sciensano

HEALTH INFORMATION

EBOD-FL

Guidelines for mapping the environmental burden of disease in Flanders

ARNO PAUWELS • CLAIRE DEMOURY • EVA DE CLERCQ • BRECHT DEVLEESSCHAUWER

2024

healthy all life long

WHO WE ARE

Sciensano can count on more than 900 staff members who commit themselves, day after day, to achieve our motto: Healthy all life long.
As our name suggests, science and health are central to our mission. Sciensano's strength and uniqueness lie within the holistic and multidisciplinary approach to health. More particularly we focus on the close and indissoluble interconnection between human and animal health and their environment (the "One health" concept). By combining different research perspectives within this framework, Sciensano contributes in a unique way to everybody's health.
For this, Sciensano builds on the more than 100 years of scientific expertise.

Sciensano

Epidemiology and public health – Health information

Chemical and physical health risks – Risk and health impact assessment

Mapping the Environmental Burden of Disease in Flanders

March 2025 • Brussels • Belgium
Approved by: Brecht Devleesschauwer, head of service

Arno Pauwels[1,2]

•

Claire Demoury[2]

•

Eva De Clercq[2]

•

Brecht Devleesschauwer[1]

1 Sciensano, Epidemiology and public health, Health information, Brussels
2 Sciensano, Chemical and physical health risks, Risk and health impact assessment, Brussels

Contact person: Arno Pauwels • arno.pauwels@sciensano.be

In collaboration with

Joke De Backer • Katrien Tersago • Hilde Van De Maele • Hanne Vandenbossche • Stefan Acke • Bart Bautmans
Departement Zorg

Please cite as: Arno Pauwels, Claire Demoury, Eva De Clercq, Brecht Devleesschauwer. EBoD-FL. Guidelines for mapping the environmental burden of disease in Flanders, 2024. Brussels, Belgium: Sciensano; 2025, 98p.

EXECUTIVE SUMMARY

The environment poses a diverse range of health risks. Environmental burden of disease (EBD) studies try to estimate the impact of environmental stressors in terms of mortality or morbidity on a population level. Although environmental risks have been studied in Flanders, an effort to routinely quantify the environmental disease burden completely and coherently has thus far not been established. For this reason, Sciensano and Departement Zorg are partnering up in a project to map the Environmental Burden of Disease in Flanders (EBoD-FL).

The aim of the research is to inventory the burden of disease attributable to all relevant environmental stressors according to a coherent framework. To tackle this objective, the disease burden attributable to environmental stressors is estimated using comparative risk assessment (CRA). As this method determines the attributable burden proportionally, figures for the total disease burden are required as a baseline to obtain absolute estimates. In EBoD-FL, the EBD is quantified as disability-adjusted life years (DALYs), a summary measure that combines both mortality and morbidity.

In EBoD-FL, a novel approach is developed where the EBD is calculated locally at the level of the statistical sector. This approach adds geographic detail to the EBD estimates, and allows to mutually compare small areas and local populations. Additionally, the local results can be aggregated to wider areas and larger populations, which allows to extract estimates for any part of the Flemish Region in a flexible manner. As collecting the necessary data on this fine-scale level poses a challenge, a parallel track of calculations was set up, where the EBD is determined 'globally' on the level of Flanders. Data on this aggregated level (Flanders) are relatively easy to obtain, which allows to complete the steps in the analysis more swiftly.

Given the extensive list of potential risk factor-health outcome pairs, a set of priorities was defined in terms of environmental stressors and health outcomes. The risk factors that were prioritised are those related to air quality, environmental noise and extreme temperature. In terms of outcomes, priority was given to all-cause mortality, respiratory diseases and cardiovascular diseases. This report outlines the CRA methodology in general, and the application on the risk-outcome pairs that have been given priority. The basic steps of CRA are:

1. Selection of risk factors: Which risk factors are included in the study and how is exposure quantified as a metric?
2. Exposure assessment: how to measure or model exposure to the risk factors in the population?
3. Identification of risk-outcome pairs: which health outcomes are caused by the risk factors?
4. Quantification of the risk-outcome relation: what is the risk of developing the outcome in function of exposure?
5. Calculation of the population attributable fraction: what is the proportion of the disease burden attributed to one or multiple risk factors?

The purpose of this report is to outline the general methodology used to tackle the objective of EBoD-FL and to apply the CRA methodology to the stressors that are prioritized. Additionally, possibilities for the application of the results for evidence-based policy are explored, as well as some challenges and limitations.

SAMENVATTING

Het milieu brengt een grote verscheidenheid aan gezondheidsrisico's met zich mee. Studies van de ziektelast door milieublootstelling (environmental burden of disease, EBD) proberen de impact van milieustressoren in termen van mortaliteit of morbiditeit in te schatten op populatieniveau. Hoewel milieurisico's in Vlaanderen reeds bestudeerd werden, bestaat er tot nu toe geen initiatief om de ziektelast van het milieu routinematig, volledig en coherent te becijferen. Daarom werken Sciensano en het Departement Zorg samen in een project om de bijdrage van milieustressoren aan de ziektelast in Vlaanderen in kaart brengen (Mapping the Environmental Burden of Disease in Flanders, EBoD-FL).

De doelstelling van het onderzoek is het inventariseren van de ziektelast die kan worden toegerekend aan alle relevante milieustressoren, en dit binnen een consistent kader. Om het doel te bereiken wordt de milieuziektelast geschat met behulp van vergelijkende risicobeoordeling (comparative risk assessment, CRA). Aangezien deze methode de toerekenbare ziektelast proportioneel bepaalt, zijn er cijfers voor de totale ziektelast nodig als basis voor absolute schattingen. In EBoD-FL wordt de ziektelast gekwantificeerd als het aantal verloren gezonde levensjaren (disability-adjusted life years, DALY's), een samenvattende maat die zowel mortaliteit als morbiditeit in rekening brengt.

In EBoD-FL is een nieuwe aanpak ontwikkeld waarbij de EBD lokaal wordt berekend op het niveau van de statistische sector. Deze aanpak voegt geografische details toe aan de EBD-schattingen en maakt het mogelijk om kleine gebieden en lokale populaties onderling te vergelijken. Bovendien kunnen de lokale resultaten geaggregeerd worden naar bredere gebieden en grotere populaties, wat toelaat om op een flexibele manier schattingen te maken voor eender welk deel van het Vlaamse Gewest. Omdat het verzamelen van de nodige gegevens op dit fijnmazige niveau een uitdaging vormt, werd een parallel traject van berekeningen opgezet, waarbij de EBD 'globaal' wordt bepaald op het niveau van Vlaanderen. Geaggregeerde gegevens zijn relatief gemakkelijk te verkrijgen, wat toelaat om de stappen in de analyse sneller te doorlopen.

Aangezien de lijst van potentiële combinaties van risicofactoren en gezondheidseindpunten zeer uitgebreid is, werd een reeks prioriteiten gesteld. De risicofactoren die prioriteit kregen hebben betrekking tot luchtkwaliteit, omgevingslawaai en temperatuurextremen. In termen van eindpunten werd prioriteit gegeven aan algemene sterfte, ademhalingsaandoeningen en hart- en vaatziekten. Dit rapport beschrijft de CRA-methodologie in het algemeen en de toepassing op de prioritaire risico-eindpuntparen. De basisstappen van CRA zijn:

1. Selectie van risicofactoren: Welke risicofactoren worden meegenomen in het onderzoek en welke indicators worden gebruikt om de blootstelling te bepalen?
2. Blootstellingsbepaling: hoe wordt de blootstelling aan de risicofactoren in de populatie gemeten of gemodelleerd?
3. Identificatie van risico-eindpuntparen: welke gezondheidseffecten worden veroorzaakt door de risicofactoren?
4. Kwantificering van de risico-eindpuntrelatie: wat is het risico op het ontwikkelen van de uitkomst in functie van de blootstelling?
5. Berekening van de toerekenbare fractie voor de bevolking: wat is het aandeel van de ziektelast dat wordt toegeschreven aan één of meerdere risicofactoren?

Het opzet van dit rapport is om de algemene methodologie van EBoD-FL te schetsen en om de CRA-methode toe te passen op de prioritaire stressoren. Daarnaast worden mogelijkheden voor de toepassing van de resultaten voor wetenschappelijk onderbouwd beleid verkend, evenals enkele uitdagingen en beperkingen.

TABLE OF CONTENTS

ABBREVIATIONS

AQG	Air Quality Guidelines
BeBOD	Belgian National Burden of Disease Study
BOD	Burden of disease
COD	Cause of death
COPD	Chronic obstructive pulmonary disease
CRA	Comparative risk assessment
CRD	Chronic respiratory disease
CVD	Cardiovascular disease
DALY	Disability-adjusted life year
DW	Disability weight
DZ	Departement Zorg
EBD	Environmental burden of disease
E-HIS	Environment-Health Impact Simulator
END	Environmental Noise Directive
ENG	Environmental Noise Guidelines
ERF	Exposure response function
FPS Health	Federal Public Service Health, Food Chain Safety and Environment
GBD	Global Burden of Diseases, Injuries, and Risk Factors Study
HIA	Health impact assessment
HDD	Hospital discharge data
ICD	International Statistical Classification of Diseases and Related Health Problems
IHD	Ischaemic heart disease
IMA	InterMutualistic Agency
ISA	Integrated Science Assessment
MMT	Minimum mortality temperature / minimum morbidity temperature
PAF	Population attributable fraction
PM	Particulate matter
RMI	Royal Meteorological Institute of Belgium
RR	Relative risk
SMPH	Summary measure of population health
TMREL	Theoretical minimum risk exposure level
VITO	Vlaamse Instelling voor Technologisch Onderzoek
WHO	World Health Organisation
YLD	Years lived with disability
YLL	Years of life lost

INTRODUCTION

1. Background

A growing body of evidence demonstrates how the environment can have adverse effects on health. Our surroundings pose a diverse range of risks, in the form of polluting substances, harmful radiation, disrupting noise and many other factors. Epidemiological studies (typically cohort or case-control studies) are conducted to identify relationships between environmental exposure and increased risk of disease or mortality. An example is ELAPSE, a multicentre cohort study assessing the link between low-level air pollution and mortality in seven European countries, including Belgium. Contrary to individual epidemiologic studies, meta-analyses pool the results of multiple studies collected in a systematic review of relevant literature. As such, a meta-analysis synthesizes a large amount of evidence to overcome the errors and bias in the individual studies and obtain a more accurate relationship.

In contrast to epidemiological studies, that examine the association between exposure and health outcomes, **burden of disease** (BOD) studies use these relationships to estimate the contribution of risk factors to mortality or morbidity on a population level. A well-known example is the **Global Burden of Diseases, Injuries, and Risk Factors Study** (GBD), initiated in the early 1990's. The GBD is "a systematic scientific effort to quantify the comparative magnitude of health loss from diseases, injuries, and risks by age, sex, and population over time" (Murray & Lopez, 2017). The GBD study classifies risk factors most broadly as behavioral, environmental/occupational and metabolic risks. The most recent iteration of the study (Murray et al., 2020a) examines 87 risk factors in 204 countries and territories. Although the GBD now provides results for all WHO member states, including Belgium, (sub)national studies still have advantages (De Pauw et al., 2023):

- Ownership of the results and the sustainability of the study are guaranteed.
- The research can be tailored to the country- or region-specific context and based on the best available local data, which is often inaccessible to international institutions. The methodology can be adapted to the needs of local researchers, authorities and policymakers.
- Since the research is conducted 'at home', it stimulates the appraisal of local data and expertise, and thereby leads to scientific capacity building.

For these reasons, the **Belgian National Burden of Disease Study** (BeBOD) was initiated, which aims to establish a coherent framework for routinely quantifying the disease burden in Belgium using uniform metrics. A local study provides flexibility in terms of formulating research objectives and priorities. For instance, risks that are not important globally and therefore ignored, can be relevant for specific countries and included in a national study. Conversely, globally important stressors can be ignored if irrelevant in a local context. Additionally, results can be alternatively presented for separate regions or other subnational entities. Particular areas of interest can be isolated and examined in more detail as well as mutually compared.

In Belgium, there are several national and regional initiatives that assess the burden of disease attributable to environmental risks. In the frame of the EBoDE-project (Environmental Burden of Disease in the European region), Hänninen & Knol (2011) estimated the burden for nine environmental stressors

in six countries, including Belgium. For Flanders specifically, Torfs (2003) calculated the BOD and external costs related to various environmental risks. In a similar exercise, Buekers et al. (2012) assessed the disease burden and external costs for Flanders of 18 environmental stressors, where the estimates have since been updated (Buekers et al., 2021).

Aside from comprehensive studies, BOD calculations are also performed for specific environmental risks. In the Flemish Region, the disease burden related to airborne particulate matter is calculated on a routine basis, with estimates revised on a yearly basis (Statistics Flanders, n.d.). Premature mortality linked to three air pollutants are published yearly by the Environmental Department (Vlaamse Milieumaatschappij, 2023a, 2023c, 2023b). With regard to noise pollution Dekoninck & Botteldooren (2019) generated a time series of the fraction of the Flemish population that is potentially severely annoyed by environmental noise. In the Brussels Capital Region, similar efforts are pursued for air pollution, and the burden of annoyance and sleep disturbance due to environmental noise was estimated in the frame of the noise plan Quiet.Brussels (Leefmilieu Brussel, 2018).

What currently lacks is a coherent and global overview of the contribution of environmental risks to the burden of disease in Flanders. Such an overview would amount to an inventory of all relevant risk factors and the associated mortality and morbidity, which sums up to the total environmental burden of disease. As part of a collaboration agreement with **Departement Zorg** (DZ), Sciensano will develop a **Mapping of the Environmental Burden of Disease in Flanders** (EBoD-FL). This research can be situated within the intention of the Flemish government to prevent and detect environmental impact on health. The project is scheduled for the years 2022 to 2026, and will build on expertise developed within BeBOD.

EBoD-FL as a research initiative fits well within the One Health approach, where the health of humans, animals and their environment is studied within a single framework. The project could foster the adoption of health in all policies, by demonstrating how components of the modifiable environment affect disease and mortality outcomes. The estimates EBoD-FL will produce would serve as indicators for monitoring progress in the environmental healthcare objective of ensuring a favourable trend in the environmental burden of disease in Flanders by 2030.

2. Objectives

The overall objective of EBoD-FL is to provide a complete overview of the contribution of environmental risk factors to the total burden of disease in Flanders according to one coherent framework. This means, on the one hand, that the research considers all of the environmental stressors that are significant within the Flemish context. The aim is thus to quantify the total **environmental burden of disease** (EBD). On the other hand, the resulting estimates are uniform expressed using a single metric, namely a summary measure that combines premature mortality and reduced life quality due to living with disease or injury. This will allow mutual comparison and ranking, an essential property if the results of EBoD-FL are to be used for determining priorities in public health policy.

The methodology of EBoD-FL is **comparative risk assessment** (CRA). CRA estimates the proportion of the disease burden that can be attributed to stressors of interest. This top-down approach ensures that the estimates never exceed the observed BOD figures. This is in contrast to a 'regular' bottom-up risk assessment approach**,** where disease burden is determined in absolute terms by combining population exposure and dose-response relationships**.** This study will rely solely on CRA, and never on regular risk assessment or a mixture of methods, as is the case for other BOD studies in Belgium and Flanders (e.g., Buekers et al., 2012; Dekoninck & Botteldooren, 2019; Hänninen & Knol, 2011).

CRA allows to determine the proportional contribution to disease burden by comparing the actual population exposure to environmental stressors and the associated risks with a theoretical situation of

minimal risk. This approach thus disregards whether achieving minimal risk is at all realistic or feasible, which sets CRA apart from **health impact assessment** (HIA). HIA is a tool to examine the potential consequences of proposed policy measures or interventions. The scenarios considered in HIA take into account technological possibilities and as such can be integrated into a cost-benefit analysis.

The domain of this study is Flanders**.** In the main track, the EBD will be calculated locally at the level of the statistical sector, the smallest territorial and population subdivision in Belgium. The initial results are generated on this local level, and can easily be aggregated to wider areas and populations in a flexible manner. Collecting the necessary data on this fine-scale level poses a challenge, as it is often not readily available in the required format and therefore needs to be requested specifically for the ends of the research project. In the case of health or mortality related data, this information is considered sensitive, certainly in combination with the small scale of the statistical sector. For this reason, a formal approval is required before any data is made available, which needs a thorough motivation and a guaranty that any sensitive information can never be traced back to individuals. In view of these challenges, a second track was proposed, where the EBD will be determined 'globally' on the level of the Flanders in addition to the local approach. Data on this aggregated level are relatively easy to obtain, which would speed up the process and allow to move through the analysis and obtain estimates faster compared to the local approach.

The aim of the research is to map the environmental burden of disease in Flanders. However, defining Flanders in this context is not straightforward, as it can refer to a geographic area (the Flemish Region) as well as a linguistic population (the Flemish Community). Exposure to environmental risks has a regional territorial character, while the Flemish population resides in the Flemish as well as the bilingual Brussels Capital Region. To deal with this ambiguity, the analysis will include both regions, with the option in- or exclude results depending on the needs.

In the context of EBoD-FL, what is understood as 'the environment' refers to all the physical, chemical and biological determinants of health external to a human being. The social environment is thus excluded from this study. The list of what are typically considered environmental risk factors is extensive and diverse. Relative importance of the various stressors strongly depends on geographic region, degree of economic development and industrialization. As counterpart to the long list of risk factors, a large collection of disease outcomes is potentially associated with environmental exposure, ranging from cancer, respiratory and cardiovascular diseases, to metabolic disorders, neurological effects and sleep disturbance. Aside from cause-specific effects, total all-cause or non-accidental mortality is commonly included as health outcome.

Due to the extensive scope of EBoD-FL – the large number of environmental risks, each linked to one or multiple health outcomes – choices have to be made with regard to which stressor-outcome pairs deserve priority for disease burden investigation in Flanders. Consequently, three proofs-of-concept (POCs) have been proposed:

1. Determine and visualize the contribution of environmental stressors to all-cause mortality and years of life lost
2. Determine and visualize the contribution of environmental stressors to the occurrence/prevalence and disease burden of cardiovascular diseases
3. Determine and visualize the contribution of environmental stressors to the occurrence/prevalence and disease burden of chronic respiratory diseases.

The POCs determine which health outcomes have priority in the research. In making the choice of the environmental stressors that are treated first, results of previous BOD studies in Flanders can be consulted to infer which risks are associated with high impact. In consultation with DZ, it was agreed to start with:

1. Ambient air quality

2. Environmental noise
3. Extreme temperatures

The approach to quantify the EBD depends on whether exposure is examined in the short-term (hours to days) for acute health effects, or in the long-term (one to several years) for chronic risks. Initially, the analysis will be limited to long-term exposure and outcomes. Chronic exposure is generally considered to have the largest attributable burden, and the data needed for exposure assessment are more readily available as compared to what is required for acute exposure.

The environmental stressors and health outcomes mentioned so far are those that will be studied in a first phase of the project. As the aim is to provide a complete and coherent overview of the EBD in Flanders, the scope of the research will be gradually expanded to include additional risk factors, mortality and morbidity outcomes and a more complete assessment of long-term and short-term effects. This expansion will also occur in time, as the results will be updated when new data become available. As such, the content of EBoD-FL will continuously evolve as the project becomes more comprehensive and when the findings are routinely actualized according to new information and scientific insights.

The purpose of this report is to outline the methodology used to tackle the objective of EBoD-FL to map the environmental disease burden in Flanders. It explains in general terms how the burden of disease is calculated, and how the attribution to risk factors is approached. Additionally, possibilities for interpretation, visualisation and application of the results for policy are discussed, as well as some challenges and limitations. The general methodology is applied to the specific cases of the prioritised health outcomes and risk factors in dedicated annexes.

METHODS

1. Burden of disease

1.1. Disability-adjusted life years

Given the complex and multifaceted nature of public health, there are a multitude of ways to measure and quantify the BOD. Initially, indicators focused on either morbidity (e.g., disease incidence or prevalence) or mortality (e.g., life expectancy, mortality rates). The previous decades saw an extensive development of **summary measures of population health** (SMPHs), indicators that combine both mortality and morbidity into a single figure. A key advantage is that health impacts of different diseases, injuries or risk factors can each be captured in one figure and mutually compared, which makes evident the use of SMPHs for setting priorities in public health interventions and other policy domains.

The SMPH that is perhaps most widely used is the **disability-adjusted life year** (DALY). The DALY is a gap metric, meaning that it measures the difference between actual population health and a stated norm or goal, usually an ideal situation where the entire population lives to life expectancy in perfect health (Murray et al., 2000).

The method for calculating DALYs applied here, is consistent with the guidelines proposed by BeBOD (De Pauw et al., 2023). DALYs are composed of standard expected **years of life lost** (*YLL*) due to premature mortality and **years lived with disability** (*YLD*, eq. 1):

$$DALY = YLL + YLD \qquad (\text{eq. } 1)$$

The YLL component integrates the impact of mortality. For each considered cause of death, YLLs are equal to the age-specific number of deaths M_i multiplied with the standard expected residual life expectancy at age of death RLE_i, summed over all age groups (eq. 2):

$$YLL = \sum_{i=1}^{n} M_i * RLE_i \qquad (\text{eq. } 2)$$

with i = 1, …, n the considered age groups. The YLD component integrates the impact of morbidity A prevalence approach can be applied for estimating YLDs for non-communicable diseases (eq. 3):

$$YLD = p * DW \qquad (\text{eq. } 3)$$

where p is the prevalence of the outcome and DW the associated disability weight. As with the residual life expectancy, the disability weights are sourced from the GBD.

DALY calculation in the GBD originally incorporated age-weighting and time discounting, but these practices were later dropped because of ethical reasons (Murray & Lopez, 2017). Conversely, no age-weighting and time discounting will be applied in this research.

1.2. Disease models

Health outcomes are commonly conceptualized with the help of a disease model. A disease model is a hierarchical representation of a disease or injury, where the health outcome is composed of multiple health states (e.g., ‘chronic’ or ‘acute’), that can in turn be stratified according to severity (e.g., ‘mild’, ‘moderate’ or ‘severe’). As such, a disease model can be thought of as an outcome tree: the health

outcome or ‘parent node’ splits into multiple ‘child nodes’, where the total number of cases is divided over the child nodes according to predetermined proportions. The number of cases per health state and (if applicable) severity level is obtained by multiplying the total number of disease cases with the fraction corresponding to each split. A hypothetical disease model is illustrated in Fig. 1.

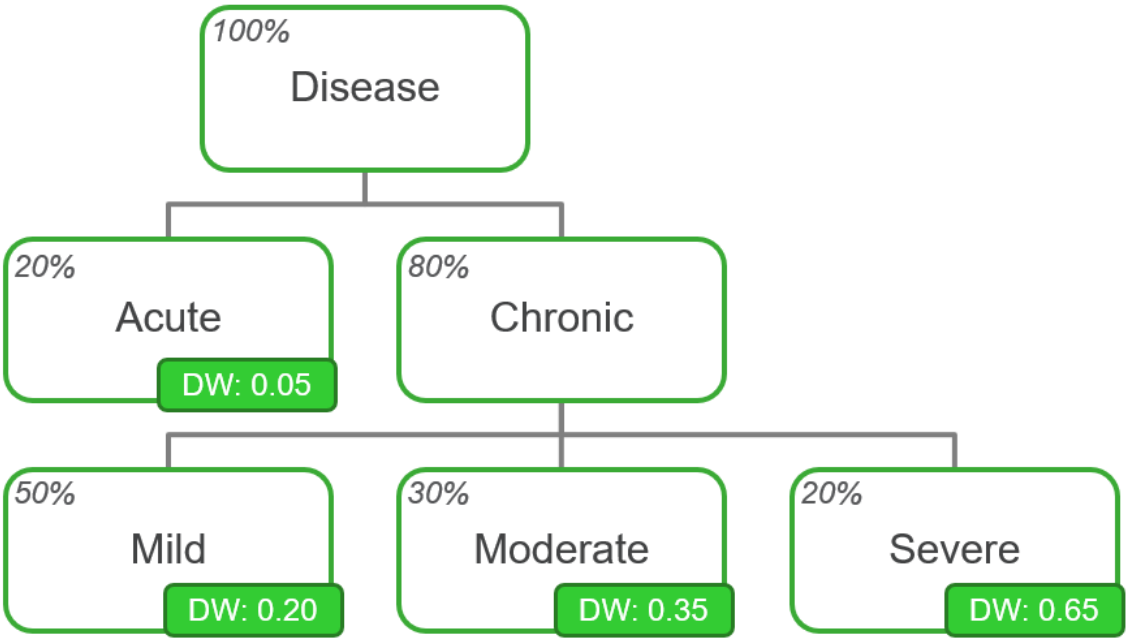

Figure 1 • Hypothetical disease model

In case a health outcome exists out of multiple health states, where each state is possibly stratified according to severity, a separate **disability weight** (DW) is assigned to each of the individual health states and potential severity levels. In this case, the DW of the overarching disease is calculated as a so-called ‘severity-weighted average’, where the proportions of cases in each of the (stratified) health states serve as weights. For the hypothetical disease model of Fig. 1, the severity-weighted DW of the disease is calculated as (eq. 1):

$$DW = \frac{20}{100} \times 0.05 + \frac{80}{100} \times \frac{50}{100} \times 0.20 + \frac{80}{100} \times \frac{30}{100} \times 0.35 + \frac{80}{100} \times \frac{20}{100} \times 0.65 = 0.278 \qquad eq.1$$

An overview of disease models and DWs can be found in the BeBOD guidelines (De Pauw et al., 2023).

