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Indoor and Outdoor Road Traffic Noise and Incident Diabetes Mellitus

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Summary

Diabetes (short for "diabetes mellitus") represents a severe and chronic disease which causes a substantial public health burden. Epidemiologic data indicates increasing incidences worldwide including the European region. Diabetes comprises a group of conditions underlying different etiologies, with type 2 diabetes mellitus (T2DM) as the prevailing diagnosis. Besides individual-level risk-factors, the environmental risk factors ambient air pollution and noise exposure have been suggested to be related to the development of diabetes. The gathered epidemiological evidence suggests that environmental noise exposure has multiple adverse health consequences, ranging from noise annoyance up to cardiometabolic outcomes, such as diabetes. However, the currently available epidemiological studies do not systmatically consider air pollution as potentially confounding co-pollutant and lack approaches to limit exposure misclassification with regard to noise assessment. The main objectives of the prospective cohort study, being part of this dissertation, was first, to study the association between residential outdoor road traffic noise exposure and the incidence of T2DM. Secondly, the study aimed at examining air pollution exposure as a potential confounder of the association between road traffic noise exposure and T2DM. Thirdly, the study aimed at investigating potential exposure misclassification by taking factors into account that modify noise propagation into the interior of the residence. and thus analyzing the relationship between estimated indoor road traffic noise exposure and T2DM.

Participants of the study were aged 45 to 75 years, lived in the Ruhr Area and were part of the Heinz Nixdorf Recall study. Data from 3,396 non-diabetic participants at baseline examination (2002-2003) who also participated in the first follow-up examination (2005-2008) were included. Long-term exposure to road traffic noise was assessed according to the European Environmental Noise Directive 2002/49/EC, using the indicator L_{den} for the level of averaged weighed 24-hour mean road traffic noise and L_{night} for the level of averaged mean night-time road traffic noise for the year 2006, assigned to the participants' residential addresses. Information on the participants' bedroom and living room orientation and window insulation of the apartment, as well as ventilation behavior, were assessed through a self-administered questionnaire and integrated to estimate indoor road traffic noise exposure. Required data was provided by 2,697 participants. Poisson regression analyses adapted to binary outcomes were applied to model the association between road traffic noise exposure and incident T2DM. The effect estimates were given as relative risks (RRs). The model was adjusted for sociodemographic characteristics and lifestyle covariates. In multipollutant models, potential confounding by fine particulate matter (aerodynamic diameter ≤ 2.5 µm, $PM_{2.5}$) and nitrogen dioxide (NO_2) was studied. Further analyses explored the role of potential effect modifiers, which were analyzed by means of multiplicative interactive terms.

The fully adjusted single-exposure model yielded an increase of incident T2DM per 10 A-weighted decibel (dB[A]) L_{den} outdoor road traffic noise of RR 1.09 (95% confidence interval (CI), 0.96-1.24). Multipollutant models for L_{den} adjusting for air pollution showed similar effect estimates yielding RRs of 1.09 (95% CI: 0.96-1.24) upon adjustment for $PM_{2.5}$ and 1.11 (95% CI: 0.97-1.11) upon adjustment for NO_2. Models for estimated indoor road traffic noise exposures yielded comparable RRs with smaller confidence intervals: RR 1.11 (95% CI: 1.01-1.21) per 10 dB(A) L_{den}.

In conclusion, this study indicates that long-term exposure to road traffic noise assessed outside and indoors may be associated with the development of T2DM. This association appears to be independent of the co-exposure to air pollution. The approach to consider factors that modulate noise propagation towards the inside of the residence appeared promising to tackle exposure misclassification. Further epidemiological studies, as well as the assumed biological pathomechanisms and experimental studies, support the findings. Alongside the accumulation of evidence in recent years, policies to monitor and mitigate noise exposure need to be updated in order to protect the population against adverse effects of noise.

Zusammenfassung

Diabetes (kurz für „Diabetes mellitus“) ist eine schwerwiegende chronische Erkrankung, die eine substanzielle Krankheitslast für öffentliche Gesundheitssysteme darstellt. Epidemiologische Daten zeigen steigende Zahlen weltweit, einschließlich dem europäischen Raum. Diabetes beinhaltet eine Gruppe von Erkrankungen mit unterschiedlichen Pathomechanismen, von denen Typ 2 Diabetes mellitus (T2DM) die überwiegend vorherrschende Diagnose darstellt. Neben individuellen Risikofaktoren werden die Umweltfaktoren Luftverschmutzung und Lärmbelastung mit der Entstehung von Diabetes in Verbindung gebracht. Die bisherige Evidenz weist darauf hin, dass Umgebungslärm die Gesundheit auf vielfache Weise schädigt, angenfangen beim Endpunkt Lärmbelästigung, bis hin zu kardiometabolischen Endpunkten wie Diabetes. Die aktuell verfügbaren epidemiologischen Studien sind jedoch insofern limitiert, dass Luftverschmutzung als assoziierter Umweltschadstoff und potenzieller Confounder nicht systematisch berücksichtigt wird und Methoden zur Verringerung der Expositions-Misklassifikation hinsichtlich Lärmerfassung fehlen. Hauptziel der in dieser Dissertation vorgestellten prospektiven Kohortenstudie war es, den Zusammenhang zwischen wohnort-bezogenem Straßenverkehrslärm und der Inzidenz von T2DM zu untersuchen. Zweitens zielte die Studie darauf ab, die Exposition gegenüber Luftschadstoffen als möglichen Confounder für die Assoziation zwischen Straßenverkehrslärm und T2DM zu untersuchen. Ein drittes Ziel der Studie war es, die potenzielle Misklassifikation der Lärmexposition zu verringern, indem Faktoren berücksichtigt wurden, die die Lärmausbreitung in die Innenräume beeinflussen, wie z.B. Fensterisolation. Für die so geschätzte Straßenverkehrslärmbelastung im Innenraum sollte ebenfalls der Zusammenhang mit der Inzidenz von T2DM untersucht werden.

Die Teilnehmer der Studie waren 45- bis 75-jährige Teilnehmer der Heinz Nixdorf Recall Studie und lebten im Ruhrgebiet. Die Daten basierten auf 3.396 nicht von Diabetes betroffenen Personen, die an der Baselineuntersuchung (2002-2003), und der ersten Follow-up Untersuchung (2005-2008) teilgenommen haben. Die Langzeit-Exposition gegenüber Straßenverkehrslärm wurde gemäß der europäischen Umgebungslärmrichtlinie 2002/49/EC erhoben, anhand der Indikatoren L_{den} für den durchschnittlichen mittleren gewichteten 24-Stunden Straßenverkehrslärms und L_{night} für den durchschnittlichen mittleren Straßenverkehrslärm nachts im Jahr 2006. Die Lärmwerte wurden den Teilnehmern über die Wohnadresse zugewiesen. Informationen zur Schlaf- und Wohnzimmerausrichtung, zur Fensterisolierung sowie zum Lüftungsverhalten der Teilnehmer wurden über einen selbst-auszufüllenden Fragebogen erhoben und verwendet, um die Straßenverkehrslärmbelastung im Inneren abzuschätzen. Hierfür standen Daten von 2.697 Teilnehmern zur Verfügung. Die Assoziation zwischen Straßenverkehrslärm und inzidenter T2DM wurde mittels Poisson-Regression untersucht. Die Effektschätzer wurden als relative Risiken (RR) angegeben. Das Modell wurde hinsichtlich soziodemographischer Charakteristiken und Lebensstil-Faktoren adjustiert. In Mehrschadstoff-Modellen wurde der Einfluss von Feinstaub (aerodynamischer Durchmesser ≤ 2,5 µm, $PM_{2.5}$) und Stickstoffdioxid (NO_2) untersucht. In separaten Modellen wurden potentielle Effektmodifikatoren über mutliple Interaktionsterme untersucht.

Das volladjustierte Einschadstoff-Modell ergab eine Steigerung der T2DM-Inzidenz um ein RR von 1,09 (95% Konfidenzintervall (KI): 0,96-1,24) pro 10 A-gewichtete Dezibel (dB(A)) L_{den} Straßenverkehrslärm, gemessen an der Außenfassade. Mehrschadstoff-Modelle mit L_{den}, adjustiert für Luftschadstoffe zeigten ähnliche Effektschätzer mit einem RR von 1,09 (95% KI: 0,96-1,24) nach Adjustierung für $PM_{2.5}$ und 1,11 (95% KI: 0,97-1,11) nach Adjustierung für NO_2. Modelle für Straßenverkehrslärmbelastung im Innenraum ergab vergleichbare RR mit kleineren KI: RR 1,11 (95% KI: 1,01-1,21) pro 10 dB(A) L_{den}.

In der Zusammenschau deutet die Studie auf eine Assoziation zwischen einer Langzeitbelastung gegenüber Straßenverkehrslärm und der Entstehung von T2DM hin. Dieser Zusammenhang scheint unabhängig von der Co-Exposition gegenüber Luftverschmutzung zu sein. Der Ansatz, Faktoren zu berücksichtigen, welche die Ausbreitung von der Fassade ins Innere des Gebäudes modifizieren, erweist sich als vielversprechend. Weitere epidemiologische Studien, vermutete biologische Pathomechanismen sowie experimentelle Studien untermauern die Ergebnisse. Vor dem Hintergrund der in den letzten Jahren gewachsenen Evidenz ist es an der Zeit, die politischen Voraussetzungen wie z.B. die europäische Richtlinie hinsichtlich Monitoring und Grenzwerten anzupassen, um die Bevölkerung wirksam vor den schädlichen Effekten von Umgebungslärm zu schützen.

List of Abbreviations

Abbreviation	Definition
BMI	body mass index
CI	confidence interval
dB	decibel
dB(A)	A-weighted decibel
DAG	directed acyclic graph
DM	diabetes mellitus
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
EEA	European environment agency
EMI	dietary pattern index (Ernährungsmusterindex)
END	Environmental Noise Directive
ESCAPE	European study of cohorts for air pollution effects
GRADE	grading quality of evidence and strength of recommendations
HPA	hypothalamic-pituitary-adrenal
HNR	Heinz Nixdorf Recall
hr	hour
IFG	impaired fasting glucose
IGT	impaired glucose tolerance
IHD	ischaemic heart disease
L_{Aeq}	A-weighted, equivalent sound level
L_{Amax}	maximum sound pressure level occurring in an interval, usually the passage of a vehicle
L_{day}	day noise level
L_{den}	day–evening–night (24-hr) noise level
L_{night}	night noise level
LUR	land use regression
NO_2	nitrogen dioxide
NO	nitrogen monoxide / nitric oxide
NO_x	nitrogen oxides
OR	odds ratio
PM	particulate matter
$PM_{2.5}$	particulate matter with aerodynamic diameter≤ 2.5 μm
RR	relative risk
SAM	sympathetic-adrenal-medullary
SAPALDIA	Swiss cohort study on air pollution and lung and heart diseases in adults
SEL	sound exposure level = sound pressure level over an interval normalized to 1 second
SES	socioeconomic status
SHS	secondhand smoke
UFP	ultrafine particles
USD	US dollar
WC	waist circumference
WHO	World Health Organization

Table of Contents

Summary ..... **i**

List of Abbreviations ..... **iii**

Table of Contents ..... **iv**

1. Introduction **1**

1.1 Background 1

1.2 Diabetes mellitus 1

1.2.1 Definition and classification of diabetes 2

1.2.2 Etiology of diabetes 3

1.2.3 Diabetes symptoms and diagnostic criteria 4

1.2.3 Determinants, risk factors and prevention of diabetes 5

1.2.4 Epidemiology of diabetes 6

1.2.5 Complications and resulting health burden 7

1.3 Noise 8

1.3.1 Environmental noise exposure 8

1.3.2 Indoor noise exposure 12

1.3.4 Health impacts of noise exposures 12

1.3.1. Environmental noise regulations and recommendations 14

1.3.2 Population exposure to environmental noise 16

1.4 Potential associations between noise exposure and diabetes incidence 17

1.4.1 Pathomechanism 18

1.4.2 The role of environmental air pollution 19

1.5 Aims of the study 20

1.5.1 Specific aims and hypotheses 21

2. Publication - Indoor and outdoor road traffic noise and incident diabetes mellitus: Results from a longitudinal German cohort study **22**

2.1 Publication appendix 31

3. Discussion **37**

3.1 Comparison to other studies 37

3.1.1 Outdoor noise exposure and incidence of T2DM 37

3.1.2 Potential confounding by co-pollutantion of air pollution exposure 38

3.1.3 Indoor versus outdoor noise exposure 40

3.1.4 Effect modification analyses 40

3.1.5 Sensitivity analyses 41

3.1.5 Varying noise exposure models 42

3.2 Biological pathways – theoretical concepts and empirical evidence 43

3.3 Quality of evidence and future research needs....44
3.4 Public health implications of the findings....45
3.4.1 Standardized and updated noise mapping procedures....45
3.4.2 Clinical relevance....47
3.4.3 Outlook and future perspectives....47
3.5 Strengths and Limitations....48
4. Conclusions....50
5. References....51
6. Acknowledgement....59

1. Introduction

1.1 Background

Diabetes mellitus (in the following, named "diabetes") is a substantial public health burden. Diabetes is a major risk-factor for severere health complications, specifically cardiovascular diseases, end-stage renal disease, retinopathy, neuropathy or lower-extremity amputations (World Health Organization 2020). The number of individuals affected by diabetes has been increasing in the last decades: Worldwide diabetes incidence has risen from 11.3 million (95% Confidence Interval (CI): 10.5-12.1) in 1990 up to 22.9 million (95% CI: 21.1-25.4) in 2017, corresponding to an increase of 102.9% (Lin et al. 2020). Age-standardized incidence numbers equal a trend from 233.6 (95% CI: 218.4-249.4) to 284.6 (95% CI: 262.2-309.7) in the same time period, which corresponds to an increase of 21.8%. In Germany, the number of type 2 diabetes mellitus (T2DM) cases is projected to rise between 54 and 77% by the year 2040, depending on different incidence and mortality scenarios (Tönnies et al. 2019). This trend is hypothized to relate to aging populations, as well as cultural, occupational and environmental changes (e.g., increased urbanization), which influences individual-level behavioural factors such as overweight, obesity and sedentary lifestyles. Noise is one of the environmental exposures prevailing in modern living conditions which is hypothized to contribute to the increasing diabetes burden (Dendup et al. 2018). Beyond fine particulate matter which is rated as the first cause, noise is rated as second relevant environmental stressor causing illness in Western Europe (Hänninen et al. 2014): Road traffic noise exposure represents the major noise burden in the European Region: 113 million people, or 20% of the European population are estimated to being exposed to harmful levels of road traffic noise (European Environment Agency 2020b). With expanding urbanization, population exposures to noise are on the rise: Experts forecast 80% of the European population to live in cities by 2050, and two thirds of the population worldwide (Koceva et al. 2016). In the last decades, the impact of environmental noise on health has been studied. Environmental noise is estimated to account for 12,000 cases of premature deaths and 48,000 cases of ischaemic heart diseases across Europe every year. The burden of disease due to environmental noise exposure per year is estimated to cause a loss of 1.0 to 1.6 million healthy life years in Western Europe (World Health Organization, Regional Office for Europe 2011). The relationship between environmental noise exposure and cardiometabolic diseases, in specific diabetes, has not been investigated until 2013 (Dzhambov 2015). Consequently, evidence in this field is still scarce.

1.2 Diabetes mellitus

Diabetes is a severe, chronic disease characterized by increased glucose levels, due to a lack of insuline – a hormone regulating blood glucose, produced by the pancreas – and / or due to a dysfunctional use of the produced insulin (World Health Organization 2020). If undetected or not

appropriately managed, diabetes is accompanied by chronically increased glucose levels in the blood, which may lead to life-threatening and disabling health complications (World Health Organization 2016). As stated above, for reasons of simplicity and readability, the short term "diabetes" instead of "diabetes mellitus" will be used in the following text, if not specific forms of diabetes (e.g., T2DM) are addressed.

1.2.1 Definition and classification of diabetes

Diabetes is defined as "a group of metabolic disorders characterized and identified by the presence of hyperglycemia in the absence of treatment. […] (with) defects in insulin secretion, insulin action, or both, and disturbances of carbohydrate, fat and protein metabolism" (World Health Organization 2019, p. 6). Diabetes is mainly classified into the following categories:

Type 1 diabetes mellitus (T1DM; formerly called insulin-dependent or juvenile-onset diabetes) represents the major cause of diabetes in children. Even if T1DM mostly occurs in childhood or youth, it can develop at any age. T1DM characterizes insulin deficiency due to ß-cell desctruction. To date, prevention of T1DM is not possible. Therapy includes regular testing of blood glucose, supply of insulin, education and surveillance (International Diabetes Federation 2019).

T2DM (formerly called non-insulin-dependent or childhood onset diabetes) is responsible for the majority of diabetes disorders in the world (approximately 90%). T2DM characterizes a state in which the body is unable to effectively metabolize insulin, and / or ß-cells inefficiently produce insulin. T2DM is caused by e.g., unhealthy eating patterns, increased body weight or sedentary lifestyle. The impact of (epi-)genetic predisposition is not clear yet. Mostly, adults are affected, but lately also adolescents suffer from T2DM and even the proportion of affected children is increasing. Often, T2DM remains undetected for several years (International Diabetes Federation 2019; World Health Organization 2019). The therapy of T2DM varies depending on the severity of the disease and includes lifestyle management, oral medication or insuline injections. Besides the regular control of blood glucose levels, also other metabolic risk factors have to be surveilled, e.g. blood pressure, or blood lipids (International Diabetes Federation 2019).

Hyperglycemia in pregnancy is classified either as gestational diabetes or diabetes in pregnancy (World Health Organization 2019; International Diabetes Federation 2019). Diabetes in pregnancy is related to hormonal changes during pregnancy, genetic and lifestyle factors. The diagnosis applies to women who have had diabetes before pregnancy or have hyperglycemia that is diagnosed during pregnancy according to the diagnostic criteria also used in non-pregnant persons. Gestational diabetes is diagnosed according to updated glucose-level thresholds, which are lower than for non-pregnant persons (World Health Organization 2019). Screening for gestational diabetes is recommended by means of an oral glucose tolerance test between pregnancy week 24 and 28, diagnostic criteria vary across the guidelines of different organizations. Both forms

of hyperglycemia in pregnancy may occur at any time during pregnancy (International Diabetes Federation 2019). It is estimated that gestational diabetes predominates hyperglycemia in pregnancy cases with a proportion of 75-90 % (International Diabetes Federation 2019). Risk factors for gestational diabetes are e.g. overweight and obesity, high weight gain during pregnancy, family history of diabetes or older age. Gestational diabetes usually resolves after pregnancy, but bears a risk for developing gestational diabetes in further pregnancies or T2TM. As hyperglycema in pregnancy bears short- and long-term elevated risks for both mother and child, a rigorous control of blood glucose levels is essential (International Diabetes Federation 2019).

