adipokine levels were altered (Rao et al. 2015). The presence of particles at other organs is known to initiate local inflammatory processes and affect oxidative stress processes, results which may contribute to worsening insulin sensitivity and glucose control (Teichert and Herder 2016).

5.3 Mediation Analysis

To our knowledge, Study III was the first epidemiologic study to see evidence that decreased adiponectin levels may mediate part of the association between long-term AP exposure and incident DM. Because studies on AP and adiponectin are so few, further work corroborating this link in other populations is needed before we can conclude that our results reflect true causal mechanisms. With the recent inclusion and expansion of mediation procedures in many software suites (e.g., SAS, R), we hope to see the number of epidemiologic studies including mediation techniques increase in the next few years. For the mechanistic connections between AP and DM, there are several other pathways that would be interesting to evaluate with these methods in future studies (e.g., vascular dysfunction and oxidative potential).

For a valid mediation analysis, strong assumptions must be met, including that there are no intermediate confounders. In this case, it is known that adiponectin levels decrease with increases in BMI. Should AP exposure cause increases in BMI, for which epidemiologic evidence is mixed (An et al. 2018), the assumption of no intermediate confounders would therefore be violated and the results of our mediation analyses would be invalidated. Nevertheless, we do not believe that strong assumptions should scare epidemiologists away from attempting to answer research questions using mediation methods. Instead, these methods can provide informative results when studies are designed to collect information on

all potential confounders (i.e., exposure-mediator, mediator-outcome, and exposure-outcome), the research question is well-suited to the necessary assumptions (e.g., relatively short time between exposure and mediator), and these assumptions are explicitly stated alongside the results.

5.4 Source-Specific Exposures

PM continues to be frequently used as a marker of AP because of the consistent associations it has shown with health outcomes across various disciplines (World Health Organization 2006). Nevertheless, there remains uncertainty as to which components of PM are particularly toxic. This is particularly complicated to determine because the composition can vary widely depending on primary and secondary emission sources along with weather conditions. With improvements in exposure modeling and measurement devices in recent years, an increasing number of studies focusing on source-specific exposures have been published (Hime et al. 2018).

Many source-specific studies have focused on road traffic-related AP (TRAP), as road transport is a major source of AP worldwide and diesel exhaust is a known carcinogen (Health Effects Institute 2010; International Agency for Research on Cancer 2013). Anenberg et al. (2019) estimated that 11.6% of $PM_{2.5}$ worldwide in 2015 came from transportation tailpipe emissions. In Germany, the attributable fraction from road transport was even higher at 31%, a byproduct of the high number of diesel vehicles (Anenberg et al. 2019). Internal combustion engines produce PM (including a large number of UFP), carbon monoxide, NO_x, carbon dioxide, and unburned hydrocarbons, but road transportation is also responsible for particles from break and tire wear as well as re-suspended dust during road travel (Health Effects Institute 2010). It has been hypothesized that TRAP may be particularly toxic due to its high metal content, the large number of UFP produced, and its oxidative potential (Hime et al. 2018). A recent report by the International Council on Clean Transport estimated that in 2015, vehicle tailpipe emissions were responsible for 5.38 deaths per 100,000 people globally and approximately $1 trillion USD in health costs (Anenberg et al. 2019).

In Study III, we used the TRAP exposure estimates generated by the EURAD model to investigate whether AP from this particular source was more or less toxic than the overall mixture. Most prior studies that have examined TRAP and DM have used traffic load, NO_2 exposure, or distance to nearest roadway as proxies for traffic exposure with mixed results (e.g., Dijkema et al. 2011; Weinmayr et al. 2015; Dzhambov and Dimitrova 2016). Some have also used chemistry transport modeling (Weinmayr et al. 2015) or emission inventories

(Krämer et al. 2010) to estimate traffic exposures, and these studies have generally seen increased DM risk with higher TRAP exposure. Weinmayr et al. (2015), a study also conducted in the HNR using the EURAD model, observed weak evidence that $PM_{10\text{-}TRA}$ increased DM risk more than total PM_{10} (RR: 1.36 [95% CI: 0.98, 1.89] vs. 1.05 [95% CI: 1.00, 1.10] per 1 $\mu g/m^3$, respectively). Krämer et al. (2010) also observed a positive association between PM_{10} and NO_2 from traffic emissions and incident DM, though it was not clear whether these associations were significantly stronger than total exposures. While we observed a slightly larger point estimate for traffic-specific $PM_{2.5}$ than all-source $PM_{2.5}$, AP from traffic sources was not more strongly associated with DM in our cohort. This could be due to the 1 km^2 resolution of the EURAD model, as TRAP levels are known to drop off quickly even 200 m away from roadways and the model may thus not capture the true variability in traffic exposures. Further studies are needed before conclusions can be drawn that this source of AP is particularly important for increasing DM risk.