1.3. Local and global approach

The main unit of analysis in EBoD-FL is the statistical sector, aka census tracts that are a subdivision of the municipality. The statistical sector is the smallest geographical unit in Belgium, established in the early 1970s to collect demographic and socio-economic data on a more refined scale. The sectors were delineated in a way that minimises internal differences in social, economic, urban or morphological characteristics or structural features, with the aim of creating homogenous units.

As CRA estimates the risk factor-related burden in a proportional way, figures for the total burden of disease are required to convert these fractions into absolute numbers. Given the approach of EBoD-FL to estimate the EBD on the level of the statistical sector, there is a need for BOD figures at this level. According to the POCs, the outcomes to be analyzed in the initial stage are all-cause mortality, **cardiovascular diseases** (CVDs) and **chronic respiratory diseases** (CRDs). The first of these endpoints only has a mortality component, while the latter two are associated with both morbidity and mortality. As POC1 specifies all-cause mortality as outcome, local mortality data are required to

calculate YLLs on the level of the statistical sector. For this end, a request was made to Statistics Belgium (Statbel) for the supply of **cause of death** (COD) microdata.

Aside from mortality figures and YLLs, data on disease incidence or prevalence are needed to quantify morbidity, or YLDs. For this end, new requests have to be submitted in a next phase of the project. For this end, a request for **hospital discharge data** (HDD) was submitted. The HDD contain information on patients hospitalised for specific health conditions, and can therefore provide a basis to estimate the incidence or prevalence of certain diseases and injuries. The HDD are managed by the **Federal Public Service Health, Food Chain Safety and Environment** (FPS Health). By default, only the postal code is recorded in the HDD, which requires a linkage with data managed by Statbel to obtain a dataset that includes the statistical sector. Additionally, data managed by the **InterMutualistic Agency** (IMA) will be explored as a potential source for health outcomes at the statistical sector level. The details of the COD and HDD are elaborated upon in appendix 1.

The local approach allows to calculate the EBD on a fine geographical scale. This approach makes it possible to relate spatial variation of exposure to location-specific mortality figures and disease incidence, which make the EBD estimates in theory more accurate. The local approach adds geographic detail to the EBD estimates, and allows to internally compare small areas and local populations. Additionally, the local results can be aggregated to wider areas and larger populations, which allows to extract estimates for any part of the Flemish Region in a flexible manner.

Parallel to the local approach, EBD estimates are calculated for Flanders as a whole. In such 'global' (as opposed to 'local') approach, a single representative estimate of population exposure is used to estimate the burden attributable to risk factors. The global, Flanders-wide approach offers the advantage that the data for exposure assessment and health outcomes are relatively easily obtainable. In terms of burden figures, BeBOD estimates for the Flemish Region are used as a baseline. The advantage of relying on BeBOD is that deaths, disease prevalence and DALYs are readily available for a large number of health outcomes. This means the calculations in the global track are not constrained to the outcomes defined in the POCs, but are carried out for all risk-outcome pairs.

2. Comparative risk assessment

Comparative risk assessment (CRA) is a top-down method for determining the proportion of the burden of disease related to specified risk factors. In CRA, the contribution of risk factors is determined by comparing the existing disease burden to the burden that would be expected in a theoretical ('counterfactual') situation with a different level of population exposure. The counterfactual can be set to any exposure level of choosing, and does not necessarily have to be realistically obtainable. Setting the counterfactual to a level of minimal risk, referred to as the **theoretical minimum risk exposure level** (TMREL), allows to estimate the full extent of the burden attributable to the risk factor (Ezzati et al., 2002). When this fraction is multiplied with observed burden figures (e.g., DALYs), it yields an absolute estimate of the BOD. This is opposed to the quantification of the attributable BOD in the risk assessment paradigm, where data on population exposure are combined with dose-response relationships to obtain figures in a bottom-up manner. As a consequence, latter method might result in an attributable burden that is higher than the total value.

The following components are required to estimate the attributable disease burden with CRA:

- Exposure of the population to the risk factor and a theoretical minimum risk exposure level
- Relationship that gives the risk of a health outcome in function of exposure
- Estimates of disease burden causally linked to the risk factor

Exposure assessment consists of determining the level of exposure in the population, which is then contrasted with the TMREL. If the risk increase in function of exposure is known, this allows to estimate

the expected relative increase in disease burden caused by raising the population exposure from the theoretical minimum to the actual level. Such a dose-response relationship can be derived from epidemiologic studies. The calculated relative increase corresponds to the **population attributable fraction** (PAF): the proportion of the disease burden caused by exposure to the stressor. The PAF is multiplied with the total burden, which yields an estimate in absolute numbers, for example expressed in DALYs (Fig. 2).

Generally, CRA consists of five steps (Plass et al., 2022):

1. Selection of risk factors: Which risk factors are included in the study and how is exposure quantified as a metric?
2. Exposure assessment: how to measure or model exposure to the risk factors in the population?
3. Identification of risk-outcome pairs: which health outcomes are caused by the risk factors?
4. Quantification of the risk-outcome relation: what is the risk of developing the outcome in function of exposure?
5. Calculation of the PAF: what is the proportion of a disease burden attributed to one or multiple risk factors?

The remainder of this chapter outlines the general CRA methodology. The application to the various stressors is added in appendix 2.

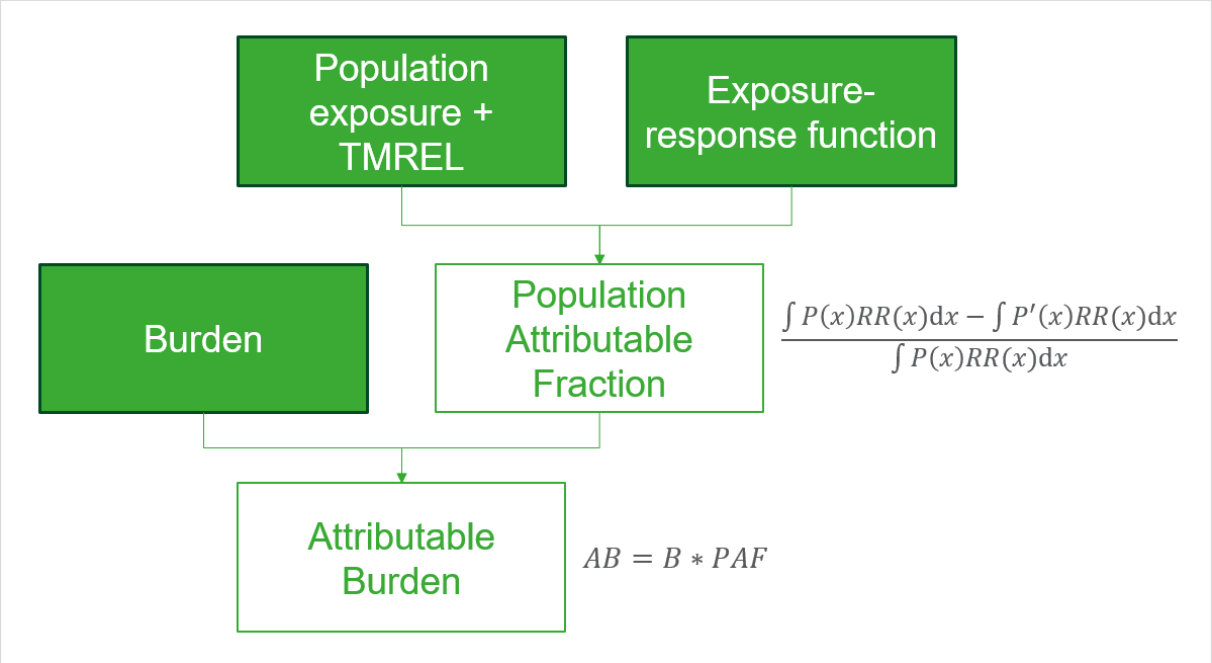

Figure 2 • Flow chart describing the procedure for calculating the attributable burden of disease by means of comparative risk assessment (CRA).

2.1. Risk factor selection

In deciding which risk factors should be included, the first question to address is what exactly constitutes 'the environment' in a health context. The WHO defines the environment as "the congregation of all the physical, chemical and biological factors external to a person, and all related behaviours, but excluding those natural environments that cannot reasonably be modified" (Prüss-Üstün et al., 2018). This definition thus excludes socio-economic and cultural factors, genetics and parts of the natural surroundings (e.g., natural breeding grounds for disease vectors, pollen). Although an exhaustive list of what can be classified as environmental risk factors does not exist, some typical examples include (indoor or ambient) air pollution (e.g., particulate matter, ozone), non-optimal temperature, occupational risks, unsafe water and sanitation (Murray et al., 2020a); carcinogens (e.g., benzene, dioxins,

formaldehyde), environmental noise (e.g., from traffic, industry), heavy metals (e.g., lead), radon, second-hand tobacco smoke (Hänninen & Knol, 2011); dampness and mold, electromagnetic fields and ultraviolet radiation (Buekers et al., 2012).

The relative importance of these factors varies greatly by region and level of industrialization and socio-economic development. According to the GBD, the top environmental risk factors in Belgium are particulate matter, low temperature, occupational carcinogens, lead exposure and occupational ergonomic factors, accounting for 16% of total disease burden and 89% of environmental/occupational burden (IHME, 2022). The GBD list of environmental risks might overlook certain stressors that are negligible on a global scale but important in specific regions or countries. The European perspective EBD study by Hänninen & Knol (2011) shows that second-hand tobacco smoke and traffic noise come in second respectively fifth of the 9 environmental stressors examined, and are also substantial contributors in the other countries that were studied. Noise and environmental tobacco smoke also rank high in the Flanders EBD study by Buekers et al. (2012) and Buekers et al. (2021) who additionally consider dampness and mold, UV and electromagnetic fields.

From the previous paragraphs, it becomes clear that the collection of candidate environmental stressors is extensive and diverse. As a result, there is a need to prioritize a select number of risk factors to be assessed in the first phase. In consultation with DZ, a selection of risk factors was made (Table 1). These risks have been shown to be important contributors to the disease burden in Flanders (Buekers et al., 2012, 2021).

Table 1 • Risk factors prioritized in EBoD-FL

Ambient air pollution	Environmental noise	Extreme temperature
Particulate matter (PM) Nitrogen dioxide (NO_2) Ozone (O_3)	Road traffic noise Railway traffic noise Air traffic noise	Heat Cold

For each stressor, a metric can be selected by consulting epidemiologic studies that examine the link between exposure and health outcomes. As environmental risks can be very different in nature, the chosen metric strongly depends on the type of environmental risk. For example, the approach to quantify the exposure to particulate matter cannot be applied to road traffic noise. Even within one type of risk factor (e.g., air pollution) there are different ways to express exposure (e.g., the ozone metric differs from the other air pollutants; see appendix). The metrics for the selected air pollutants and sources of environmental noise are outlined in the dedicated sections in appendix 2. For extreme temperature, further research is needed prior to applying CRA to the related stressors.

2.2. Exposure assessment

When a decision on the inclusion of risk factors is made, the next step is to devise a strategy to estimate the distribution of exposure in the population. As a burden of disease study relies on dose-response relationships that are derived in epidemiologic studies, one can consult the literature on how exposure of the participants is measured. Ideally, the approach to assess population exposure should be as close as possible to the methodology applied to derive the dose-response relationship.

In the main track, the unit of analysis is the statistical sector. In this case, exposure assessment is approached as a local area-level value, or as a distribution of the local population over discrete exposure classes. In the second track, the EBD is determined on a regional level, as a distribution or as a single global value that summarizes exposure in the Flemish population.

For any given stressor, the approach of exposure assessment varies depending on whether chronic or acute health effects are studied. For chronic effects, the risk of developing an outcome is linked to a long-term mean or cumulative level of exposure. Correspondingly, the level of exposure is quantified as

an annual or seasonal average or cumulative value. For the short-term approach, correlation in time is important, and as such exposure peaks have to be identified in a time series of e.g., hourly or daily values, that can be linked to acute effects.

Aside from estimating the existing population exposure, CRA relies on the definition of a theoretical minimum risk exposure level. The TMREL is used as a benchmark, which allows to determine the fraction of the BOD associated with the increased risk from a population exposure in excess of this level. Defining the TMREL for risk factors is not always straightforward. For air quality and environmental noise, one could assume that the TMREL is equal to zero pollution and a lack of noise from traffic, respectively. Another possibility is the existence of an exposure threshold, a level under which no adverse effects occur. Whether or not to include a cut-off value affects the burden calculation, as it shifts the benchmark to which population exposure is compared. The inclusion of an exposure threshold is further discussed in the section on the selection of dose-response relationships.

2.3. Identification of risk-outcome pairs

After the selection of stressors and exposure assessment, the next step is to determine which health outcomes are causally linked to the selected risk factors. In this context, a risk-outcome pair refers to an exposure and a related health effect. A randomized controlled trial (RCT) is often considered the gold standard for inferring causality, but in practice it might be unfeasible or unethical to conduct such a study (Plass et al., 2022). In case an RCT is not possible, an alternative is to assess the evidence produced by various studies. In this sense, a risk-outcome pair should be included if there is sufficiently strong evidence supporting a causal relationship. The considerations proposed by Hill are in this respect useful guidelines (Hill, 1965):

- **Strength**: The larger the effect size, the more likely that the association is causal.
- **Consistency**: The more independent studies producing similar findings, the more likely that the association is causal.
- **Specificity**: The more specific exposure and outcome are defined, the more likely that the association is causal.
- **Temporality**: The outcome has to occur after the exposure, possibly after some delay.
- **Biological gradient**: Higher exposure should be associated with more cases of the outcome, indicative of a dose-response relationship.
- **Plausibility**: There should be a plausible mechanism between exposure and outcome.
- **Coherence**: The fewer contradictory findings in other fields of study, the more likely that the association is causal.
- **Experiment**: Do changes in exposure, for example through preventive action, have an effect on the frequency of the outcome?
- **Analogy**: A causal relationship is supported if there are similar risk-outcome pairs.

Applying (some) of these considerations as criteria to evaluate a risk-outcome pair amounts in practice to grading the relevant evidence collected in a systematic review. Examples of such assessments:

- Integrated Science Assessments published by the US Environmental Protection Agency for air pollution health effects.
- The monographs published the International Agency for Research on Cancer (IARC) for the causal links with cancer outcomes.

The GBD also performed causality assessments to decide on the inclusion of risk-outcome pairs in previous cycles (Murray et al., 2020b), which are based on the grading system of the World Cancer Research Fund (Wiseman, 2008). Risk-outcome pairs are included if convincing or probable evidence exists that supports a causal relationship:

- **Convincing evidence**: Convincing evidence is evidence based on epidemiological studies showing consistent associations between exposure and disease and includes little or no evidence to the contrary. The available evidence is based on a substantial number of studies

including prospective observational studies and, where relevant, RCTs of sufficient size, duration, and quality that show consistent effects. The association should be biologically plausible.

- **Probable evidence**: Probable evidence is evidence based on epidemiological studies showing fairly consistent associations between exposure and disease, but for which perceived shortcomings in the available evidence exist or some evidence to the contrary precludes a more definite judgment. Shortcomings in the evidence may be any of the following: insufficient duration of trials (or studies); insufficient trials (or studies) available; inadequate sample sizes; or incomplete follow-up. Laboratory evidence is usually supportive. The association should be biologically plausible.
- **Possible evidence**: Possible evidence is evidence based mainly on findings from case-control and cross-sectional studies. Insufficient RCTs, observational studies, or non-randomised controlled trials are available. Evidence based on non-epidemiological studies, such as clinical and laboratory investigations, is supportive. More trials are needed to support the tentative associations, which should be biologically plausible.
- **Insufficient evidence**: Insufficient evidence is evidence based on findings of a few studies which are suggestive but insufficient to establish an association between exposure and disease. Little or no evidence is available from RCTs. More well-designed research is needed to support the tentative association.

Since GBD 2021, new potential risk-outcome pairs are identified as receiving at minimum one star in the newly introduced burden of proof risk function methodology. The candidate pair is included if the "relative risk (RR) estimate's 95% uncertainty interval, conventionally calculated, without accounting for unexplained between-study heterogeneity, does not cross the null RR value of 1" (Brauer et al., 2024).

According to POCs, the prioritized outcomes are all-cause mortality and respiratory and cardiovascular diseases. The evidence of causality for these outcomes and the stressors selected for this study are discussed in the dedicated sections in appendix 2.

2.4. Quantification of the risk-outcome relation

Once the causal risk-outcome pairs are established, a relationship is needed that relates exposure dose to increased risk for developing an outcome, i.e., a dose-response or **exposure-response function** (ERF). An ERF for a certain stressor-outcome pair returns the relative risk (or other effect measures like the odds ratio or hazard ratio) of developing the outcome at a certain level of exposure. ERFs can be sourced from the epidemiologic literature, where the relationship between exposure and relative risk is derived in longitudinal (cohort, case-control) and ecological studies. Alternatively, the ERF can be meta-analytic, meaning that it is a pooled estimate from the results of multiple studies collected in a systematic review.

The following aspects should be considered when selecting an ERF for a risk-outcome pair:

- **Accessibility**: Can the information be easily extracted?
  - From the article text?
  - From the supplementary materials?
- **Transparency**: Are the methodology and underlying data clearly described?
  - Which health data are used?
  - How is the health outcome defined?
  - How is exposure assessed?
  - Which information is available for the study's subjects?
    - Age and sex
    - Socio-economic status
    - Smoking behaviour

        - BMI
        - Physical activity level
    - Is the information on subjects individual or area-level?
    - Which confounding factors are taken into account?
    - In case of a systematic review and meta-analysis:
        - Is the search strategy documented?
        - What are the inclusion and exclusion criteria?
        - Which studies are included in the review?
        - Which information is extracted?

- **Reliability**: Is the analysis methodology sound and appropriate?
    - Is exposure assessment unbiased?
    - Is the outcome definition appropriate?
    - Are analyses performed for relevant subgroups?
    - Is the relationship adjusted for all possible confounding factors?
    - Are single or multiple exposure models used?
    - In case of a systematic review and meta-analysis:
        - Was there publication bias detected?
        - How high is the heterogeneity of the results between the studies?

- **Evidence**: Is the quality and quantity of the data used in the analysis sufficient?
    - What is the sample size?
    - Is the sample representative of the population?
    - What is the study design?
        - Systematic review
        - Randomized control trial
        - Cohort study
        - Case-control study
        - Ecological study
    - In case of a systematic review and meta-analysis:
        - Are all included studies relevant?
        - Are all relevant studies included?
        - Does the review consider the most recent evidence?

- **Relevance**: Are the findings representative of the (Belgian/Flemish) population?
    - Do the health outcome definitions match?
    - Does the definition of exposure match?
    - Are the population characteristics similar?
    - What is the geographical extent of the study?
    - What is the observed exposure range?

Critical components are the shape of the ERF and the possible existence of a threshold below which no risk increase is observed. Some studies find complex ERF shapes, by fitting a polynomial curve to the collected data. These curves can serve directly as ERF, or more commonly, can be discretized so that regular intervals of exposure correspond to a relative risk value (an integrated ERF). On the other hand, other studies approximate the complex ERF curve with a with (log-)linear relationship, where the effect measure increases by a factor per increment in exposure.

The inclusion of an exposure threshold relates to the definition of the TMREL. Since the TMREL is a counterfactual exposure distribution that corresponds to no increased risk, the RR at this level equals 1. The TMREL is used as benchmark, which allows to determine the fraction of the BOD resulting from the increased risk of the actual population exposure in excess of this level. In the case of environmental risks, the TMREL can be set to zero exposure (e.g., zero concentration of air pollutants, no detectable noise levels). Another possibility is the existence of a threshold exposure level under which no adverse

effects occur. Such a threshold is difficult to identify in epidemiologic studies, as samples in the low extreme of the exposure range are scarce. If this is the case, there are two options:

1. A first option would be to refrain from calculating BOD below the bottom exposure value. One could argue that, as the ERF is based on a certain range of observations, the relationship is only valid for exposure values that fall within that range, and it is not justified to extrapolate down to zero exposure. The bottom value could be set to the lowest exposure value observed in the epidemiologic study, or more robustly, to a lower quantile (e.g., the 5th percentile).
2. A second option is to perform BOD calculations for the entire range of exposure values. This practice could be justified in case there is no indication of a threshold. This can be verified by examining the shape of the ERF.

The selection of ERFs for the different risk-outcome pairs and possible inclusion of an exposure threshold are discussed in the dedicated sections in appendix 2.

2.5. Calculation of the population attributable fraction

The final step in CRA is to combine all of the information outlined in the previous steps to calculate the PAF, the proportion of health outcome Y due to exposure to X in the population. For a continuous exposure, the PAF can be calculated as follows (eq. 4; Plass et al., 2022):

$$PAF = \frac{\int P(x)\, RR(x)\, dx - \int P'(x)\, RR(x)\, dx}{\int P(x)\, RR(x)\, dx} \qquad (\text{eq. } 4)$$

with *P(x)* the actual distribution of exposure in the population, *P'(x)* the counterfactual exposure distribution, and *RR(x)* the relative risk of the outcome in function of exposure level *x*. In case exposure is categorical, the PAF can be calculated as (eq. 5):

$$PAF = \frac{\sum_{i=1}^{n} P_i RR_i - \sum_{i=1}^{n} P_i' RR_i}{\sum_{i=1}^{n} P_i RR_i} \qquad (\text{eq. } 5)$$

with P_i the observed prevalence of exposure class *i*, P'_i the counterfactual prevalence of exposure class *i*, and RR_i the relative risk of exposure class *i* compared to the reference class.

In case the counterfactual exposure distribution is the TMREL, and exposure is assumed to be uniform across the population (P_i and P'_i both equal 1), eq. 5 can be reduced to eq. 6:

$$PAF = \frac{RR - 1}{RR} \qquad (\text{eq. } 6)$$

The way the RR is calculated depends on whether the ERF is a simple log-linear relationship, or derived from a complex risk curve. If the ERF is log-linear, and a threshold value is included, the RR is calculated as (eq. 7):

$$RR(x) = \exp\left(\frac{\ln(RR_{incr})}{incr} \times (x - TH)\right) \qquad (\text{eq. } 7)$$

with *x* the exposure value, *TH* the exposure threshold, and RR_{incr} the increase in relative risk for an increment value *incr*. The exposure threshold refers the a level of population exposure below which no health effects are expected to occur. If population exposure is at or below the exposure threshold, the RR is assumed to be equal to the null value of 1.0. In case the ERF is a complex curve, the curve is usually discretised to a set of points, giving the RR value at specific levels of exposure. The RR at any level of exposure can then be approximated by a linear interpolation between two adjacent points.

In case a specific health outcome is associated with more than one risk factor, the corresponding PAF needs to be combined prior to multiplication with the observed disease burden. This can be achieved by applying the following formula (eq. 8):

$$PAF_{combi} = 1 - \prod_{i=1}^{n}(1 - PAF_i) \qquad (\text{eq. } 8)$$

with *i* = 1, …, *n* the risk factors associated with the outcome of interest.

Uncertainty on the PAF is a function of the uncertainty on the ERF and the exposure assessment. Analytical formulas exist to correctly determine the PAF confidence interval, but these tend to be unwieldy. Alternative approaches are Monte Carlo simulation, based on the repeated sampling from distributions that approximate the 'true' distribution, or bootstrapping, where the original set of observations is sampled with replacement as to mimic actual population sampling. Applied to CRA, the basic principle can be explained as follows: If exposure value x and RR_0 are point estimates, the value of the PAF corresponds to the central estimate. In Monte Carlo simulation or bootstrapping, the point estimates of x and RR_0 are replaced with probability distributions or the original set of observations respectively, so that repeated sampling and calculation yields a wide range (typically 1000) of PAF estimates. Based on this set of values, the mean and standard deviation or the confidence interval can be derived (Greenland, 2004).

DISCUSSION

—

1. Possibilities

1.1. Policy implications of DALYs

The main rationale for computing DALYs or other SMPHs is that it provides a coherent framework in which the impacts of different diseases, injuries and risk factors can be integrated. As such, BOD and CRA offer a quantitative basis for evidence-based public health interventions. Attributable disease burden estimates allow to identify and compare important groups of diseases and risk factors, and as such determine priorities for prevention policies and further research. The multidimensionality and layering of the EBD inventory means flexibility in terms of extracting figures. Different subsets of the inventory can be extracted, depending on the information of interest. For instance, instead of comparing the total disease burden, only the contributions to specific outcomes can be considered. The analysis can be limited to a selected category of risk factors, or exclusively to mortality or morbidity.