Hybrid forms of diabetes are often diabetes types difficult to differentiate between T1DM and T2DM and include slowly evolving immune-mediated diabetes and ketosis-prone T2DM.

The category *unclassified diabetes* is mostly used temporarily for newly diagnosed, unclear cases until a definite diagnosis has been made.

The diagnosis *prediabetes* (alternatively called "non-diabetic hyperglycemia" or "intermediate hyperglycemia") characterizes impaired glucose tolerance (IGT) and / or impaired fasting glucose (IFG), and means an elevated risk for the development of T2DM (International Diabetes Federation 2019). Prediabetes is relevant as IGT and IGF already present an elevated risk for the development of cardiovascular diseases. A progression towards the development of T2DM within 5 years after the diagnosis of IGT or IFG is estimated to range between 26% and 50% (International Diabetes Federation 2019).

1.2.2 Etiology of diabetes

All types of diabetes are characterized by a pathologically disturbed glucose metabolism. The glucose metabolism is controlled by the polypeptide hormone insulin, which is predominantly produced by the ß-cells in the islets of Langerhans of the pancreas (Rahman et al. 2021). Insulin has several crucial functions in the complex metabolism of glucose, fat and protein:

- Blood glucose metabolism: Insulin is the single blood glucose-lowering hormone.
- Lipid metabolism: Insulin (and other hormones) promotes the uptake of lipids into the cells and inhibits lipolysis in the liver.
- Protein metabolism: Insulin promotes the secretion of proteins and the uptake of aminoacids into the cells.

The role of insulin in the pathophysiology of diabetes mainly relates to its function in the blood glucose metabolism: Food intake causes elevated blood glucose levels. In healthy individuals, elevated blood glucose levels induce the secretion of insulin into the bloodstream. In the following, the uptake of glucose (as glycogen) by liver cells, adipose tissue and skeletal muscles (insulin

action) is promoted. Simulteneously, glucose output of the liver is inhibited. (Cantley and Ashcroft 2015). Thereupon, blood glucose levels return to baseline values (Rahman et al. 2021).

In *T2DM* affected individuals, body cells lose insulin sensitivity (reduced insulin action of the cells) and tries to compensate with increased insulin secretion in the pancreas (Zheng et al. 2018). This condition is described as prediabetic. In the course of the disease, which can take several years, ß-cells cannot keep up with the high insulin secretion and lose their secretional function. Hereby caused increased blood glucose levels (hyperglycemia) mark the progression to T2DM (International Diabetes Federation 2019; Dendup et al. 2018). Determinants and major risk factors for the development of T2DM are presented below (1.2.3 Determinants, risk factors).

T1DM develops after an autoimmune-related destruction of pancreatic ß-cells hampering insulin secretion. If the body is unable to utilize glucose as an energy source, body fat is used as energy supply. This state may trigger the secretion of ketones and lead to the life threatening complication ketoacidosis (Rahman et al. 2021). The destruction of ß-cells is predominantly caused by genetically-or environmental related autoimmune processes, e.g. virus infections. The role of non-immune related ß-cell destruction is still unclear (World Health Organization 2019). T1DM affected individuals are dependent on regular (daily) insulin injections.

This dissertation investigates the incidence of an elderly cohort aged over 45 years at study entry. Together with the knowledge of T2DM generally being responsible for the vast majority of diabetes cases in particular at this age, we assume that incident diabetes in our study represent T2DM diagnoses. Therefore, this dissertation focuses on the outcome T2DM, and the following text relates mainly to this condition.

1.2.3 Diabetes symptoms and diagnostic criteria

Particulary during the early phases of disease manifestation, symptoms are not always correctly interpreted and a diagnosis is delayed. Typical symptoms of diabetes include excessive thirst, frequent urination, fatigue or a blurred vision. Symptoms for T1DM and T2DM are similar, but due to a longer latency period, T2DM symptoms are less obvious. Therefore, T2DM often remains unrecognized, i.d. has a long pre-diagnostic phase.

The World Health Organization (WHO) (2019) currently recommends the use of four diagnostic tests to detect one of the three conditions in symptomatic individuals: Impaired fasting glucose (IFG), impaired glucose tolerance (IGT) or diabetes (Table 1). In asymptomatic individuals, the test result should be validated by a further test on another day (World Health Organization 2019).

Table 1 Diagnostic criteria for Impaired fasting glucose, impaired glucose tolerance and diabetes, adaped from (International Diabetes Federation 2019)

	Criterion / Definition	Impaired fasting glucose (A and B[a])	Impaired glucose tolerance (A and B)	Diabetes (A or B or C or D)
A	Fasting plasma glucose	6.1 - 6.9	< 7.0 mmol/L	≥ 7.0 mmol/L
B	2-hour post-load plasma glucose[b]	< 7.8 mmol/L	≥ 7.8 and < 11.1 mmol/L	≥ 11.1 mmol/L
C	HbA1c			≥ 48 mmol/mol (6.5 %)
D	Random plasma glucose[c]			> 11.1 mmol/mol

a: if measured; b: after a 75 g oral glucose tolerance test; c: in the presence of symptoms of hyperglycemia

HbAic: Hemoglobin A1C, L: liter, mmol/L: millimole per liter

After a diagnostic confirmation of diabetes, physicians determine the type of diabetes by considering factors, such as family history, age and physical findings.

1.2.3 Determinants, risk factors and prevention of diabetes

The development of T2DM is understood as a complex interplay between individual-level factors and environmental factors. Relevant individual-level determinants consist of socioeconomic, demographic, biological (genetic predisponitions) and lifestyle factors while environmental determinants include physical and social environment factors, such as green spaces, infrastructure (e.g., walkability, public transport, physical activity resources), density of buildings and perceived safety / violence (Dendup et al. 2018). These environmental determinants are major contributors to the environmental risk factors air pollution and noise pollution and also influence individual risk factors. Individual level lifestyle risk factors relate to energy-dense diet and physical inactivity, smoking, as well as sleep disorders, social isolation or fear. Further, stress and depression have been linked to diabetes incidence (Dendup et al. 2018; Kolb and Martin 2017). Evidence of the proportions of genetic factors is lacking. However, the increasing rate of diabetes prevalence in the past 60 years indicate a strong influence of environmental and lifestyle factors (Cantley and Ashcroft 2015).

Intermedate conditions preceding the final manifestation of T2DM are obesity, hypertension, prediabetes and elevated blood lipid levels (Shin et al. 2013; Dendup et al. 2018). Often, several of these intermediate outcomes occur simultaneously. This condition is called metabolic syndrome (Shin et al. 2013).

While primary prevention of T1DM is currently not feasible due to limited knowledge of the etiology, several randomized controlled trials have shown that T2DM prevention is feasible and effective: By means of tackling modifiable risk factors (e.g., sedentary lifestyle, unhealthy diet) alone or in combination with pharmacotherapies (e.g., metformin) reduce the risk of T2DM by 30 to more than 50% in high-risk persons (International Diabetes Federation 2019). Beyond individual-level prevention stategies, structural public health measures, such as taxes on sugar-sweetened drinks are promising approaches to prevent diabetes on the population level. Thus, a multi-modal approach seems promising (International Diabetes Federation 2019).

1.2.4 Epidemiology of diabetes

Due to differing underlying diagnostic criteria and definitions, estimated numbers of diabetes vary. The IDF (2019) estimates the worldwide diabetes prevalence to amount 463 million or 9.3% in adults between 20 and 79 in the year 2019, including type 1 and type 2 diabetes as well as diagnosed and non-diagnosed diabetes. Global number of deaths related to diabetes and its consequences is estimated to amount to 4.2 million or 11.3% of all-cause mortality in the age range of 20-79 years (International Diabetes Federation 2019).

In the European Region, about 60 million persons are affected by diabetes including undiagnosed cases, which equals sex-specific prevalence rates of 9.6% for women and 10.3% for men (World Health Organization, Regional Office for Europe 2020; International Diabetes Federation 2019). In 2019, diabetes was attributable to 465,900 deaths in the European region, which accounts for 8.4 % of all-cause-mortality. In Germany, the age-standardized prevalence of people diagnosed with diabetes was 9.9 %, based on statutory health insurance data of 2010. A large proportion is contributed by T2DM with a prevalence rate of 7.1%. T1DM was present in 0.3% of diabetes cases. Unclear diagnoses were documented in statutory health data of 2.5% of all diabetes cases. Stratified by sex and age, 7.4 % of men and 7.0 % of women aged above 40 years, were affected by T2DM. (Tamayo et al. 2016). Survey data from 1997-1999 and 2008-2011 support the total diabetes estimates and further showed a decrease in undiagnosed diabetes from 27.7 to 20.8% (Heidemann et al. 2016). T2DM-related death rates were are about 140,000 per year.

The epidemiologic key measures of diabetes vary, among others, according to the income classifications defined by the World Bank. The prevalence rates related to both diagnosed and undiagnosed diabetes in 20 to 79-year-olds range from 4.0% (2.8-6.7) in low-income countries over 9.5% (7.6-12.3) in middle-income countries up to 10.4% (8.6-13.3) in high income-countries. In low-income countries, the proportion of undiagnosed diabetes is highest with 66.8%, compared to 52.6% and 38.3% in middle- and high-income countries (International Diabetes Federation 2019).

1.2.5 Complications and resulting health burden

Firstly, diabetes is directly linked to mortality: Diabetes is estimated to account for 4.2 million deaths in total or 11.3% of deaths worldwide in adults aged between 20 to 79 years. In Europe, a third of deaths occurring before the age of 60 years are attributable to diabetes (International Diabetes Federation 2019).

Diabetes is regarded as lifelong condition requiring multidimensional care. The risk for diabetes related complications rises in individuals which are not appropriately managed. By means of an adequate care including blood glucose control, assessment of metabolic control and screening for potential complications, diabetes-related complications may be effectively delayed or prevented (International Diabetes Federation 2019). In addition, individuals with undiagnosed diabetes are particularly affected by complications, these individuals sould be detected as early as possible by tailored screening programs (Chatterjee et al. 2017).

Acute complications of diabetes include hypoglycemia, hyperglycemic crisis and infections. Hypoglycemia defines extremely low blood glucose levels due to low food intake, excess physical activity or overdosage with insulin or oral hypoglycemic substances. It can lead to serious brain damage and cardiovascular events. Hyperglycemic crises followed by ketoacidosis which may lead to death more often affects individuals with T1DM, while hyperglycemic hyperosmolar state also occurs in T2DM (International Diabetes Federation 2019).

Chronically elevated blood glucose concentrations, mostly accompanied by insulin resistance, inflammation and endothelial dysfunction together increase the risk of *chronic complications* (Cade 2008). Macrovascular complications include cardiovascular diseases (e.g., coronary heart disease, myocardial infarction, or ischemic stroke) and are major contributors to diabetes-related morbidity, hospitalizations and death. (Cade 2008; Harding et al. 2019). Diabetes approximately doubles the risk of cardiovascular diseases (International Diabetes Federation 2019) and doubles to quadruples the risk for cardiovascular mortality in comparison to non-diabetic individuals worldwide (Harding et al. 2019). Major microvascular diabetes-related complications include diabetic foot complications (lower-extremity amputations), kidney disease (end-stage renal diseases), diabetic eye disease (retinopathy) and vascular / nerval damage (neuropathy) (Harding et al. 2019). Various other diseases are related to diabetes as for example oral, musculoskeletal or mental health conditions (Cade 2008). Further, data suggests increased mortality from other diseases, e.g. cancers, liver diseases, infections, falls, chronic obstructive pulmonary disease, pneumonia, digestive system disorders (Harding et al. 2019).

Comorbidities often prevalent in individuals with T2DM – dislipidaemia, hypertension, and obesity (metabolic syndrome) – as well as behavioural risk factors (namely smoking and low physical activity) further amplify the risk for long-term complications.

The global economic health burden associated with diabetes and its related complications is enormous. It has risen from 232 billion US dollars (USD) in 2007 up to 760 billion USD in 2019. Assuming that the average health costs per person and diabetes prevalence remain stable, projections forecast a rise of 11.2% (845 USD in total numbers) until 2045. Depending on the global regions, diabetes accounts for 8.3% of total health expenditures in the IDF European Region up to 15.2 in the South and Central American Region in 2019 (International Diabetes Federation 2019). By country level and absolute costs, the USA leads the rank list (264.9 billion US dollars USD), followed by China (109.0 USD), Brazil (52.3 USD) and Germany (43.8 USD).

1.3 Noise

Sound is a physical phenomenon which results from vibrations and propagates in the air or other medias through sound waves. Noise exposure is measured as decibel (dB), on a logarithmic scale. This means that a 10-fold increase of sound energy equals a 10 dB-increase, perceived as a doubling of loudness (Basner et al. 2014). Consequently, noise levels cannot be simply added.

Within the auditory system in the brain a sound is subjectively perceived as a pleasant sound or as unwanted sound, in this context named as "noise" (e.g., music) (Muzet 2007). Sounds are composed of various frequencies (i.e. vibrations per seconds), measured in Hertz (Hz) (World Health Organization 1999). Humans are usually able to perceive sounds from 20 to 20,000 Hz. As the average hearing capacities vary according to the different frequencies of environmental noise, a special weighting of noise frequencies has been introduced to approximate the human hearing system. The so-called A-weighting system is usually applied to environmental noise indicators. Depending on the source, noise covers a spectrum from single sound levels to continuous noise events within a given time period. Typical environmental noise sources and its corresponding dB(A) noise levels are presented in Table 2.

1.3.1 Environmental noise exposure

Environmental noise describes sounds occurring outside in relation to industry, transportation or workplaces and neighbourhood/ recreational sources, varying by definition (European Environment Agency 2020b). Noise originating from wind turbines complements the picture.

Industrial noise occurs in a great variety of sound frequencies and patterns depending of the type of machinery, such as rotating or stamping sounds. Its intensity correlates with the power of machines (World Health Organization 1999). It affects workers, and thus represents an occupational noise setting. However, also close residential areas may be affected.

Even if **construction / building services noise** is a temporary noise source, the relating noise can reach substantial levels. It is characterized by a broad range of noise types, relating to hammering,

welding, cranes or cement mixery. Regular services (e.g., garbage disposal or street cleaning) often take place at times that interfere with sleep.

Table 2: Environmental noise levels, contents retrieved and adapted from Münzel et al. (2017)

	Noise / Sound sources	Decibel scale dB(A)
	Aircraft take off	120
	Jackhammer	100
	Truck	90
	Passenger car	70
	Quiet living room	40
	Whisper	30
	Rustling leaves	20

dB (A): A-weighted decibel

Transportation noise represents the major source of environmental noise nuisance in urban agglomerations and include air, railway and road traffic noise (World Health Organization 1999).

- *Road traffic noise* mainly results from the engine of the vehicle on road surfaces. With increasing speed, the friction of the tyres with the surface of the road contributes to the noise. (Muzet 2007). The sound level and frequency spectrum produced by vehicles depends on the type of the road surface, the traffic flow rate, the average speed of the vehicles and the proportion of heavy vehicles (World Health Organization 1999). Other factors, such as meteorological conditions, intersections and the topography contribute to the magnitude and spectrum of road traffic noise.
- *Railway traffic noise* equally results from the engine (World Health Organization 1999). According to the type of train, it varies greatly in relation to the engine type and speed, and further influenced by the wagons and the nature of wheels and rails. For example,

high speed trains exceeding 250 km/h generate perceived noise levels similar to aircrafts (Muzet 2007).

- *Aircraft traffic noise* occurs in relation to take off and landing operations in the context of civil, private or military flights. Besides aircraft, also helicopters may generate enormous noise levels. Due to intensive research, noise emitted from single aircrafts has been decreased considerably during the last decades. At the same time, the volume of air traffic has increased (World Health Organization 1999; Muzet 2007).

Neighbourhood noise occurs from various sources, mostly of anthropogenic origin, on private premises, e.g. mechanical devices (ventilation systems), equipments (lawn mover), voices, foot steps, animals or music. Neighbourhood noise increases with residential density and a lack of insulation. Due to the high informative content and potential negative attitudes towards the source, neighbourhood noise has a high potential to cause annoyance (Muzet 2007; World Health Organization 1999).

Across the different noise sources, the perception of noise depends on

- the pattern of the noise,
- the frequency content and loudness of the noise,
- the time of day,
- the interfering activity,
- the attitude towards the source and individual factors
- the building quality, surface and green space.

This dissertation focuses on transportation noise, specifically road traffic noise.

Assessing environmental noise immission

Noise levels at a certain immission point can be measured or calculated. In particular for railway and road traffic noise, calculation of noise exposure is applied to outweigh temporal fluctuations. The German noise immission protection guideline for roads and railways explicitly requires the calculation of sound immissions (Bundesministerium der Justiz und Verbraucherschutz; Bundesamt für Justiz 6/12/1990).

The Environmental Noise Directive (END) specifies the following noise indicators referring to A-weighted long-term average sound levels for all day periods of a year.

L_{den}	day-evening-night noise indicator (24 hours)
L_{day}	day-noise indicator (12 hours):
$L_{evening}$	evening-noise indicator (4 hours)
L_{night}	night-noise indicator (8 hours)
L_{Amax} / sound exposure level (SEL)	if appropriate and necessary, for example in situations where noise events take place in less than 20% of the period of the year

According to the END noise levels should be generally measured at a height of 4.0 ± 0.2 metres at the most exposed façade of the residential building. To estimate the immission at the buildings, noise assessment models capture numerous factors that influence the propagation from the source (motorized vehicules) to the residential buildings. These include measures to reduce noise at the source (e.g., special road surfaces) or between noise source and residential buildings (e.g., noise barriers). Also meteorological and terrestrial (unevenness of the surface) factors are taken into account (BMU 2006). Most countries define the distance of the noise measurement in relation to the the open window (Peeters and Nusselder Rosan 2019). In Germany, a distance of 0.5 metres was chosen. A strategic noise map for L_{den} road traffic noise the study region of the included publication is presented in Figure 1.