While less studied than traffic, industry remains an important source of AP around the world (European Environment Agency 2018). The majority of studies on industry-specific exposures have focused on respiratory and cardiovascular outcomes (e.g., Golshahi et al. 2016; Bergstra et al. 2018), with few studies having examined the effect of industry-specific AP on diabetes risk (Eom et al. 2018; Orru et al. 2018). In a study on residents of industrial areas in Korea, Eom et al. (2018) observed no association between region of residence (industrial vs. control) and diabetes prevalence (OR: 0.99 [95% CI: 0.91, 1.08]). Orru et al. (2018) conducted a similar study in Estonia, but they observed higher DM prevalence in the area with greater industrial AP. While effects were not larger than those for all-source or traffic-specific exposures, we did observe positive associations between industry-specific AP and incident diabetes within Study III. As NO_2 is a gas whose composition is unaffected by source, it is possible that the association for industry-specific NO_2 also reflects related air pollutants that are co-emitted during industrial processes. Just as for TRAP, further prospective studies looking at industry-specific exposures and DM incidence are needed.

5.5 Ultrafine Particle Exposure

As described in the Introduction, ambient UFP have risen in importance as a potentially harmful AP exposure in the last few decades due to their large relative surface area and ability to penetrate deeply into the respiratory system (Traboulsi et al. 2017; Bai et al. 2018). While PN_{AM} exposures in Studies I, II, and III reflect particles slightly larger than UFP, the strong associations we observed in all three studies indicates that further research into these

associations for UFP is merited. To date, only one small study of Danish households by Karrotki et al. (2014) has investigated UFP and HbA1c and observed a positive association 48-hour indoor PNC but not for outdoor PNC. No other studies have investigated the associations between various time windows of exposure to submicron PNC and glucose-related measures. While there are no known prior studies on UFP exposure and adiponectin and IL-1RA, the few studies on UFP and pulmonary inflammation (and to a lesser extent, systemic inflammation) seem to suggest an association may exist (Ohlwein et al. 2019b).

While recent meta-analyses on AP and DM did not include UFP or quasi-UFP exposures, the association we observed in Study III between PN_{AM} and incident DM is in line with results from a prospective cohort study by Bai et al. (2018). They observed a positive association between long-term UFP and incident DM among Canadian adults (HR: 1.06 [95% CI: 1.05, 1.08] per 9,694.1 particles/mL). To our knowledge, the only other study on UFP found no association between residential UFP and prevalent diabetes (Li et al. 2017). At present, too few studies have examined this issue to make conclusions about the importance of UFP for DM risk, but it is likely that further studies will emerge as more research groups and monitoring centers begin to measure and model UFP levels.

5.6 Implications for Policy and Public Health

The results of this dissertation have several important implications for public health and public health policy. First, the studies included here demonstrate that AP levels at or below EU regulations (e.g., 40 $\mu g/m^3$ for NO_2; Table 1.1), as is experienced in the Ruhr area of Germany today, continue to adversely affect human health. The results of Study III add to the evidence that low-level AP remains a risk factor for diabetes, a conclusion made by several other studies conducted in areas of North America and Europe with AP levels below those experienced in the Ruhr area (e.g., Andersen et al. 2012; Chen et al. 2013; Requia et al. 2017; Bai et al. 2018). Furthermore, meta-analyses on low-level air pollution and cardio-respiratory outcomes (Papadogeorgou et al. 2019) as well as mortality (Chen and Hoek 2020) show that no level of air pollution exposure, even that below the stricter WHO AQG (e.g., 10 $\mu g/m^3$ for $PM_{2.5}$), is known to be safe for human health.