Examples of the types of questions that the results of EBoD-FL can answer are:

- Which environmental risks have a major health impact in Flanders?
- How does the environmental burden of disease compare to the total burden?
- Which stressors are mostly responsible for premature mortality?
- Which stressors are mostly responsible chronic disease burden?
- In which environmental domains contain the potential for substantial improvements in public health?
- For which stressors have exposure and attributable burden declined over the past years?
- For which stressors have exposure and attributable burden increased or remained stable?
- How do short-term and long-term impacts compare for a single risk factor?

EBoD-FL as a research initiative fits well within the One Health approach, which stresses the strong interconnectedness of the health of humans, animals and their environment. Specifically, the project focusses on the nexus between environmental and human health. The environment is approached holistically, with attention going to its varying components including quality of air, water and soil, diverse sources of human-made pollution such as heavy metals, persistent chemicals, traffic noise and ionizing radiation, and climatic factors including temperature, humidity and solar radiation. Attention will go to interactions between environmental components in their effect on health, and local approach especially offers the possibility to take this into consideration. As such, EBoD-FL could play a part in realizing the ambition of the Flemish government to realize health in all policies, specifically the domains related to environment, mobility, energy and industry, and nature conservation.

Environmental DALYs could serve as indicators for monitoring progress in environmental health objectives and targets. The main objective in the environmental healthcare objectives proposed by DZ is to ensure a favourable trend in EBD in Flanders by 2030. This overarching aim is composed of three themes, being climate-health (which concerns among others heat), quality of the living environment (concerning among others air pollution and environmental noise) and substances of high concern (concerning among others heavy metals, pesticides and endocrine-disrupting chemicals). Since the health objectives are meant to be specific and measurable, there is a need for quantitative estimates of the disease burden related to environmental stressors. In this context, the results of EBoD-FL could be well suited. The global, region-scale estimates lend themselves well in the context of defining strategic goals on the level of the Flemish Region. In this case the target audience is researchers and policy-makers active in national or regional governmental institutions.

The results of EBoD-FL are expressed uniquely in terms of health impacts, or 'human cost'. The attributable disease burden estimates are expressed in the form of DALYs or one of its components. The related economic costs will not be calculated as part of EBoD-FL. Various methods exist to convert BOD estimates into external costs, such as the 'value of a life year' (Desaigues et al., 2011) and 'value of statistical life' (OECD, 2012) approaches for mortality, and the quantification of the costs of hospital admission, work absenteeism and loss of wealth due to disease suffering for morbidity. As such, the results of EBoD-FL could serve as a starting point for an analysis of economic costs.

1.2. Benefits of the local approach

In the local approach to EBD, estimates are generated at small-scale geographical entities, in this case statistical sectors. In contrast to a global approach, where a single estimate summarizes the health state for the whole population and territory, the local method allows to examine how the EBD varies in space and across the population.

The local-scale approach also offers a great deal of freedom in terms of spatial aggregation. Local results can be added up to obtain estimates for wider regions and larger populations. In this way, estimates can be generated for each administrative subdivision of Flanders, such as municipalities, cities, districts, provinces and so on. Similarly, estimates can also be obtained for territorial units that are specific to the health system, such as *zorgregio's* and *eerstelijnszones*. This way, subregional entities in Flanders can be studied in isolation and mutually compared.

Aggregation is not restricted to official administrative boundaries, and can be implemented in a flexible manner to obtain estimates for virtually any region or subpopulation imaginable. This allows to study the disease burden in self-defined areas of interest, such as *milieugezondheidskundige aandachtsgebieden*. Estimates can be generated in an ad-hoc fashion for any geographical area of concern, which allows to anticipate future needs. The fine-scale approach means that EBoD-FL can deliver estimates at a scale that is meaningful to local authorities and public health professionals, such as *MMKs, LOGO's,* or *zorgraden*.

A local approach renders it possible to stratify EBD estimates. Similar to aggregating local estimates to wider areas of interest, one could aggregate results separately for different population strata. Depending on the data available on the level of the statistical sector, estimates can be stratified according to demographic characteristics (e.g., age, sex, ethnicity) or socio-economic status (e.g., income, educational, employment). This allows to study and compare different population subgroups in terms of exposure and the related EBD. As an example, one could focus on vulnerable groups such as children, the elderly or socioeconomically deprived persons.

As exposure assessment is carried out locally, risk factor interactions and the effect on the related BOD can be addressed. For example, both particulate matter and heat are known to impact health separately, and are for instance linked with premature mortality. Additionally, evidence indicates that these stressors interact and reinforce each other, which means their combined effect might be stronger than their individual contributions to mortality. If the strength of the synergetic effect depends on the levels of the individual risk factors, a local exposure assessment is able to take this into account.

As a final benefit mentioned, the local EBD estimates can be used to investigate correlations with other variables. In this case, the individual sectors correspond to datapoints, which allows to investigate statistical associations between for instance the EBD related to different stressors, or with socioeconomic variables to infer if there are inequalities in the disease burden.

1.3. Knowledge translation and visualisation

As EBoD-FL aims for an exhaustive inventory of the EBD in Flanders, the set of estimates will be broad in scope and multi-layered. The principal dimensions are the risk factors and the health outcomes, where EBD results are available for the relevant combinations. Additionally, the estimate for each risk-outcome pair can be extended into a mortality (YLL) and morbidity (YLD) component, and a long-term and short-term component where relevant. Multiple ways exist to group single risk-outcome pair estimates into wider categories. In terms of stressors, the individual risk factors can be grouped into broader categories, e.g., PM, NO_2 and O_3 into air pollution or noise from roads, railways and airports into traffic noise. This is similar for the health endpoints, e.g., ischaemic heart disease and stroke can both be placed in the cardiovascular category.

The EBoD-FL inventory presents a large body of material that can be translated into knowledge useful to policy makers and other stakeholders. This can be achieved by means of visualisation, in the form of graphs, diagrams and maps. Line plots are suited to represent the evolution of EBD over time. This could provide a basis for monitoring, where a sufficiently long time series would allow to infer trends. Charts are suited for comparing burden over different groups and entities, such as geographical regions, age groups and sexes. Alternatively, risk factors can be compared, and each bar can be subdivided into cause-specific burden, or show the relative share of mortality versus morbidity. Treemaps are another option often considered for visualising the total disease burden and the share of stressors. An overview of the burden related to all considered diseases and injuries is presented in the form of a tiling, where each tile corresponds to a health outcome and its size to its relative contribution to the total burden.

Maps are another powerful way to visualise results, suited for comparing the across geographical areas and to study spatial patterns. As the burden calculation is conducted on the small-scale level of the statistical sector, the choices for spatial aggregation are virtually unlimited. Burden figures of different sectors are simply added to generate estimates for larger areas. Aside from fixed administrative entities, custom regions of interest can be defined and examined.

Given the large size of the inventory, combined with multiple options for visualisation, an interactive tool that generates a visualisation based on user input could be suitable. To provide an example and a starting point for further discussion, Sciensano has developed an interactive visualisation tool, implemented in R Shiny. The online BeBOD tool, which provides several options to visualise the BOD in Belgium and its regions, has been considered for inspiration (Sciensano, 2022). Interactive tools could be combined with a functionality to generate reports. Based on a template, and adapted to user settings, a document is automatically generated that combines graphics with a short descriptive text. Examples are Gemeente-Stadsmonitor and provincies.incijfers.be, which allow to select a city or municipality to create an overview of a range if indicators, including health related. The user is able to select a benchmark, which could be the wider reference region, province or the whole Flemish Region.

1.4. Comparison with E-HIS

What sets apart EBoD-FL from other research projects, is the combination of its objective and wide scope. Other comprehensive EBD studies have been conducted for Flanders (e.g., Buekers et al., 2012) or the wider area (e.g., Hänninen & Knol, 2011). While these studies considered a wide range of environmental stressors, they were to a large extent a one-off endeavor. On the contrary, EBoD-FL will continuously expand in scope, and its results routinely actualized. Other routine EBD exercises exist (e.g., the DALY calculations for PM in Flanders), but these are focused on only one or a couple of environmental risks, and thus lack the wide scope of EBoD-FL.

The project that EBoD-FL perhaps shares most similarities with, is the **Environment-Health Impact Simulator** (E-HIS), developed by VITO by order of DZ (Hooyberghs et al., 2021). The aim of E-HIS is to determine the disease burden and related economic costs of air pollution and environmental noise in Flanders. Their methodology shares some similarities with EBoD-FL, as they estimate the disease

burden in a top-down manner, and also work with the statistical sector as unit of analysis. The difference however lies again with the objective and scope of the projects. E-HIS is an implementation of HIA, as it enables to project the health impact and related economic costs of different policy measures and interventions for air quality and environmental noise. In this sense, E-HIS is a prospective tool, that allows to estimate the EBD under different future scenarios.

EBoD-FL, on the other hand, relies on CRA with the objective to create and maintain a complete inventory of the existing EBD. In this sense, EBoD-FL is retrospective, as it estimates current disease burden caused by past exposure to risk factors. Important attributes of EBoD-FL are the aims for completeness and coherence. In contrast to E-HIS, it is not limited to air and noise pollution, but tries to evaluate all environmental risks in order to fully capture the EBD. While E-HIS only considers long-term exposure, EBoD-FL will include short-term analyses where this is relevant. Disease burden in E-HIS is primarily quantified as attributable disease incidence or mortality. DALYs are not consistently calculated, but only in some cases as an intermediary between disease burden and external costs. This limits the comparability of the estimates in terms of health impacts, which is one of the pillars of EBoD-FL. All of these differences in terms of methodology and approach point to the distinct aim and applicability of the two projects.

Table 2 outlines the differences and similarities between E-HIS and EBoD-FL.

Table 2 • Comparison of Environment-Health Impact Simulator (E-HIS) and Mapping the Environmental Burden of Disease in Flanders (EBoD-FL).

	E-HIS	EBoD-FL
Stressors	• Air quality: $PM_{2.5}$, PM_{10}, NO_2, O_3 • Traffic noise: roads	All environmental stressors. Priority: • Air quality: $PM_{2.5}$, PM_{10}, NO_2 • Traffic noise: roads, railways, airports • Extreme temperatures: heat, cold
Outcomes	• Mortality • Disease incidence • Sleep disturbance • Annoyance	All health outcomes associated with environmental stressors. Priority: • All-cause mortality • Cardiovasculair diseases • Chronic respiratory diseases
Output	• Number of cases • External costs	• All-cause deaths • DALYs
Scale	Statistical sector, postal code, municipality, district, eerstelijnszone, vervoerregio, province, region	• Statistical sector + aggregations (to be determined) • Region
Period	• Present + past • Expert version: prospective BAU and BEL scenario 2030 air quality	• Present + past
Methods	• Air quality: CRA • Traffic noise: CRA + annoyance functions	• CRA

2. Challenges

2.1. Challenges of the local approach

As a flipside to the benefits outlined in the previous section, the local approach comes with certain challenges as well. A first challenge relates to collecting data at the small scale of the statistical sector. Generally, data availability decreases with increasing resolution. With regard to data on environmental stressors, the national or regional level is often available as open access, in some cases down to the municipal level but rarely on a sector scale. As a result, environmental data need to be requested in a format tailored to the specific needs of the research, where the data providers are in some cases unable or unwilling to do so. If exposure assessment is based on a sample and statistical extrapolation, such as for biomonitoring data, the sector level is unattainable.

Similar problems arise in the collection of the health outcome data, with the added difficulty of potential privacy issues. The data required to calculate baseline disease burden are effectively personal data, in this case considered especially sensitive due to their medical nature. Requesting such data usually requires a formal approval from an advisory board, such the Information Security Committee, which amounts to an arduous and time-consuming procedure. The fine scale of the statistical sectors further complicates things, as it poses a small cell risk where aggregated data can still be traced back to individuals in sectors where populations are small and disease or mortality cases rare. In the case of morbidity outcomes, some of the underlying data sources are not available on the level of the statistical sector. For instance, in the case of the Health Interview Survey or a GP sentinel network like Intego, extrapolation to the wider population is impossible based on the available samples.

A second challenge relates to the small population size of the sectors, with a mean population count of around 500 inhabitants. Estimating the PAF and attributable burden rely on general statistical relationships, representative for a large, diverse population. Local groups might show a distribution of relevant confounders that is skewed compared to the general population, in which case applying these relationships as ERF would result in biased estimates. In some sectors, with very small populations and very few cases of mortality or disease incidence, the use of ERFs would amount to ecological fallacy, where the statistical relationships that hold for groups are interpreted as to hold for individuals as well. A possible remediation for the local result bias is to aggregate sectors to larger areas and populations. In doing so, the individual biases would nullify each other and the aggerated estimate would become accurate.

2.2. Establishing decision criteria

Developing a methodological protocol for the inclusion of risk-outcome pairs poses a challenge. As mentioned in the previous chapter on the methodology, one can consult studies that assess the causality between environmental exposures and health outcomes. In practice, such assessments are not always conclusive, or even non-existent for some risk-outcome pairs. In case an assessment on causality is available, there are several scenarios. The two straightforward scenarios are when causality is either proven or disproven, in which case the risk-outcome pair should be included or excluded respectively. In the remaining scenario, the evidence on causality is inconclusive. In this case, the question is whether a statistically significant association can be found in the epidemiologic literature, and if so, whether the risk-outcome pair should then be included or not.

Another point of contention relates to what constitutes the most appropriate ERF. One point of view is that the dose-response relationship should be based on a sample that is as large and diverse as possible. Preference is given to meta-analyses that include effect measures from multiple studies, as to cover as much of the world's population as possible. A contrary view is that the ERF should be based on a source population (sampled in the epidemiologic study) that is close as possible to the target population (of interest in the BOD study). The underlying idea is that ERFs are context-dependent, and

the results from one population are not transferable to another. In this case, the ERF is ideally sourced from a large cohort study confined to the population of interest.

2.3. Integrating estimates

Summing burden estimates from individual risk-outcome pairs is not always straightforward. A first challenge relates to integrating short-term (ST) and long-term (LT) exposure into one coherent and comparative framework. When the same stressor is associated with both ST and LT effects, there are two scenarios with respect to the associated outcomes:

- Scenario 1: the ST and LT effects of the stressor concern different outcomes, i.e., the risk-outcome pairs are unique in terms of ST and LT effects. The solution here is to aggregate the ST and LT burden to the same period, after which the results are comparable and additive.
- Scenario 2: the ST and LT effects of the stressor concern the same outcome, i.e., some risk-outcome pairs are associated with both ST and LT effects. This situation is more tricky, and multiple solutions are possible:
  - Solution 1: aggregate the ST and LT burden to the same period, equivalent to the solution in the first scenario. However, this might be problematic, as there could be overlap in the disease burden of the ST and LT estimates. As a consequence, the results are possibly not comparable and additive.
  - Solution 2: limit the burden calculation for the risk-outcome pairs to either the ST or LT approach. The issue here is to establish criteria to decide which approach is best suited. Additionally, if only ST or LT effects are quantified, the question is whether those effects alone account for all of the related EBD, or whether the EBD is underestimated.

In case of a scenario 2, the second solution will be pursuit. A ST or LT approach is developed depending on which of these effects is best supported by the available evidence.

A second challenge pertains to aggregating the burden attributable to exposures that are correlated. If PAFs are calculated based on ERFs that are not corrected for combined exposures, overlap will exist in the attributable burden and adding these estimates will result in partial double-counting. There are several potential strategies to accommodate this challenge:

- In an ideal scenario, the PAFs are calculated with ERFs from multi-exposure models, meaning that the effect of correlated exposures is accounted for in the effect estimate. However, even multi-exposure models cannot fully in untangle the health effects of stressors that are highly correlated.
- If ERFs from multi-exposure models are unavailable, single-pollutant ERFs can be corrected with a factor taken from the scientific literature to correct for the overlap. This factor is based on the results of older studies, where both single and multi-exposure models are applied and can be compared. Aggregating estimates is then approached as calculating the attributable burden for the correlated stressors separately, using the corrected ERFs, and subsequently summing up the estimates.
- As an alternative to summing estimates, one could rely on a multiplicative model to calculate the PAF (see eq. 8). In this approach, the PAFs from different risk factors are combined prior to multiplying with the baseline burden. This ensures that the PAF never exceeds 1, but does not account for overlap in the estimates.
- As a final strategy, aggregating estimates over stressors can simply be avoided. Estimates are then only presented separately for each risk factor, and it is underlined that one should not sum estimates of different stressors. This is of course problematic when interested in comparing the burden attributable to broader categories of stressors (e.g., air pollution or environmental noise), or to obtain an overall estimate of the environmental burden of disease.

3. Limitations

The overall objective of EBoD-FL is to provide a complete overview of the environmental burden of disease in Flanders. In practice, however, the contribution of environmental risk factors to the disease burden is most likely greater than what is feasible to estimate based on the available data and scientific information. The CRA framework requires reliable data to assess the extent of population exposure, which are unavailable for certain environmental stressors, especially on the statistical sector scale. Attributable burden estimation is also dependent on ERFs to quantify the PAF. The existence of reliable effect estimates is tied to state of the epidemiologic literature, which is advanced for some stressors, while only emerging in the case of others. For these reasons, the aim of obtaining a 'complete overview' should be interpreted as an ultimate objective to strive for, rather then an identifiable end goal to be achieved.

Generating attributable disease burden estimates inevitably relies on a set of assumptions, and is subject to a degree of uncertainty. Some of these uncertainties have already been referred to, such as those related to exposure assessment and the use of ERFs. These sources of uncertainty can be quantified, for instance by implementing a Monte Carlo simulation. This not the case for other uncertainties, where it is not possible to estimate their extent. One of such sources are possible errors in the data used to map the stressors. These data consist of model output, and although there might be efforts to validate their results, a degree of bias is still probable. Other examples are the shape of the ERF, which is not always examined, and the possibility of an exposure threshold, for which the data often lack. Under these circumstances, one is left to assume a linear ERF, and to include or exclude a threshold based on own assessment or expert opinion.

Another limitation is that population exposure is solely addressed based on place of residence. As there is no information on occupation or place of work, occupational exposure to e.g., workplace carcinogens or ergonomic stressors cannot be addressed. Additionally, information on location is usually limited to the current or last-known official place of residence. As a result, exposure changes due to people moving cannot be taken into account. The approach for exposure assessment is thus 'static': the effect of occupational exposure, changing address, commuting, traveling or a second residence is not registered.

CONCLUSION

The ultimate objective of EBoD-FL, a complete and coherent inventory of the environmental burden of disease in Flanders, is ambitious and extensive in scope. As a starting point, priority was given to stressors related to ambient air quality, traffic noise and extreme temperatures, that will be quantified in terms of their contribution to all-cause mortality, cardiovascular diseases and chronic respiratory diseases as a proof of concept. The scope of the project will gradually extend to include more risk factors and health outcomes. All estimates are expressed as disability-adjusted life years, which ensures that both mortality and morbidity impacts of environmental risks are captured and that the estimates are mutually comparable.

What differentiates EBoD-FL from other research projects, is the combination of its objective and wide scope. While other comprehensive studies of the EBD in Flanders have been conducted, they were to a large extent a one-off endeavor. On the other hand, routine EBD exercises exist, but these are limited to a select number of environmental risks. On the contrary, EBoD-FL will quantify the disease burden related to a wide range of environmental risk factors using a consistent framework. The project will continuously expand in scope, and its results will be routinely updated. The research will allow to monitor the evolution of the EBD and the progress in proposed targets. Other projects similar to EBoD-FL are ongoing, such as the Environment Health Impact Simulator developed by VITO. Although distinct in aim, contact will be maintained with other institutions to ensure a better alignment and to avoid a duplication of efforts.

The local approach of the research offers several advantages, including generating estimates for self-defined areas and population subgroups in a flexible, ad-hoc manner. Various options for visualisation and knowledge translation will be explored, such as diagrams, graphs and maps, which could be realised in an interactive format such as an R Shiny application. As such, EBoD-FL could serve as a basis for evidence-based public health interventions, addressing questions related to environmental health impact in a quantitative way. The results can aid the integration of a health perspective into environmental policy, and to set priorities for prevention and further research.

In order to achieve these goals, some challenges have to be overcome. The fine scale of the statistical sector interferes with collecting the data, which are generally less available or simply do not exist. For this reason, a parallel track of calculations on the level of the Flemish Region will be pursued, where data availability is not constrained by the sector level. Another difficulty is to establish clear and substantiated criteria for including risk-outcome pairs and to select the most suitable ERF. Another relates to the fact that individual estimates are not always additive, which hampers integration into one comparative framework. Continued research is required to deal with these challenges, as well as moments of consultation with partners and institutions involved with similar research to devise appropriate and supported solutions.

REFERENCES

Alemayehu Ali, E., Cox, B., Van de Vel, K., Verachtert, E., Vaes, B., Gabriel Beerten, S., Duarte, E., Scheerens, C., Aerts, R., & Van Pottelbergh, G. (2024). Associations of heat with diseases and specific symptoms in Flanders, Belgium: An 8-year retrospective study of general practitioner registration data. *Environment International*, *193*, 109097. https://doi.org/10.1016/j.envint.2024.109097

Bouchama, A., Mündel, T., & Laitano, O. (2024). Beyond heatwaves: A nuanced view of temperature-related mortality. *Temperature*, *11*(3), 190–202. https://doi.org/10.1080/23328940.2024.2310459

Brauer, M., Roth, G. A., Aravkin, A. Y., Zheng, P., Abate, K. H., Abate, Y. H., Abbafati, C., Abbasgholizadeh, R., Abbasi, M. A., Abbasian, M., Abbasifard, M., Abbasi-Kangevari, M., ElHafeez, S. A., Abd-Elsalam, S., Abdi, P., Abdollahi, M., Abdoun, M., Abdulah, D. M., Abdullahi, A., … Gakidou, E. (2024). Global burden and strength of evidence for 88 risk factors in 204 countries and 811 subnational locations, 1990–2021: A systematic analysis for the Global Burden of Disease Study 2021. *The Lancet*, *403*(10440), 2162–2203. https://doi.org/10.1016/S0140-6736(24)00933-4

Brunekreef, B., Strak, M., Chen, J., Andersen, Z. J., Atkinson, R., Carey, I., Cesaroni, G., Forastiere, F., Fecht, D., Gulliver, J., Hertel, O., Hoffmann, B., de Hoogh, K., Houthuijs, D., Hvidtfeldt, U., Klompmaker, J., Krog, N. H., Liu, S., Ljungman, P., … Hoek, G. (2021). *Mortality and Morbidity Effects of Long-Term Exposure to Low-Level PM2.5, BC, NO2, and O3: An Analysis of European Cohorts in the ELAPSE Project*. 150.

Buekers, J., Torfs, R., Deutsch, F., Lefebvre, W., & Bossuyt, M. (2012). *Inschatting ziektelast en externe kosten veroorzaakt door verschillende milieufactoren in Vlaanderen, studie uitgevoerd in opdracht van de Vlaamse Milieumaatschappij* (p. 135). VITO.

Buekers, J., Van de Vel, K., & Cops, J. (2021). *Actualisatie indicator verloren gezonde levensjaren (DALY's) door milieuverstoringen in Vlaanderen* (Studie in Opdracht van Milieurapport Vlaanderen, Vlaamse Milieumaatschappij).

Burkart, K. G., Brauer, M., Aravkin, A. Y., Godwin, W. W., Hay, S. I., He, J., Iannucci, V. C., Larson, S. L., Lim, S. S., Liu, J., Murray, C. J. L., Zheng, P., Zhou, M., & Stanaway, J. D. (2021). Estimating the cause-specific relative risks of non-optimal temperature on daily mortality: A two-part modelling approach applied to the Global Burden of Disease Study. *The Lancet*, *398*(10301), 685–697. https://doi.org/10.1016/S0140-6736(21)01700-1

Cai, Y., Ramakrishnan, R., & Rahimi, K. (2021). Long-term exposure to traffic noise and mortality: A systematic review and meta-analysis of epidemiological evidence between 2000 and 2020. *Environmental Pollution*, *269*, 116222. https://doi.org/10.1016/j.envpol.2020.116222

Chen, J., & Hoek, G. (2020). Long-term exposure to PM and all-cause and cause-specific mortality: A systematic review and meta-analysis. *Environment International*, *143*, 105974. https://doi.org/10.1016/j.envint.2020.105974

Cheng, J., Xu, Z., Bambrick, H., Prescott, V., Wang, N., Zhang, Y., Su, H., Tong, S., & Hu, W. (2019). Cardiorespiratory effects of heatwaves: A systematic review and meta-analysis of global epidemiological evidence. *Environmental Research*, *177*, 108610. https://doi.org/10.1016/j.envres.2019.108610

De Pauw, R., Gorasso, V., & Devleesschauwer, B. (2023). *Belgian National Burden of Disease Study. Guidelines for the calculation of DALYs in Belgium*.