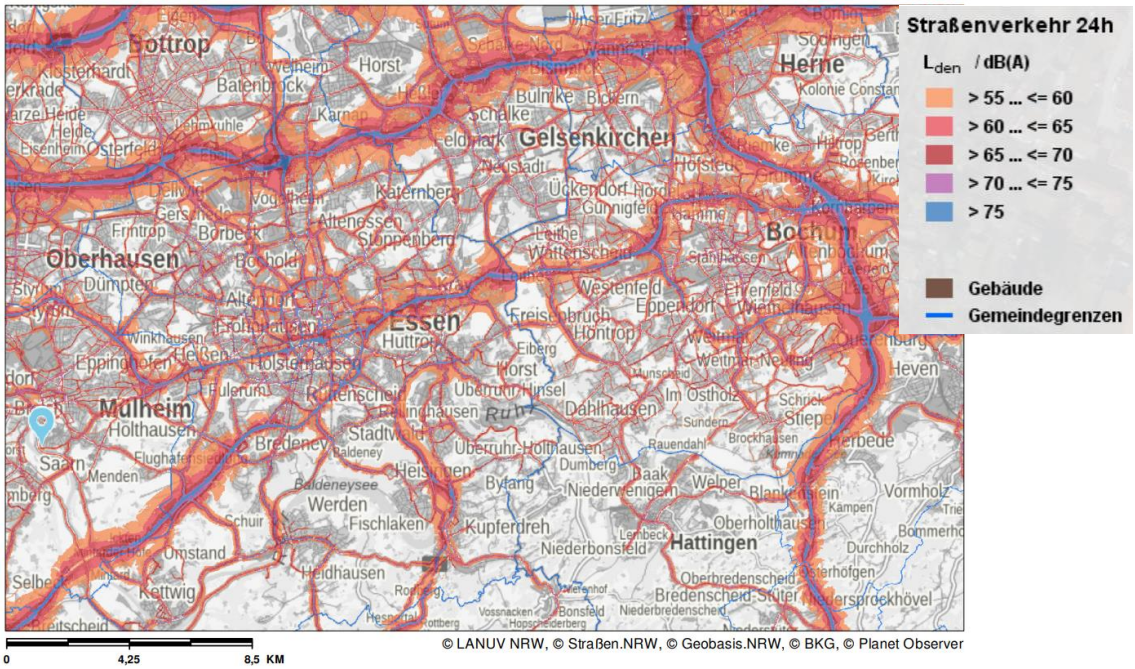

Figure 1: Noise map according to the END for the Ruhr Area in Northrhine Westphalia, publicily available, derived from https://www.umgebungslaerm-kartierung.nrw.de/

dB(A): A-weighted decibel, h: hour, L_{den}: day-evening-night noise level

1.3.2 Indoor noise exposure

Noise prediction models used to study health effects in association with noise exposure usually apply outside exposure levels (Locher et al. 2018). Thus, season-related ventilation behaviour, building-related factors like insulation of windows, the orientation of living rooms / bedrooms are not considered. However, these aspects are particularly relevant in relation to noise-induced sleep disturbance, as the majority of residents stays indoors during the night. To some extent, factors determining indoor noise apply also to daytime noise exposure. With rising noise levels, residents adapt their behaviour and close the windows. Consequently, noise exposure depends on window insulation. In the WHO night noise guideline (World Health Organization, Regional Office for Europe 2009), the insulation effect of closed windows are estimated to reach 24 dB for simple insulation up to 45 dB for most insulated window facades. These values vary across countries. For central Europe, an average window frame reduces noise exposure by 30 dB to 35 dB. However, European residents prefer to sleep with slightly opened windows (World Health Organization 1999).

1.3.4 Health impacts of noise exposures

Harmful health effects of noise were first recognized as auditory effects in occupational settings, where workers were exposed to very high levels of noise. The invention of gunpowder had grave consequences on the hearing ability of military workers. Also, coppersmiths and corn workers were affected. Later, workers in the steel industry suffered from noise-induced hearing loss (Thurston 2013). Meanwhile, a huge evidence base for the harmful effects of noise has been built. To investigate the current evidence for the updated WHO noise guidelines, the WHO initiated reviews to analyze the association between environmental noise and annoyance (Guski et al. 2017), sleep disturbance (Basner and McGuire 2018), adverse birth outcomes (Nieuwenhuijsen et al. 2017), cognition (Clark and Paunovic 2018a), cardiovascular and metabolic effects (van Kempen et al. 2018), sleep, quality of life, wellbeing and mental health (Clark and Paunovic 2018b) and tinnitus and hearing loss (Śliwińska-Kowalska and Zaborowski 2017).

Noise impacts are classified into auditory and non-auditory effects (Basner et al. 2014). The most obvious effects of noise relate to the auditory system. Single intense noise exposures or frequently elevated noise levels may result in hearing impairment, hearing loss or tinnitus through irreversible damage of the sensory cells in the cochlea (Basner et al. 2014). These exposures occur mostly in occupational or leisure settings (eg., nightclubs or per sonal listening devices) (Śliwińska-Kowalska and Zaborowski 2017). The specific noise levels causing auditory damage are not standardized. Recommendations in industrial settings suggest thresholds of 80 to 90 dB over a period of 8 hours above which protection measures are required (Basner et al. 2014).

Non-auditory effects of noise describe noise effects beyond the auditory system. Epidemiologic studies generally investigate health effects of long-term noise exposure, even for sleep-related health outcomes (Basner and McGuire 2018). The following paragraphs describe annoyance, sleep disturbance and cardiometabolic effects of noise as these health effects have the closest relation to diabetes as the outcome of interest in this thesis.

Annoyance as one of the most common effect of noise is a complex reaction including subjective factors like noise sensitivity and age (European Environment Agency 2010; World Health Organization, Regional Office for Europe 2011). The perception or appraisal of noise does not only depend on the level of noise but also the quality and the timing of the noise as it interferes with other activities or tranquility, eg during work (King and Davis 2003; Basner et al. 2014). According to a psychological stress model by Stallen (1999), the perceived noise disturbance acts together with the perceived control of the noise and is further determined by coping behaviour and personal attitudes. Generally, annoyance is assessed by a questionnaire recommended by the International Committee for the Biological Effects of Noise (ICBEN). A standard outcome of annoyance studies is the percentage of highly annoyed participants. A recent meta-analysis (Guski et al. 2017) for the updated WHO guideline including 62 studies calculated source-related exposure-response-functions and summary estimates. A 10 dB increase (50 dB to 60 dB) in traffic noise was associated with an odds ratio (OR) of 2.7 (95% CI: 1.9-4.0) for road, 3.4 (95% CI: 2.1-5.6) for railway and 3.4 (95% CI: 2.4-4.8) for aircraft in relation to highly annoyed, based on empirical data.

The second most prevalent health effect of environmental noise is sleep disturbance (World Health Organization, Regional Office for Europe 2011). Sleep is a complex and active process crucial for health and wellbeing. Due to direct interactions between sensory hearing nerves and the central nervous system, noise disturbs sleeps consciously or unconsciously, and the body does not fully habituate to the noise (Basner et al. 2014; Recio et al. 2016). Environmental noise can have various short-term adverse effects on sleep latency, total sleep time, sleep efficiency and number of awakenings (World Health Organization 1999), manifesting in sleep disturbances, insomnia, followed by daytime fatigue and somnolence. Long-term exposure to environmental noise have been linked to mental-health related endpoints to noise like anxiety and depression (Hegewald et al. 2020). Further, chronically disturbed or restricted sleep is known to alter immune function, glucose metabolism, appetit regulation and endothelial function. A vast amount of literature demonstrates the adverse effects of noise-related sleep disturbances. Field studies examined the impact of noise on sleep measured by polysomnography, recording phases of arousal, vegetative arousal, and the time spent in waking stage, specific sleep stages (including slow-wave-sleep and rapid-eye-movement sleep (REM)). Even noise levels of 33 dB L_{Amax} have shown to cause motor, autonomic or corticoid arousals (Basner et al. 2014). A recent systematic review and meta-analysis gathering evidence for the updated WHO guidelines found significant association between an

increase of 10 dB L_{night} and the percentage of highly sleep disturbed assessed by means of questionnaires. OR was 1.9 (95% CI: 1.6-2.3) for aircraft noise, 2.1 (95% CI: 1.8-2.5) for road traffic noise and 3.1 (95% CI: 2.4-3.9) for railway noise (Basner and McGuire 2018). Acute effects of noise, i.e. awakenings, assessed by polysomnographic studies, showed smaller but more precise associations, with ORs for aircraft 1.35 (95% CI: 1.22-1.50), for road 1.36 (95% CI: 1.2-1.6) and rail 1.35 (95% CI: 1.2-1.5).

Beyond the obvious impacts of noise on daily activities and sleep leading to annoyance and sleep disturbance, noise also affects the cardiovascular conditions. As illustrated (Figure 2), noise-induced stress represents the main explanation, accompanied by noise-induced adverse behaviour (alcohol consumption, smoking) (van Kempen 2018). Sleep disturbance due to noise exposure during night may also represent a risk factor for cardiometabolic diseases. In the systematic review by van Kempen et al. (2018) the current evidence was analyzed. The most studied cardiovascular outcomes in response to environmental noise were hypertension (37 cross-sectional and 2 cohort studies included in meta-analysis) and ischaemic heart disease (IHD; 22 studies, mostly cross-sectional). Road raffic noise was significantly associated with prevalence of hypertension per 10 dB (RR 1.06, 95% CI: 1.02-1.06). However, the quality of evidence was rated mainly very low. For the relationship between road traffic noise and the incidence of IHD the authors found significant associations (RR 1.08, 95% CI: 1.01-1.15 per 10 dB). The quality of the evidence was rated as high. The evidence for the association between aircraft and railway noise with IHD was rated as low, due to the low number of studies. Further, the meta-analysis showed an association between road traffic noise and diabetes (RR 1.08, 95% CI: 1.02-1.14) per 10 dB (see 1.4.1).

1.3.1. Environmental noise regulations and recommendations

In 2018, the WHO Euro published updated environmental noise guidelines for the 53 member countries in the European Region (World Health Organization, Regional Office for Europe 2018; Jarosińska et al. 2018), replacing the guidelines for community noise from 1999 (World Health Organization 1999). The recommendations refer to road traffic noise, railway noise, aircraft noise, wind turbine noise and leisure noise and are specified as "strong" or "conditional", according to the feasibility and the net benefit depending on quality of evidence and resource implications (Table 3). In cases where no recommendation is given, evidence is still too low (World Health Organization, Regional Office for Europe 2018).

To protect the public from the harmful and annoying effect of noise a fundamental framework for noise policy monitoring and regulation on European level was adopted by the European Noise Directive (END) in 2002 (END 2002/49/EC). The END is supposed to "provide a basis for developing and completing the existing set of Community measures concerning noise emitted by the major sources (…) in short, medium and long term." (Council of the European Union, European

Parliament 7/25/2002). The END promotes standardized assessment of noise exposure by formulating concise definitions and indicators.

Table 3: Environmental noise guidelines for the European Region (World Health Organization, Regional Office for Europe 2018)

	Average noise exposure[a]	**Night noise exposure**
Road traffic	**53 dB L_{den}**	**45 dB L_{night}**
Railway	**54 dB L_{den}**	**44 dB L_{night}**
Aircraft	**45 dB L_{den}**	**40 dB L_{night}**
Wind turbine	45 dB L_{den}	-
Leisure noise	70 dB $L_{Aeq, 24h}$	-

a: strong recommendations are printed in bold and conditional recommendations in non-bold letters

$L_{Aeq, 24h}$: A-weighted, equivalent sound level, L_{den}: day–evening–night (24-hr) noise level, L_{night}: night noise level

The specified noise indicators apply (for the timeframe between 2010-2014)

- *within* urban areas for all roads, railways, airports and industries in agglomerations populated by more than 100,000 residents (250,000 for the years 2005-2009) with a density determined by the member country as urban and
- *outside* urban areas for major roads (frequented by more than three million vehicles; more than six million vehicles for the years 2005-2009), major railways (railways frequented by more than 30,000 trains) and major airports (with more than 10,000 movements, ie take-off or landing) per year.

Member countries are requested to use the specifications to regularly report the number of population exposed to noise levels of 55-59, 60-64, 65-69, 70-74 and >75 dB L_{den}. For L_{night}, the lowest category is 50-54 dB and the highest equals >70 dB. The European Environment Agency (EEA) publishes the results regularly (Jarosińska et al. 2018; European Environment Agency 2020b). The agency reports noise levels above of 55 dB (L_{den}) and 50dB (L_{night}) in categories of 5 dB, as proposed in the END and depending on the data provided.Further, the END specifies measures to tackle noise pollution (strategic noise mapping, action plans) and communication stategies to the public.

The END builds the framework for harmonized noise policies and demands national strategic noise maps and action plans, and further requires the countries to set national limit values. (Peeters and

Nusselder Rosan 2019). However, no concise limit values are given. By stating thresholds above which noise data has to be sent to the EC, most member states use these thresholds. 90% of the countries apply their own national noise policies, mostly including limit / target values and sometimes using legal consequences in cases of exceedance. The majority of national limit / target values significantly exceed the noise levels recommended by the WHO noise guideline, legal consequences are not consistently applied. They are most common for industrial noise exposure (Peeters and Nusselder Rosan 2019; European Environment Agency 2020b).

In Germany, as regulated by the Traffic Noise Protection Ordinance § 2 Abs 1, limit values for traffic road noise exposure at residential areas are also beyond the WHO recommened limit values for new or significantly changed residence areas (59 dB L_{day} up to 64 dB L_{day} and 49 up to 54 dB L_{night}). For existing residence areas noise abating measures (e.g. noise insulation windows or noise barriers) may be granted if following limit values are exceeded: 64 up to 66 dB $L_{day,}$ 54 up to 56 dB L_{night} (Bundesministerium der Justiz und Verbraucherschutz; Bundesamt für Justiz 6/12/1990; Bundesministerium für Verkehr und digitale Infrastruktur 2018).

1.3.2 Population exposure to environmental noise

In Europe, exposure to noise levels exceeding 55 dB L_{den} as surveyed by the EEA is dominated by road traffic noise: 113 million people are affected by road traffic noise, followed by railway noise (22 million), aircraft noise (4 million) and industrial noise (< 1 million) (European Environment Agency 2020b). The distribution of sources affecting people by night noise levels above 50 dB draws a similar picture. With regard to road traffic noise, at least 20% of the European population is affected by noise levels exceeding 55 dB. In general, i.e. across all noise sources, more people in urban areas are exposed to noise levels above 55 dB $L_{den.}$ For example, within urban areas, approximately 50% of the population is exposed to these levels (European Environment Agency 2020b).

In Germany, 19.4% and 13.2% of the population was affected by traffic noise above 55 dB L_{den} and above 50 dB L_{night}, respectively, in 2017. With 10.3% and 6.7%, the major source was road traffic noise, followed by railway (7.8% and 6.3%) and aircraft noise (1.0% and 0.3%) (Umweltbundesamt 2020a). However, the German Federal Environmental Agency (UBA) estimates that, considering the noise which is not assessed by means of the current noise mapping strategy (e.g. agglomerations with fewer than 250,000 habitants) half of the German population is affected by traffic noise above 55 dB Lden and 45 dB Lnight. Further the UBA estimates that 15% of the German population are exposed to noise levels exceeding 65 dB L_{den} and 55 L_{night} (Umweltbundesamt 2020b).

1.4 Potential associations between noise exposure and diabetes incidence

In the last decade, noise exposure has been linked to metabolic diseases, in particularly obesity and diabetes. The first cohort study on the association between road traffic noise and the incidence of diabetes was published in 2013 (Sørensen et al. 2013). A first review on the association between environmental noise exposure and diabetes (Dzhambov 2015) including three cohort and two case-control studies found a significant association (RR 1.22, 95% CI: 1.09-1.37) for an exposure exceeding 60 dB versus less than 64 dB (the dB range between 60 and 64 named by the author as "grey area"). However, the pooled effect was mainly based on a single cohort study from Denmark (Sørensen et al. 2013). In the WHO review (van Kempen et al. 2018) only one cohort study (the aforementioned Danish study) met the inclusion criteria for the relationship between road traffic noise and diabetes *incidence*. The review found significant associations (RR 1.08, 95% CI: 1.02-1.14 per 10 dB increase). While the quality of effect was rated as moderate, the magnitude of effect was rated as low (van Kempen et al. 2018). The quality of evidence of the relationship between traffic noise and *prevalence* of diabetes was rated as very low. A review by Wang et al. (2020) on long-term noise exposure (including transportation, residential and occupational noise) and incident diabetes, based on five cohort and three cross-sectional studies resulted in similar estimates (OR 1.08, 95% CI: 1.03-1.12, increment not stated) as van Kempen and colleagues. In a subsample only including cohort studies (four on transportation noise, one smaller study on aircraft noise) associations were comparable. Further cohort studies published after the literature searches of the systematic reviews support the suggestive evidence on the association between road traffic noise exposure and incident diabetes (Jørgensen et al. 2019; Clark et al. 2017; Eze et al. 2017; Roswall et al. 2018; Shin et al. 2020). In addition, a recent Danish cohort study found a suggestive association between long-term exposure to road traffic noise and mortality from diabetes (Cole-Hunter et al. 2022).

Most cohort studies address potential confounding for the association between exposure (traffic noise) and outcome (diabetes incidence) by taking into account individual-level socio-demographic factors that have been identified by literature (see also 1.2.3 Determinants, risk factors). These potentially confounding factors can be evaluated by means of causal diagrams called directed acyclic graphs (DAG) e.g. with special automized software tools (e.g. DAGitty). As a result of this graphical and mathematical approach, adjustment sets for the statistical models are buildt (Textor et al. 2011) and thus, the risk for bias is reduced.

A main limitation of the existing epidemiological studies on the association between long-term road traffic noise and diabetes incidence is that potential confounding by co-exposure of air pollution is not consistently and thorougly taken into account (Zare Sakhvidi et al. 2018). Even if most studies adjust for at least one air pollution exposures, studies vary in the choice of air pollutant, assessment,assignment and statistical modeling methods.