Because adverse health effects are observed at all levels of AP as well as for both short- and long-term exposures, it is important that countries critically evaluate and revise their policies to reflect the current scientific knowledge and to better protect their citizens. For long-term AP levels, reduction is usually achieved through the introduction of fixed limit values (e.g., mean annual $PM_{2.5}$ levels must be below 25 $\mu g/m^3$) or through binding relative

exposure reduction requirements (e.g., $PM_{2.5}$ levels must decrease by 5% each year until a set value is reached). In the case of the EU, critical revision of the current air quality guidelines is particularly needed, as the EU Ambient Air Quality Directive (AAQD; European Parliament, Council of the European Union 2008) has much higher limit values for annual $PM_{2.5}$ and PM_{10} than recommended in the WHO AQG (e.g., 25 $\mu g/m^3$ vs. 10 $\mu g/m^3$ for $PM_{2.5}$; World Health Organization 2006). Within Europe, most urban populations remain exposed to AP levels above the WHO AQG (Fig. 5.1; European Environment Agency 2019c), and an estimated 412,000 premature deaths were caused by $PM_{2.5}$ exposure in 2016 (European Environment Agency 2019a). While stricter than the EU AAQD, the most recent WHO guidelines were established in 2005 and are currently undergoing revision, which may result in even stronger recommendations for certain pollutants. The EU, as acknowledged in a recent "fitness check" report by the EU Commission, needs to strengthen their air quality guidelines and lower limits to better align with WHO standards (European Commission 2019a). Based on the strategy put forth within the European Green Deal, this may happen as soon as 2021 (European Commission 2019b).