De Pauw, R., Gorasso, V., Scohy, A., Nayani, S., Claerman, R., Van den Borre, L., & Devleesschauwer, B. (2024). *BeBOD estimates of mortality, years of life lost, prevalence, years lived with disability, and disability-adjusted life years for 38 causes, 2013-2021 (v2024-08-27) [Data set]*. Zenodo. https://doi.org/10.5281/zenodo.13378154

Dekoninck, L., & Botteldooren, D. (2019). *Actualisatie geluidshinderindicatoren 2019*. 28.

Demoury, C., Aerts, R., Vandeninden, B., Van Schaeybroeck, B., & De Clercq, E. M. (2022). Impact of Short-Term Exposure to Extreme Temperatures on Mortality: A Multi-City Study in Belgium. *International Journal of Environmental Research and Public Health*, *19*(7), 3763. https://doi.org/10.3390/ijerph19073763

Desaigues, B., Ami, D., Bartczak, A., Braun-Kohlová, M., Chilton, S., Czajkowski, M., Farreras, V., Hunt, A., Hutchison, M., Jeanrenaud, C., Kaderjak, P., Máca, V., Markiewicz, O., Markowska, A., Metcalf, H., Navrud, S., Nielsen, J. S., Ortiz, R., Pellegrini, S., … Urban, J. (2011). Economic valuation of air pollution mortality: A 9-country contingent valuation survey of value of a life year (VOLY). *Ecological Indicators*, *11*(3), 902–910. https://doi.org/10.1016/j.ecolind.2010.12.006

Devleesschauwer, B., Scohy, A., De Pauw, R., Gorasso, V., Kongs, A., Neirynck, E., Verduyckt, P., Wyper, G. M. A., & Van den Borre, L. (2023). Investigating years of life lost in Belgium, 2004–2019: A comprehensive analysis using a probabilistic redistribution approach. *Archives of Public Health*, *81*(1), 160. https://doi.org/10.1186/s13690-023-01163-7

European Environment Agency. (2010). *Good practice guide on noise exposure and potential health effects.* Publications Office. https://data.europa.eu/doi/10.2800/54080

Ezzati, M., Lopez, A. D., Rodgers, A., Vander Hoorn, S., & Murray, C. J. (2002). Selected major risk factors and global and regional burden of disease. *The Lancet*, *360*(9343), 1347–1360. https://doi.org/10.1016/S0140-6736(02)11403-6

Gao, D., Friedman, S., Hosler, A., Sheridan, S., Zhang, W., & Lin, S. (2022). Association between extreme ambient heat exposure and diabetes-related hospital admissions and emergency department visits: A systematic review. *Hygiene and Environmental Health Advances*, *4*, 100031. https://doi.org/10.1016/j.heha.2022.100031

Greenland, S. (2004). Interval estimation by simulation as an alternative to and extension of confidence intervals. *International Journal of Epidemiology*, *33*(6), 1389–1397. https://doi.org/10.1093/ije/dyh276

Guo, Y., Li, S., Zhang, Y., Armstrong, B., Jaakkola, J. J. K., Tong, S., & Pan, X. (2013). Extremely cold and hot temperatures increase the risk of ischaemic heart disease mortality: Epidemiological evidence from China. *Heart*, *99*(3), 195–203. https://doi.org/10.1136/heartjnl-2012-302518

Hahad, O., Kröller-Schön, S., Daiber, A., & Münzel, T. (2019). The Cardiovascular Effects of Noise. *Deutsches Ärzteblatt International*. https://doi.org/10.3238/arztebl.2019.0245

Halonen, J. I., Hansell, A. L., Gulliver, J., Morley, D., Blangiardo, M., Fecht, D., Toledano, M. B., Beevers, S. D., Anderson, H. R., Kelly, F. J., & Tonne, C. (2015). Road traffic noise is associated with increased cardiovascular morbidity and mortality and all-cause mortality in London. *European Heart Journal*, *36*(39), 2653–2661. https://doi.org/10.1093/eurheartj/ehv216

Hänninen, O., & Knol, A. (2011). *European perspectives on environmental burden of disease: Estimates for nine stressors in six European countries.* National Institute for Health and Welfare.

Hao, G., Zuo, L., Weng, X., Fei, Q., Zhang, Z., Chen, L., Wang, Z., & Jing, C. (2022). Associations of road traffic noise with cardiovascular diseases and mortality: Longitudinal results from UK Biobank and meta-analysis. *Environmental Research*, *212*, 113129. https://doi.org/10.1016/j.envres.2022.113129

Hill, A. B. (1965). The Environment and Disease: Association or Causation? *Proceedings of the Royal Society of Medicine*, *58*(5), 295.

Hoffmann, B., Boogaard, H., de Nazelle, A., Andersen, Z. J., Abramson, M., Brauer, M., Brunekreef, B., Forastiere, F., Huang, W., Kan, H., Kaufman, J. D., Katsouyanni, K., Krzyzanowski, M., Kuenzli, N., Laden, F., Nieuwenhuijsen, M., Mustapha, A., Powell, P., Rice, M., … Thurston, G. (2021). WHO Air Quality Guidelines 2021–Aiming for Healthier Air for all: A Joint Statement by Medical, Public Health, Scientific Societies and Patient Representative Organisations. *International Journal of Public Health*, *66*, 1604465. https://doi.org/10.3389/ijph.2021.1604465

Hooyberghs, H., Van de Vel, K., Deutsch, F., De Nocker, L., Beckx, C., & Van Holderbeke, M. (2021). *Overzichtsrapport Environment Health Impact Simulator (E-HIS)* (2020/RMA/R/2133). VITO.

Houthuijs, D., Swart, W., & van Kempen, E. (2019). *Implications of environmental noise on health and wellbeing in Europe. Based on data from the second (2012) and third (2017) round of noise assessment in the framework of the European Noise Directive* (ETC/ACM 2018/10; Eionet Report). European Topic Centre on Air Pollution and Climate Change Mitigation.

Huangfu, P., & Atkinson, R. (2020). Long-term exposure to NO2 and O3 and all-cause and respiratory mortality: A systematic review and meta-analysis. *Environment International*, *144*, 105998. https://doi.org/10.1016/j.envint.2020.105998

IHME. (2022). *GHDx*. https://vizhub.healthdata.org/gbd-results/

Leefmilieu Brussel. (2018). *QUIET.BRUSSELS. Plan voor de preventie en bestrijding van geluidshinder en trillingen in een stedelijke omgeving. Milieueffectenrapport van het ontwerp-plan*.

Lian, H., Ruan, Y., Liang, R., Liu, X., & Fan, Z. (2015). Short-Term Effect of Ambient Temperature and the Risk of Stroke: A Systematic Review and Meta-Analysis. *International Journal of Environmental Research and Public Health*, *12*(8), 9068–9088. https://doi.org/10.3390/ijerph120809068

Liu, J., Varghese, B. M., Hansen, A., Xiang, J., Zhang, Y., Dear, K., Gourley, M., Driscoll, T., Morgan, G., Capon, A., & Bi, P. (2021). Is there an association between hot weather and poor mental health outcomes? A systematic review and meta-analysis. *Environment International*, *153*, 106533. https://doi.org/10.1016/j.envint.2021.106533

Liu, J., Varghese, B. M., Hansen, A., Zhang, Y., Driscoll, T., Morgan, G., Dear, K., Gourley, M., Capon, A., & Bi, P. (2022). Heat exposure and cardiovascular health outcomes: A systematic review and meta-analysis. *The Lancet Planetary Health*, *6*(6), e484–e495. https://doi.org/10.1016/S2542-5196(22)00117-6

Murray, C. J. L., Aravkin, A. Y., Zheng, P., Abbafati, C., Abbas, K. M., Abbasi-Kangevari, M., Abd-Allah, F., Abdelalim, A., Abdollahi, M., Abdollahpour, I., Abegaz, K. H., Abolhassani, H., Aboyans, V., Abreu, L. G., Abrigo, M. R. M., Abualhasan, A., Abu-Raddad, L. J., Abushouk, A. I., Adabi, M., … Lim, S. S. (2020a). Global burden of 87 risk factors in 204 countries and territories, 1990–2019: A systematic analysis for the Global Burden of Disease Study 2019. *The Lancet*, *396*(10258), 1223–1249. https://doi.org/10.1016/S0140-6736(20)30752-2

Murray, C. J. L., Aravkin, A. Y., Zheng, P., Abbafati, C., Abbas, K. M., Abbasi-Kangevari, M., Abd-Allah, F., Abdelalim, A., Abdollahi, M., Abdollahpour, I., Abegaz, K. H., Abolhassani, H., Aboyans, V., Abreu, L. G., Abrigo, M. R. M., Abualhasan, A., Abu-Raddad, L. J., Abushouk, A. I., Adabi, M., … Lim, S. S. (2020b). Global burden of 87 risk factors in 204 countries and territories, 1990–2019: A systematic analysis for the Global Burden of Disease Study 2019. *The Lancet*, *396*(10258), 1223–1249. https://doi.org/10.1016/S0140-6736(20)30752-2

Murray, C. J. L., & Lopez, A. D. (2017). Measuring global health: Motivation and evolution of the Global Burden of Disease Study. *The Lancet*, *390*(10100), 1460–1464. https://doi.org/10.1016/S0140-6736(17)32367-X

Murray, C. J. L., Salomon, J. A., & Mathers, C. (2000). A critical examination of summary measures of population health. *Bulletin of the World Health Organization*, 14.

Nieuwenhuijsen, M., Gascon, M., Martinez, D., Ponjoan, A., Blanch, J., Garcia-Gil, M., Ramos, R., Foraster, M., Mueller, N., Espinosa, A., Cirach, M., Khreis, H., Dadvand, P., & Basagaña, X. (2018). Air Pollution, Noise, Blue Space, and Green Space and Premature Mortality in Barcelona: A Mega Cohort. *International Journal of Environmental Research and Public Health*, *15*(11), 2405. https://doi.org/10.3390/ijerph15112405

OECD. (2012). *Mortality risk valuation in environment, health and transport policies*. OECD Publishing.

Plass, D., Hilderink, H., Lehtomäki, H., Øverland, S., Eikemo, T. A., Lai, T., Gorasso, V., & Devleesschauwer, B. (2022). Estimating risk factor attributable burden – challenges and potential solutions when using the comparative risk assessment methodology. *Archives of Public Health*, *80*(1), 148. https://doi.org/10.1186/s13690-022-00900-8

Prüss-Üstün, A., Wolf, J., Corvalán, C., Bos, R., & Neira, M. (2018). *Preventing disease through healthy environments: Towards an estimate of the environmental burden of disease: A global assessment of the burden of disease from environmental risks*. WHO Regional Office for the Western Pacific. http://iris.wpro.who.int/handle/10665.1/14040

Pyko, A., Roswall, N., Ögren, M., Oudin, A., Rosengren, A., Eriksson, C., Segersson, D., Rizzuto, D., Andersson, E. M., Aasvang, G. M., Engström, G., Gudjonsdottir, H., Jørgensen, J. T., Selander, J., Christensen, J. H., Brandt, J., Leander, K., Overvad, K., Eneroth, K., … Pershagen, G. (2023). Long-Term Exposure to Transportation Noise and Ischemic Heart Disease: A Pooled Analysis of Nine Scandinavian Cohorts. *Environmental Health Perspectives*, *131*(1), 017003. https://doi.org/10.1289/EHP10745

Roswall, N., Pyko, A., Ögren, M., Oudin, A., Rosengren, A., Lager, A., Poulsen, A. H., Eriksson, C., Segersson, D., Rizzuto, D., Andersson, E. M., Aasvang, G. M., Engström, G., Jørgensen, J. T., Selander, J., Christensen, J. H., Thacher, J., Leander, K., Overvad, K., … Sørensen, M. (2021).

Long-Term Exposure to Transportation Noise and Risk of Incident Stroke: A Pooled Study of Nine Scandinavian Cohorts. *Environmental Health Perspectives*, *129*(10), 107002. https://doi.org/10.1289/EHP8949

Royal Meteorological Institute. (n.d.). *Gridded observational data*. Retrieved December 20, 2024, from https://opendata.meteo.be/geonetwork/srv/eng/catalog.search#/metadata/RMI_DATASET_GRIDDEDOBS

Sciensano. (2022, October 27). *BeBOD estimates of the burden of disease*. Belgian National Burden of Disease Study. https://burden.sciensano.be/shiny/daly/

Statistics Flanders. (n.d.). *Healthy life years lost due to fine particles*. Retrieved June 7, 2022, from https://www.vlaanderen.be/en/statistics-flanders/environment-and-nature/healthy-life-years-lost-due-to-fine-particles

Thacher, J. D., Hvidtfeldt, U. A., Poulsen, A. H., Raaschou-Nielsen, O., Ketzel, M., Brandt, J., Jensen, S. S., Overvad, K., Tjønneland, A., Münzel, T., & Sørensen, M. (2020). Long-term residential road traffic noise and mortality in a Danish cohort. *Environmental Research*, *187*, 109633. https://doi.org/10.1016/j.envres.2020.109633

Thompson, R., Hornigold, R., Page, L., & Waite, T. (2018). Associations between high ambient temperatures and heat waves with mental health outcomes: A systematic review. *Public Health*, *161*, 171–191. https://doi.org/10.1016/j.puhe.2018.06.008

Torfs, R. (2003). *Kwantificering van gezondheidsrisico's aan de hand van DALYs en externe gezondheidskosten*.

U.S. Environmental Protection Agency. (2015). *Preamble to the Integrated Science Assessments*. National Center for Environmental Assessment—RTP Division. Office of Research and Development.

U.S. Environmental Protection Agency. (2016). *Integrated Science Assessment for Oxides of Nitrogen–Health Criteria*. Center for Public Health and Environmental Assessment.

U.S. Environmental Protection Agency. (2019). *Integrated Science Assessment for Particulate Matter*. Center for Public Health and Environmental Assessment.

U.S. Environmental Protection Agency. (2020). *Integrated Science Assessment for Ozone and Related Photochemical Oxidants*. Center for Public Health and Environmental Assessment.

van Kempen, E., Casas, M., Pershagen, G., & Foraster, M. (2018). WHO Environmental Noise Guidelines for the European Region: A Systematic Review on Environmental Noise and Cardiovascular and Metabolic Effects: A Summary. *International Journal of Environmental Research and Public Health*, *15*(2), 379. https://doi.org/10.3390/ijerph15020379

Verachtert, E., Faes, C., Lauwaet, D., De Nocker, L., Van Esch, L., Van de Vel, K., Janssen, L., Stouthuysen, P., & Duarte, E. (2023). *Instrumenten voor evaluatie van gezondheidsimpact door hitte in Vlaanderen, nu en in de toekomst*. Studie uitgevoerd door VITO en UHasselt i.o.v. Departement Zorg, Vlaamse Overheid.

Vienneau, D., Eze, I. C., Probst-Hensch, N., & Röösli, M. (2019). *Association between transportation noise and cardio-metabolic diseases: An update of the WHO meta-analysis*.

Vlaamse Milieumaatschappij. (2023a). *Blootstelling en gezondheidseffecten van fijn stof (PM_{10} en $PM_{2,5}$)*. https://www.vmm.be/lucht/fijn-stof/blootstelling-en-gezondheidseffecten-fijn-stof

Vlaamse Milieumaatschappij. (2023b). *Blootstelling en gezondheidseffecten van ozon (O_3)*. https://www.vmm.be/lucht/ozon/blootstelling-en-gezondheidseffecten-ozon

Vlaamse Milieumaatschappij. (2023c). *Blootstelling en gezondheidseffecten van stikstofdioxide (NO_2)*. https://www.vmm.be/lucht/stikstof/blootstelling-en-gezondheidseffecten-stikstofdioxide

WHO Regional Office for Europe. (2018). *Environmental noise guidelines for European Region*. WHO Regional Office for Europe.

WHO Regional Office for Europe & JRC European Commission. (2011). *Burden of disease from environmental noise: Quantification of healthy life years lost in Europe*. World Health Organization, Regional Office for Europe.

Wiseman, M. (2008). The second World Cancer Research Fund/American Institute for Cancer Research expert report. Food, nutrition, physical activity, and the prevention of cancer: A global

perspective. *The Proceedings of the Nutrition Society*, *67*(3), 253–256. https://doi.org/10.1017/S002966510800712X

World Health Organization. (2021). *WHO global air quality guidelines: Particulate matter (PM2.5 and PM10), ozone, nitrogen dioxide, sulfur dioxide and carbon monoxide*. World Health Organization. https://apps.who.int/iris/handle/10665/345329

ANNEXES

—

1. Health outcomes

1.1. Total and cause-specific mortality

According to the POCs, the outcomes to be analyzed in the initial stage are all-cause mortality, cardiovascular diseases and chronic respiratory diseases. As each of these endpoints have a mortality component, local mortality data are required to calculate YLLs on the level of the statistical sector. For this end, a request was made to Statistics Belgium (Statbel) for the supply of **cause of death** (COD) microdata. The word microdata refers to records of individual instances, in this case deaths. These microdata are based on information in death certificates, filled out by the medical doctor that certifies the death. The death certificates are then collected and coded by the regions, and afterwards compiled by Statbel into a single database.

As the COD microdata concern privacy-sensitive information, the request to Statbel had to be well-motivated, involving extensive negotiation, and the signing of a confidentiality contract. An agreement was reached to deliver COD data for the whole of Belgium starting with the year 2000, ending in 2019, the most recent year available. Yearly updates will be delivered until 2026 (i.e., the time range will be extended to reference year 2023), after which a prolongation of the contract can be requested through a simplified procedure. The received microdata are a combination of two datasets:

- MD1A: Deaths of people who were less than one year old ('infant mortality'). These records include perinatal indicators, which can be used to assess confounding factors.
- PD1A: Deaths of people who were over one year old ('adult mortality').

The variables of the COD microdata include:

- COD ID: a pseudonym that serves as a unique identifier
- Basic demographics: age, sex, country of birth and date of death
- Cause of death: specified according to the **International Statistical Classification of Diseases and Related Health Problems** (ICD), 10th revision. In the ICD, CODs are coded hierarchically, where the first digit (a roman numeral) refers a broad category of diseases or injuries, and the subsequent digits progressively specify the cause. At the insistence of Statbel, the number of digits was limited for causes that are considered to be extra sensitive. There are several ways to specify the COD:
  - Underlying cause: the cause that is ultimately responsible for the death. The underlying cause is of prime interest, and also the one that is reported in COD statistics.
  - Immediate cause: this refers to the final event before death. Additionally, up to two intermediate causes can be specified, but these are not necessarily filled out.
  - Associated causes: up to three associated causes can be specified, but these are not necessarily filled out.
  - External cause: a separate field is reserved in case the underlying COD is external. Additionally, the type of death is specified, meaning natural or a type of external cause (accident, suicide, homicide).
- Statistical sector: the place of residence of the deceased person is given in the form of the statistical sector code.

The COD dataset contains two fields which specify the underlying cause: *COD_UNDRLG* and *CD_UCOD*. The first mentioned corresponds to what the doctor filled out in the death certificate. The

latter is filled out by Statbel, and is equal to *COD_UNDRLG* except for ICD codes that are not accepted as COD in statistics (namely those belonging to the S and T categories in ICD-10: 'Injury, poisoning and certain other consequences of external causes'). In this case, Statbel recodes the ICD code filled out by the doctor. The estimates in EBoD-FL for cause-specific mortality will use *CD_UCOD* to specify the COD. In rare cases (less than 0.1%) the *CD_UCOD* field is empty, in which case *COD_UNDRLG* will be used.

The COD microdata allow to compute total mortality figures, such as number of deaths, mortality rates, and years of life lost, the mortality component of the DALY. As the underlying cause of death is specified, cause-specific mortality can be addressed. The ICD codes specify the COD with varying detail, depending on how many digits are given. For CVDs and CRDs, the following ICD codes can be considered:

- Cardiovascular diseases: I00-I99
  - Hypertension: I10-I15
  - Ischemic heart disease: I25
  - Stroke: I60-I64
- Chronic respiratory diseases: J00-J99
  - Chronic obstructive pulmonary disease: J40-J44, J47
  - Lower respiratory infections: J09-J18

The use of COD data to address cause-specific mortality comes with certain caveats. First, the codes filled out by the doctor are subject to human error, and are therefore not always reliable. Furthermore, a significant proportion of reported codes are ill-defined, and therefore not suited for any analysis of cause specific deaths. As an indication, approximately 2.5% of reported underlying causes in the requested dataset correspond to R99 ('Unknown cause of mortality'), and this fraction does not include other potential 'garbage codes'. A possible remedy for ill-defined deaths is to redistribute those deaths over meaningful COD codes, for example using a probabilistic redistribution approach such as used in BeBOD (Devleesschauwer et al., 2023).

To assess the EBD of long-term exposure, the mortality figures can be summed over one or multiple years. As the full date of death is given, short-term effects can be examined as well. For acute outcomes, correlation in time is important, as exposure and mortality follow each other in a time span of days to weeks. The attributable cases can then be summed over one or multiple years to compare them to the chronic burden. The COD microdata only allow to address the mortality component (YLL) of the EBD. For this reason, a request for local incidence data to account for morbidity (YLD) is in process.

1.2. Incidence and prevalence of diseases

To assess the local impact of morbidity, information on the occurrence of diseases at the level of the statistical sector are required. Sources that are typically considered when estimating disease incidence or prevalence, are national registries, hospital discharge data, medical prescription and health care reimbursement data, sentinel networks of general practitioners, population screening programs and survey results. These sources however differ in the extent to which they allow estimating disease occurrence at the level of the statistical sector. In a first phase, we therefore focus on sources that are exhaustive and have nationwide coverage – including the hospital discharge data and medical reimbursement data.

First, hospital discharge data (HDD) are requested for patients admitted for cardiovascular or chronic respiratory disease diagnoses, in accordance with the outcomes prioritised in the POCs. By relying on these data, the burden can be expressed in terms of the incidence of hospitalisations for specific diseases and injuries within those categories. For outcomes that have a high hospitalisation rate, HDD can be considered as a proxy for total disease incidence or prevalence. Other strengths of HDD are nationwide coverage and diagnosis by a medical doctor (De Pauw et al., 2023).

The HDD are managed by the FPS Health. By default, only the postal code is recorded in the HDD, which means a linkage with national registry data managed by Statbel is required to obtain data that includes the statistical sector of the patient's residence. Analogous to the COD data, the HDD are microdata of patients admitted to a hospital in Belgium, where the cause of death is replaced by the diagnosis considered the main reason for admission.

The variables of the HDD microdata include:

- Cproject: a pseudonym that serves as a unique identifier allowing to identify patients across hospitals and years
- Basic demographics: age, sex
- Diagnosis: specified according to ICD codes. Diagnoses in reference years before 2015 are specified according to version 9 of the ICD, those after 2015 according to version 10. No data are made available for reference year 2015 itself, because due to the switch from ICD-9 to ICD-10 the diagnosis codes are considered unreliable. For each speciality the patient was admitted to during his or her stay, a primary diagnosis is specified, as well as optional secondary diagnoses.
- Statistical sector: the place of residence of the patient is given in the form of the statistical sector code. This requires a linkage with national registry data managed by Statbel.

Additionally, data managed by the **InterMutualistic Agency** (IMA) will be explored as a potential source for health outcomes at the statistical sector level.

1.3. BeBOD estimates of the burden of disease

Complementary to the local approach to EBD calculations, estimates are obtained globally at the level of the Flemish Region. A major advantage to this parallel track is that baseline disease burden estimates for Flanders are already available from BeBOD. In the BeBOD estimates, DALYs are available for 38 health outcomes, including CVD and CRD (Fig. 3). As total burden estimates can be extracted for additional outcomes besides those prioritised in the POCs, the calculations in the global track do not have to be restricted to CVD and CRD, but can be extended to all available outcomes linked to the environmental stressors. In addition to DALYs, estimates are available for the fatal burden of 131 causes of death and the non-fatal burden of 57 cancer sites. All estimates are available for download from an open-access repository (De Pauw et al., 2024), and details on the calculations and data sources can be found in the BeBOD protocol (De Pauw et al., 2023).