Another limitation of the current evidence is that studies rely on noise exposures modeled at the façade of the buildings. However, factors that modify the propagation of noise modeled at the façade of the residence with regard to noise immission indoors may bias the true exposure to road traffic noise (Locher et al. 2018). These noise modulating factors include noise barriers such as window insulation, as well as the orientation of mainly used rooms (living room and bedroom) or the individual season-related ventilation behavior during the different season. This aspect may be particularly relevant with regard to noise exposure during nighttime as individuals spend the majority of the nighttime indoors.

1.4.1 Pathomechanism

According to the noise – stress model introduced by Babisch (2002), non-auditory effects of environmental noise are explained by a *direct* and an *indirect* pathway (Figure 2): The *direct* pathway describes the mere physiological reaction to noise, e.g. during sleep. In contrast, the *indirect* pathway includes a cognitive and emotional appraisal of the environmental stressor. Both pathways induce physiological stress reactions, marked by an activation of the autonomic nerve system and of the endocrine system through the hypothalamic-pituitary-adrenalin (HPA) axis followed by the secretion of stress hormones / glucocorticoids, such as cortisone, adrenalin and noradrenalin (Münzel et al. 2021; van Kempen et al. 2017; Recio et al. 2016). Chronic noise exposure may lead to an autonomic imbalance and HPA axis activation cascade of physiological changes. Adverse consequences include increased blood pressure and heart rate. Increased cortisol levels may inhibit the secretion of insulin and the sensitivity of insulin (van Kempen et al. 2018; Münzel et al. 2021). Chronically increased glucocorticoids cause an activation of other neurohormonal mechanisms in the kidneys and thus increase systemic inflammation and oxidative stress (Münzel et al. 2021). In conclusion, long-term exposure to noise may chronically deregulate cardiometabolic functions and manifest in cardiometabolic risk factors and diseases (e.g., obesity, hypertension and atherosclerosis). Further, noise induced sleep disturbance is hypothized to modulate fasting glucose and appetite regulation and thus lead to disturbed endocrine and metabolic functions. In addition, studies indicate that noise contributes to unhealthy lifestyles, specifically through reduced physical activity, und unhealthy behaviour increased smoking and alcohol consumption. However, the evidence is still limited (Münzel et al. 2021).

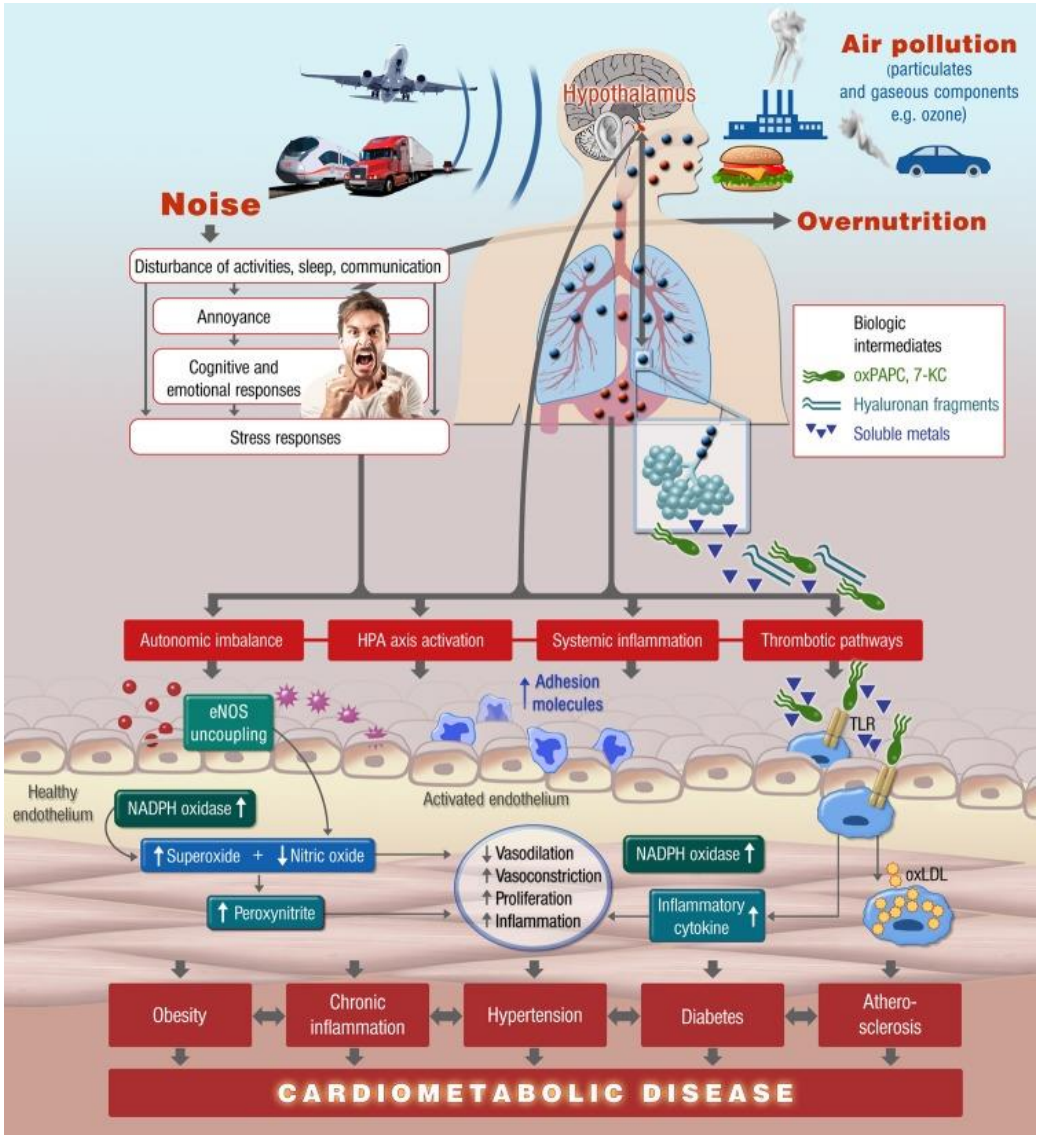

Figure 2: Transportation noise-induced effects on the cardiometabolic system, from (Münzel et al. 2017)

1.4.2 The role of environmental air pollution

Air pollution rated as most important environmental health burden is linked to noise due to their common source, i.e. transportation, notably in urban areas. In epidemiological studies assessing both noise and air pollution exposure, road traffic noise exposure is stronger correlated with nitrogen dioxide (NO_2) compared to particulate matter (PM). E.g., in Eze et al. (2017): 0.43 versus 0.23 spearman correlation between L_{den} and NO_2 and $PM_{2.5}$, respectively, or in our study (spearman correlation 0.37 verusus 0.30).

Further the hypothized physiological mechanisms between air pollution and noise in relation to diabetes overlap to some extent, (Figure 2). Both noise and air pollution exposure lead to an activation of the autonomous nervous system, linked to cardiometabolicrisk factors, such as endothelial dysfunction, hypertension or inflammation.

The association between environmental air pollution and diabetes has been studied increasingly in the past years (Puett et al. 2019; He et al. 2017). Mostly, PM matter sized up to 2.5 ($PM_{2.5}$) or 10 µm (PM_{10}) in diameter have been assessed, as well as NO_2. For PM, the evidence suggests an association between environmental air pollution and diabetes, while the evidence for the association between NO_2 and diabetes is low (Puett et al. 2019).

In recent epidemiological studies examining associations between noise and health endpoints, statistical models address potential confounding of air pollution by adjusting the regression models for air pollution as an approach to disentangle the separate effects of noise. Tétreault and colleagues (2013) performed a systematic review to untangle the effects by reviewing noise studies controlled for air pollution and vice versa. Most of the 9 noise studies related to cardiovascular endpoints showed a change in effect of < 10% upon adjustment for air pollution, indicating independent effects. Studies published after the review show less consistent results (Pickford et al. 2020). As an example in relation to cardiometabolic endpoints, Foraster et al. (2018) found similar effect estimates for the association between road traffic noise and metabolic endpoints upon adjustment for NO_2 exposure (OR 1.17, 95% CI: 1.03-1.33) versus 1.13, 95% CI: 1.01-1.27).

Another statistical approach, namely effect modification analyses, investigate effects of joint exposure of noise and air pollution, resulting for example in additive or synergistic effects. Subgroup-specific associations between noise exposure and incident diabetes may be examined, e.g., by reporting associations for subgroups of individuals highly exposed to air pollution versus those less exposed to air pollution. To date, studies report generally inconsistent results from epidemiological studies applying effect modification analysis (Pickford et al. 2020).

1.5 Aims of the study

The evidence of environmental road traffic noise in relation to the incidence of T2DM is still scarce and inconsistent with a limited number of cohort and cross-sectional studies. Therefore, this dissertation investigates the association between road traffic noise exposure and T2DM incidence. Further, this dissertation addresses potential confounding by air pollution co-exposure, which has not been studied systematically. Another knowledge gap being addressed is exposure misclassification originating from the difference between noise modeled at the façade and noise immission indoors. To this end, data from the Heinz Nixdorf Recall cohort was used, representing a population-based study in the densely populated Ruhr Area, namely the three cities Mülheim, Essen and Bochum. The randomly selected 4,814 individuales aged 45 to 75 years underwent several examinations comprising numerous laboratory tests, interviews and questionnaires at baseline (2002- 2003) and first follow-up examinations (2006-2008). The study was approved by the Ethics Commission of the University Hospital Essen (ethics vote reference numbers: 99-69-1200; 11-4678).

1.5.1 Specific aims and hypotheses

- The first aim of the study was to investigate the association between residential long-term daily-averaged (L_{den}) and night (L_{night}) road traffic noise exposure and incident T2DM – assessed by blood glucose concentrations, reported physician's diagnosis and diabetes medication - in adults between baseline (2002-2003) and the first follow-up (2006-2008).
- The second aim of the study was to analyse the role of air pollution, namely NO_2 and $PM_{2.5}$, as a potential confounder for the association between long-term road-traffic noise exposure and incident T2DM in order to gain insight in the independence of the association in relation to air pollution exposure.
- The third aim of the study was to investigate potential exposure misclassification by taking into account factors modulating the difference between exposure modeled at the façade of the residential building and noise immission indoors. On that basis, the aim was to examine the association between long-term residential long-term daily-averaged (L_{den}) and night (L_{night}) road traffic noise exposure indoors and incident diabetes.

2. Publication - Indoor and outdoor road traffic noise and incident diabetes mellitus: Results from a longitudinal German cohort study

Ohlwein S, Hennig F, Lucht S, Matthiessen C, Pundt N, Moebus S, Jöckel KH, Hoffmann B. Indoor and outdoor road traffic noise and incident diabetes mellitus: Results from a longitudinal German cohort study. Environ Epidemiol. 2019 Feb 12;3(1):e037. doi: 10.1097/EE9.0000000000000037. PMID: 33778334; PMCID: PMC7952109.

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Indoor and outdoor road traffic noise and incident diabetes mellitus: Results from a longitudinal German cohort study

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Background: Road traffic noise affects a large number of people in urbanized areas. Recent epidemiological evidence indicates that environmental noise exposure may not only be associated with cardiovascular but also with cardio-metabolic outcomes. This prospective cohort study investigated the effect of outdoor and indoor residential road traffic noise on incident type 2 diabetes mellitus (T2DM).
Methods: We used data from 3,396 participants of age 45–75 years of the Heinz Nixdorf Recall study being non-diabetic at baseline (2000–2003). T2DM was defined via blood glucose level, incident intake of an anti-diabetic drug during follow-up or self-reported physician diagnosis at follow-up examination (2005–2008). Weighted 24-h (L_{dan}) and night-time (L_{night}) mean road traffic noise was assessed according to the European Union directive 2002/49/EC. Road traffic noise exposure indoors was modeled taking into account the participants' room orientation, ventilation behavior and window insulation (n = 2,697). We applied Poisson regression analyses to estimate relative risks (RRs) of incident T2DM, adjusting for demographic characteristics, lifestyle factors, and air pollution exposure (NO_2 or $PM_{2.5}$).
Results: A 10-dB(A) increase in outdoor road traffic noise (L_{dan}) was associated with an RR of 1.09 (95% confidence interval, 0.96–1.24) for T2DM in the fully adjusted model. Models including $PM_{2.5}$ or NO_2 yielded RRs of 1.09 (0.96–1.24) and 1.11 (0.97–1.27), respectively. In analyses with road traffic noise (L_{dan}) exposure indoors, we observed similar RRs with smaller confidence intervals (1.11 [1.01–1.21]).
Conclusions: Our analyses suggest that long-term exposure to indoor and outdoor road traffic noise may increase the risk of developing T2DM, independent of air pollution exposure.

Introduction

Noise is a growing environmental health problem causing at least 10,000 premature deaths in Europe annually.[1] Surpassing railway, aircraft, and industry, road traffic represents the most ubiquitous source of noise in Europe both inside and outside urban areas: In 2012, about 100 million Europeans were affected by road-traffic noise exceeding the recommended day, evening, and night noise levels of 55 decibels (dB(A)).[2] In the last few decades, evidence supporting a harmful association between noise exposure and various aspects of cardiovascular health has accumulated.[3] Recently, first epidemiologic studies investigated associations between noise and metabolic outcomes, observing positive associations between road traffic noise and type 2 diabetes mellitus (T2DM).[4–7] Potential biological pathways of traffic noise–related health effects include noise-induced stress, activating the autonomic nervous system/hypothalamus–pituitary–adrenal (HPA) axis both directly and through the personal perception of noise as a stressor, the so-called noise annoyance. A second pathway links exposure to ambient night noise to sleep disturbances, which may also lead to altered metabolic functions.[8,9] Epidemiologic studies support this theory, showing that both short-term and long-term exposure to environmental traffic noise was associated with an increase in body mass index (BMI) and/or waist circumference (WC).[10–13] Imprecise exposure assessment to road traffic noise may originate from noise-abating factors of the outer shell of the residence. The three studies that previously investigated indoor noise exposure differed from our study in that they evaluated other endpoints (e.g., blood pressure[14] and markers of obesity[13] or used only the bedroom orientation as a surrogate marker for indoor noise exposure.[5,13] The use of indoor noise levels has the advantage of less exposure misclassification and less correlation with air pollution (AP) levels and thus reduced potential confounding

What this study adds

- Our study adds to prior evidence that traffic noise is associated with cardio-metabolic disease.
- Estimates for noise exposure were robust to air pollution adjustment, indicating independence of associations.
- Using modeled indoor noise by including information on window orientation and insulation can improve estimation of traffic noise exposure.

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Availability of Data and Code: Data of the Heinz Nixdorf Recall (HNR) cohort can be provided upon agreement of the Institute of Medical Informatics, Biometry and Epidemiology in Essen by the corresponding author. The code for reproduction of the analyses can be obtained through contacting the corresponding author.

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by AP. As AP and traffic noise exposure share traffic as a common source, considering only one of the two exposures in an analysis may lead to confounded associations.[15] This is of particular relevance when researching cardio-metabolic outcomes, as current evidence suggests a possible positive association between AP and T2DM.[16–18] The aim of this study was to investigate the association between long-term residential exposure to road traffic noise and incident T2DM during a mean follow-up period of 5 years, using several measures of noise exposure outside and inside the residence within the German population-based Heinz Nixdorf Recall (HNR) cohort.

Materials and methods

Study population

We used data from the population-based longitudinal HNR (Risk factors, evaluation of coronary calcium and lifestyle) cohort study located in three adjacent cities (Bochum, Essen, and Mülheim/Ruhr) within the highly urbanized German Ruhr Area. Information on the study design has been described elsewhere.[19,20] In short, 4,814 participants (45–75 years of age), randomly selected (age-stratified) from municipal population registries, were recruited at baseline (response rate 56.0%) between December 2000 and August 2003 (Figure 2). About 5 years later (2006–2008), the first follow-up examination was performed including 4,157 participants (response rate of eligible participants 90.2%). Assessments included self-administered questionnaires, face-to-face interviews, clinical examinations, and comprehensive laboratory analyses. The HNR study was approved by the ethics committee of the University Hospital Essen. All participants gave their written informed consent.

Noise assessment

Outdoor road traffic noise was modeled according to the 2002/49/EC Directive.[21] Noise modeling was performed on behalf of the local city administrations who supplied source-specific traffic noise values applying the VBUS/RLS-90[22] method and using the software CadnA.[23] For the year 2006, averaged day–evening–night (24-hour) noise levels (L_{den}) and averaged levels of nighttime noise (L_{night}, 22:00–06:00 hour) were modeled considering the following factors: small-scale topography of the area, building dimensions, noise barriers, street axis, type-specific vehicle traffic density, speed limit, and type of road surface.[22] The indicator L_{den} is a weighted noise value integrating 12 hours for day (6:00–18:00), 6 hours for evening (18:00–22:00), and 8 hours for nighttime (22:00–6:00). L_{den} considers increased annoyance reactions toward traffic noise during evening and night hours, by adding a penalty of 5 dB to evening noise levels and a penalty of 10 dB to night noise levels. The immission of noise at the participant's residence was estimated at a height of 4 ± 0.2 m selecting the highest estimated noise level within a buffer of 10 m from the residence. In the HNR study, we used noise values estimated at the residential addresses of study participants at baseline (2000–2003), applying the geographic information system ArcGIS. We thereby assumed that average noise levels were relatively stable over time in terms of spatial distribution and exposure level.

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Indoor noise from outside sources (i.e., traffic) was estimated for 2,697 study participants through combining outdoor noise values (L_{den} and L_{night}) with individual apartment information, which was collected in the 3- to 4-year follow-up questionnaire. Indoor noise values for the living room (Indoor L_{den}) and the bedroom (Indoor L_{night}) were derived from outdoor noise estimates through information on room and window orientation, window opening/closing habits, and window type[14] (Figure 1). If the room was facing a street other than the postal address street or a side street, 20 dB(A) were subtracted from the outdoor noise level, according to a model for traffic noise in cities.[24] Otherwise, room-specific outdoor noise estimates were assumed

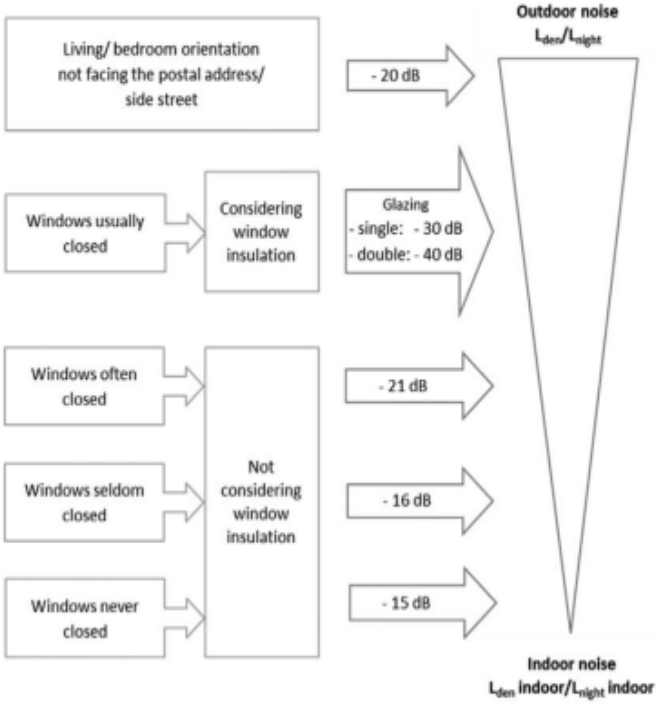

Figure 1. Indoor noise model.