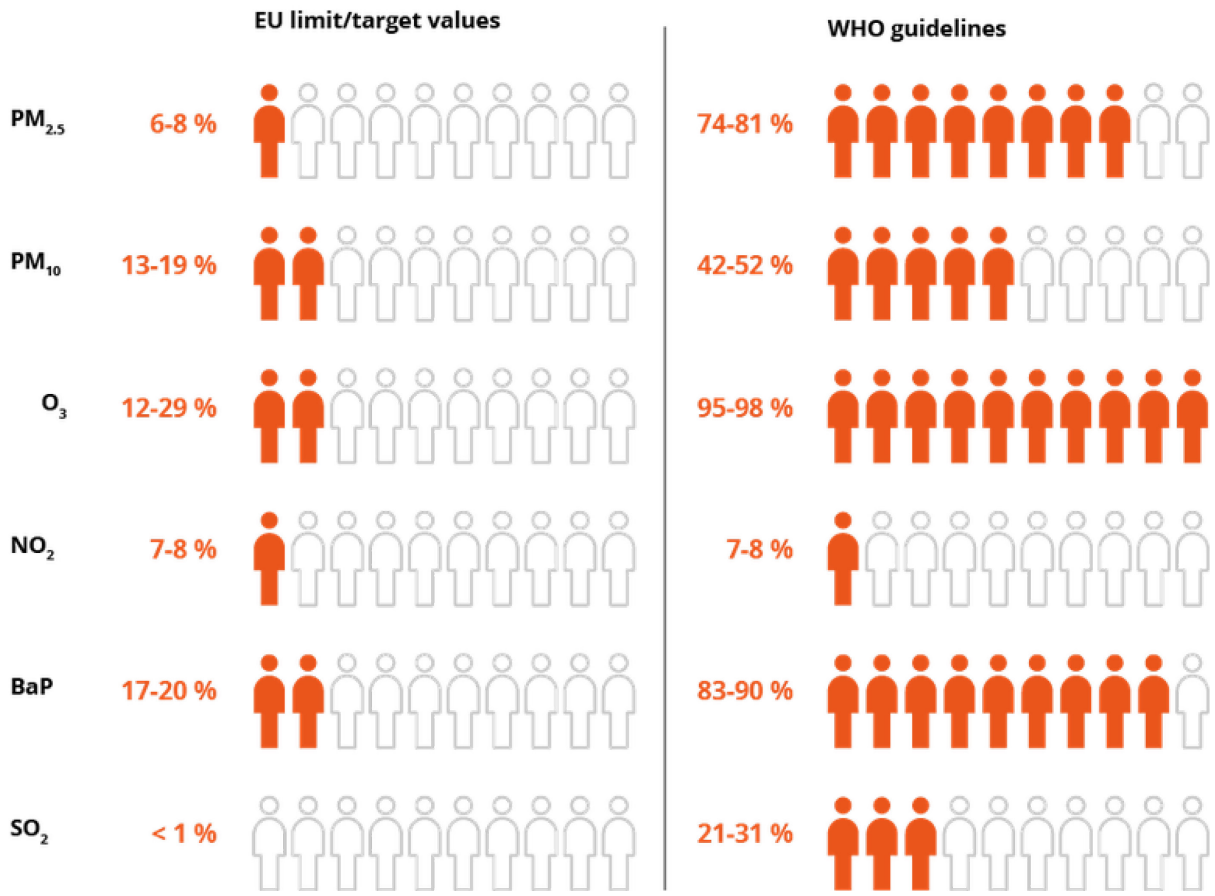

Fig. 5.1: Share of the European Union (EU) urban population exposed to air pollutant concentrations above EU and World Health Organization (WHO) reference values in 2015-2017. Figure from the European Environment Agency (2019c). Abbreviations: BaP, benzo[a]pyrene; EU, European Union; NO_2, nitrogen dioxide; O_3, ozone; $PM_{2.5}$, particulate matter with aerodynamic diameter ≤ 2.5 µm; PM_{10}, particulate matter with aerodynamic diameter ≤ 10 µm; SO_2, sulfur dioxide; WHO, World Health Organization.

Alongside revision of the EU's AAQD limit values, policies instituting binding relative exposure reductions should also be implemented. Within the EU, several areas remain above the limits set by the more lenient EU AAQD (e.g., Poland and Northern Italy for $PM_{2.5}$; European Environment Agency 2019a), and sudden requirements to meet WHO AQG levels in the coming years would be very expensive. The implementation of binding percentage decreases in average exposure indices (e.g., three-year average for $PM_{2.5}$) would provide concrete and obtainable steps for countries with higher AP to reach WHO AQGs while also requiring less polluted EU areas (e.g., Sweden, Denmark) to continue reducing AP levels. As the current scientific evidence shows adverse health effects down to very low levels of AP exposure (Papadogeorgou et al. 2019; Chen and Hoek 2020), even small decreases in AP would yield population-level health benefits. Average exposure indices were proposed but not instituted into law in the 2008 version of the EU guidelines, therefore careful attention should be paid to including these in the upcoming revision of the European AAQD.

Legislation surrounding clean air in Europe not only involves the AAQD but also emission and energy efficiency standards, which target key sources, and the National Emissions Ceilings Directive (European Parliament, Council of the European Union 2016), which establishes emission limits for specific sectors and pollutants. In order to further reduce AP, it is necessary to tighten and/or institute stricter regulations on the sources responsible for the majority of the pollution. In 2017, the commercial, institutional and household sector was the largest contributor to $PM_{2.5}$ and PM_{10} emissions (56% and 39%, respectively) whereas road transport was the largest contributor to NO_x emissions (39%; European Environment Agency 2019b). Agriculture continues to produce almost all of the EU's ammonia emissions (92%), a pollutant which is known to play an important role in the production of secondary PM but has not decreased since 2010 (European Environment Agency 2019b). Strategies at both the national and the EU level should be developed for further decreasing emissions from these sectors and improving overall air quality.

While measures for reducing AP can require significant financial investment, lowering AP levels brings with it many benefits. In 2016, it is estimated that $PM_{2.5}$ contributed to 3.2 million incident cases of DM worldwide (Bowe et al. 2018). As persons with diabetes typically face significantly higher medical costs, reducing the global burden through prevention could result in significant savings and reduce the burden on the health system. This is particularly important in low- and middle-income countries, where only one in three countries report having the medical infrastructure required for properly diagnosing and managing diabetes in primary care facilities (World Health Organization 2016b). Reducing AP would also decrease the incidence of ischemic heart disease, stroke, lung cancer, and chronic obstructive pulmonary disease as well as other conditions associated with AP exposure (World Health Organization 2016a). Importantly, greenhouse gases and air pollutants share sources and measures reducing air pollutant emissions will reduce global warming (European Environment Agency 2019a).