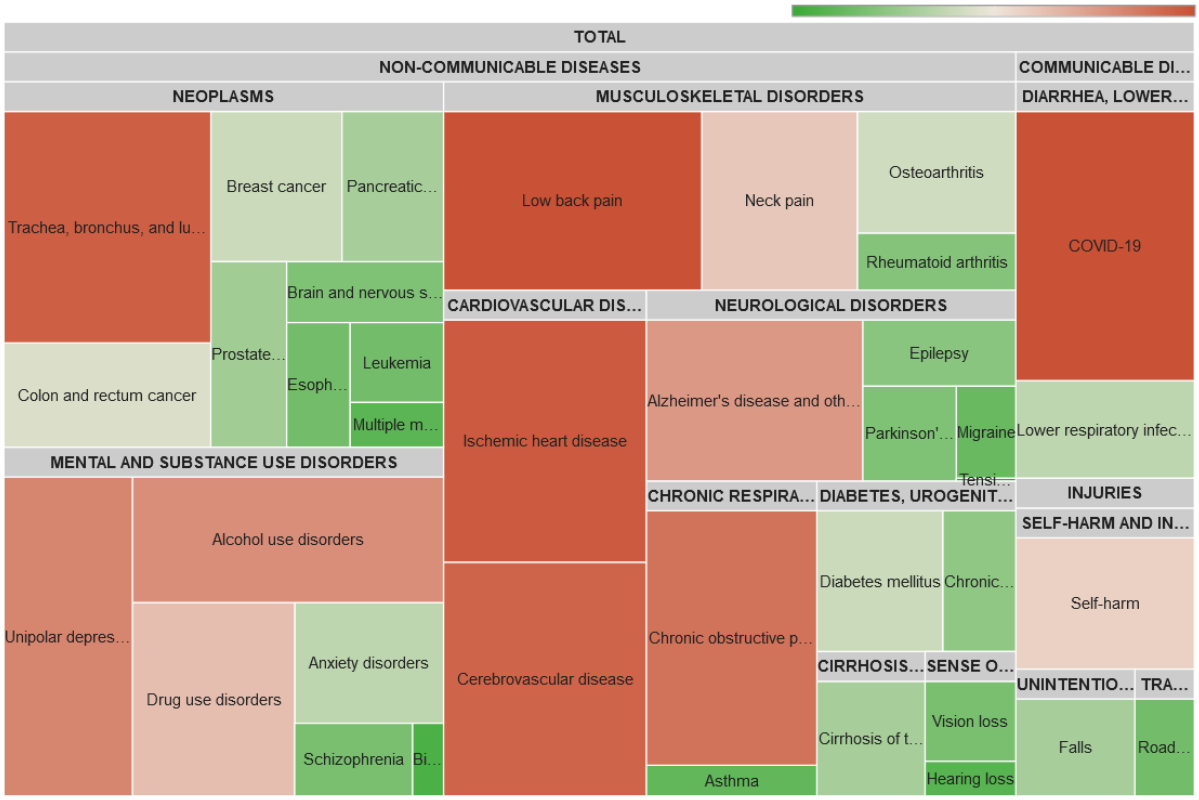

Figure 3 • Treemap of DALYs in Flanders, 2021 for 38 health outcomes (Sciensano, 2022).

2. Risk factors

2.1. Air quality

2.1.1. Risk factor selection

For air quality, the selected risk factors are **particulate matter** (PM) with a diameter smaller than 10 micrometers (PM_{10}) and with a diameter smaller than 2.5 micrometers ($PM_{2.5}$), nitrogen dioxide (NO_2) and ozone (O_3). PM refers to all of the fine microscopic particles suspended in the air. As $PM_{2.5}$ only contains the smaller particles of PM, its composition and health effects are different compared to PM_{10}. NO_2 is a gas formed by combustion, as occurring in car engines and power plants. O_3 is not emitted directly but formed in the atmosphere by photochemical reactions. Each of these stressors is counted among the 'classical air pollutants' by the WHO (World Health Organization, 2021). The GBD only considers $PM_{2.5}$ and O_3, but the EBD study by Buekers et al. (2012) considers all four.

The metric used to assess long-term exposure is the annual mean concentration, expressed in the form of a mass concentration as micrograms per cubic meter ($\mu g\ m^{-3}$). Ozone forms an exception, for which a simple yearly average concentration is inadequate because of its strong seasonal and diurnal variation. A more complex metric is used, labelled 'peak season ozone' and is defined as the average of daily maximum 8-hour mean O_3 concentration in the six consecutive months with the highest six-month running-average O_3 concentration. For Belgium, the ozone peak season corresponds to the months April to September. Black/elemental carbon will not be studied because of a strong overlap with NO_2 in terms of exposure, and with $PM_{2.5}$ in terms of mortality. The short-term approach is essential for some stressors, such as ozone and heat, and has to be addressed in a future phase.

2.1.2. Exposure assessment

Population exposure to the air pollutants is based on high-resolution concentration maps for Belgium provided by IRCEL-CELINE. These air quality maps are produced by state-of-the-art models, calibrated against actual measurements but still subject to a degree of uncertainty. The output used for assessing PM_{10}, $PM_{2.5}$ and NO_2 exposure is from ATMO-Street, which is the interpolation-dispersion model RIO-IFDM (used for O_3) expanded with a street canyon module. Both models have a 10 m grid spacing. For the domain of Flanders plus the Brussels Region, ATMO-Street is available for the years 2016-2021 (2017-2021 also include the Walloon Region). Prior years (2009-2015) are modeled with RIO-IFDM, which means results for these years are not comparable with 2016-2020 output.

The estimation of population exposure relies on a geospatial approach. Local exposure is determined as an area-level average, by overlaying the air quality maps with a vector file representing the statistical sectors. The exposure value for each sector is then calculated as the spatial mean concentration. Given their small size, and the fact that statistical sectors were defined with internal homogeneity in mind, this average value is assumed to be representative for the local population. The uncertainty on the local exposure can be addressed using bootstrapping: for a sector that overlaps with N pollution values, this set is sampled with replacement to generate hundreds of sets of size N, corresponding to hundreds of means, i.e., exposure values. The collection of resampled means forms a distribution of exposure values, characterised by a certain spread.

To estimate global exposure in the Flemish population as a whole, a spatial average concentration would be inadequate given its size. The reason is that, if inhabitants would reside in areas that are on average either more or less polluted, a simple average concentration would not be representative for exposure in the population. To counter this bias, one can compute a global average concentration weighted by population density. The population-weighted average here is calculated by summing all local sector exposures, weighted by the fraction of the population residing in each sector.

While exploring the air pollution rasters (both RIO-IFDM and ATMO-Street) overlaid with statistical sector vector file, it became apparent that the rasters do not fully cover the territory of Flanders. The result is that certain sectors (N = 550) near the national border do not fully overlap with the pollution rasters. The ‘missing value problem’ is limited for most of these sectors, but in the most extreme cases more than half of the sector’s territory is not covered. As was personally communicated by an IRCEL collaborator, the problem occurred when the original model output was clipped to the extent of the Belgian territory. To mitigate this issue, IRCEL provided us with the unclipped rasters. These maps are split into the Flemish and Brussels region on the one hand, and the Walloon regions on the other, as these domains are modelled separately. These maps differ slightly from the results for Belgium as a whole that are available as open data. The rasters for O_3 (expressed in the peak season metric) have been requested as well, as the maps publicly available rely on another unit.

Local exposure for each statistical sector is calculated straightforwardly as a spatial average, and not as a population-weighted average that takes into account residential addresses and number of residents per address. In the supplementary materials of Chen & Hoek (2020) and Huangfu & Atkinson (2020), the meta-analyses referenced in the WHO air quality guidelines, the exposure assessment method of each of the reviewed studies is briefly outlined. In the majority of the cases, exposure of the subjects is quantified by linking the participant’s address to a pollution raster, most of which have a relatively low resolution of a few hundred meters or even more than a kilometer. Alternatively, the address location is linked to the nearest monitoring station, or if the exact address is unknown, an average concentration value for the district or municipality is used as exposure value. In each of these cases, exposure is estimated with a considerable deal of uncertainty. Therefore, we argue that our chosen method, using the spatial average of the statistical sector as exposure assessment, already goes beyond the state of the art, and that calculating population-weighted average exposure within each statistical sector offers no advantage over a spatial average in this case.

2.1.3. Identification of risk-outcome pairs

The EPA's **Integrated Science Assessments (ISAs)**[1] were consulted to assess the causality between long-term exposure to air pollution and the outcomes specified in the POCs. ISAs are available for the four air pollutants considered ($PM_{2.5}$, PM_{10}, NO_2 and O_3). These assessments study the relationships with various health outcomes, including total non-accidental (all-cause) mortality, respiratory effects and cardiovascular effects. Depending on the available evidence, the relationship is rated as causal, likely to be causal, suggestive of causality, inadequate to infer causality, and not likely to be causal (U.S. Environmental Protection Agency, 2015). The conclusions of the ISAs for the risk-outcome pairs for long-term exposure that are relevant at this stage of the research are summarized in Table 2 (U.S. Environmental Protection Agency, 2016, 2019, 2020). Alternatively, one can consult the monographs by the International Agency for Research on Cancer (IARC) for the causal links with cancer outcomes. The IARC classifies air pollution, and more specifically particulate matter, as carcinogenic.

Table 3 • Conclusions on the causality between long-term exposure to selected air pollutants and health outcomes, based on the U.S. EPA's ISAs.

Outcome	$PM_{2.5}$	PM_{10}	NO_2	O_3
All-cause mortality	Causal	Suggestive	Suggestive	Suggestive
Respiratory effects	Likely	Inadequate	Likely	Likely
Cardiovascular effects	Causal	Suggestive	Suggestive	Suggestive

Of course, a causal relationship between air pollutants and respiratory and cardiovascular effects does not indicate a causal link between these risks and more specific CRDs and CVDs. In case the evidence points (suggestive) causality for these effects, the epidemiologic literature can be searched for ERFs that link exposure and more specific outcomes such as COPD, asthma, IHD and stroke. If such studies find a statistically significant association and are sufficiently corrected for confounding, including these risk-outcome pairs would be justified.

2.1.4. Quantification of the risk-outcome relation

The first option for ERFs are those integrated in the most recent **Air Quality Guidelines** (AQGs) published by the WHO (World Health Organization, 2021). These ERFs are comprised of a meta-analytic effect derived from multiple epidemiologic studies identified in systematic reviews. These reviews consider the health effects of the 'classical air pollutants' in terms of total and cause-specific mortality outcomes. The health effects of both PM types are similar, although more pronounced for $PM_{2.5}$ compared to PM_{10} (Chen & Hoek, 2020). This finding fits the results of the causality assessment by the U.S. EPA. For chronic NO_2 exposure, only all-cause and respiratory mortality outcomes are examined, although the ISA for this stressor finds the evidence suggestive of causality for the link with cardiovascular effects. This indicates that it might be necessary to consult other reviews that do study this risk-outcome pair. For long-term O_3, the dose-response relationships are even weaker. The AQGs do include the ERF for O_3 and all-cause mortality, where the bottom of the 95 % CI coincides with a RR of 1.00 (Huangfu & Atkinson, 2020). Consequently, a choice must be made to include all-cause mortality of chronic O_3, or to limit the study to acute mortality.

A second option is ELAPSE, a large pooled European cohort study (Brunekreef et al., 2021). This study considers a wide range of pollutants and health outcomes, and pulls from broad and recent evidence base where the exposure assessment, outcome definition and confounder adjustment are consistent across the cohorts. The research focuses on the effects down to low levels of air pollution, which means

[1] www.epa.gov/isa

the observed exposure range covers Flanders well. The study found mostly negative associations with O_3, which is possibly due to this pollutants strong negative correlation with NO_2 and black carbon. As this study came out after the WHO reviews were conducted, it is not included in their meta-analyses.

A third option are the ERFs applied in the most recent iteration of the GBD (Brauer et al., 2024). For air pollution, the GBD applies complex curve ERFs generated by a tool called meta-regression Bayesian, regularised, trimmed (MR-BRT), which synthesis the epidemiologic evidence collected in systematic reviews. The GBD considers a wide range of outcomes for $PM_{2.5}$, but is limited for the other pollutants.

A detailed comparison of the ERF options for air pollution can be found in appendix 3.1. Only statistically significant ERFs are taken (i.e., lower bound of the confidence interval above the null value). Because of aforementioned reasons, the WHO ERFs were chosen to quantify all-cause mortality, while the cause-specific burden is quantified using the ELAPSE ERFs. If mortality and morbidity-specific effect estimates are available, those will be applied separately for the fatal and non-fatal burden, respectively. For O_3, only COPD is quantified using the GBD's ERF, as this is the only significant association.

Regarding the shape, the (all-cause and cause specific) mortality ERFs for $PM_{2.5}$, PM_{10}, NO_2 and O_3 are generally either linear or supra-linear (i.e., a steeper curve at lower concentration). In the systematic reviews performed in the context of the AQGs, the meta-analytic effect is calculated using the inverse variance method assuming linear dose-response relationships (World Health Organization, 2021). For PM, some individual studies reported non-linear functions Chen & Hoek (2020), while Huangfu & Atkinson (2020) did not find strong evidence to reject the linearity assumption for NO_2 and O_3. In light of this, we propose to apply a linear ERF to calculate the PAF. This approach differs from the GBD, which uses integrated ERFs, based on non-linear functions.

With regard to an exposure threshold, most studies for PM do not find indication of a cut-off value (Chen & Hoek, 2020). In Huangfu & Atkinson (2020), it is not mentioned whether the individual studies find evidence for a threshold. As a consequence, we suggest that an exposure threshold should not be applied to long-term EBD calculation for the air pollutants. This is congruent with a joint statement released by medical, public health, scientific societies and patient representative organizations, stating that "harmful health effects [of air pollution] can be observed all the way down to very low concentration levels, with no observable thresholds below which exposure can be considered safe" (Hoffmann et al., 2021).

2.1.5. Calculation of the population attributable fraction

In the case of ambient air pollution, the entire population is exposed to the risk factor, either estimated as a local area-level concentration, or as global population-weighted average. As such, the PAFs for the air pollutants can be calculated with the simplified formula (eq. 6), where the relative risk is calculated linearly without the inclusion of an exposure threshold (eq. 7).

2.2. Environmental noise

2.2.1. Risk factor selection

Environmental noise can result from different sources, such as transportation (road traffic, railway and aircraft), wind turbines and leisure activities (e.g., concerts, nightclubs). The Environmental noise guidelines for European Region provide recommendations for protecting human health from exposure to environmental noise (WHO Regional Office for Europe, 2018). Based on the evidence quality and the expected efficacy of reducing exposure, the recommendations are strong or conditional. As the recommendations formulated are strong for traffic noise and mostly conditional for the other sources, we propose to start with noise from road, railway and air traffic, and to optionally extend this list with industrial, wind turbine and leisure noise at a later stage.

The health effects of environmental noise are addressed by relying on a long-term approach. As such, the indicator used is usually a yearly average sound pressure level, calculated for specific hours of the day (daytime, evening or night) or for the day as a whole. A common metric is the A-weighted (corrected for the sensitivity of the human ear) sound level taken over the day, evening and night (L_{den}), expressed in decibels (dB). In the calculation of L_{den}, the evening value gets a penalty of 5 dB and the night value of 10 dB, as noise exposure during these hours is considered to have a larger impact (eq. 9; European Environment Agency, 2010).

$$L_{den} = 10 \log \frac{1}{24} \left(12 * 10^{\frac{L_{day}}{10}} + 4 * 10^{\frac{L_{evening}+5}{10}} + 8 * 10^{\frac{L_{night}+10}{10}} \right) \qquad (eq. 9)$$

with L_{day} the average annual mean sound level during the day (with a duration of 12 hours), $L_{evening}$ during the evening (duration 4 hours) and L_{night} during the night (duration 8 hours). L_{den} is annoyance based, and therefore not the most suited indicator to study the link with cardiovascular outcomes (WHO Regional Office for Europe & JRC European Commission, 2011).

2.2.2. Exposure assessment

Population exposure assessment is based on the traffic noise exposure numbers reported to the EU in the frame of the **Environmental Noise Directive** (END). In the publicly accessible format, these data concern the number of exposed persons over 5 dB classes for the indicators L_{den} and L_{night}, available for the Regions separately. Exposure in this case is defined as the noise level at the most exposed facade of the subject's dwellings (WHO Regional Office for Europe, 2018). The levels are estimated by acoustic models, that take into account the distribution of noise sources with differing properties and the geometry of the surroundings. The estimates are updated every 5 years, currently available for the reference years 2011, 2016 and 2021.

In the END data, exposure to noise from road, rail and air traffic, as well as industrial noise are available. Exposure numbers are reported separately for large agglomerations (urban areas with populations exceeding 100.000 inhabitants) on one hand, and the areas outside these agglomerations on the other. Noise modelling in the large agglomerations is done comprehensively for all roads, railways and airports, and includes other sources as well, such as trams and industry (including ports). For Flanders, the agglomerations that qualify for separate detailed modelling are Antwerp, Ghent and Bruges, and since 2021 Leuven is included as well. The Brussels Capital Region (BCR) is modelled as agglomeration, and as such has detailed noise data available.

The modelling outside large agglomerations is limited to major sources of environmental noise, and as such does not cover all sources comprehensively. The major sources accounted for in the exposure numbers are:

- Road traffic, for routes with more than 3 million vehicles per year;
- Rail traffic, for railways with more than 30.000 passages per year;
- Aircraft traffic, for airports with more than 50.000 aircraft movements per year, excluding training flights with light aircraft.

The exposure assessment is thus limited to major highways and busy railways. The requirement for airports only applies to Brussels Airport in Zaventem, although data for the airports of Antwerp and Oostende are also made available by their respective companies in the form of noise contour maps. To ensure a consistent assessment of noise exposure across Flanders, the exposure numbers reported for major sources including agglomerations will be used. The downside of using these numbers is that they reported in wide band (>55, >65, >75 dB), instead of the more refined 5 dB categories available for the separate reporting of agglomerations and the regions outside these.

As the exposure numbers are reported by Region, these data are not suited to assess exposure locally. For this reason, a request was made with Departement Omgeving, who procures the road and railway noise exposure data for Flanders, to obtain the figures in a format tailored to the needs of the research. An agreement was reached for the delivery of the number of exposed people over 1 dB bands per statistical sector in the most recent reference year 2021. In addition, the same request was made to the large agglomerations in Flanders, and data by statistical sector was obtained Antwerp, Ghent and Leuven, while the exposure numbers for Bruges could only be made available in aggregated format. For Brussels airport, noise data were made available in the form of contour maps. As such, a geospatial method will be developed to derive local exposure values.

There are important limitations to the use of the END data for burden of disease studies:

- The modelling outside the agglomerations is limited to major sources. As this approach omits sources that could potentially emit harmful levels of environmental noise, exposure in the population could be underestimated.
- The END focuses on the number of people exposed to noise levels of 55 dB or higher during the day-evening-night period and to night-time noise levels of 50 dB or higher. These reporting thresholds are above the values recommended by the WHO in their environmental noise guidelines (WHO Regional Office for Europe, 2018), which means that more people may be suffering negative health impacts than estimated based on the END data. However, methods exist to estimate the number of exposed in categories below 55 dB L_{den}, calculated as a fraction of the number exposed above 55 dB (Houthuijs et al., 2019).
- Exposure numbers of the END are released in five-year cycles, which means no data are available for the years in between. Because of differences in the modelling methodologies, the results for the different reference years are not comparable, which hampers the study of time trends. Given the absence of an alternative, the values from each END reporting year are taken “as is”, and exposure numbers for the in-between years are obtained by interpolation using a binomial statistical model.

2.2.3. Identification of risk-outcome pairs

The assessment of causality between noise exposure and health outcomes is not as well established as for air pollution. With regard to cardiovascular effects, a plausible pathway is that exposure to environmental noise induces a stress reaction, which in turn can impact the circulatory system. Another possibility is that nighttime noise leads to sleep deprivation, which can also be linked to cardiovascular outcomes (Hahad et al., 2019). As certain cardiovascular conditions can lead to death, exposure to environmental noise can in theory be linked to all-cause mortality as well.

2.2.4. Quantification of the risk-outcome relation

The most recent **Environmental Noise Guidelines** (ENGs) for the European Region (WHO Regional Office for Europe, 2018) do not consider all-cause mortality as health outcome when deriving advised noise levels for traffic noise. When consulting the epidemiologic literature, it appears that a consensus regarding traffic noise and all-cause mortality has not been reached. A positive correlation for road traffic exposure was identified in one meta-analysis by Hao et al. (2022) (who pooled the results of their cohort study with other effect estimates collected in a systematic review), in a large cohort study from two Danish cities (Thacher et al., 2020), and a weak correlation in a London cohort study (Halonen et al., 2015). The study by Hao et al. (2022) suffers from some limitations, as the ERF identified by their ‘main model’ does not adjust for all confounding factors, and their meta-analysis includes studies that overlap in population. On the other hand, no significant association was found in another meta-analysis by (Cai et al., 2021), and in a ‘mega-cohort’ study from Barcelona (Nieuwenhuijsen et al., 2018). According to Cai et al. (2021), there are few studies for railway and aircraft noise, and those that do exist find no relationship with mortality.

With regard to cardiovascular outcomes, the WHO's ENGs consider the incidence of IHD as outcome. Based on the commissioned systematic review and meta-analysis of the cardiovascular and metabolic effects of traffic noise (van Kempen et al., 2018), they report a significant ERF for IHD incidence and traffic noise from roads and aircraft. For railway noise, the study found no evidence to support a link with IHD. The review by van Kempen et al. (2018) also examines stroke as health outcome, but found no significant correlation with any of the traffic noise sources.

Based on the review featured in the ENGs, only the associations of noise from road traffic with IHD and stroke are significant. The evidence quality for the link with IHD is graded as high, while the association with stroke is graded moderate evidence quality and based on only one study. The review by van Kempen et al. (2018) only considers studies up to 2014. An update of the WHO review is available for IHD and diabetes (Vienneau et al., 2019). In this updated review, the evidence base of the WHO review is supplemented with more recent studies, which especially significant for diabetes as outcome. For IHD on the other hand, the updated pooled estimate is no longer strictly significant (lower bound of the confidence interval equal to the null). Aside from the original review, the updated version can be considered as a source for ERFs.

A third option are the ERFs derived in the NordSOUND project, based on a large pooled Scandinavian cohort. Outcomes included in the project are IHD (Pyko et al., 2023) and stroke (Roswall et al., 2021). Similar to ELAPSE, this research pulls from broad and recent evidence base where exposure assessment, outcome definition and confounder adjustment are consistent across the cohorts.

A detailed comparison of the ERFs considered for the noise stressors is included in appendix 3.2. It was decided to include only road traffic noise at this time, as no significant associations are found for other traffic noise sources. Noise from aircrafts and railways could be included in the future, when more reliable ERFs become available. For IHD, the ERF from the original WHO review is selected, while the ERF for diabetes is taken from the updated review. For stroke, the ERF from NordSOUND is taken, as this is cohort study is larger and more comprehensive compared to the study featured in the WHO review. Because of a lack of (statistically significant) effect estimates for mortality and morbidity separately, the same ERF is applied to both types of outcomes. As exposure threshold, the value from the ENGs is taken (53 dB L_{den}).

2.2.5. Calculation of the population attributable fraction

As noise exposure data are available in the format of the number of people exposed to a certain range of decibels, the categorical formula (eq. 5) is suited to compute the PAF. In the local approach, the tailored data delivered by Departement Omgeving and the city authorities data will be used for exposure assessment. The PAF can then be calculated at the level of the statistical sector, and used for a local assessment of the burden attributable to environmental noise. Additionally, the health impacts in the large agglomerations can be inspected more comprehensively, as the noise modelling there considers all source of noise. A downside is that estimates will only be available for the year 2021.

In the global approach, the exposure numbers reported under the END will be used. As these data are available for the years 2011, 2016 and 2021, with the numbers for in-between years obtained by interpolation, trends in time can be examined. The downside here is that only major noise sources are accounted for, thus likely underestimating true population exposure.

2.3. Extreme temperatures

2.3.1. Risk factor selection

Extreme or non-optimal temperatures can be defined as short-term (e.g., daily mean, minimum or maximum) temperatures that deviate from the optimal temperature associated with a minimal risk of adverse health outcomes. In this sense, temperatures below this optimal level pose risks associated

with cold weather, while temperatures above this level are associated with the effects of heat. The optimal temperature is referred to as either the **minimum mortality** or **minimum morbidity temperature** (MMT), depending on whether fatal or non-fatal outcomes are considered. As the populations in different climate zones are adapted to different temperature ranges, the MMT is location-dependent.

Different opinions exist on whether either extreme temperatures or either non-optimal temperatures should be considered as the risk factor:

- Non-optimal temperatures refer to temperatures that deviate to any extent from the MMT. From this point of view, health effects are attributed to any deviation of the temperature from the optimal value, however small. This is the approach of e.g., the GBD (Brauer et al., 2024; Burkart et al., 2021).
- Extreme temperatures refer to values at both extremes of the annual temperature distribution. No fixed definition of 'extreme' exists in this context, but extreme temperatures could for instance be defined as values below a low quantile or above a high quantile (e.g., the 2.5 and 97.5 percentiles). From this point of view, only the extreme values pose a risk, while in between lies a range of temperatures to which the population is able to adapt and avoid any health consequences.

2.3.2. Exposure assessment

Exposure in the population can be assessed spatially using ambient surface air temperature, usually expressed in kelvin or degrees Celsius (conversions are easily made). The required temperature data can be extracted from the gridded observational data provided by the **Royal Meteorological Institute of Belgium** (RMI). The continuous grid results from the interpolation of observations from meteorological stations. Interpolation in this sense is a statistical prediction method, relying on ancillary data in addition to the observations. In the case of air temperature, correlated variables such as the terrain elevation and the proximity of water surfaces are integrated in the interpolation model (Royal Meteorological Institute, n.d.).