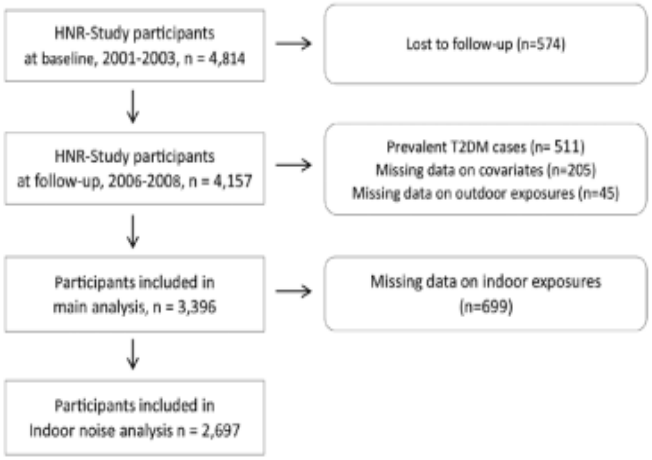

Figure 2. Flowchart of the study population.

to be similar to the noise estimates at the participants' postal address. In addition, participants were asked about their seasonal ventilation behavior. Two separate noise values were then calculated considering days with average temperatures above 10°C, which is the approximate mean temperature in the study area, as warm season (265 days) and days with average temperatures below 10°C (100 days) as cold season. If the windows were usually closed, we subtracted 30 dB(A) from the estimated room-specific outdoor noise level for single- or double-glazed windows and 40 dB(A) for sound-proof windows, according to the Good Practice Guide on Noise Exposure and Potential Health Effects (EEA 2010). "Often" (75% of the time), "seldom" (25% of the time) or "never" closed windows were taken into account by subtracting 21, 16, and 15 dB, respectively, from the room-specific noise estimates, without considering the window type. Any negative indoor noise estimates were set to zero.

Air pollution assessment

AP exposure levels for fine particulate matter ($PM_{2.5}$) and nitrogen dioxide (NO_2) were assessed by a land use regression model (LUR). The LUR model was established according to the European Study of Cohorts for Air Pollution Effects (ESCAPE) standardized procedure (ESCAPE-LUR) to estimate point-specific long-term outdoor AP.[20,25] The models performed well with R^2 of 0.88 and 0.89 for $PM_{2.5}$ and NO_2, respectively. For details, see Supplement; http://links.lww.com/EE/A29.

Assessment of type 2 diabetes mellitus

Blood glucose was assessed by glucose measurements at baseline and follow-up examinations in the University Hospital of Essen according to standardized procedures. Incident T2DM at follow-up was identified if one of the three criteria were met: (1) random blood glucose ≥200 mg/dL or fasting blood glucose ≥126 mg/dL, (2) intake of an anti-diabetic drug (ATC code A10) during follow-up, or (3) self-reported physician diagnosis after baseline assessed at follow-up examination[18] in those free of diabetes mellitus at baseline. Baseline T2DM cases were identified applying the same criteria. As study participants were aged over 45 years at baseline examinations, we assume most incident diabetes diagnoses likely to be T2DM.

Covariates

Socioeconomic, demographic and behavioral characteristics of the study population were assessed at baseline via standardized interviews and self-administered questionnaires. Height, weight, and WC were obtained from standardized anthropogenic measurements performed during the clinical examination. BMI was calculated as weight in kilograms per square meter. The individual socioeconomic status (SES) was defined as years of education according to the International Standard Classification of Education 1997[26] and was categorized into four groups (≤10, 11–13, 14–17, and ≥18 years). In addition, neighborhood SES was assessed as the unemployment rate of the neighborhood for each residential neighborhood according to administrative bounds (median size: 11,263 inhabitants). Smoking status was categorized as current smoker (during the past year), former smoker, and never smoker. Lifetime cumulative smoking exposure was assessed in pack-years. Self-reported exposure to secondhand smoke (SHS) at home, at the work place, or in other places was combined into one variable. Nutrition was assessed using a food frequency questionnaire and included in this analysis as a 26-point score (categorized in quantiles as <10, 10–12, 13–14, 15–23), with low scores characterizing a poor diet and high scores characterizing high-quality diet.[27,28] Alcohol consumption was considered as regular consumption of alcoholic drinks per week, classified as <3, 3–6, 7–20, and >20 drinks. Physical activity was assessed as binary outcome variable representing at least 30 minutes physical activity per week as well as continuous variable of weekly hours of metabolically relevant exercise. High depressive symptoms during the previous week were assessed using the 15-item short-form questionnaire of the Center for Epidemiologic Studies Depression Scale (CES-D) and included as binary variable (score of <17 versus ≥17).[29,30] Employment status was categorized as employed, pensioner, or unemployed/inactive/housewife. Annoyance due to road traffic noise during the day and at night was assessed via questionnaire in five categories. Hypertension was defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or intake of blood pressure–lowering medication.

Statistical methods

We compared participants being less exposed to median noise levels (<52.25 dB) versus participants exposed to noise levels equal or above median (52.25 dB). Furthermore, we compared participants excluded due to missing data on covariates and/or exposures (n = 250) to the main study population (3,396), investigating differences in the baseline characteristics. Due to missing information on indoor noise exposure in a part of the study population, a reduced analysis sample (n = 2,697) was used for analysis of indoor noise and incident T2DM. Spearman correlation coefficients were calculated between estimated levels of

noise and AP. We used Poisson regression adapted to binary outcomes to estimate the relative risks (RRs) and 95% confidence intervals (95% CIs) for incident T2DM per 10 dB(A) increase for each noise exposure.[31] Noise exposures were included as continuous variables. For the analysis of the association of noise with T2DM, we used threshold models 45 dB for L_{den} and 35 dB for L_{night}, based on previous findings on potential health effects.[32,33] Threshold values for indoor noise originating from outdoor traffic (20 dB [L_{den}] and 10 dB [L_{night}]) were selected according to the distribution of the outdoor noise thresholds (approximately 16% of the values were below the threshold). All noise values lower than the defined threshold values were equated to the threshold value. According to current epidemiologic and clinical evidence, we identified potential confounders for inclusion in our models following the construction of a directed acyclic graph (eFigure S1; http://links.lww.com/EE/A29). Single-pollutant models were built with increasing covariate adjustment. Model 1 included age, sex, individual, and neighborhood SES; the fully adjusted model 2 was additionally adjusted for smoking status, pack-years, SHS, any regular physical activity, weekly physical activity, alcohol consumption, and nutrition index. Multipollutant models additionally included $PM_{2.5}$ or NO_2. In separate models, we included WC, BMI, and depressive symptoms as possible mediators. Linearity assumptions for continuous noise variables and covariates were evaluated using polynomials and comparing the models via Wald tests. For WC, nonlinearity was present ($P = 0.03$ compared to the nonfitted), and we therefore added a squared term to the model.

Effect modification

Multiplicative interaction terms were constructed to investigate possible effect modification of noise exposure by age (<65 and ≥65 years), sex (male/female), hypertension (yes/no), smoking status (never/former/current), SHS (no/yes), annoyance (not at all or slightly versus moderately or very or extremely annoyed), distance to a major road (>150/<150 m), and educational level (≤13 years/≥14 years).

Sensitivity analyses

We performed sensitivity analyses for the main models excluding participants who changed their residential addresses between baseline and follow-up examination to minimize exposure misclassification. Since evidence on possible noise thresholds for metabolic diseases is scarce, we further performed sensitivity analyses using different outdoor noise threshold values (55 dB for L_{den} and 45 dB for L_{night}). Additionally, we analyzed noise exposures as categorical variables using quantiles (<46.7, 46.7–52.3, 52.3–61.1, >61.1 dB). Analyses were performed with R version 2.13.1 (R Core Team 2013) software.

Results

We included 3,396 participants free of diabetes mellitus at baseline (Figure 1), of whom 305 (9.0 %) developed T2DM over a mean follow-up time of 5.1 years, with 162 participants self-reporting onset of T2DM or receiving antidiabetic medication and 211 participants having elevated blood glucose levels. The participants had a mean age of 58.8 years (SD 7.6; Table 1). According to the definition of the World Health Organization (based on BMI), 22.4% of the participants were obese and 47.2% overweight.[34] 5.3% and 2.5% of our participants were very or extremely annoyed by traffic noise at daytime and nighttime, respectively. Highly exposed participants reported more unfavorable health behaviors or conditions with, for example fewer education years, higher actual or former smoking rates, and less physical activity. The main study population differs in several ways from participants excluded due to missings on covariates or exposure data (n = 250). Excluded participants tended to be older, to be less educated, to have a higher WC, to be less physically active, to have worse dietary habits, and tended to live in a neighborhood with a higher unemployment rate (eTable S1; http://links.lww.com/EE/A29). Mean noise exposure values at the baseline home address were 53.9 dB for the weighted 24-hour average and 45.1 dB at night (Table 2; eFigure S2; http://links.lww.com/EE/A29). Indoor noise levels were on average 20 dB lower than the outdoor values (means for L_{den} and L_{night} indoor: 35.0 and 27.2, respectively) analyses. eTable S2; http://links.lww.com/EE/A29 showed moderate correlations between indoor and outdoor noise (0.43–0.50). AP exposures were moderately correlated with outdoor noise exposures (0.30–0.37) and weakly correlated with indoor noise levels (0.15–0.22).

Table 1

Baseline characteristics of the study population (n = 3,396), stratified by median noise exposure.

Characteristics	L_{den} < 52.25 (n = 1,698)	L_{den} ≥ 52.25 (n = 1,698)	*P* value[a]
Age (years), mean ± SD	58.8 ± 7.6	58.8 + 7.6	0.96
Sex (male), N (%)	810 (47.7)	808 (47.6)	0.97
Employment status, N (%)[b]			
Employed	756 (44.5)	753 (44.4)	0.34
Inactive/housewife/pensioner/unemployed	941 (55.5)	944 (55.6)	
Education, N (%)			
≤10 years	141 (8.3)	158 (9.3)	<0.01
11–13 years	917 (54.0)	995 (58.6)	
14–17 years	399 (23.5)	369 (21.7)	
≥18 years	241 (14.2)	176 (10.4)	
Unemployment rate in neighborhood (%), mean ± SD	11.8 ± 3.3	12.9 ± 3.4	<0.001
BMI (kg/m²), mean ± SD	27.4 ± 4.2	27.4 ± 4.4	0.62
BMI, N (%)			
<25	505 (29.7)	525 (30.9)	0.27
25–30	825 (48.6)	779 (45.9)	
>30	368 (21.7)	394 (23.2)	
Waist circumference men (cm), mean ± SD	99.1 + 10.0	98.82 + 10.3	0.11
Waist circumference women (cm), mean ± SD	86.5 + 11.5	87.1 + 12.3	0.13
Weekly physical activity, N (%)	1,022 (60.2)	955 (56.2)	<0.05
Metabolic effective activity/week (hours), mean ± SD	12.1 + 22.0	11.5 + 24.79	0.46
Nutrition score, mean ± SD	12.7 + 3.0	12.6 + 3.2	0.71
Drinks/week, mean ± SD	5.8 + 10.1	5.5 + 9.9	0.48
Smoking status, N (%)			
Never smoker	759 (44.7)	723 (42.6)	<0.05
Former smoker	593 (34.9)	568 (33.5)	
Current smoker	346 (20.4)	407 (24.0)	
Pack-years of current/former smokers, mean ± SD	30.1 + 21.2	31.5 + 24.7	0.14
Exposure to second-hand smoke	561 (33)	655 (38.6)	<0.01
Daytime annoyance, N (%)[c]			
Not at all annoyed	997 (66.7)	583 (37.8)	<0.001
Slightly/moderately annoyed	474 (31.7)	822 (53.3)	
Very/extremely annoyed	23 (1.5)	137 (8.9)	
Nighttime annoyance, N (%)[d]			
Not at all annoyed	1,241 (83.0)	961 (62.6)	<0.001
Slightly/moderately annoyed	245 (16.4)	507 (33.1)	
Very/extremely annoyed	10 (0.7)	66 (4.3)	

[a]*P* values were derived from (a) Student's *t* tests for continuous variables and (b) Wilcoxon signed-rank tests for categorial variables.
[b]Two missings.
[c]Two hundred four of 196 missings for those exposed to L_{den} < 52.25 and ≥52.25, respectively.
[d]Two hundred two of 164 missings for those exposed to L_{den} < 52.25 and ≥52.25, respectively.

Associations between noise and T2DM

Our regression analyses showed overall weak positive but nonsignificant associations between outdoor road traffic noise and T2DM incidence in all models (Table 3). For example, a 10 dB

Table 2

Description of noise and air pollution exposures (2008–2009 annual means) assigned to the home address of study participants at baseline (n = 3,396)

Exposures	Min	Q1	Median	Q3	Max	Mean ± SD	IQR
L_{den} (dB)	25.9	46.7	52.3	61.1	84.6	53.9 ± 9.4	14.4
L_{night} (dB)	16.8	38.2	43.6	52.0	76.3	45.1 ± 9.1	13.8
L_{den}, indoors[a] (dB)	0.0	24.0	34.8	45.6	78.1	35.0 ± 15.3	21.6
L_{night}, indoors[a] (dB)	0.0	15.4	27.2	39.3	67.0	27.2 ± 15.7	23.9
$PM_{2.5}$ (µg/m³)	16.1	17.6	18.3	19.1	21.5	18.4 ± 1.1	1.5
NO_2 (µg/m³)	19.8	26.8	29.5	33.0	62.4	30.2 ± 4.9	6.2

[a]Indoor noise values refer to the participants with information on apartment characteristics and ventilation behavior (n = 2,697). 0 values originate from the indoor estimation method. In the regression models, 20 dB and 10 dB were chosen as lowest cutpoints for minimum indoor L_{den} and indoor L_{night} levels, respectively.
NO_2, nitrogen dioxide; $PM_{2.5}$, fine particulate matter.

Table 3

Relative risks and 95% confidence intervals for T2DM per 10 dB increase of outdoor noise exposure in the Heinz-Nixdorf-Recall Study Population (n = 3,396)

	L_{den}	L_{night}
Crude	1.12 (0.99–1.26)	1.12 (0.99–1.27)
M1[a]	1.09 (0.96–1.24)	1.09 (0.96–1.24)
M2[b]	1.09 (0.96–1.24)	1.09 (0.96–1.23)
Multipollutant analyses		
M2 + $PM_{2.5}$	1.09 (0.96–1.24)	1.09 (0.96–1.24)
M2 + NO_2	1.11 (0.97–1.27)	1.11 (0.97–1.27)
Mediation analyses		
M2 + WC	1.07 (0.95–1.21)	1.07 (0.95–1.21)
M2 + BMI	1.08 (0.96–1.23)	1.08 (0.96–1.23)
M2 + depressive symptoms	1.09 (0.96–1.24)	1.09 (0.96–1.24)

[a]Adjusted for age and sex.
[b]Additionally adjusted for education and neighborhood unemployment rate.
[c]Additionally adjusted for nutrition, alcohol consumption, smoking status, pack-years, SHS, physical activity (yes/no), weekly metabolic physical activity.
NO_2, nitrogen dioxide; $PM_{2.5}$, fine particulate matter.

increase in L_{den} resulted in an RR of 1.09 (0.96–1.24) in the fully adjusted model (M2). Multipollutant models including $PM_{2.5}$ or NO_2 resulted in similar RRs (e.g., for L_{den} RR 1.09 [CIs, 0.96–1.24] and 1.11 [CIs, 0.97–1.27], respectively). Due to their high correlation (0.99), results for L_{den} and L_{night} were very similar. Including WC, BMI, or depressive symptoms in the analysis did not change the estimates substantially. Results of categorical analyses and Wald tests suggested a linear relationship between outdoor noise and T2DM. In the analysis of indoor noise exposures (n = 2,697; 233 [8.6%] incident cases of T2DM at follow-up), we found similar point estimates, but the CIs were smaller (Table 4). Sensitivity analyses excluding 560 participants who had moved between baseline and follow-up examinations led to slightly increased point estimates, for example, RR for L_{den} in the fully adjusted model (M2) was 1.14 (0.99–1.30; eTable S3; http://links.lww.com/EE/A29). Analyses considering noise variables with 10 dB higher thresholds for L_{den} (55 dB) and L_{night} (45 dB) also showed higher RRs, for example, 1.15 (0.95–1.39) for L_{den} (eTable S4; http://links.lww.com/EE/A29). Analyses using noise categories showed increasing point estimates with higher noise levels. However, CIs were very large (eTable S5; http://links.lww.com/EE/A29). Effect estimates were higher for physically active ($P = 0.01$) and employed participants ($P = 0.09$) than for physically inactive and pensioners/housewives/unemployed participants (eFigure S3; http://links.lww.com/EE/A29). Most interaction analyses did not yield clear results due to wide CIs, specifically for effect modification by annoyance.

Discussion

In our population-based study, we found a positive association between road traffic noise exposure and incident T2DM. This association was independent of concurrent AP exposure. We observed similar point estimates with smaller CIs in an analysis with indoor noise exposure in a reduced sample. Sensitivity analyses with different noise thresholds and subgroups supported our conclusions.