5.7 Strengths and Limitations

There are several important strengths in the studies included in this dissertation. The Heinz Nixdorf Recall study is a well-characterized cohort study, in which demographic and lifestyle information has been collected in great detail over many years. When combining this cohort data with the spatially and temporally flexible EURAD model, we were able to evaluate how short-, medium-, and long-term AP exposures influenced metabolism and inflammation. Additionally, we were able to expand the literature on several biomarkers (IL-

1RA, adiponectin) involved in both metabolism and inflammation but largely unstudied in the area of AP and DM. By focusing on how AP influences persons without diabetes, Studies I and II increased understanding of how AP may further DM development and informed the mediation analysis of Study III, a technique which has been implemented in few prior studies on AP and DM.

The studies presented in this dissertation also have several limitations. The EURAD model is able to estimate air pollution on a 1 km^2 grid, as opposed to on an address-specific level, and therefore it is likely that estimates contain some exposure error. Nevertheless, this limitation may be somewhat of an advantage, as persons do not spend their time exclusively at home and a 1 km^2 estimate may provide a good estimate of AP exposure for a person's time at home as well as performing activities in the area (e.g., jogging or running errands). For the EURAD model, there are no assimilated estimates for $PM_{2.5}$ and PN_{AM} exposures, and therefore greater error in these exposure estimates is expected. Future efforts to validate and improve these modeled exposures is needed, but it is reassuring that model estimates for unassimilated exposures did not vary wildly from those of the assimilated exposures (i.e., PM_{10} and NO_2). All three studies were conducted within the same German HNR cohort, whose participants are predominantly Caucasian and older, therefore our results may not be generalizable to other populations where AP exposure levels and/or demographics are different.

5.8 Future Directions

The short- and long-term associations between AP, various markers of glucose and inflammation, and diabetes that we observed in this dissertation provide preliminary data to support a connection between AP and DM, but further studies in other cohorts and parts of the world are needed to confirm these results. Additionally, there are many markers of inflammation and those included in these studies were measured in blood. Studies on AP exposures and localized inflammatory responses, such as in the pancreas, would provide potentially useful information on whether inflammation can be observed in what are believed to be the biologically relevant organs. While the number of studies examining associations between various AP exposures and DM has increased in recent years, further studies using mediation techniques are needed to investigate whether hypothetical mechanisms can also be seen in observational data.

5.9 Conclusions

The studies presented in this dissertation support the hypothesis that long-term exposure to air pollution increases the risk of incident diabetes. Short-, medium-, and long-term air pollution exposures were associated with changes in blood glucose, metabolic, and inflammatory markers among healthy people, suggesting that air pollution exposure may influence DM development. This was further supported in mediation analyses for adiponectin. With these results and the growing literature on air pollution and diabetes in mind, measures should be taken to decrease air pollution levels and thereby reduce diabetes risk worldwide, as this would bring with it wide-reaching health and financial benefits.

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7 Appendices

7.1 Study I Appendix

Supplementary material for Study I can be found under the following citation:

Lucht, S.A., Hennig, F., Matthiessen, C., Ohlwein, S., Icks, A., Moebus, S., Jöckel, K.-H., Hoffmann, B., (2018), Air pollution and glucose metabolism: An analysis in non-diabetic participants of the Heinz Nixdorf Recall study. *Environmental Health Perspectives*, 126(4): 47001.

7.2 Study II Appendix

Supplementary material for Study II can be found under the following citation:

Lucht, S., Hennig, F., Moebus, S., Führer-Sakel, D., Herder, C., Jöckel, K.-H., Hoffmann, B., (2019), Air pollution and diabetes-related biomarkers in non-diabetic adults: A pathway to impaired glucose metabolism? *Environment International*, 124: 370–392.

7.3 Study III Appendix

Supplementary material for Study III can be found under the following citation:

Lucht, S., Hennig, F., Moebus, S., Ohlwein, S., Herder, C., Kowall, B., Jöckel, K.-H., Hoffmann, B., (2020), All-source and source-specific air pollution and 10-year diabetes incidence: Total effect and mediation analyses in the Heinz Nixdorf Recall study. *Environment International*, 136: 105493.

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