This dataset covers Belgium at a spatial resolution of 5 km, available since 1961 and continuously updated. It contains several meteorological variables, including air temperature, available at different temporal resolutions, including daily values as well as long-term climate averages. Its spatial extent (covering Flanders), the availability of short-term values as well as long-term averages, and the prospect of being continued into the future make this dataset well suited for exposure assessment in the framework of EBoD-FL. As the gridded observations are not available as open data, a request was made to access the data.

2.3.3. Identification of risk-outcome pairs

A thorough and systematic evidence grading of the causality of extreme temperatures and health effects could not be retrieved. As an alternative starting point for selecting risk-outcome pairs, the GBD was used. The GBD derives cause-specific ERFs for non-optimal temperatures by linking modelled daily temperature data to COD data, available for nine countries in their mortality database. As the MMT depends on the climate, annual mean temperature was included in model as a variable, resulting in temperature zone-specific ERFs for each risk-outcome pair (Burkart et al., 2021).

The selection of risk-outcome pairs for temperature in GBD is based on a scoring. For each level 3 outcome and temperature zone, a risk curve is derived and subsequently normalised to obtain a RR equal to 1.0 at the MMT. Each curve is then log-transformed, and the score is then calculated as the area between the lower bound of the 95% uncertainty interval and the null (i.e., a log-RR of 0.0). Regions of the risk curve where the RR uncertainty intervals includes the null result in negative scores, and regions that exclude the null result in positive scores. If the mean score over all temperature zones exceeds zero, the risk-outcome pair is included. For CVD and CRD, this results in the inclusion of IHD,

stroke and COPD, as well as hypertensive heart disease and cardiomyopathy and myocarditis, as outcomes related to extreme temperatures (Table 4; Burkart et al., 2021).

Table 4 • Inclusion of non-optimal temperature outcomes for CVD and CRD in GBD based on risk-outcome scores.

Outcome	Average score
IHD	0.084
Stroke	0.072
Hypertensive heart disease	0.051
Cardiomyopathy and myocarditis	0.044
COPD	0.106

An overview of the evidence for CVD and CRD temperature health effects:

- The meta-analysis by Cheng et al. (2019) found significant associations between heatwaves and cardiovascular and respiratory mortality, and specifically IHD, stroke, heart failure and COPD.
- The meta-analysis by Liu et al. (2022) reports significant associations between heat and cardiovascular disease mortality (and sub-outcomes coronary heart disease, heart failure and stroke) and CVD morbidity (and sub-outcome coronary heart disease).
- The meta-analysis by Lian et al. (2015), reviewing stroke in general and more specific subtypes, found a significant association between cold with stroke morbidity and mortality, and heat with stroke mortality. On the other hand, heat acts as protective factor for haemorrhagic stroke.
- A large cohort from China (Guo et al., 2013) identified increased risk of IHD mortality at both cold and hot temperatures.

An overview of the evidence for other outcomes:

- The meta-analysis by Gao et al. (2022) reports a significant association between extreme ambient heat exposure and diabetes-related hospital admissions and emergency department visits.
- The meta-analysis by Liu et al. (2021) found a significant association between hot weather and mental health-related mortality and morbidity. More specifically, heat is associated with substance-related mental disorders, organic mental disorders, mood disorders, schizophrenia, and neurotic and anxiety disorders.
- The systematic review by Thompson et al. (2018) concludes that the available evidence points to an increased risk of suicide with heat.

Recent literature appears to be more focused on heat rather than extreme or non-optimal temperatures in general (including cold weather), given the concerns about the increased frequency and intensity of hot weather extremes in a warming climate. In some cases, exposure to heatwaves is assessed (binary exposure: heatwave vs. no heatwave) instead of temperature as a continuous variable.

2.3.4. Quantification of the risk-outcome relation

Associations between temperature and health outcomes generally show a higher risk at both cold and hot extremes. In this sense, temperature risk curves are typically U or J-shaped, where the relative risk decreases with temperature in the range below the MMT and increases beyond the MMT.

The relative risk of temperature-related outcomes needs to be quantified with ERFs adapted to the Belgian climate. Climate in this sense can be defined as the long-term mean temperature, typically calculated over a period spanning several decades. As the climate in this sense can vary across the territory, a long-term mean temperature can be calculated for each temperature pixel covering the

Flemish Region. In case of a (substantial) variation, different ERFs can be selected based on the local temperature zone.

As a first option, the risk curves of the GBD could by applied (Burkart et al., 2021). These are available as graphs in supplementary materials of the article, but not as integrated dose-response curves. As the GBD is able to derive ERFs for cause-specific mortality only, only fatal outcomes are included in their non-optimal temperature estimates. In case GBD ERFs are used in EBoD-FL, the assumption is that these apply to non-fatal outcomes as well.

Another option would be to adopt ERFs derived specifically for Belgium or Flanders:

- Demoury et al. (2022) derived risk curves and log-linear approximations of mortality due to all causes, IHD, stroke and COPD, based on data from nine urban agglomerations in Belgium.
- Verachtert et al. (2023) derived risk curves of all-cause, respiratory and cardiovascular mortality in Flanders.
- Alemayehu Ali et al. (2024) derived risk curves and log-linear approximations of morbidity due to a.o. stroke/cerebrovascular accident, pneumonia, COPD and asthma, based on Flemish GP data (ICPC2 codes).

The implementation of exposure thresholds (as extreme temperature quantiles) is closely linked to the question of whether risk is posed by all non-optimal temperatures or only by extreme temperatures. In case an integrated non-linear ERF is used, the RR will increase in function of temperature according to the curve, and no thresholds would be needed in principle. Following this approach, burden will be attributed over the entire temperature range, only excepting the MMT. According to some authors, this will likely result in an overestimation of the temperature-related burden, as the population is adapted to a 'normal' temperature range, and only the extreme temperatures outside of this range pose a risk (Bouchama et al., 2024).

2.3.5. Calculation of the population attributable fraction

To calculate the PAF of extreme temperatures, the temperature grid is overlaid with the vector file of the statistical sectors, and a temperature is assigned to each sector based on the pixel with the largest overlap. The temperature-attributable burden calculation follows a short-term exposure approach. As such, a PAF is calculated for each day of the year based on the daily mean temperature.

As the population in each sector is assumed to be exposed to the same ambient temperature, the PAF can be calculated with the simplified formula (eq. 6). The relative risk is calculated with eq. 7 in case of a log-linear relationship, or with an integrated ERF in case a risk curve is used. The inclusion of an exposure threshold depends on whether the risk is constrained to extreme temperatures, or whether burden is attributed over the whole non-optimal temperature range.

If the daily mean temperature is below the MMT, the burden is attributed to cold, while a temperature above the MMT results in heat-attributable burden. The PAFs for heat and cold are then aggregated separately to yearly values, to match with the annual burden estimates. To achieve this, the daily PAFs for a given outcome are weighted with the daily number of temperature-attributable deaths due to the same outcome, as a fraction of the total.

In the local approach, the temperature-attributable disease burden is calculated by multiplying the PAF of each sector with the corresponding local burden estimate. In the global approach, two approaches are possible. In one, the sector PAFs are aggregated to Flanders, using the population in the sector as a fraction of the total population as a weight. This takes into account the possibility of different temperature zones, as different ERFs can be applied depending on the long-term mean temperature in the sector. In case the whole of Flanders belongs to the same or a similar temperature zone, there is no

need for locally adapted ERFs. In such a scenario, a global PAF can be calculated based on the population-weighted mean temperature in Flanders.

3. Exposure-response function evaluation sheets

3.1. Air quality

3.1.1. $PM_{2.5}$

Table . Dose-response function evaluation grid for long-term exposure to $PM_{2.5}$ and all-cause mortality.

	WHO 2021	ELAPSE	GBD 2021
Value	Mortality: 1.08 (1.06, 1.09) per 10 µg m^{-3}	Mortality: 1.130 (1.106, 1.155) per 5 µg m^{-3}	/
Accessibility	Log-linear RR with confidence interval, available from article text.	Log-linear HR with confidence interval, available from article text.	/
Transparency	Meta-analysis of 107 studies (25 for all-cause mortality). Review registered in PROSPERO (ID: CRD42018082577). Information extracted on study type, study population, exposure assessment, outcome definition, confounder adjustment, single and two-pollutant models and subgroup analyses.	Detailed information available on study population, exposure assessment, outcome definition, confounder adjustment, single and two-pollutant models and subgroup analyses.	/
Reliability	Based on adult population. No subgroup analyses for this outcome. Outcome define d as COD specified by ICD codes. "The exposure assessment methods varied across the studies, from assigned exposure to the nearest monitoring station, to land use regression or dispersion models. Exposures were assigned on very different spatial scales, ranging from residential address to US county." "Studies further differ in the detail of information available on potential confounders." High degree of statistical heterogeneity (I^2 = 88.9%)	Based on adult population. Identification of outcomes by linkage with registries for mortality, cancer incidence, hospital discharge, and physician-based adjudication of cases, specified by ICD codes. Exposure assessment is based on LUR models, which incorporate monitoring data, land use, and traffic data supplemented with satellite observations and dispersion model estimates. The exposure models had moderate-to-good performance in holdout validation and validation with external data.	/ .

		The main model is single-pollutant model, adjusted for cohort ID, age, sex, year of baseline visit, smoking (status, duration, intensity, and intensity squared), BMI, marital status, employment status, and 2001 neighborhood-level mean income. Several subgroup analyses were performed: age at baseline (<65 vs. ≥65 years), smoking status (current, ever, or never) and BMI (cut points at 18.5, 24.9, and 29.9 kg/m^2).	
Evidence	Risk of Bias: Most included studies showed Low-Risk, some Moderate-risk and few High-risk. Adapted GRADE tool: “High certainty of evidence”. Review includes all studies until October 2018. Missing some important recent studies (e.g., ELAPSE).	The analysis relied on a large European pooled cohort study. For mortality: Eight cohorts in Stockholm area, Denmark, the Netherlands, German Ruhr area and Augsburg area, France, Vorarlberg (Austria), with a total of 325,367 participants (47,131 deaths). For morbidity: Six cohorts in Stockholm area, Denmark, the Netherlands, German Ruhr and Augsburg areas, with a total of 137,148 participants (10,071 events).	/
Relevance	The results of the meta-analysis are relevant in terms of exposure assessment (annual average concentration in µg m^{-3}) and outcome definition (specified in ICD codes). The results are not necessarily relevant when regarding geographical extent, population characteristics and observed exposure range, as the review includes studies worldwide (62 from North America, 25 from Europe, 19 from Asia).	The results of the European cohort study are relevant in terms of exposure assessment (annual average concentration in µg m^{-3}) and outcome definition (specified in ICD codes), geographical extent, population characteristics and observed exposure range.	/

Table . Dose-response function evaluation grid for long-term exposure to $PM_{2.5}$ and IHD.

	WHO 2021	ELAPSE pooled cohort (main model)	GBD 2021
Value	Mortality: 1.16 (1.10, 1.21) per 10 µg m^{-3}	Mortality: 1.111 (1.056, 1.169) per 5 µg m^{-3}	

		Morbidity: 1.02 (0.95, 1.10) per 5 μg m^{-3}	*1 integrated dose-response function for both mortality and morbidity*
Accessibility	Log-linear RR with confidence interval, available from article text.	Log-linear HR with confidence interval, available from article text.	Integrated risk curve with confidence interval, available from the GHDx.
Transparency	Meta-analysis of 107 studies (22 for IHD). Review registered in PROSPERO (ID: CRD42018082577). Information extracted on study type, study population, exposure assessment, outcome definition, confounder adjustment, single and two-pollutant models and subgroup analyses.	Detailed information available on study population, exposure assessment, outcome definition, confounder adjustment, single and two-pollutant models and subgroup analyses.	List of sources included in the meta-analysis (MR-BRT model) available in supplementary materials. Information extracted on representativeness of the study population, exposure, outcome, reverse causation, control for confounding and selection bias, included in the Burden of Proof risk function.
Reliability	Based on adult population. No subgroup analyses for this outcome. Outcome define d as COD specified by ICD codes. "The exposure assessment methods varied across the studies, from assigned exposure to the nearest monitoring station, to land use regression or dispersion models. Exposures were assigned on very different spatial scales, ranging from residential address to US county." "Studies further differ in the detail of information available on potential confounders." High degree of statistical heterogeneity (I^2 = 77.5%)	Based on adult population. Identification of outcomes by linkage with registries for mortality, cancer incidence, hospital discharge, and physician-based adjudication of cases, specified by ICD codes. Exposure assessment is based on LUR models, which incorporate monitoring data, land use, and traffic data supplemented with satellite observations and dispersion model estimates. The exposure models had moderate-to-good performance in holdout validation and validation with external data. The main model is single-pollutant model, adjusted for cohort ID, age, sex, year of baseline visit, smoking (status, duration, intensity, and intensity squared), BMI, marital status, employment status, and 2001 neighborhood-level mean income. Several subgroup analyses were performed: age at baseline (<65 vs. ≥65 years), smoking	No distinction between mortality or morbidity of the outcome. Publication bias was detected. .

		status (current, ever, or never) and BMI (cut points at 18.5, 24.9, and 29.9 kg/m^2).	
Evidence	Risk of Bias: Most included studies showed Low-Risk, some Moderate-risk and no High-risk. Adapted GRADE tool: “High certainty of evidence”. Review includes all studies until October 2018. Missing some important recent studies (e.g., ELAPSE).	The analysis relied on a large European pooled cohort study. For mortality: Eight cohorts in Stockholm area, Denmark, the Netherlands, German Ruhr area and Augsburg area, France, Vorarlberg (Austria), with a total of 325,367 participants (47,131 deaths). For morbidity: Six cohorts in Stockholm area, Denmark, the Netherlands, German Ruhr and Augsburg areas, with a total of 137,148 participants (10,071 events).	Burden of Proof risk function: The risk-outcome pair received a score of 0.259, corresponding to a rating of 3 out of 5 stars.
Relevance	The results of the meta-analysis are relevant in terms of exposure assessment (annual average concentration in µg m^{-3}) and outcome definition (specified in ICD codes). The results are not necessarily relevant when regarding geographical extent, population characteristics and observed exposure range, as the review includes studies worldwide (62 from North America, 25 from Europe, 19 from Asia).	The results of the European cohort study are relevant in terms of exposure assessment (annual average concentration in µg m^{-3}) and outcome definition (specified in ICD codes), geographical extent, population characteristics and observed exposure range.	The results of the meta-analysis are relevant in terms of exposure assessment (annual average concentration in µg m^{-3}) and outcome definition (specified in ICD codes). The results are not necessarily relevant when regarding geographical extent, population characteristics and observed exposure range, as the review includes studies worldwide.

Table . Dose-response function evaluation grid for long-term exposure to $PM_{2.5}$ and stroke.

	WHO 2021	ELAPSE pooled cohort (main model)	GBD 2021
Value	Mortality: 1.11 (1.04, 1.18) per 10 µg m^{-3}	Mortality: 1.128 (1.048, 1.214) per 5 µg m^{-3} Morbidity: 1.10 (1.01, 1.21) per 5 µg m^{-3}	*1 integrated dose-response function for both mortality and morbidity*
Accessibility	Log-linear RR with confidence interval, available from article text	Log-linear HR with confidence interval, available from article text	Integrated risk curve with confidence interval, available from the GHDx.
Transparency	Meta-analysis of 107 studies (16 for stroke). Review registered in PROSPERO (ID: CRD42018082577). Information extracted on study type, study population, exposure	Detailed information available on study population, exposure assessment, outcome definition, confounder adjustment, single and two-pollutant models and subgroup analyses.	List of sources included in the meta-analysis (MR-BRT model) available in supplementary materials. Information extracted on representativeness of the study population,

	assessment, outcome definition, confounder adjustment, single and two-pollutant models and subgroup analyses.		exposure, outcome, reverse causation, control for confounding and selection bias, included in the Burden of Proof risk function.
Reliability	Based on adult population. No subgroup analyses for this outcome. Outcome defined as COD specified by ICD codes. "The exposure assessment methods varied across the studies, from assigned exposure to the nearest monitoring station, to land use regression or dispersion models. Exposures were assigned on very different spatial scales, ranging from residential address to US county." "Studies further differ in the detail of information available on potential confounders." High degree of statistical heterogeneity (I^2 = 84.7%)	Based on adult population. Identification of outcomes by linkage with registries for mortality, cancer incidence, hospital discharge, and physician-based adjudication of cases, specified by ICD codes. Exposure assessment is based on LUR models, which incorporate monitoring data, land use, and traffic data supplemented with satellite observations and dispersion model estimates. The exposure models had moderate-to-good performance in holdout validation and validation with external data. The main model is single-pollutant model, adjusted for cohort ID, age, sex, year of baseline visit, smoking (status, duration, intensity, and intensity squared), BMI, marital status, employment status, and 2001 neighborhood-level mean income. Several subgroup analyses were performed: age at baseline (<65 vs. ≥65 years), smoking status (current, ever, or never) and BMI (cut points at 18.5, 24.9, and 29.9 kg/m^2). For stroke, effect modification for education (low, medium, or high) was also assessed.	No distinction between mortality or morbidity of the outcome. No publication bias was detected.
Evidence	Risk of Bias: Most included studies showed Low-Risk, some Moderate-risk and a few High-risk. Adapted GRADE tool: "High certainty of evidence".	The analysis relied on a large European pooled cohort study. For mortality: Eight cohorts in Stockholm area, Denmark, the Netherlands, German Ruhr area and Augsburg area, France, Vorarlberg (Austria), with a total of 325,367 participants (47,131 deaths). For morbidity: Six	Burden of Proof risk function: The risk-outcome pair received a score of 0.167, corresponding to a rating of 3 out of 5 stars.

	Review includes all studies until October 2018. Missing some important recent studies (e.g., ELAPSE).	cohorts in Stockholm area, Denmark, the Netherlands, German Ruhr and Augsburg areas, with a total of 137,148 participants (10,071 events).	
Relevance	The results of the meta-analysis are relevant in terms of exposure assessment (annual average concentration in µg m^{-3}) and outcome definition (specified in ICD codes). The results are not necessarily relevant when regarding geographical extent, population characteristics and observed exposure range, as the review includes studies worldwide (62 from North America, 25 from Europe, 19 from Asia).	The results of the European cohort study are relevant in terms of exposure assessment (annual average concentration in µg m^{-3}) and outcome definition (specified in ICD codes), geographical extent, population characteristics and observed exposure range.	The results of the meta-analysis are relevant in terms of exposure assessment (annual average concentration in µg m^{-3}) and outcome definition (specified in ICD codes). The results are not necessarily relevant when regarding geographical extent, population characteristics and observed exposure range, as the review includes studies worldwide.

Table . Dose-response function evaluation grid for long-term exposure to $PM_{2.5}$ and asthma.

	WHO 2021	ELAPSE pooled cohort (main model)	GBD 2021
Value	/	Mortality: / Morbidity: 1.22 (1.04, 1.43) per 5 µg m^{-3}	/
Accessibility	/	Log-linear HR with confidence interval, available from article text	/
Transparency	/	Detailed information available on study population, exposure assessment, outcome definition, confounder adjustment, single and two-pollutant models and subgroup analyses.	/
Reliability	/	Based on adult population. Identification of outcomes by linkage with registries for mortality, cancer incidence, hospital discharge, and physician-based adjudication of cases, specified by ICD codes. Exposure assessment is based on LUR models, which incorporate monitoring data, land use, and traffic data supplemented with satellite observations and dispersion model	/

		estimates. The exposure models had moderate-to-good performance in holdout validation and validation with external data. The main model is single-pollutant model, adjusted for cohort ID, age, sex, year of baseline visit, smoking (status, duration, intensity, and intensity squared), BMI, marital status, employment status, and 2001 neighborhood-level mean income. Several subgroup analyses were performed: age at baseline (<65 vs. ≥65 years), smoking status (current, ever, or never) and BMI (cut points at 18.5, 24.9, and 29.9 kg/m^2).	
Evidence	/	The analysis relied on a large European pooled cohort study. For mortality: Eight cohorts in Stockholm area, Denmark, the Netherlands, German Ruhr area and Augsburg area, France, Vorarlberg (Austria), with a total of 325,367 participants (47,131 deaths). For morbidity: Six cohorts in Stockholm area, Denmark, the Netherlands, German Ruhr and Augsburg areas, with a total of 137,148 participants (10,071 events).	/
Relevance	/	The results of the European cohort study are relevant in terms of exposure assessment (annual average concentration in µg m^{-3}) and outcome definition (specified in ICD codes), geographical extent, population characteristics and observed exposure range.	/

Table . Dose-response function evaluation grid for long-term exposure to $PM_{2.5}$ and COPD.

	WHO 2021	ELAPSE pooled cohort (main model)	GBD 2021

Value	Mortality: 1.11 (1.05, 1.17) per 10 µg m^{-3}	Mortality: 1.131 (1.002, 1.278) per 5 µg m^{-3} Morbidity: 1.17 (1.06, 1.29) per 5 µg m^{-3}	*1 integrated dose-response function for both mortality and morbidity*
Accessibility	Log-linear RR with confidence interval, available from article text	Log-linear HR with confidence interval, available from article text	Integrated risk curve with confidence interval, available from the GHDx.
Transparency	Meta-analysis of 107 studies (11 for COPD). Review registered in PROSPERO (ID: CRD42018082577). Information extracted on study type, study population, exposure assessment, outcome definition, confounder adjustment, single and two-pollutant models and subgroup analyses.	Detailed information available on study population, exposure assessment, outcome definition, confounder adjustment, single and two-pollutant models and subgroup analyses.	List of sources included in the meta-analysis (MR-BRT model) available in supplementary materials. Information extracted on representativeness of the study population, exposure, outcome, reverse causation, control for confounding and selection bias, included in the Burden of Proof risk function.
Reliability	Based on adult population. No subgroup analyses for this outcome. Outcome defined as COD specified by ICD codes. "The exposure assessment methods varied across the studies, from assigned exposure to the nearest monitoring station, to land use regression or dispersion models. Exposures were assigned on very different spatial scales, ranging from residential address to US county." "Studies further differ in the detail of information available on potential confounders." Moderate degree of statistical heterogeneity (I^2 = 49.6%)	Based on adult population. Identification of outcomes by linkage with registries for mortality, cancer incidence, hospital discharge, and physician-based adjudication of cases, specified by ICD codes. Exposure assessment is based on LUR models, which incorporate monitoring data, land use, and traffic data supplemented with satellite observations and dispersion model estimates. The exposure models had moderate-to-good performance in holdout validation and validation with external data. The main model is single-pollutant model, adjusted for cohort ID, age, sex, year of baseline visit, smoking (status, duration, intensity, and intensity squared), BMI, marital status, employment status, and 2001 neighborhood-level mean income. Several subgroup analyses were performed: age at baseline (<65 vs. ≥65 years), smoking status (current, ever, or never) and BMI (cut points at 18.5, 24.9, and 29.9 kg/m^2). For	No distinction between mortality or morbidity of the outcome. No publication bias was detected.

		COPD effect modification for education (low, medium, or high) was also assessed.	
Evidence	Risk of Bias: Most included studies showed Low-Risk, some Moderate-risk and no High-risk. Adapted GRADE tool: “High certainty of evidence”. Review includes all studies until October 2018. Missing some important recent studies (e.g., ELAPSE).	The analysis relied on a large European pooled cohort study. For mortality: Eight cohorts in Stockholm area, Denmark, the Netherlands, German Ruhr area and Augsburg area, France, Vorarlberg (Austria), with a total of 325,367 participants (47,131 deaths). For morbidity: Six cohorts in Stockholm area, Denmark, the Netherlands, German Ruhr and Augsburg areas, with a total of 137,148 participants (10,071 events).	Burden of Proof risk function: The risk-outcome pair received a score of 0.441, corresponding to a rating of 4 out of 5 stars.
Relevance	The results of the meta-analysis are relevant in terms of exposure assessment (annual average concentration in µg m^{-3}) and outcome definition (specified in ICD codes). The results are not necessarily relevant when regarding geographical extent, population characteristics and observed exposure range, as the review includes studies worldwide (62 from North America, 25 from Europe, 19 from Asia).	The results of the European cohort study are relevant in terms of exposure assessment (annual average concentration in µg m^{-3}) and outcome definition (specified in ICD codes), geographical extent, population characteristics and observed exposure range.	The results of the meta-analysis are relevant in terms of exposure assessment (annual average concentration in µg m^{-3}) and outcome definition (specified in ICD codes). The results are not necessarily relevant when regarding geographical extent, population characteristics and observed exposure range, as the review includes studies worldwide.

Table . Dose-response function evaluation grid for long-term exposure to $PM_{2.5}$ and lung cancer.