Pathomechanisms

A large body of evidence has accumulated on the effects of noise on health.[35] The activation of the autonomic nervous system and the HPA axis are main components of an unspecific stress response, which in turn induces pathophysiological metabolic mechanisms in several organ systems (Münzel et al. 2016a).[36] Metabolic dysregulation promotes the secretion of the adrenal glucocorticoid cortisol. Besides an increase in blood pressure, viscosity, and clotting, chronically elevated glucocorticoid levels may in particular inhibit pancreatic insulin secretion and decrease insulin sensitivity in skeletal muscle, liver, and adipose tissue.[36] The contribution of acute inflammation processes and oxidative stress is still under discussion.[36,37] Experimental studies in rats underscore the role of stress-induced responses on the metabolic system, mediated by inflammatory processes: Exposure to noise was related to increased levels in inflammatory markers, elevated glucocorticoid levels, and decreased hepatic insulin sensitivity.[38–40] A recent toxicological study in mice[39] observed reduced weight gain and adipose tissue gain in mice chronically exposed to noise compared to mice without noise exposure. However, noise-exposed mice had increased blood levels of free fatty acids, indicating a poor glycemic control, probably induced by high levels of stress hormones. A second pathway emphasizes the role of sleep disturbances, which may be partly caused by nighttime traffic noise. Noise may provoke both unconscious and conscious physiologic arousals at night, causing sleep disturbances that lead to multiple physiological, psychological, and social health consequences.[41] Specifically, sleep deprivation is known to alter energy metabolism, resulting in dysregulated glucose and appetite regulation, both representing potential mediators in the development of diabetes.[8,36,42]

Comparison to other studies

Three recently published prospective cohort studies investigating the association between road traffic noise and incident T2DM showed similar or even more pronounced results in comparison to ours.[5,6,43] In contrast, a study investigating the effect of aircraft noise on pre-diabetes and T2DM reported unclear associations.[10] This might be a consequence of different noise patterns of aircraft noise compared to road traffic noise. Second, Eriksson et al.[10,13] also included psychological distress which could have acted as a mediator and therefore attenuated risk estimates. In line with our results, two studies[10,13] observed increased effect estimates for those participants who did not move during the study period.

Table 4

Relative risks with 95% CIs for T2DM per 10 dB increase of outdoor and indoor noise exposure in the Heinz-Nixdorf-Recall study population (n = 2,697)

	L_{DEN}		L_{NIGHT}	
	Outdoor	Indoor	Outdoor	Indoor
Crude	1.12 (0.97–1.29)	1.11 (1.01–1.21)	1.12 (0.97–1.29)	1.10 (0.99–1.23)
M1[a]	1.10 (0.95–1.27)	1.10 (1.00–1.20)	1.10 (0.95–1.27)	1.11 (1.00–1.23)
M2[b]	1.10 (0.95–1.27)	1.11 (1.01–1.21)	1.10 (0.95–1.27)	1.11 (1.00–1.24)
Multipollutant analyses				
M2 + $PM_{2.5}$	1.09 (0.93–1.25)	1.10 (1.01–1.21)	1.10 (0.94–1.27)	1.11 (1.00–1.24)
M2 + NO_2	1.11 (0.96–1.30)	1.11 (1.01–1.22)	1.11 (0.96–1.30)	1.12 (1.01–1.24)
Mediation analyses				
M2 + WC	1.08 (0.93–1.24)	1.07 (0.98–1.17)	1.08 (0.93–1.24)	1.09 (0.98–1.20)
M2 + BMI	1.09 (0.95–1.26)	1.08 (0.98–1.18)	1.09 (0.95–1.26)	1.08 (0.98–1.20)
M2 + depressive symptoms	1.10 (0.95–1.27)	1.11 (1.01–1.21)	1.10 (0.95–1.27)	1.11 (1.00–1.24)

[a]Adjusted for age and sex.

[b]Additionally adjusted for education and neighborhood unemployment rate.

[c]Additionally adjusted for nutrition, alcohol consumption, smoking status, pack-years, SHS, physical activity (yes/no), weekly metabolic physical activity.

$PM_{2.5}$, fine particulate matter; NO_2, nitrogen dioxide.

Mediating factors

The evidence base of overweight/obesity being a possible mediator for the association between road traffic noise and T2DM remains conflicting, with several epidemiological studies observing positive associations between noise and the obesity markers BMI and/or WC[10,13] or both,[11] while others found no associations for BMI[10,12] or any markers of obesity.[13] Our study indicates a minor mediating role of obesity assessed by WC as a marker of central adipose tissue or BMI, with hardly reduced effect estimates in the models adjusted for WC or BMI. Another factor influencing the relationship between noise and T2DM might be high depressive symptoms through annoyance, sleeping disorders, and/or several physiological stress effects: A depression-related activation of the autonomic nervous system and the HPA axis may promote inflammatory processes which could contribute to the development of T2DM.[44] The evidence base for the link between noise and depression is very limited, while the evidence regarding the association between depression and T2DM is conflicting.[41,42] In our study, there was no sign of high depressive symptoms mediating the association between road traffic noise and T2DM.

Noise exposure in the context of AP

While the underlying pathomechanisms of noise and AP with regard to metabolic health effects overlap to some extent, they differ in several ways. Exposure to AP and noise both increase the activation of the nervous system able to induce metabolic imbalance, but noise perception partly represents a psychological stressor, whereas AP acts without major personal perception. Furthermore, originating from traffic as a common source, road traffic noise and AP are highly interrelated, due to diverging dispersion patterns. Although AP dispersion depends highly on meteorological conditions, noise is influenced strongly by noise barriers and buildings. Specifically, the building density influences correlations of noise and AP with street canyons, leading to higher correlations.[43] Furthermore, traffic attributes as volume, speed, and vehicle type lead to different dispersion patterns.[15,43] Two review articles point out the need to disentangle these potentially mutually confounded exposures.[15,44] In our study, participants were affected by noise and AP differently with only a moderate correlation. Upon mutual adjustment, estimates remained stable, indicating independence of noise effects from AP in our study area.

Indoor noise exposure and T2DM

Indoor noise exposure may better reflect the true personal exposure and is less correlated with ambient AP exposure. While a few studies have analyzed indoor noise exposures with cardiovascular and metabolic health outcomes, to our knowledge, there is no other study investigating indoor noise exposures with T2DM. One cross-sectional study in Spain focused on noise-related hypertension and blood pressure.[14] In this study area, outdoor road traffic noise and ambient AP were highly correlated, leading to instable results in mutually adjusted regression analyses. However, when using indoor noise estimates, they found more consistent associations for indoor noise than for outdoor noise exposure. In comparison, our outdoor noise exposures are less correlated with AP exposures than in Foraster's study (0.37 vs. 0.75), which may explain why our indoor and outdoor noise exposure-related RRs in the two-pollutant models are similar. Importantly, both Forasters' and our study observed more precise effect estimates when using indoor noise exposure estimates. Similarly, a Swiss study by Eze et al.[5] observed stronger associations between road traffic noise and T2DM in participants with bedrooms facing the street or sleeping with open windows.[5] Another study investigating the association between road traffic noise and markers of obesity found positive associations for the subset of participants with bedrooms facing a road.[13] Overall, our study and the other studies mentioned above suggest that derived indoor noise estimates may reduce exposure estimation error and may be a more precise marker for the actual noise exposure of individuals than outdoor noise and may help disentangle overlapping effects of ambient AP and ambient noise, specifically in situations of high correlation.

Strengths and limitations

A strength of our study is the prospective design in a population-based cohort with detailed assessment of demographic and lifestyle factors. In addition, we were able to use both indoor and outdoor noise variables for this analysis. We further were able to use two-exposure models with both PM and NO_2. One limitation with regard to our results is that our study had limited statistical power to find significant associations between noise and T2DM. Another limitation is that information on family history of diabetes and/or metabolic diseases was not available. Furthermore, we had no information on hearing aid use or aural deficits among our participants. In addition, we lacked information on traffic noise from railway traffic. Aircraft noise was not included in this analysis, because only a very small part of the study population (less than 1%) was estimated to be exposed to elevated noise levels from aircraft traffic. Moreover, indoor noise models have not been validated yet. We also had no information on noise exposure at work or time spent at the residence.

Finally, a possible selection effect toward healthier and better-educated participants at baseline and a possible healthy survivor effect may have biased our effect estimates.

Conclusions

Our analyses of a population-based prospective cohort study suggest that long-term exposure to indoor and outdoor road traffic noise may increase the risk of developing T2DM, independent of AP exposure. Using estimated indoor noise exposures derived from individual apartment information improves estimation of noise effects

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Conflict of interest statement

The authors declare that they have no conflicts of interest with regard to the content of this report.

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2.1 Publication appendix

Supplement

Assessment of air pollution

Fine particulate matter (PM) of aerodynamic diameter less than 2.5 µm ($PM_{2.5}$) was measured at 20 sites, and nitrogen oxides (NO_2) was measured at 40 sites in three separate two-week periods (to cover different seasons) over one year (Beelen et al. 2013; 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 and to predict concentrations at each participant's address. In the Ruhr Area, the models explained 88% of the variability in the annual concentrations of $PM_{2.5}$ and 89% of that for NO_2 (Beelen 2013; Eeftens et al. 2012; Hennig et al. 2016).

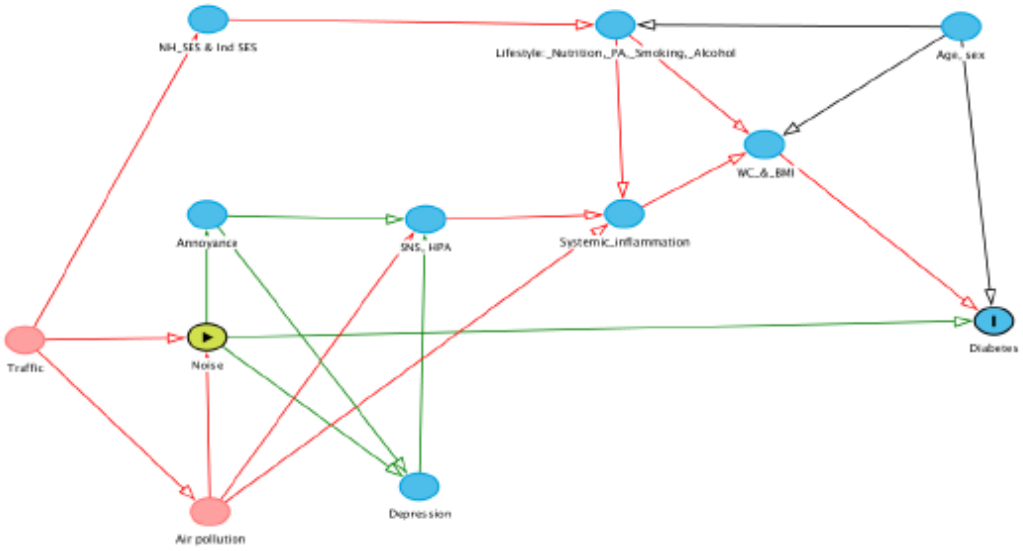

Figure S1: Directed acyclic graph (DAG) for the relationship between Noise and T2D

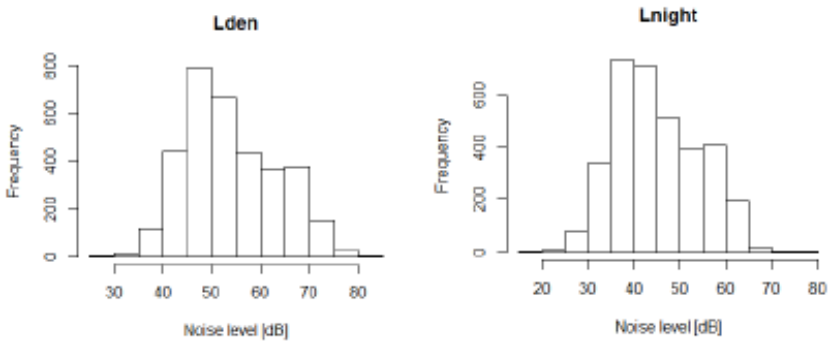

Figure S2: Distribution of the outdoor noise levels L_{den} and L_{night} in the main study population (3,646)

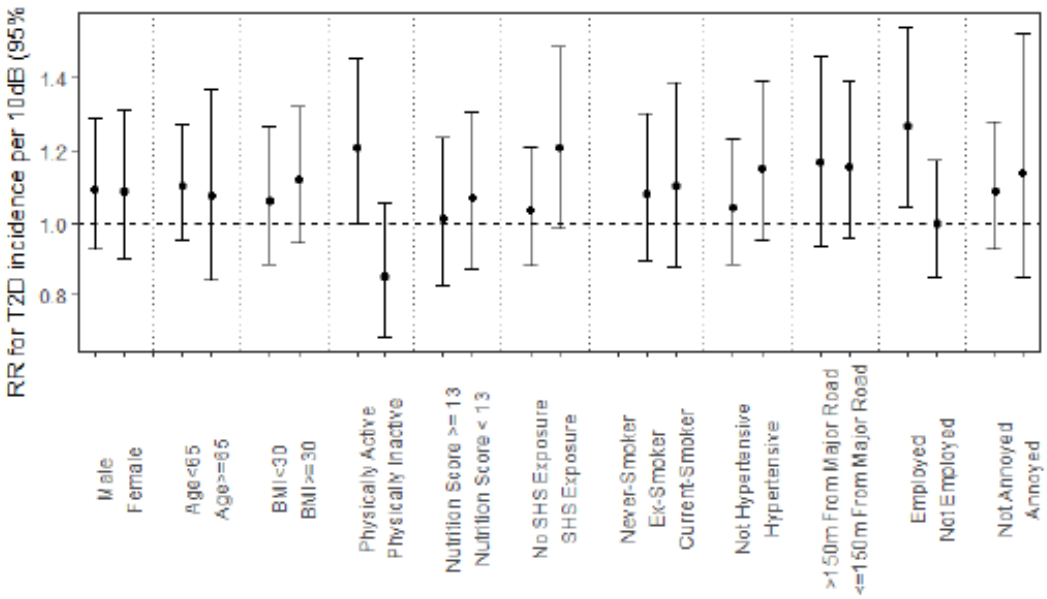

Figure S3: Interaction-based relative risks (RR (95% CI)) for T2DM per 10 dB increase of L_{night} in the study population (n=3,396). Models with versus without interaction terms were compared using Wald tests. P-values < 0.05 were considered as an indicator for effect modification.

Table S1: Comparison of the main study population and those participants excluded due to missing exposure and covariate data (3,646)

Baseline Characteristics	Main study population (n=3,396)	Missing values	Participants excluded due to missing data (n=250)	Missing values	P-value[a]
Age [years]; mean ± SD	58.8 ± 7.6	0	61.2 ± 8.0	0	<0.001
Sex (male); N (%)	1,618 (47.6)	0	108 (43.2)	0	0.196
Education years, N (%)					
≤10 years	299 (8.8)	0	58 (23.7)	5	<0.001
11-13 years	1,912 (56.3)		126 (51.4)		
14-17 years	768 (22.6)		45 (18.4)		
≥18 years	417 (12.3)		16 (6.5)		
Unemployment rate in neighborhood; mean ± SD	12.3 ± 3.4	0	13.0 ± 3.6	0	<0.01
BMI [kg/m²]; mean ± SD	27.5 ± 4.3	0	27.9 ± 4.6	15	0.14
BMI < 25; N (%)	1,030 (30.3)	0	65 (27.7)	15	0.48
BMI 25-30; N (%)	1,604 (47.2)		110 (46.8)		
BMI > 30; N (%)	762 (22.4)		60 (25.5)		
Waist circumference [cm]; mean ± SD	92.6 ± 12.6	0	94.2 ± 14.2	10	0.09
Weekly physical activity; N (%)	1,977 (58.2)	0	119 (47.6)	0	<0.01
Metabolic effective activity/week [hours]; mean ± SD	11.8 ± 23.4	0	8.6 ± 18.9	11	<0.05
Nutrition index; mean ± SD	12.6 ± 3.1	0	13.2 ± 3.4	55	<0.05
Smoking status; N (%)					
Non-smoker	1,482 (43.6)	0	106 (42.4)	0	0.93
Ex-smoker	1,161 (34.2)		87 (34.8)		
Current smoker	753 (22.2)		57 (22.8)		
Packyears; mean ± SD	14.9 ± 24.0	0	15.1 ± 22.0	28	0.92
Secondhand smoke; N (%)	1,216 (35.8)	0	81 (33.1)	5	0.42
Annoyance day; N (%)					
Not annoyed	1,580 (52.0)	360	116 (58.3)	51	0.22

Slightly/ moderately annoyed	1,296 (42.7)		73 (36.7)		
Very/ extremely annoyed	160 (5.3)		10 (5.0)		
Annoyance night; N (%)					
Not annoyed	2,202 (72.7)	366	158 (77.8)	47	0.19
Slightly/ moderately annoyed	752 (24.8)		39 (19.2)		
Very/ extremely annoyed	76 (2.5)		6 (3.0)		

*P-values were derived from a) Student's t-tests for continuous variables and b) Wilcoxon signed-rank tests for categorial variables

Table S2: Correlations between noise and AP exposures at baseline (n=3,396)

	L_{den}	L_{night}	L_{den}, indoor	L_{night}, indoor	$PM_{2.5}$	NO_2
L_{den}	1	0.99	0.50	0.43	0.30	0.37
L_{night}		1	0.50	0.43	0.31	0.37
L_{den}, indoor			1	0.42	0.18	0.22
L_{night}, indoor				1	0.15	0.18
$PM_{2.5}$					1	0.65
NO_2						1

$PM_{2.5}$: Fine particulate matter, NO_2: Nitrogen dioxide

Table S3: Relative risks (95% CI) for T2D per 10 dB increase in the Heinz-Nixdorf-Recall study population after excluding movers between baseline and follow-up examinations (n=2,836)

	L_{den}	L_{night}
Crude	1.15 (1.01-1.31)	1.15 (1.00-1.31)
M1[a]	1.13 (0.98-1.29)	1.12 (0.98-1.29)
M2[b]	1.14 (0.99-1.30)	1.13 (0.99-1.30)
Multi-pollutant analyses		
M2+ $PM_{2.5}$	1.13 (0.99-1.30)	1.13 (0.99-1.30)
M2+ NO_2	1.15 (0.99-1.33)	1.15 (0.99-1.33)

Mediation analyses		
M2+ WC	1.11 (0.97-1.27)	1.11 (0.97-1.27)
M2+ BMI	1.12 (0.98-1.29)	1.12 (0.98-1.29)
M2+ Depressive symptoms	1.14 (0.99-1.30)	1.14 (0.99-1.30)

$PM_{2.5}$: Fine particulate matter, NO_2: Nitrogen dioxide

[a]adjusted for age and sex, education and neighborhood unemployment rate, [b]additionally adjusted for nutrition, alcohol consumption, smoking status, pack-years, SHS, physical activity (yes/ no), weekly metabolic physical activity.