	WHO 2021	ELAPSE pooled cohort (main model)	GBD 2021
Value	Mortality: 1.12 (1.07, 1.16) per 10 µg m^{-3}	Mortality: / Morbidity: 1.13 (1.05, 1.23) per 5 µg m^{-3}	*1 integrated dose-response function for both mortality and morbidity*
Accessibility	Log-linear RR with confidence interval, available from article text	Log-linear HR with confidence interval, available from article text	Integrated risk curve with confidence interval, available from the GHDx.
Transparency	Meta-analysis of 107 studies (15 for lung cancer). Review registered in PROSPERO (ID: CRD42018082577). Information extracted on study type, study population, exposure assessment, outcome definition, confounder	Detailed information available on study population, exposure assessment, outcome definition, confounder adjustment, single and two-pollutant models and subgroup analyses.	List of sources included in the meta-analysis (MR-BRT model) available in supplementary materials. Information extracted on representativeness of the study population, exposure, outcome, reverse causation, control

	adjustment, single and two-pollutant models and subgroup analyses.		for confounding and selection bias, included in the Burden of Proof risk function.
Reliability	Based on adult population. No subgroup analyses for this outcome. Outcome defined as COD specified by ICD codes. "The exposure assessment methods varied across the studies, from assigned exposure to the nearest monitoring station, to land use regression or dispersion models. Exposures were assigned on very different spatial scales, ranging from residential address to US county." "Studies further differ in the detail of information available on potential confounders." Moderate degree of statistical heterogeneity (I^2 = 39.4%)	Based on adult population. Identification of outcomes by linkage with registries for mortality, cancer incidence, hospital discharge, and physician-based adjudication of cases, specified by ICD codes. Exposure assessment is based on LUR models, which incorporate monitoring data, land use, and traffic data supplemented with satellite observations and dispersion model estimates. The exposure models had moderate-to-good performance in holdout validation and validation with external data. The main model is single-pollutant model, adjusted for cohort ID, age, sex, year of baseline visit, smoking (status, duration, intensity, and intensity squared), BMI, marital status, employment status, and 2001 neighborhood-level mean income. Several subgroup analyses were performed: age at baseline (<65 vs. ≥65 years), smoking status (current, ever, or never) and BMI (cut points at 18.5, 24.9, and 29.9 kg/m^2).	No distinction between mortality or morbidity of the outcome. No publication bias was detected.
Evidence	Risk of Bias: Most included studies showed Low-Risk, some Moderate-risk and one High-risk. Adapted GRADE tool: "High certainty of evidence". Review includes all studies until October 2018. Missing some important recent studies (e.g., ELAPSE).	The analysis relied on a large European pooled cohort study. For mortality: Eight cohorts in Stockholm area, Denmark, the Netherlands, German Ruhr area and Augsburg area, France, Vorarlberg (Austria), with a total of 325,367 participants (47,131 deaths). For morbidity: Six cohorts in Stockholm area, Denmark, the Netherlands, German Ruhr and Augsburg	Burden of Proof risk function: The risk-outcome pair received a score of 0.342, corresponding to a rating of 3 out of 5 stars.

		areas, with a total of 137,148 participants (10,071 events).	
Relevance	The results of the meta-analysis are relevant in terms of exposure assessment (annual average concentration in µg m^{-3}) and outcome definition (specified in ICD codes). The results are not necessarily relevant when regarding geographical extent, population characteristics and observed exposure range, as the review includes studies worldwide (62 from North America, 25 from Europe, 19 from Asia).	The results of the European cohort study are relevant in terms of exposure assessment (annual average concentration in µg m^{-3}) and outcome definition (specified in ICD codes), geographical extent, population characteristics and observed exposure range.	The results of the meta-analysis are relevant in terms of exposure assessment (annual average concentration in µg m^{-3}) and outcome definition (specified in ICD codes). The results are not necessarily relevant when regarding geographical extent, population characteristics and observed exposure range, as the review includes studies worldwide.

Table . Dose-response function evaluation grid for long-term exposure to $PM_{2.5}$ and diabetes.

	WHO 2021	ELAPSE pooled cohort	GBD 2021
Value	/	Mortality: 1.316 (1.144, 1.514) per 5 µg m^{-3} Morbidity: /	*1 integrated dose-response function for both mortality and morbidity*
Accessibility	/	Log-linear HR with confidence interval, available from article text	Integrated risk curve with confidence interval, available from the GHDx.
Transparency	/	Detailed information available on study population, exposure assessment, outcome definition, confounder adjustment, single and two-pollutant models and subgroup analyses.	List of sources included in the meta-analysis (MR-BRT model) available in supplementary materials. Information extracted on representativeness of the study population, exposure, outcome, reverse causation, control for confounding and selection bias, included in the Burden of Proof risk function.
Reliability	/	Based on adult population. Identification of outcomes by linkage with registries for mortality, cancer incidence, hospital discharge, and physician-based adjudication of cases, specified by ICD codes. Exposure assessment is based on LUR models, which incorporate monitoring data, land use, and traffic data supplemented with	No distinction between mortality or morbidity of the outcome. Publication bias was detected.

		satellite observations and dispersion model estimates. The exposure models had moderate-to-good performance in holdout validation and validation with external data. The main model is single-pollutant model, adjusted for cohort ID, age, sex, year of baseline visit, smoking (status, duration, intensity, and intensity squared), BMI, marital status, employment status, and 2001 neighborhood-level mean income. Several subgroup analyses were performed: age at baseline (<65 vs. ≥65 years), smoking status (current, ever, or never) and BMI (cut points at 18.5, 24.9, and 29.9 kg/m^2).	
Evidence	/	The analysis relied on a large European pooled cohort study. For mortality: Eight cohorts in Stockholm area, Denmark, the Netherlands, German Ruhr area and Augsburg area, France, Vorarlberg (Austria), with a total of 325,367 participants (47,131 deaths). For morbidity: Six cohorts in Stockholm area, Denmark, the Netherlands, German Ruhr and Augsburg areas, with a total of 137,148 participants (10,071 events).	Burden of Proof risk function: The risk-outcome pair received a score of 0.188, corresponding to a rating of 3 out of 5 stars.
Relevance	/	The results of the European cohort study are relevant in terms of exposure assessment (annual average concentration in µg m^{-3}) and outcome definition (specified in ICD codes), geographical extent, population characteristics and observed exposure range.	The results of the meta-analysis are relevant in terms of exposure assessment (annual average concentration in µg m^{-3}) and outcome definition (specified in ICD codes). The results are not necessarily relevant when regarding geographical extent, population characteristics and observed exposure range, as the review includes studies worldwide.

3.1.2. NO_2

Table . Dose-response function evaluation grid for long-term exposure to NO_2 and all-cause mortality.

	WHO 2021	ELAPSE pooled cohort (main model)	GBD 2021
Value	Mortality: 1.02 (1.01, 1.04) per 10 µg m^{-3}	Mortality: 1.086 (1.070, 1.102) per 10 µg m^{-3}	/
Accessibility	Log-linear RR with confidence interval, available from article text	Log-linear HR with confidence interval, available from article text	/
Transparency	Meta-analysis of 46 studies (9 for COPD). Review registered in PROSPERO (ID: CRD42018089853). Information extracted on citation details (title, authors, date of publication); cohort details (name, country, patient/ population group, follow up period(s)); subject characteristics (age at recruitment, sex, occupation); confounders measured; exposure assessment method (e.g. monitor, land use regression model); mean and concentration range of the pollutant (e.g. 5th & 95th percentile or minimum/ maximum or 25th/75th percentile values); outcome assessment (e.g. death records, ICD coding); and details of the risk estimates including exposure unit of measurement, metric description (e.g. annual mean), period of year of exposure assessment (all-year or 'warm/peak season'), and 95% confidence interval (CI) of the risk estimates for relevant outcomes; and details on co-pollutant models.	Detailed information available on study population, exposure assessment, outcome definition, confounder adjustment, single and two-pollutant models and subgroup analyses.	/
Reliability	Based on adult population. Sub-groups were defined by: 1) cohorts comprised of patient group versus general population cohorts; 2) cohorts able to control for individual measures of BMI, smoking and SES; 3) WHO region (Region of the Americas (AMR); European	Based on adult population. Identification of outcomes by linkage with registries for mortality, cancer incidence, hospital discharge,	/

	Region (EUR); Western Pacific Region (WPR)); and 4) by low/high RoB. Outcome defined as COD specified by ICD codes. "Studies included used various methods in exposure assessment, including local monitoring networks, atmospheric dispersion models, and land use regression model." Very high degree of statistical heterogeneity (I^2 = 96.9%)	and physician-based adjudication of cases, specified by ICD codes. Exposure assessment is based on LUR models, which incorporate monitoring data, land use, and traffic data supplemented with satellite observations and dispersion model estimates. The exposure models had moderate-to-good performance in holdout validation and validation with external data. The main model is single-pollutant model, adjusted for cohort ID, age, sex, year of baseline visit, smoking (status, duration, intensity, and intensity squared), BMI, marital status, employment status, and 2001 neighborhood-level mean income. Several subgroup analyses were performed: age at baseline (<65 vs. ≥65 years), smoking status (current, ever, or never) and BMI (cut points at 18.5, 24.9, and 29.9 kg/m^2).	
Evidence	Risk of Bias: Most included studies showed Low-Risk, some Moderate-risk and few High-risk. Adapted GRADE tool: "Moderate certainty of evidence". Review includes all studies until September 2018. Missing some important recent studies (e.g., ELAPSE).	The analysis relied on a large European pooled cohort study. For mortality: Eight cohorts in Stockholm area, Denmark, the Netherlands, German Ruhr area and Augsburg area, France, Vorarlberg (Austria), with a total of 325,367 participants (47,131 deaths). For morbidity: Six cohorts in Stockholm area, Denmark, the Netherlands, German Ruhr and Augsburg areas, with a total of 137,148 participants (10,071 events).	/.
Relevance	The results of the meta-analysis are relevant in terms of exposure assessment (annual average concentration in µg m^{-3}) and outcome definition (specified in ICD codes). The results are not necessarily relevant when regarding	The results of the European cohort study are relevant in terms of exposure assessment (annual average concentration in µg m^{-3}) and outcome definition (specified in ICD codes),	/

	geographical extent, population characteristics and observed exposure range, as the review includes studies worldwide (22 from North America, 19 from Europe, and 5 from Asia)	geographical extent, population characteristics and observed exposure range.

Table . Dose-response function evaluation grid for long-term exposure to NO_2 and IHD.

	WHO 2021	ELAPSE pooled cohort (main model)	GBD 2021
Value	/	Mortality: 1.098 (1.053, 1.145) per 10 µg m^{-3} Morbidity: 1.04 (1.01, 1.07) per 10 µg m^{-3}	/
Accessibility	/	Log-linear HR with confidence interval, available from article text.	/
Transparency	/	Detailed information available on study population, exposure assessment, outcome definition, confounder adjustment, single and two-pollutant models and subgroup analyses.	/
Reliability	/	Based on adult population. Identification of outcomes by linkage with registries for mortality, cancer incidence, hospital discharge, and physician-based adjudication of cases, specified by ICD codes. Exposure assessment is based on LUR models, which incorporate monitoring data, land use, and traffic data supplemented with satellite observations and dispersion model estimates. The exposure models had moderate-to-good performance in holdout validation and validation with external data. The main model is single-pollutant model, adjusted for cohort ID, age, sex, year of baseline visit, smoking (status, duration, intensity, and	/ .

		intensity squared), BMI, marital status, employment status, and 2001 neighborhood-level mean income. Several subgroup analyses were performed: age at baseline (<65 vs. ≥65 years), smoking status (current, ever, or never) and BMI (cut points at 18.5, 24.9, and 29.9 kg/m^2).	
Evidence	/	The analysis relied on a large European pooled cohort study. For mortality: Eight cohorts in Stockholm area, Denmark, the Netherlands, German Ruhr area and Augsburg area, France, Vorarlberg (Austria), with a total of 325,367 participants (47,131 deaths). For morbidity: Six cohorts in Stockholm area, Denmark, the Netherlands, German Ruhr and Augsburg areas, with a total of 137,148 participants (10,071 events).	/
Relevance	/	The results of the European cohort study are relevant in terms of exposure assessment (annual average concentration in µg m^{-3}) and outcome definition (specified in ICD codes), geographical extent, population characteristics and observed exposure range.	/

Table . Dose-response function evaluation grid for long-term exposure to NO_2 and stroke.

	WHO 2021	ELAPSE pooled cohort (main model)	GBD 2021
Value	/	Mortality: 1.068 (1.011, 1.129) per 10 µg m^{-3}	/
		Morbidity: 1.08 (1.04, 1.12) per 10 µg m^{-3}	
Accessibility	/	Log-linear HR with confidence interval, available from article text	/

Transparency	/	Detailed information available on study population, exposure assessment, outcome definition, confounder adjustment, single and two-pollutant models and subgroup analyses.	/
Reliability	/	Based on adult population. Identification of outcomes by linkage with registries for mortality, cancer incidence, hospital discharge, and physician-based adjudication of cases, specified by ICD codes. Exposure assessment is based on LUR models, which incorporate monitoring data, land use, and traffic data supplemented with satellite observations and dispersion model estimates. The exposure models had moderate-to-good performance in holdout validation and validation with external data. The main model is single-pollutant model, adjusted for cohort ID, age, sex, year of baseline visit, smoking (status, duration, intensity, and intensity squared), BMI, marital status, employment status, and 2001 neighborhood-level mean income. Several subgroup analyses were performed: age at baseline (<65 vs. ≥65 years), smoking status (current, ever, or never) and BMI (cut points at 18.5, 24.9, and 29.9 kg/m^2). For stroke, effect modification for education (low, medium, or high) was also assessed.	/
Evidence	/	The analysis relied on a large European pooled cohort study. For mortality: Eight cohorts in Stockholm area, Denmark, the Netherlands, German Ruhr area and Augsburg area, France, Vorarlberg (Austria), with a total of 325,367	/

		participants (47,131 deaths). For morbidity: Six cohorts in Stockholm area, Denmark, the Netherlands, German Ruhr and Augsburg areas, with a total of 137,148 participants (10,071 events).	
Relevance	/	The results of the European cohort study are relevant in terms of exposure assessment (annual average concentration in µg m^{-3}) and outcome definition (specified in ICD codes), geographical extent, population characteristics and observed exposure range.	/

Table . Dose-response function evaluation grid for long-term exposure to NO_2 and asthma.

	WHO 2021	ELAPSE pooled cohort (main model)	GBD 2021
Value	/	Mortality: /	*1 integrated dose-response function for both mortality and morbidity*
		Morbidity: 1.17 (1.10, 1.25) per 10 µg m^{-3}	
Accessibility	/	Log-linear HR with confidence interval, available from article text	Integrated risk curve with confidence interval, available from the GHDx.
Transparency	/	Detailed information available on study population, exposure assessment, outcome definition, confounder adjustment, single and two-pollutant models and subgroup analyses.	Meta-analysis of 27 studies. List of sources included in the meta-analysis (MR-BRT model) available in supplementary materials. Information extracted on representativeness of the study population, exposure, outcome, reverse causation, control for confounding and selection bias, included in the Burden of Proof risk function.
Reliability	/	Based on adult population. Identification of outcomes by linkage with registries for mortality, cancer incidence, hospital discharge,	No distinction between mortality or morbidity of the outcome. Publication bias was detected.

		and physician-based adjudication of cases, specified by ICD codes. Exposure assessment is based on LUR models, which incorporate monitoring data, land use, and traffic data supplemented with satellite observations and dispersion model estimates. The exposure models had moderate-to-good performance in holdout validation and validation with external data. The main model is single-pollutant model, adjusted for cohort ID, age, sex, year of baseline visit, smoking (status, duration, intensity, and intensity squared), BMI, marital status, employment status, and 2001 neighborhood-level mean income. Several subgroup analyses were performed: age at baseline (<65 vs. ≥65 years), smoking status (current, ever, or never) and BMI (cut points at 18.5, 24.9, and 29.9 kg/m^2).	
Evidence	/	The analysis relied on a large European pooled cohort study. For mortality: Eight cohorts in Stockholm area, Denmark, the Netherlands, German Ruhr area and Augsburg area, France, Vorarlberg (Austria), with a total of 325,367 participants (47,131 deaths). For morbidity: Six cohorts in Stockholm area, Denmark, the Netherlands, German Ruhr and Augsburg areas, with a total of 137,148 participants (10,071 events).	Burden of Proof risk function: The risk-outcome pair received a score of -0.51, corresponding to a rating of 1 out of 5 stars.
Relevance	/	The results of the European cohort study are relevant in terms of exposure assessment (annual average concentration in µg m^{-3}) and outcome definition (specified in ICD codes),	The results of the meta-analysis are relevant in terms of exposure assessment (annual average concentration in µg m^{-3}) and outcome definition (specified in ICD codes). The results are not necessarily relevant when regarding

		geographical extent, population characteristics and observed exposure range.	geographical extent, population characteristics and observed exposure range, as the review includes studies worldwide.

Table . Dose-response function evaluation grid for long-term exposure to NO_2 and COPD.

	WHO 2021	ELAPSE pooled cohort (main model)	GBD 2021
Value	Mortality: 1.03 (1.01, 1.04) per 10 µg m^{-3}	Mortality: 1.141 (1.056, 1.233) per 10 µg m^{-3} Morbidity: 1.11 (1.06, 1.16) per 10 µg m^{-3}	/
Accessibility	Log-linear RR with confidence interval, available from article text	Log-linear HR with confidence interval, available from article text	/
Transparency	Meta-analysis of 46 studies (9 for COPD). Review registered in PROSPERO (ID: CRD42018089853). Information extracted on citation details (title, authors, date of publication); cohort details (name, country, patient/ population group, follow up period(s)); subject characteristics (age at recruitment, sex, occupation); confounders measured; exposure assessment method (e.g. monitor, land use regression model); mean and concentration range of the pollutant (e.g. 5th & 95th percentile or minimum/ maximum or 25th/75th percentile values); outcome assessment (e.g. death records, ICD coding); and details of the risk estimates including exposure unit of measurement, metric description (e.g. annual mean), period of year of exposure assessment (all-year or 'warm/peak season'), and 95% confidence interval (CI) of the risk estimates for relevant outcomes; and details on co-pollutant models.	Detailed information available on study population, exposure assessment, outcome definition, confounder adjustment, single and two-pollutant models and subgroup analyses.	/
Reliability	Based on adult population. No subgroup analyses for this outcome. Outcome defined as COD specified by ICD codes.	Based on adult population. Identification of outcomes by linkage with registries for mortality, cancer incidence, hospital discharge,	/

	"Studies included used various methods in exposure assessment, including local monitoring networks, atmospheric dispersion models, and land use regression model." Low degree of statistical heterogeneity (I^2 = 22.7%)	and physician-based adjudication of cases, specified by ICD codes. Exposure assessment is based on LUR models, which incorporate monitoring data, land use, and traffic data supplemented with satellite observations and dispersion model estimates. The exposure models had moderate-to-good performance in holdout validation and validation with external data. The main model is single-pollutant model, adjusted for cohort ID, age, sex, year of baseline visit, smoking (status, duration, intensity, and intensity squared), BMI, marital status, employment status, and 2001 neighborhood-level mean income. Several subgroup analyses were performed: age at baseline (<65 vs. ≥65 years), smoking status (current, ever, or never) and BMI (cut points at 18.5, 24.9, and 29.9 kg/m^2). For COPD effect modification for education (low, medium, or high) was also assessed.	
Evidence	Risk of Bias: Most included studies showed Low-Risk, some Moderate-risk and few High-risk. Adapted GRADE tool: "High certainty of evidence". Review includes all studies until September 2018. Missing some important recent studies (e.g., ELAPSE).	The analysis relied on a large European pooled cohort study. For mortality: Eight cohorts in Stockholm area, Denmark, the Netherlands, German Ruhr area and Augsburg area, France, Vorarlberg (Austria), with a total of 325,367 participants (47,131 deaths). For morbidity: Six cohorts in Stockholm area, Denmark, the Netherlands, German Ruhr and Augsburg areas, with a total of 137,148 participants (10,071 events).	/.
Relevance	The results of the meta-analysis are relevant in terms of exposure assessment (annual average concentration in µg m^{-3}) and outcome	The results of the European cohort study are relevant in terms of exposure assessment	/

	definition (specified in ICD codes). The results are not necessarily relevant when regarding geographical extent, population characteristics and observed exposure range, as the review includes studies worldwide (22 from North America, 19 from Europe, and 5 from Asia)	(annual average concentration in µg m^{-3}) and outcome definition (specified in ICD codes), geographical extent, population characteristics and observed exposure range.	

Table . Dose-response function evaluation grid for long-term exposure to NO_2 and lung cancer.

	WHO 2021	ELAPSE pooled cohort (main model)	GBD 2021
Value	/	Mortality: / Morbidity: 1.02 (0.97, 1.07) per 10 µg m^{-3}	/
Accessibility	Log-linear RR with confidence interval, available from article text	Log-linear HR with confidence interval, available from article text	/
Transparency	Meta-analysis of 107 studies (15 for lung cancer). Review registered in PROSPERO (ID: CRD42018082577). Information extracted on study type, study population, exposure assessment, outcome definition, confounder adjustment, single and two-pollutant models and subgroup analyses.	Detailed information available on study population, exposure assessment, outcome definition, confounder adjustment, single and two-pollutant models and subgroup analyses.	/
Reliability	Based on adult population. No subgroup analyses for this outcome. Outcome defined as COD specified by ICD codes. "The exposure assessment methods varied across the studies, from assigned exposure to the nearest monitoring station, to land use regression or dispersion models. Exposures were assigned on very different spatial scales, ranging from residential address to US county." "Studies further differ in the detail of information available on potential confounders." Moderate degree of statistical heterogeneity (I^2 = 39.4%)	Based on adult population. Identification of outcomes by linkage with registries for mortality, cancer incidence, hospital discharge, and physician-based adjudication of cases, specified by ICD codes. Exposure assessment is based on LUR models, which incorporate monitoring data, land use, and traffic data supplemented with satellite observations and dispersion model estimates. The exposure models had moderate-to-good performance in holdout validation and validation with external data.	/

		The main model is single-pollutant model, adjusted for cohort ID, age, sex, year of baseline visit, smoking (status, duration, intensity, and intensity squared), BMI, marital status, employment status, and 2001 neighborhood-level mean income. Several subgroup analyses were performed: age at baseline (<65 vs. ≥65 years), smoking status (current, ever, or never) and BMI (cut points at 18.5, 24.9, and 29.9 kg/m^2).	
Evidence	Risk of Bias: Most included studies showed Low-Risk, some Moderate-risk and one High-risk. Adapted GRADE tool: "High certainty of evidence". Review includes all studies until October 2018. Missing some important recent studies (e.g., ELAPSE).	The analysis relied on a large European pooled cohort study. For mortality: Eight cohorts in Stockholm area, Denmark, the Netherlands, German Ruhr area and Augsburg area, France, Vorarlberg (Austria), with a total of 325,367 participants (47,131 deaths). For morbidity: Six cohorts in Stockholm area, Denmark, the Netherlands, German Ruhr and Augsburg areas, with a total of 137,148 participants (10,071 events).	/.
Relevance	The results of the meta-analysis are relevant in terms of exposure assessment (annual average concentration in µg m^{-3}) and outcome definition (specified in ICD codes). The results are not necessarily relevant when regarding geographical extent, population characteristics and observed exposure range, as the review includes studies worldwide (62 from North America, 25 from Europe, 19 from Asia).	The results of the European cohort study are relevant in terms of exposure assessment (annual average concentration in µg m^{-3}) and outcome definition (specified in ICD codes), geographical extent, population characteristics and observed exposure range.	/

Table . Dose-response function evaluation grid for long-term exposure to NO_2 and diabetes.

	WHO 2021	ELAPSE pooled cohort	GBD 2021
Value	/	Mortality: 1.238 (1.112, 1.378) per 10 µg m^{-3} Morbidity: /	/

Accessibility	/	Log-linear HR with confidence interval, available from article text	/
Transparency	/	Detailed information available on study population, exposure assessment, outcome definition, confounder adjustment, single and two-pollutant models and subgroup analyses.	/
Reliability	/	Based on adult population. Identification of outcomes by linkage with registries for mortality, cancer incidence, hospital discharge, and physician-based adjudication of cases, specified by ICD codes. Exposure assessment is based on LUR models, which incorporate monitoring data, land use, and traffic data supplemented with satellite observations and dispersion model estimates. The exposure models had moderate-to-good performance in holdout validation and validation with external data. The main model is single-pollutant model, adjusted for cohort ID, age, sex, year of baseline visit, smoking (status, duration, intensity, and intensity squared), BMI, marital status, employment status, and 2001 neighborhood-level mean income. Several subgroup analyses were performed: age at baseline (<65 vs. ≥65 years), smoking status (current, ever, or never) and BMI (cut points at 18.5, 24.9, and 29.9 kg/m^2).	/
Evidence	/	The analysis relied on a large European pooled cohort study. For mortality: Eight cohorts in Stockholm area, Denmark, the Netherlands, German Ruhr area and Augsburg area, France,	/

		Vorarlberg (Austria), with a total of 325,367 participants (47,131 deaths). For morbidity: Six cohorts in Stockholm area, Denmark, the Netherlands, German Ruhr and Augsburg areas, with a total of 137,148 participants (10,071 events).	
Relevance	/	The results of the European cohort study are relevant in terms of exposure assessment (annual average concentration in µg m^{-3}) and outcome definition (specified in ICD codes), geographical extent, population characteristics and observed exposure range.	/

3.1.3. O_3

Table . Dose-response function evaluation grid for long-term peak exposure to O_3 and all-cause mortality.