Table S4: Relative risks (95% CI) for T2D per 10 dB increase in the Heinz-Nixdorf-Recall study population (n=3,396) with higher outdoor noise thresholds

	L_{den} t55[d]	L_{night} t45[e]
Crude	1.19 (0.99-1.42)	1.18 (0.99-1.41)
M1[a]	1.15 (0.95-1.38)	1.14 (0.95-1.37)
M2[b]	1.15 (0.95-1.39)	1.14 (0.95-1.37)
Multi-pollutant analyses		
M2[1]+ PM2.5	1.15 (0.95-1.39)	1.14 (0.95-1.37)
M2+ NO2	1.18 (0.97-1.44)	1.18 (0.97-1.43)
Mediation analyses		
M2+ WC	1.13 (0.94-1.36)	1.12 (1.94-1.34)
M2+ BMI	1.15 (0.96-1.38)	1.14 (0.95-1.36)
M2+depressive symptoms	1.15 (0.95-1.39)	1.14 (0.95-1.37)

$PM_{2.5}$: Fine particulate matter, NO_2: Nitrogen dioxide

[a]adjusted for age and sex, education and neighborhood unemployment rate, [b]additionally adjusted for nutrition, alcohol consumption, smoking status, pack-years, SHS, physical activity (yes/ no), weekly metabolic physical activity.
,[d]t55: threshold value: 55 dB, [e]t45: threshold value: 45dB

Table S5: Relative risks (95% CI) for exposure to L_{den} on T2D per categorical analysis (quantiles; reference category: <46.7 dB) of the Heinz-Nixdorf-Recall study participants (n=3,396).

	46.7≤ L_{den} < 52.2 dB	**52.2 ≤ L_{den} < 61.1 dB**	**L_{den} ≥ 61.1 dB**
Crude	0.80 (0.56-1.14)	1.10 (0.79-1.51)	1.22 (0.89-1.68)
M1[a]	0.78 (0.55-1.12)	1.07 (0.78-1.48)	1.15 (0.78-1.48)
M2[b]	0.79 (0.55-1.13)	1.07 (0.78-1.48)	1.18 (0.85-1.63)
Multi-pollutant analyses			
M2 + PM2.5	0.78 (0.55-1.12)	1.06 (0.76-1.47)	1.16 (0.83-1.62)
M2 + NO2	0.79 (0.56-1.13)	1.07 (0.78-1.49)	1.19 (0.85-1.66)
Mediation analyses			
M2+ WC	0.72 (0.54-1.09)	0.98 (0.75-1.41)	0.97 (0.80-1.51)
M2+ BMI	0.79 (0.55-1.13)	1.05 (0.76-1.45)	1.16 (0.84-1.59)
M2 + depressive symptoms	0.79 (0.56-1.13)	1.07 (0.78-1.49)	1.18 (0.85-1.63)

$PM_{2.5}$: Fine particulate matter, NO_2: Nitrogen dioxide

[a]adjusted for age and sex, education and neighborhood unemployment rate, [b]additionally adjusted for nutrition, alcohol consumption, smoking status, pack-years, SHS, physical activity (yes/ no), weekly metabolic physical activity.

3. Discussion

The study presented in this dissertation indicated that outdoor and indoor road traffic noise may be adversely associated with T2DM. The observed association appears to be independent from air pollution exposures. The approach to consider additional factors that modify the outdoor noise exposure modelled at the façade of the residences in relation to noise immission indoors appeared promising and resulted in more precise estimates. Results concerning potential effect modifying factors remained unclear.

3.1 Comparison to other studies

3.1.1 Outdoor noise exposure and incidence of T2DM

The included study suggests a weak positive association between outdoor environmental noise and T2DM incidence (RR 1.09, 95% CI: 0.96-1.24). The overall results of a comprehensive systematic review and meta-analysis for the WHO Environmental Noise Guidelines – analyzing studies on cardiovascular and metabolic effects of environmental noise published by October 2014 (van Kempen et al. 2017, 2018) – support the findings of the included study. The review authors rated the level of evidence for the association between road traffic noise and incident diabetes as "moderate" according to the GRADE (Grading quality of evidence and strength of recommendations) criteria due to the limited evidence of only one included study from Denmark (Sørensen et al. 2013). Results with follow-up data of the Danish study (Roswall et al. 2018) as well as findings from other prospective cohort studies published after the WHO review showed similar results (Table 4): Two Canadian studies used data from public registries (Shin et al. 2020; Clark et al. 2017), the other four studies – including the publication integrated in the dissertation – were based on cohorts recruited for scientific purposes (Jørgensen et al. 2019; Eze et al. 2017; Roswall et al. 2018). Overall, the availability of participants' data in order to adjust the models for potential confounders, or to apply appropriately powered effect-modification analyses, differed widely across the studies. Some studies (Clark et al. 2017; Jørgensen et al. 2019), merely investigated noise indicators integrating day, evening and night exposures (L_{den} or $A_{eq,\ 24h}$). Other studies (Eze et al. 2017; Shin et al. 2020) including our study additionally investigated nighttime noise exposure (L_{night}). The results of the latter studies suggest similar associations for L_{night} compared to L_{den}. While the two registry-based studies (Clark et al. 2017; Shin et al. 2020) assigned noise values on postal code level, the included and the other cohort studies assigned noise values to the participants' residential addresses. With regard to residential history, our study applied stratified analyses to explore the relationship between environmental noise and incident diabetes for a subsample of participants who did not move between baseline and follow-up examination (n = 2,836). As a result, slightly increased effect estimates (e.g. fully adjusted model: RR 1.14 (95% CI: 0.99-1.30) per 10 dB L_{den}) were observed. Eze et al. (2017) only included study participants who

had not moved during the study period to reduce exposure misclassification. Other studies (Jørgensen et al. 2019; Roswall et al. 2017; Clark et al. 2017; Shin et al. 2020) used different strategies to take into account the exposures at different residences.

Despite different methodologies not only regarding noise assessment, but also regarding length of follow-up period or model adjustments, the studies found consistently positive associations.

Table 4: Short description of prospective studies stuying the association between outdoor noise exposure and diabetes incidence.

Author	Country	Study design	Follow-up (years)	Study population (n)	Effect estimate (95% CI)[c]	Increment of effect estimate
Clark et al. 2017	Canada	prospective cohort study	4	380,738	OR 1.08 (1.05-1.10)	6.8 dB L_{den}
Eze et al. 2017	Switzerland	prospective cohort study	8.3[b]	2,631	RR 1.20 (0.93-1.55)	10 dB L_{den}
Jørgensen et al. 2019	Denmark	prospective cohort study	25	28,731	HR 1.06 (0.96-1.40)	10 dB L_{den}
Ohlwein et al. 2019[a]	Germany	prospective cohort study	5.1	3,396	RR 1.09 (0.96-1.24)	10 dB L_{den}
Roswall et al. 2018	Denmark	prospective cohort study	15.5	50,534	RR 1.10 (1.06-1.15)	10 dB L_{den}
Shin et al. 2020	Canada	retrospective cohort study	15	914,607	HR 1.08 (1.08-1.09)	10 $L_{Aeq, 24h}$

a: study included in the dissertation, b: effect estimate refers to annual average noise level, c: effect estimates relate to the main models, respectively.

CI: confidence interval, HR: hazard ratio, L_{Aeq}: A-weighted, equivalent sound level, L_{den}: day–evening–night (24-hr) noise level, RR: relative risk

3.1.2 Potential confounding by co-pollutantion of air pollution exposure

As described above, air pollution and noise exposure partly overlap, first, with regard to their common source (Stansfeld 2015) and second, with regard to their hypothezised pathomechanisms (Münzel et al. 2018). Recent studies investigated potential confounding by air pollution for the association between environmental noise exposure and incident diabetes. However, the up-to-date literature does not draw a clear picture. First, the selection of co-pollutants differed across studies: In general, $PM_{2.5}$ is hypothized to play a more relevant role in the development of diabetes incidence than NO_2 (Liu et al. 2019; Jørgensen et al. 2019). Among the relevant studies, one study beyond our study addressed potential confounding by adjusting the models for $PM_{2.5}$ (Jørgensen et al. 2019). While effect estimates remained stable upon adjustment for $PM_{2.5}$ (RR 1.09, 95% CI: 0.96-1.24) in our study, the large-scale Danish nurse study (Jørgensen et al. 2019) oberserved attenuated associations after adjustment for $PM_{2.5}$ (HR 0.99, 95% CI: 0.91-1.08) per 10 dB L_{den}, mean follow-up of 5 years.

NO_2 is another relevant co-pollutant, as NO_2 is generally more related to traffic compared to $PM_{2.5}$ which is reflected by higher correlation values. E.g., in our study area, the correlation between averaged 24h-road-traffic noise exposure and $PM_{2.5}$ was 0.30 (Spearman correlation coefficient) compared to 0.37 for NO_2. This pattern was similar across the above named cohort studies. The studies included different types of nitrogen oxides (NO_x) as proxies of traffic-related air pollution in their role of potential confounders, e. g. NO_2 or nitrogen monoxide (NO). The role of nitrogen oxides as potential confounder for the association between road traffic noise and diabetes incidence was heterogenerous across studies: Our study observed similar associations upon adjustment for NO_2 (RR 1.11, 95% CI: 0.97-1.27) per 10 dB L_{den} road traffic noise mean follow-up 5.1 years, compared to single-exposure models. In contrast, the Danish nurse study (Jørgensen et al. 2019) observed null associations in models controlling for NO_2 (HR 1.01, 95% CI: 0.91-1.11) per 10 dB L_{den}, mean follow-up of 5 years. The Danish study by Roswall et al. (2018) yielded stable associations upon adjustment for NO_x (HR 1.12, 95% CI: 1.06-1.18). Clark et al. (2017) controlled for NO and observed slightly attenuated effect estimates (OR 1.04, 95% CI: 1.01-1.05).

Two studies did not report associations with co-pollutants separately, but reported results of co-pollution models including further exposures, namely L_{den} aircraft and L_{den} railway (Eze et al. 2017) and ultrafine particles (UPFs) (Shin et al. 2020): The Swiss cohort study (Eze et al. 2017) showed slightly stronger associations in multi-exposure models including L_{den} aircraft, L_{den} railway and NO_2 simultaneously (RR 1.35, 95% CI: 1.02-1.78) for L_{den} road traffic noise. The Canadian study (Shin et al. 2020) investigated confounding by adjusting for UFPs and NO_2 simultaneously and observed stable results compared to single-exposure noise models (HR 1.07, 95% CI: 1.06-1.08) for $L_{Aeq\ 24h}$ road traffic noise.

Further insights are given by studies investigating associations between air pollution exposure and diabetes incidence adjusting for road traffic noise as potential confounders (Clark et al. 2017; Eze et al. 2017). While Clark et al. (2017) observed modest associations between air pollution exposures (NO_2, NO, $PM_{2.5}$) in relation to diabetes incidence that attenuated upon adjustment for noise exposure, Eze et al. (2017) observed null associations for NO_2 exposure in relation to incident diabetes.

In conclusion, the literature draws a heterogeneous picture both in relation to varying selected air pollutants, to different modeling approaches and in relation to the resulting effect estimates. Therefore, it is difficult to evaluate if the suggested association between road traffic noise and incident diabetes is independent of air pollution exposure. However, the majority of the analyses on the topic indicate that the associations of road traffic noise with T2DM remain upon adjustment for various air pollutants.

3.1.3 Indoor versus outdoor noise exposure

Evidence suggests that there is a difference between road traffic noise exposure as measured at the façade of the residences (in the following named as outdoor noise exposure) and the noise perceived indoors (Locher et al. 2018; World Health Organization, Regional Office for Europe 2009). The study presented in this dissertation observed substantial differences between outdoor road traffic noise exposures and indoor road traffic noise exposure with a median difference of 17.5 for L_{den} (outdoor L_{den} 52.3 dB versus indoor L_{den} 34.8 dB) and 16.4 for L_{night} (outdoor L_{night} 43.6 dB versus indoor L_{night}: 27.2 dB) in annual-mean noise exposures. This is specifically important for the evaluation of noise exposure during nighttime, when individuals spend their time usually indoors. Research findings show that individuals also spend a substantial part of their time indoors during daytime (U.S. Environment Protection Agency 2001). The included study showed that the estimated indoor noise exposure yielded more precise effect estimates (RR 1.11, CI: 95%: 1.01-1.21), probably due to less exposure misclassification. Another reason for smaller confidence intervals might have been that indoor noise levels were less correlated with outdoor air pollution exposures. Few of the above named relevant studies integrated information on window insulation, living room / bedroom orientation or season-related ventilation behaviour into their analyses: Eze et al. (2017) only observed effects among participants sleeping with open windows (RR 1.44, 95% CI: 1.02-2.03) versus participants sleeping with closed windows (RR 0.64, 95% CI: 0.34-1.19). Unexpectedly, the study further observed stronger associations among participants whose bedroom was orientated towards the backyard (RR 1.61, 95% CI: 1.11-2.35) versus the street (RR 1.08, 95% CI: 0.64-1.83) per 10 dB L_{den}. The contradictory results were explained by the fact that participants with bedroom faced towards the backyard slept more often with open windows (Eze et al. 2017). Two studies (Foraster et al. 2018; Oftedal et al. 2015) analyzed potential effect modification by bedroom orientation for the association between long-term road traffic noise exposure and BMI change and found stronger associations among participants with bedroom orientation to the street vs. backyard.

In conclusion, the evidence is too limited to draw clear conclusions. However, our study findings are in line with the scarce literature, and suggest that considering aspects as ventilation behaviour, window insulation and room orientation are important for specifying the true indoor noise exposure of participants.

3.1.4 Effect modification analyses

Explorative effect modification analyses indicated potential interaction for physically active versus inactive participants. Further, a potential weak interaction was indicated for employed versus unemployed, pensioneers or housewives. For all other investigated effect modificators including age (> 65 verus ≤ 65), BMI, annoyance and distance to major roads, confidence intervals overlapped widely. Generally, other studies did not reveal distinct effect modification, either: Relating to

physical activity, one further study explored a potential effect modifying role (Jørgensen et al. 2019) observing no clear picture with a trend towards the opposite direction compared to our findings. In relation to obesity markers, effect modification analyses did not show consistent results in this study, either (Jørgensen et al. 2019).

While our study did not investigate effect modification by air pollution, two studies (Shin et al. 2020; Eze et al. 2017) studied a potential interaction. Shin et al. (2020) suggested a potential effect modification by UFPs and NO_2 exposure, showing weaker associations in the highest exposed quintiles. The authors suggested synergistic biological effects of air pollution and noise exposure in the higher exposed, leading to desensitized physiological reactions. In contrast, Eze et al. (2017) found no clear effect modification by NO_2, with slightly stronger associations in the subgroup of lower exposure. The authors explained that less exposure misclassification might be the reason.

3.1.5 Sensitivity analyses

Due to limited evidence, the DAG for the analyses being conducted within the framework or this study (see appendix figure S1 of the included publication) could not be specified with high certainty concerning the role of single covariates, such as obesity markers and depressive symptoms. Therefore, we applied sensitivity analyses by in- and excluding the respective covariate, namely obesity markers and depression, in the models to explore their role as potential mediating factors.

With regard to obesity markers, our study indicated a potential mediating role, showing attenuated associations upon adjustment for waist circumference (WC): RR 1.07 (95% CI: 0.95-1.21). Other studies that included obesity markers in their models (Jørgensen et al. 2019; Roswall et al. 2018; Shin et al. 2020; Eze et al. 2017) did not report separate models with and without obesity markers. While the evidence for the causal relationship between obesity and development of T2DM is widely accepted (International Diabetes Federation 2019), the link between traffic noise and obesity markers has only been studied lately: The WHO commissioned review and meta-analysis (van Kempen et al. 2017) showed weak associations for the relationship between road traffic noise and a change in BMI or WC and rated the overall evidence as very low. Studies published after the review strengthened the evidence with overall positive associations across the four cohort studies (Foraster et al. 2018; Li et al. 2021; Pyko et al. 2017; Cai et al. 2020). The most recent and largest study including 412,934 participants of three UK cohorts reported a significant BMI increase with an OR of 1.06 (95% CI: 1.04-1.08) and an increase in WC with and OR of 1.05 (95% CI: 1.04-1.07) per 10 dB L_{den} (Cai et al. 2020). The same authors updated the WHO meta-analysis found an overall increase in BMI by 0.09 kg/m² (95% CI: -0.06-0.25) and a WC increase by 0.19 cm (95% CI: -0.22-0.60) per 10 dB L_{den}. However, the heterogeneity across studies was high.

In summary, recent evidence supports a mediating role of weight and WC for the association between road traffic noise and diabetes. However, the investigation of this causal path has not been addressed adequately in studies on road traffic noise and incident diabetes.

Further, the role and causal direction of depression in relation to our exposure-outcome-relationship was not clear. Our study therefore varied the analysis by additionally adjusting the main model for depressive symptoms as another potential mediating factor. As a result, effect estimates remained unchanged (RR 1.08, 95% CI: 0.06-1.24). None of the other relevant studies on the association between road traffic noise and incident diabetes included this aspect. According to the WHO review, the evidence on the association between road traffic noise exposure and self-reported or interviewer-assessed depression was very low. A recent meta-analysis including 11 studies (Hegewald et al. 2020) found a weak association with an effect size of 1.03 (0.99-1.06) per 10 dB L_{den}, with moderate heterogeneity. The result corresponds to our unchanged effect estimates upon adjustment for depression indicating a maximal weak effect modyfing role of depression status on the investigated relationship.

In sum, sophisticated analyses to examine potential mediation are generally lacking in studies on road traffic noise exposure and diabetes incidence.

3.1.5 Varying noise exposure models

Exposure-response relationship

Analyses on exposure-response allow to explore the shape of the relationship and to estimate associations for different ranges of noise exposure. Thus, thresholds above which long-term noise exposures may cause adverse health effects may be revealed as well as noise exposure ranges, in which adverse health effects are strongest. Three up-to date studies (Shin et al. 2020; Jørgensen et al. 2019; Roswall et al. 2018, 2018; Clark et al. 2017) beyond the included publication explored dose-response relationships by applying categorical noise exposure models. In our study, such models were built using quantiles of the exposure values: < 46.7 dB L_{den} (reference category); 46.7 dB - 52.2 dB L_{den}; 52.2 dB - 61.1 dB L_{den} and > 61.1 dB L_{den}. The results indicated stronger relationships above road traffic noise levels of 52.2 dB L_{den}, suggesting a linear relationship within the noise categories above the hypothized threshold of adverse health effects. Other studies generally support our results (Shin et al. 2020; Clark et al. 2017; Jørgensen et al. 2019) and indicate a steady positive relationship. However, differing distribution-related noise categories across studies preclude detailed comparisons. Clark et al. (2017) and Eze et al. (2017) applied smoothing splines to explore the relationship indicated a linear relationship. In the study by Clark (2017), this relationship was visible in in the area between 45 and 85 dB; for extreme noise values, confidence limits were too large. In the smaller study by Eze (2017), the area for which linearity was observed was smaller.

In conclusion, the scarce evidence on exposure-response relationships in studies on diabetes related noise effects indicates a linear relationship above study-specific thresholds.

Lower noise thresholds

In the main models of the included publication, 45 dB and 35 dB were selected as threshold values for L_{den} and L_{night}, respectively, i.e. all predicted noise exposure values below these values were set to the threshold values. This approach is based on the hypothesis that noise values below the threshold values are considered not to have adverse effects on health. The assumption originates from research on the dose-effect relations between traffic noise exposure and health annoyance which start at 45 dB L_{den} (European Environment Agency 2010). A threshold approach was also applied in other studies using 40 dB (Jørgensen et al. 2019; Eze et al. 2017) or 35 dB (Roswall et al. 2017) as thresholds, stating that the threshold values reflect the minimal true noise exposure. In a sensitivity analysis, we explored models with threshold values of 55 dB L_{den} and 45 L_{night}, implicating that adverse health effects start at long-term noise levels above the values selected in the main models. The alternative threshold values resembled mean exposure values of the participants and thus enhance the contrast of participants exposed to up to mean versus higher noise levels. The analyses yielded slightly stronger, but also less precise values.

3.2 Biological pathways – theoretical concepts and empirical evidence

Decades ago, the noise-stress concept was developed explaining the biological reactions and health effects following to noise exposure (Babisch 2002; McEwen 1998). Later, it was elaborated and applied to the context of cardiometabolic health outcomes (Münzel et al. 2017; Recio et al. 2016). Auditory thalamus, auditory cortex, amygdala and hypothalamus are brain regions involved in the response to the stressor noise (Basner et al. 2014). According to current knowledge, the major hypothized mechanisms include the activation of the sympathetic-adrenal-medullary (SAM) and of the hypothalamic-pituitary-adrenalin axis (HPA). Conciously or unconsciously, the psychosocial stressor noise activates the SAM causing production of adrenaline and noradrenaline in the adrenal medulla and activates the HPA axis causing endocrine reactions. The endocrine cascade includes the secretion of corticotrophin-releasing hormone which promotes the secretion of adrenocorticotropic hormone, followed by a production of glucocorticoids (e.g., cortisol). Through elevation of cortisol levels, the HPA axis influences metabolic and immune functions, such as elevation of blood glucose levels, lipolysis and immune suppression (Eriksson and Pershagen 2018). Long-term exposure to noise accompanied by increased cortisol levels may accumulate body fat in central adipose tissue, impair insulin secretion in the pancreas and reduce the sensitivity to insulin in the liver, adipose tissue and skeletal muscle (Eriksson and Pershagen 2018; Recio et al. 2016; Münzel et al. 2017). Several experimental animal studies investigated this hypothesis, observing elevated blood corticosterone levels (Taban et al. 2016), elevated blood glucose levels and biomarkers indicating decreased insulin resistance (Cui et al. 2016; Liu et al. 2018a; Liu et al. 2018b;

Morakinyo et al. 2019) in mice or rats in response to middle-term noise exposure. The studies also analyzed underlying pathways, e.g. phosphorylation processes in the muscles as mediating pathways (Liu et al. 2018a). Some studies investigated the effect of noise on subgroups of mice with high-fed diet compared to chow-diet fed mice (Liu et al. 2018b). The modified metabolic response was particularly obvious in high-fat-diet fed mice. In this group, the authors also observed changes in the biomarkers of signaling pathways in the skeletal muscles which have been linked to insulin resistance. Some study authors also investigated the role of stress-induced inflammatory and oxidative stress processes as contributors to insulin resistance. Liu et al. (2018a) studied associations between chronic (20 days) noise exposure and inflammation as well as oxidative stress markers and observed temporarily elevated TNF-alpha, IL-6 and MDA plasma concentrations in response to chronic noise exposure which are hypothized to activate stress kinases, e.g. JNK as potential mediators to insulin resistance (Liu et al. 2018a). Similarly, Cui et al. (2016) observed persistent elevated levels of IfA, IL-13 and TNF-alpha levels in intestinal mice tissue.

As a further mechanism, sleep disturbances due to night noise exposure may activate the carbohydrate metabolism which is normally inactivated during sleep (van Kempen et al. 2017; Eriksson and Pershagen 2018). As potential regulating hormones, leptin and ghrelin have been identified. Leptin follows a circadian rhythm and regulates energy homeostasis (World Health Organization, Regional Office for Europe 2009). Disrupted sleep patterns are characterized by increased leptin concentrations enhancing appetite. Experimental studies observed increased leptin concentrations following noise exposure in rats (Chandralekha et al. 2005). A review including several studies in humans reports that acute and chronic sleep disturbances have been associated with weight gain, increased BMI and WC (Medic et al. 2017). For example, a small field study, including nine healthy volunteers, showed that sleep disruption on three consecutive nights decreased insulin sensitivity and increased blood glucose levels to a clinically high risk state (Tasali et al. 2008; Medic et al. 2017). A meta-analysis of ten studies found associations between quantity and quality of sleep and the development of T2DM (Cappuccio et al. 2010).

In sum, the evidence of the hypothized biological pathomechanisms linking environmental noise and T2DM remains scarcly elucidated. Due to the complex health effects of noise as well as the multifactorial development of T2DM, a comprehensive and detailed delineation of the relationship is challenging.

3.3 Quality of evidence and future research needs

The overall quality of evidence for the association between traffic noise in general and diabetes was rated as very low according to the GRADE approach as reported in the latest WHO review (van Kempen et al. 2018). For exposure to road traffic noise separately, the overall quality of evidence supporting an association was rated as moderate: While the quality of evidence was rated

down by one level due to the limited number of only one included study, the demonstrated exposure-response relationship led to an upgrading of the level of evidence by one level. Since the review, more partly large-scale studies in the European Region, namely in Denmark (Jørgensen et al. 2019; Roswall et al. 2017), Switzerland (Eze et al. 2017) and Canada (Clark et al. 2017; Shin et al. 2020) have examined the potential adverse effects of noise on diabetes raising the confidence in the observed associations. However, the evidence on independent associations from air pollution as co-pollutant is less consistent. Furthermore, there is an urgent need for more precise noise exposure assessments by taking factors like bedroom and living room orientation, ventilation behaviour and window insulation into account. The evidence on biological pathways on the development of diabetes is still scare. Few experimental and epidemiological studies corrobate the noise / stress hypothesis as main driver for noise-induced metabolic health consequences. Further, the scarce findings are not always consistent. Short- and middle-term epidemiological studies investigating biomarkers alongside the biological pathways might elucidate this research gap.

3.4 Public health implications of the findings

3.4.1 Standardized and updated noise mapping procedures

The adverse effects of noise exposure have been rated as second most important environmental stressor behind air pollution (Hänninen et al. 2014). Our study contributes to the still limited evidence that traffic noise affects the metabolic system and namely the incidence of diabetes. In the study area of the included study, half of the participants were exposed to road traffic noise levels above 52.3 dB L_{den} and 43.6 dB L_{night} during the studied time period. Similarily, the German Federal Environmental Agency (Umweltbundesamt) estimated that at least half of the German populations is exposed to environmental noise – which is usually dominated by road traffic noise - levels of at least 55 dB L_{den} and 45 dB L_{night} (Umweltbundesamt 2020b). Thus, about half of the German population is exposed to traffic noise levels exceeding values strongly recommended by WHO noise guidelines (53 dB L_{den} and 45 dB L_{night} for road troaffic noise) (World Health Organization, Regional Office for Europe 2018). These WHO Guidelines values do not represent the lowest-observed-adverse-effect levels above which adverse effects may arise, but values, above which adverse health effects are strongly suggested based on available evidence (Umweltbundesamt 2019; World Health Organization, Regional Office for Europe 2018). Consequently, the recommended values might not be appropriate to protect vulnerable groups (e.g., children, shift workers or ill persons). Regarding night noise limits, the WHO Guidelines claims that the evidence-based expert judgement of the Night Noise Guidelines (World Health Organization, Regional Office for Europe 2009) is still valid stating that noise exposure corresponding values of 40 dB L_{night} are levels "where adverse effects start to occur" (World Health Organization, Regional Office for Europe 2018, p. 28). According to the Guideline authors, these values aim to take the whole population into account, including vulnerable groups.

However, END noise reporting requirements do not correspond to the WHO recommendations as the lower cut-off reporting values exceed those strongly recommended by the WHO: The END specified threshold values of 55 dB L_{den} and 50 dB L_{night}, above which member countries are to report noise mapping data to the EEA. In this light, the END should be urgently updated by requiring lower cut-off values for the noise reporting (European Environment Agency 2020b). This aim has been adopted within the Seventh Environment Action Programm (EAP). However, in contrast to the legally-binding END directive, the EAP represents a non-binding commitment. Besides the current limited END requirements, noise exposure data reported by the EEA member states varies in quality and availability (World Health Organization, Regional Office for Europe 2018). For example, 30% of the national noise mapping data required by 2017 had not been provided (European Environment Agency 2020b). Regarding quality, the reported noise data may be biased due to a lack of standardization as not all countries use the same noise indicators (e.g., L_{den} versus L_{day}) so that aggregated data loose preciseness. While this divergency has been meanwhile tackeled by an approach to harmonize noise assessment measures, called Common noise assessment methods for Europe (CNOSSOS-EU) (Kephalopoulos et al. 2014), other diverging noise reporting procedures are still present (European Environment Agency 2020a): National definitions of agglomerations, as the definition of the term "urbanized area" is left to the member states, and assessment techniques (e.g. software) of noise are country-specific. As a consequence, the number of persons affected by noise exposures exceeding 55 dB as surveyed by he EEA is very heterogeneous across the 33 member countries. Further, noise mapping procedures do not cover the total territory, particularly outside urban areas. Therefore, data provided by the member countries underestimate the true numbers of persons exposed to harmful levels of noise. Another challenge concerning noise assessment refers to the selection of noise indicators. The indicators available for our study, L_{den} and L_{night}, represent yearly noise exposures and do not provide concise information on noise characteristics (e.g., short-term tonal variations, peak noise levels or impulsiveness of the noise). The END explicitly states that it might be beneficial to complement L_{den} and L_{night} by taking further indicators into account, such as L_{Amax} or sound exposure level (SEL) for nighttime noise exposure. Even if road traffic noise is generally described as a source of constant noise in contrast to other noise sources, e.g. airplanes, the constancy of road traffic noise depends on the road flow, determined by e.g., intersections or traffic light cycles. Information on number of events, peak levels of single noise events or other characteristics would be particularly relevant for epidemiological studies to assess endpoints on annoyance or sleep quality, but also for other endpoints: As sleep quality represents one hypothezised pathway for the association between noise and incident diabetes, data on noise characterristics beyond averaging noise exposure levels could gain new insights. Up to now, member states only report long-term averaging noise indicators L_{den} and L_{night}. To this end, the END methodologies should be extended with regard to further noise indicators. Among the relevant studies on road traffic noise and incident diabetes,

only one small study by Eze et al. (2017) explored the impact of noise characteristics (by taking into account the proportion of intermittency), but the estimates did not change upon adjustment. Another limitation of the data gathered by the EEA is that the separation by source complicates the aggregation of data. If people are affected by several types of sources, they would be counted double (European Environment Agency 2020b): The END guideline does not describe or specify a concept to quantitatively and qualitatively evaluate complex sound landscapes within residential areas, which often constitute of various combined noise sources.

Based on the noise mapping procedures, the END demands its member countries to develop noise action plans as a measure to mitigate noise exposures. However, the EEA states that "significant delays and the poor quality of action plans suggest that countries may not have taken the necessary steps to address noise pollution" (European Environment Agency 2020b, p. 74). This lack of compliance reflects that legally consequences are needed for the case that the required data is not provided by the member states.

To sum up, besides urgently needed standardization procedures to assess noise exposure, a redefined and comprehensive noise mapping system is urgently needed, e.g. to adapt noise reporting values below or a least according to the WHO limit values in order to precisely monitor environmental noise pollution exposure and thus being able to implement noise mitigation policies.

3.4.2 Clinical relevance

Our study suggests a risk increase of 10% per 10 dB L_{den} traffic noise exposure for the risk increase of incident diabetes referring to noise exposure levels of 45 dB up to about 85 dB L_{den}. Further epidemiological studies show similar results ranging from a 6 to 20% increase for similar noise windows. A change of 10 dB corresponds to a perceived doubling of noise exposure. In this light, a 10% increase in diabetes incidence seems clinically less relevant compared to other risk factors. However, as stated above, alongside the pathway on the development of diabetes, environmental noise exposure causes more subtle adverse health effects, such as risk factors belonging to the metabolic syndrome. These may not only lead to diabetes but also to other diseases. Thus, diabetes represents a "hard" outcome at the end of a line of diverse possible alterations in the metabolic system leading to various potential health risks.

Besides, seen from the public health perspective, even small risk increases can cause a substantial population-level health burden, if exposure is widespread. Thus, on a European level, millions of people would benefit from reductions of noise exposure.

3.4.3 Outlook and future perspectives

Eurocities stated that within the last 10 years, noise exposures have not changed considerably (Scott-Smith 2020). With people tending to move from rural areas into cities, and increasing

transportation demands, projections estimate that exposure to adverse road traffic noise exposure levels will further increase both inside and outside urban areas, by 7.8% and 16.4%, respectively, for the time frame between 2017 and 2030 (European Environment Agency 2020b). Therefore, noise reduction goals are needed to mitigate noise pollution (Scott-Smith 2020). Current trends towards sustainable urban mobility create the opportunity to reduce not only air, but also noise exposures. Among else, the spread of electronic vehicles and the development of quiet road and tyre surfaces have the potential to reduce noise emissions (Scott-Smith 2020). However, for pedestrian safety, electronic vehicles will be also equipped with (artificial) sounds.

3.5 Strengths and Limitations

One overall strength of our study is that participants of the Heinz Nixdorf Recall cohort were thoroughly investigated in relation to individual-level data, e.g., the participants' health status and other valuable data, e.g. on lifestyle related information, comorbidities (e.g., depression status) and noise sensitivity. As a consequence of the generally thorougly described cohort, we were able to investigate potential effect modification by various aspects (e.g., noise sensitivity) and further sensitivity analyses. As a trade-off in relation to the detailed individual-level-data, our analysis suffered from limited statistical power due to the limited study population. In this context, the lacking data on family history of diabetes and hearing impairment must be considered as study limitation.

Relating to exposure assessment, noise exposure values used in the included study used a reliable noise assessment methodology based on noise generation and propagation modeling according to the END directive. The models were built on complex physical methodologies and integrated numerous factors. A limitation refers to averaging noise levels of one single year: In the presented study, noise exposure levels were based on data provided by local authorities for strategic noise mapping in the year 2006. The resulting noise exposure was estimated to be stable over time. Nevertheless, there remain doubts if the year 2006 was representative for noise exposure over the whole time period during which the cohort was followed. Exposure values may be biased insofar that the selected exposure year differs from longer term averages with regard to input variables of the noise models, such as noise barriers, changed infrastructures / road network, or traffic flows. A strength in relation to exposure assessment refers to the availability of air pollution data assigned to the participants' residencies. Thus, we were able to investigate the independence of associations for the most relevant co-pollutants. Another strength of the study is, that in addition to outdoor noise assessment, information on bedroom / living room orientation, season-related ventilation behaviour and window insulation were integrated and used to estimate indoor road traffic noise. A general limitation of most epidemiologic noise studies concerns the exposure misclassification through assigning exposures to participants' addresses and thus not considering the time participants spent at work or other places, leading to non-differential bias.

Finally, the assessment of the outcome diabetes may have biased the results: As the majority of the relevant studies included participants with a mean age of around 59 years at baseline, the study authors expect the majority of indicent diabetes cases being T2DM. Further, the healthy participant effect might have biased our study results: T2DM is usually diagnosed in women and men at a mean age of 54.1 and 55.0 years, respectively. In our study, we excluded participants suffering from T2DM at baseline. At baseline, the mean participant age was 58.8 years. Thus, we included a cohort of participants in whom a T2DM diagnosis may have been delayed, potentially due to an advantageous metabolic risk profile. Correspondingly, the educational level of the participants is relatively high, with less than 9% of the participants disposing of ≤10 years of education.

4. Conclusions

The main study results are in line with a growing evidence base on studies investigating the association between outdoor road traffic noise exposure and diabetes incidence, suggesting weak but consistent associations relating to long-term noise exposure up to 25 years of follow-up. The interrelationship between road traffic noise and air pollution exposure with regard to diabetes incidence remains unresolved. Current evidence suggests rather independent associations. Our research shows that the integration of information on housing characteristics and behavioural factors (insulation, room orientation and ventilation behaviour) may improve noise exposure estimation and thereby noise effect analyses. The role of risk factors such as obesity or comorbidities (e.g., prevalent depression) for the relationship between road traffic noise and diabetes incidence is not completely clear yet. The underlying pathomechanisms have been well conceptualized, however, further experimental and epidemiological studies are needed to confirm the hypothized biological pathways. Half of the population living in the EU is estimated to be affected by exposure levels rated as harmful. However, current data is not sufficient to assess the true extent of the exposed population. Political measures need to be taken in order to prevent adverse effects of road traffic noise. The existing END needs to be revised upon the updated WHO recommendations. Adapted requirements could serve as base to initiate traffic transformation particularly in urban areas to mitigate noise alongside air pollution exposures. According to the existing evidence on the adverse effects of noise, such measures are important to protect the health of healthy but also vulnerable groups.

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