	WHO 2021	ELAPSE pooled cohort (main model)	GBD 2021
Value	Mortality: 1.01 (1.00, 1.02) per 10 µg m^{-3}	Mortality: 0.896 (0.878, 0.914) per 10 µg m^{-3}	/
Accessibility	Log-linear RR with confidence interval, available from article text.	Log-linear HR with confidence interval, available from article text.	/
Transparency	Meta-analysis of 107 studies (7 for all-cause mortality). Review registered in PROSPERO (ID: CRD42018082577). Information extracted on study type, study population, exposure assessment, outcome definition, confounder adjustment, single and two-pollutant models and subgroup analyses.	Detailed information available on study population, exposure assessment, outcome definition, confounder adjustment, single and two-pollutant models and subgroup analyses.	/
Reliability	Based on adult population. No subgroup analyses for this outcome. Outcome defined as COD specified by ICD codes. “The exposure assessment methods varied across the studies, from assigned exposure to	Based on adult population. Identification of outcomes by linkage with registries for mortality, cancer incidence, hospital discharge,	/

	the nearest monitoring station, to land use regression or dispersion models. Exposures were assigned on very different spatial scales, ranging from residential address to US county." "Studies further differ in the detail of information available on potential confounders." High degree of statistical heterogeneity (I^2 = 98%)	and physician-based adjudication of cases, specified by ICD codes. Exposure assessment is based on LUR models, which incorporate monitoring data, land use, and traffic data supplemented with satellite observations and dispersion model estimates. The exposure models had moderate-to-good performance in holdout validation and validation with external data. The main model is single-pollutant model, adjusted for cohort ID, age, sex, year of baseline visit, smoking (status, duration, intensity, and intensity squared), BMI, marital status, employment status, and 2001 neighborhood-level mean income. Several subgroup analyses were performed: age at baseline (<65 vs. ≥65 years), smoking status (current, ever, or never) and BMI (cut points at 18.5, 24.9, and 29.9 kg/m^2).	
Evidence	Risk of Bias: Most included studies showed Low-Risk, some Moderate-risk and one High-risk. Adapted GRADE tool: "Moderate certainty of evidence". Review includes all studies until October 2018. Missing some important recent studies (e.g., ELAPSE).	The analysis relied on a large European pooled cohort study. For mortality: Eight cohorts in Stockholm area, Denmark, the Netherlands, German Ruhr area and Augsburg area, France, Vorarlberg (Austria), with a total of 325,367 participants (47,131 deaths). For morbidity: Six cohorts in Stockholm area, Denmark, the Netherlands, German Ruhr and Augsburg areas, with a total of 137,148 participants (10,071 events).	/
Relevance	The results of the meta-analysis are relevant in terms of exposure assessment (annual average concentration in µg m^{-3}) and outcome	The results of the European cohort study are relevant in terms of outcome definition (specified in ICD codes), geographical extent,	/

	definition (specified in ICD codes). The results are not necessarily relevant when regarding geographical extent, population characteristics and observed exposure range, as the review includes studies worldwide (62 from North America, 25 from Europe, 19 from Asia).	population characteristics and observed exposure range. In terms of exposure assessment, the study relies on warm season averages (in µg m^{-3}), instead of the WHO's peak metric.	

Table . Dose-response function evaluation grid for long-term peak exposure to O3 and IHD.

	WHO 2021	ELAPSE pooled cohort (main model)	GBD 2021
Value	/	Mortality: 0.870 (0.821, 0.921) per 10 µg m^{-3} Morbidity: 0.94 (0.90, 0.98) per 10 µg m^{-3}	/
Accessibility	/	Log-linear HR with confidence interval, available from article text.	/
Transparency	/	Detailed information available on study population, exposure assessment, outcome definition, confounder adjustment, single and two-pollutant models and subgroup analyses.	/
Reliability	/	Based on adult population. Identification of outcomes by linkage with registries for mortality, cancer incidence, hospital discharge, and physician-based adjudication of cases, specified by ICD codes. Exposure assessment is based on LUR models, which incorporate monitoring data, land use, and traffic data supplemented with satellite observations and dispersion model estimates. The exposure models had moderate-to-good performance in holdout validation and validation with external data.	/ .

		The main model is single-pollutant model, adjusted for cohort ID, age, sex, year of baseline visit, smoking (status, duration, intensity, and intensity squared), BMI, marital status, employment status, and 2001 neighborhood-level mean income. Several subgroup analyses were performed: age at baseline (<65 vs. ≥65 years), smoking status (current, ever, or never) and BMI (cut points at 18.5, 24.9, and 29.9 kg/m^2).	
Evidence	/	The analysis relied on a large European pooled cohort study. For mortality: Eight cohorts in Stockholm area, Denmark, the Netherlands, German Ruhr area and Augsburg area, France, Vorarlberg (Austria), with a total of 325,367 participants (47,131 deaths). For morbidity: Six cohorts in Stockholm area, Denmark, the Netherlands, German Ruhr and Augsburg areas, with a total of 137,148 participants (10,071 events).	/.
Relevance	/	The results of the European cohort study are relevant in terms of outcome definition (specified in ICD codes), geographical extent, population characteristics and observed exposure range. In terms of exposure assessment, the study relies on warm season averages (in µg m^{-3}), instead of the WHO's peak metric.	/

Table . Dose-response function evaluation grid for long-term peak exposure to O_3 and stroke.

	WHO 2021	ELAPSE pooled cohort (main model)	GBD 2021

Value	/	Mortality: 0.882 (0.817, 0.953) per 10 µg m^{-3} Morbidity: 0.96 (0.91, 1.01) per 10 µg m^{-3}	/
Accessibility	/	Log-linear HR with confidence interval, available from article text	/
Transparency	/	Detailed information available on study population, exposure assessment, outcome definition, confounder adjustment, single and two-pollutant models and subgroup analyses.	/
Reliability	/	Based on adult population. Identification of outcomes by linkage with registries for mortality, cancer incidence, hospital discharge, and physician-based adjudication of cases, specified by ICD codes. Exposure assessment is based on LUR models, which incorporate monitoring data, land use, and traffic data supplemented with satellite observations and dispersion model estimates. The exposure models had moderate-to-good performance in holdout validation and validation with external data. The main model is single-pollutant model, adjusted for cohort ID, age, sex, year of baseline visit, smoking (status, duration, intensity, and intensity squared), BMI, marital status, employment status, and 2001 neighborhood-level mean income. Several subgroup analyses were performed: age at baseline (<65 vs. ≥65 years), smoking status (current, ever, or never) and BMI (cut points at 18.5, 24.9, and 29.9 kg/m^2). For	/

		stroke, effect modification for education (low, medium, or high) was also assessed.	
Evidence	/	The analysis relied on a large European pooled cohort study. For mortality: Eight cohorts in Stockholm area, Denmark, the Netherlands, German Ruhr area and Augsburg area, France, Vorarlberg (Austria), with a total of 325,367 participants (47,131 deaths). For morbidity: Six cohorts in Stockholm area, Denmark, the Netherlands, German Ruhr and Augsburg areas, with a total of 137,148 participants (10,071 events).	/
Relevance	/	The results of the European cohort study are relevant in terms of outcome definition (specified in ICD codes), geographical extent, population characteristics and observed exposure range. In terms of exposure assessment, the study relies on warm season averages (in µg m^{-3}), instead of the WHO's peak metric.	/

Table . Dose-response function evaluation grid for long-term peak exposure to O_3 and asthma.

	WHO 2021	ELAPSE pooled cohort (main model)	GBD 2021
Value	/	Mortality: / Morbidity: 0.90 (0.81, 0.99) per 5 µg m^{-3}	/
Accessibility	/	Log-linear HR with confidence interval, available from article text	/
Transparency	/	Detailed information available on study population, exposure assessment, outcome definition, confounder adjustment, single and two-pollutant models and subgroup analyses.	/

Reliability	/	Based on adult population. Identification of outcomes by linkage with registries for mortality, cancer incidence, hospital discharge, and physician-based adjudication of cases, specified by ICD codes. Exposure assessment is based on LUR models, which incorporate monitoring data, land use, and traffic data supplemented with satellite observations and dispersion model estimates. The exposure models had moderate-to-good performance in holdout validation and validation with external data. The main model is single-pollutant model, adjusted for cohort ID, age, sex, year of baseline visit, smoking (status, duration, intensity, and intensity squared), BMI, marital status, employment status, and 2001 neighborhood-level mean income. Several subgroup analyses were performed: age at baseline (<65 vs. ≥65 years), smoking status (current, ever, or never) and BMI (cut points at 18.5, 24.9, and 29.9 kg/m^2).	/
Evidence	/	The analysis relied on a large European pooled cohort study. For mortality: Eight cohorts in Stockholm area, Denmark, the Netherlands, German Ruhr area and Augsburg area, France, Vorarlberg (Austria), with a total of 325,367 participants (47,131 deaths). For morbidity: Six cohorts in Stockholm area, Denmark, the Netherlands, German Ruhr and Augsburg areas, with a total of 137,148 participants (10,071 events).	/

Relevance	/	The results of the European cohort study are relevant in terms of outcome definition (specified in ICD codes), geographical extent, population characteristics and observed exposure range. In terms of exposure assessment, the study relies on warm season averages (in µg m^{-3}), instead of the WHO's peak metric.	/

Table . Dose-response function evaluation grid for long-term peak exposure to O_3 and COPD.

	WHO 2021	ELAPSE pooled cohort (main model)	GBD 2021
Value	/	Mortality: 0.861 (0.774, 0.957) per 10 µg m^{-3} Morbidity: 0.99 (0.93, 1.05) per 10 µg m^{-3}	*1 integrated dose-response function for both mortality and morbidity*
Accessibility	/	Log-linear HR with confidence interval, available from article text	Integrated risk curve with confidence interval, available from the GHDx.
Transparency	/	Detailed information available on study population, exposure assessment, outcome definition, confounder adjustment, single and two-pollutant models and subgroup analyses.	List of sources included in the meta-analysis (MR-BRT model) available in supplementary materials. Information extracted on representativeness of the study population, exposure, outcome, reverse causation, control for confounding and selection bias, included in the Burden of Proof risk function.
Reliability	/	Based on adult population. Identification of outcomes by linkage with registries for mortality, cancer incidence, hospital discharge, and physician-based adjudication of cases, specified by ICD codes. Exposure assessment is based on LUR models, which incorporate monitoring data, land use, and traffic data supplemented with satellite observations and dispersion model estimates. The exposure models had	No distinction between mortality or morbidity of the outcome. No publication bias was detected.

		moderate-to-good performance in holdout validation and validation with external data. The main model is single-pollutant model, adjusted for cohort ID, age, sex, year of baseline visit, smoking (status, duration, intensity, and intensity squared), BMI, marital status, employment status, and 2001 neighborhood-level mean income. Several subgroup analyses were performed: age at baseline (<65 vs. ≥65 years), smoking status (current, ever, or never) and BMI (cut points at 18.5, 24.9, and 29.9 kg/m^2). For COPD effect modification for education (low, medium, or high) was also assessed.	
Evidence	/	The analysis relied on a large European pooled cohort study. For mortality: Eight cohorts in Stockholm area, Denmark, the Netherlands, German Ruhr area and Augsburg area, France, Vorarlberg (Austria), with a total of 325,367 participants (47,131 deaths). For morbidity: Six cohorts in Stockholm area, Denmark, the Netherlands, German Ruhr and Augsburg areas, with a total of 137,148 participants (10,071 events).	Burden of Proof risk function: The risk-outcome pair received a score of 0.011, corresponding to a rating of 2 out of 5 stars.
Relevance	/	The results of the European cohort study are relevant in terms of outcome definition (specified in ICD codes), geographical extent, population characteristics and observed exposure range. In terms of exposure assessment, the study relies on warm season averages (in µg m^{-3}), instead of the WHO's peak metric.	The results of the meta-analysis are relevant in terms of exposure assessment (annual average concentration in µg m^{-3}) and outcome definition (specified in ICD codes). The results are not necessarily relevant when regarding geographical extent, population characteristics and observed exposure range, as the review includes studies worldwide.

Table . Dose-response function evaluation grid for long-term peak exposure to O_3 and lung cancer.

	WHO 2021	ELAPSE pooled cohort (main model)	GBD 2021
Value	/	Mortality: / Morbidity: 0.95 (0.89, 1.02) per 10 µg m^{-3}	/
Accessibility	/	Log-linear HR with confidence interval, available from article text	/
Transparency	/	Detailed information available on study population, exposure assessment, outcome definition, confounder adjustment, single and two-pollutant models and subgroup analyses.	/
Reliability	/	Based on adult population. Identification of outcomes by linkage with registries for mortality, cancer incidence, hospital discharge, and physician-based adjudication of cases, specified by ICD codes. Exposure assessment is based on LUR models, which incorporate monitoring data, land use, and traffic data supplemented with satellite observations and dispersion model estimates. The exposure models had moderate-to-good performance in holdout validation and validation with external data. The main model is single-pollutant model, adjusted for cohort ID, age, sex, year of baseline visit, smoking (status, duration, intensity, and intensity squared), BMI, marital status, employment status, and 2001 neighborhood-level mean income. Several subgroup analyses were performed: age at baseline (<65 vs. ≥65 years), smoking	/

		status (current, ever, or never) and BMI (cut points at 18.5, 24.9, and 29.9 kg/m^2).	
Evidence	/	The analysis relied on a large European pooled cohort study. For mortality: Eight cohorts in Stockholm area, Denmark, the Netherlands, German Ruhr area and Augsburg area, France, Vorarlberg (Austria), with a total of 325,367 participants (47,131 deaths). For morbidity: Six cohorts in Stockholm area, Denmark, the Netherlands, German Ruhr and Augsburg areas, with a total of 137,148 participants (10,071 events).	/
Relevance	/	The results of the European cohort study are relevant in terms of outcome definition (specified in ICD codes), geographical extent, population characteristics and observed exposure range. In terms of exposure assessment, the study relies on warm season averages (in µg m^{-3}), instead of the WHO's peak metric.	/

Table . Dose-response function evaluation grid for long-term peak exposure to O_3 and diabetes.

	WHO 2021	ELAPSE pooled cohort	GBD 2021
Value	/	Mortality: 0.744 (0.645, 0.859) per 10 µg m^{-3} Morbidity: /	/
Accessibility	/	Log-linear HR with confidence interval, available from article text	/
Transparency	/	Detailed information available on study population, exposure assessment, outcome definition, confounder adjustment, single and two-pollutant models and subgroup analyses.	/

Reliability	/	Based on adult population. Identification of outcomes by linkage with registries for mortality, cancer incidence, hospital discharge, and physician-based adjudication of cases, specified by ICD codes. Exposure assessment is based on LUR models, which incorporate monitoring data, land use, and traffic data supplemented with satellite observations and dispersion model estimates. The exposure models had moderate-to-good performance in holdout validation and validation with external data. The main model is single-pollutant model, adjusted for cohort ID, age, sex, year of baseline visit, smoking (status, duration, intensity, and intensity squared), BMI, marital status, employment status, and 2001 neighborhood-level mean income. Several subgroup analyses were performed: age at baseline (<65 vs. ≥65 years), smoking status (current, ever, or never) and BMI (cut points at 18.5, 24.9, and 29.9 kg/m^2).	/
Evidence	/	The analysis relied on a large European pooled cohort study. For mortality: Eight cohorts in Stockholm area, Denmark, the Netherlands, German Ruhr area and Augsburg area, France, Vorarlberg (Austria), with a total of 325,367 participants (47,131 deaths). For morbidity: Six cohorts in Stockholm area, Denmark, the Netherlands, German Ruhr and Augsburg areas, with a total of 137,148 participants (10,071 events).	/

Relevance	/	The results of the European cohort study are relevant in terms of outcome definition (specified in ICD codes), geographical extent, population characteristics and observed exposure range. In terms of exposure assessment, the study relies on warm season averages (in µg m^{-3}), instead of the WHO's peak metric.	/

3.2. Environmental noise

3.2.1. Road traffic noise

Table . Dose-response function evaluation grid for long-term exposure to road traffic noise and IHD.

	WHO 2018	WHO 2018 (update)	NordSOUND
Value	Mortality: 1.05 (0.97, 1.13) per 10 dB	Mortality: /	Mortality + morbidity: 1.03 (1.00, 1.05) per 10 dB
	Morbidity: 1.08 (1.01, 1.15) per 10 dB	Morbidity: 1.02 (1.00, 1.04) per 10 dB	
Accessibility	Log-linear RR with confidence interval, available from article text.	Log-linear RR with confidence interval, available from article text.	Log-linear HR with confidence interval, available from article text.
Transparency	Meta-analysis: Inclusion of 7 studies for IHD, myocardial infarction and angina pectoris. Data extracted on general study characteristics (e.g., study design, study period, study location), population characteristics (sampling of the study population, number of participants, response and attrition rate, gender, age, exposure assessment and health outcome assessment, and the results of the study	Meta-analysis: Inclusion of 13 studies for IHD, myocardial infarction and angina pectoris. Data extracted on general study characteristics (e.g., study design, study period, study location), population characteristics (sampling of the study population, number of participants, response and attrition rate, gender, age, exposure assessment and health outcome assessment, and the results of the study	Information extracted on smoking status, smoking intensity, alcohol consumption, and leisure-time physical activity, weight and height, educational level, marital status, area-level mean income, air pollution.

Reliability	Based on adult population. No subgroup analyses for this outcome. Outcome derived from mortality register or by self-reporting, clinical interview or healthcare registration, defined by ICD codes. Varying adjustment for confounders (smoking, air pollution, SES). Exposure assessment mostly by noise models, some by measurement. No clear evidence of statistical heterogeneity.	Based on adult population. No subgroup analyses for this outcome. Outcome derived by self-reporting, clinical interview or healthcare registration, defined by ICD codes. Varying adjustment for confounders (smoking, air pollution, SES). Exposure assessment mostly by noise models, some by measurement. No clear evidence of statistical heterogeneity.	Based on adult population. Subgroup analyses available for age, sex, marital status, BMI, physical activity, smoking status, educational level, calendar year, $PM_{2.5}$, and NO_2. No distinction between mortality or morbidity of the outcome. Main model adjusted for age, cohort, sex, calendar year, educational status, marital status, area-level income, and other transportation noise sources. All cohorts modeled road traffic and railway noise using the Nordic Prediction Method or an update of this method, Nord2000.
Evidence	GRADE: High quality of evidence Review includes studies 2000-2015.	Low Risk of Bias. Review includes all studies until February 2019.	The analysis relied on a large Scandinavian pooled cohort study, with a total of 132,801 participants (22,459 events).
Relevance	The results of the meta-analysis are relevant in terms of exposure assessment (annual average sound level in dB LDEN), outcome definition (specified in ICD codes), geographical extent (all but one study from Europe), population characteristics and observed exposure range.	The results of the meta-analysis are relevant in terms of exposure assessment (annual average sound level in dB LDEN), outcome definition (specified in ICD codes), geographical extent (all but one study from Europe), population characteristics and observed exposure range.	The results of the study are relevant in terms of exposure assessment (annual average sound level in dB LDEN) and outcome definition (specified in ICD codes). The results are not necessarily relevant when regarding geographical extent, population characteristics and observed exposure range, as the study is based exclusively on Scandinavian data.

Table . Dose-response function evaluation grid for long-term exposure to road traffic noise and stroke.

	WHO 2018	WHO 2018 (update)	NordSOUND
Value	Mortality: 1.14 (1.03, 1.25) per 10 dB	/	Mortality + morbidity: 1.05 (1.03, 1.08) per 10 dB

Accessibility	Log-linear RR with confidence interval, available from article text	/	Log-linear HR with confidence interval, available from article text
Transparency	Meta-analysis: Inclusion of 1 study for IHD, myocardial infarction and angina pectoris. Data extracted on general study characteristics (e.g., study design, study period, study location), population characteristics (sampling of the study population, number of participants, response and attrition rate, gender, age, exposure assessment and health outcome assessment, and the results of the study.	/	Information extracted on smoking status, smoking intensity, alcohol consumption, and leisure-time physical activity, weight and height, educational level, marital status, area-level mean income, air pollution.
Reliability	Based on adult population. No subgroup analyses for this outcome. Outcome derived from mortality register or by self-reporting, clinical interview or healthcare registration, defined by ICD codes. Varying adjustment for confounders (smoking, air pollution, SES). Exposure assessment mostly by noise models, some by measurement. No clear evidence of statistical heterogeneity.	/	Based on adult population. Subgroup analyses available for age, sex, marital status, BMI, physical activity, smoking status, educational level, calendar year, $PM_{2.5}$, and NO_2. No distinction between mortality or morbidity of the outcome. Main model adjusted for age, cohort, sex, calendar year, educational status, marital status, area-level income, and other transportation noise sources. All cohorts modeled road traffic and railway noise using the Nordic Prediction Method or an update of this method, Nord2000.
Evidence	GRADE: Moderate quality of evidence Review includes studies 2000-2015.	/	The analysis relied on a large Scandinavian pooled cohort study, with a total of 135,951 participants (11,056 events).
Relevance	The results of the meta-analysis are relevant in terms of exposure assessment (annual average sound level in dB LDEN), outcome definition (specified in ICD codes), geographical extent (all studies from Europe), population characteristics and observed exposure range.	/	The results of the study are relevant in terms of exposure assessment (annual average sound level in dB LDEN) and outcome definition (specified in ICD codes). The results are not necessarily relevant when regarding geographical extent, population characteristics and observed exposure range, as the study is based exclusively on Scandinavian data.

Table . Dose-response function evaluation grid for long-term exposure to road traffic noise and diabetes.

	WHO 2018	WHO 2018 (update)	NordSOUND
Value	Mortality: /	Mortality: /	/
	Morbidity: 1.08 (1.02, 1.14) per 10 dB	Morbidity: 1.11 (1.08, 1.15) per 10 dB	
Accessibility	Log-linear RR with confidence interval, available from article text	Log-linear HR with confidence interval, available from article text	/
Transparency	Meta-analysis: Inclusion of 1 study for diabetes. Data extracted on general study characteristics (e.g., study design, study period, study location), population characteristics (sampling of the study population, number of participants, response and attrition rate, gender, age, exposure assessment and health outcome assessment, and the results of the study.	Meta-analysis: Inclusion of 5 studies for diabetes. Data extracted on general study characteristics (e.g., study design, study period, study location), population characteristics (sampling of the study population, number of participants, response and attrition rate, gender, age, exposure assessment and health outcome assessment, and the results of the study	/
Reliability	Based on adult population. No subgroup analyses for this outcome. Outcome derived from mortality register or by self-reporting, clinical interview or healthcare registration, defined by ICD codes. Varying adjustment for confounders (smoking, air pollution, SES). Exposure assessment mostly by noise models, some by measurement. No clear evidence of statistical heterogeneity.	Based on adult population. No subgroup analyses for this outcome. Outcome derived from mortality register or by self-reporting, clinical interview or healthcare registration, defined by ICD codes. Varying adjustment for confounders (smoking, air pollution, SES). Exposure assessment mostly by noise models, some by measurement. No clear evidence of statistical heterogeneity.	/
Evidence	GRADE: Moderate quality of evidence Review includes studies 2000-2015.	Low Risk of Bias. Review includes all studies until February 2019.	/

Relevance	The results of the meta-analysis are relevant in terms of exposure assessment (annual average sound level in dB LDEN), outcome definition (specified in ICD codes), geographical extent (all studies from Europe), population characteristics and observed exposure range.	The results of the meta-analysis are relevant in terms of exposure assessment (annual average sound level in dB LDEN), outcome definition (specified in ICD codes), geographical extent (all but one study from Europe), population characteristics and observed exposure range.	/

3.2.2. Railway traffic noise

Table . Dose-response function evaluation grid for long-term exposure to railway traffic noise and IHD.

	WHO 2018	WHO 2018 (update)	NordSOUND
Value	/	Mortality: /	Mortality + morbidity: 1.03 (1.00, 1.05) per 10 dB
	Morbidity: 1.18 (0.82, 1.68) per 10 dB	Morbidity: 1.01 (0.99, 1.03) per 10 dB	
Accessibility	Log-linear RR with confidence interval, available from article text.	Log-linear RR with confidence interval, available from article text.	Log-linear HR with confidence interval, available from article text.
Transparency	Meta-analysis: Inclusion of 4 study for morality and 2 studies for morbidity of IHD, myocardial infarction and angina pectoris. Data extracted on general study characteristics (e.g., study design, study period, study location), population characteristics (sampling of the study population, number of participants, response and attrition rate, gender, age, exposure assessment and health outcome assessment, and the results of the study	Meta-analysis: Inclusion of 3 studies for IHD, myocardial infarction and angina pectoris. Data extracted on general study characteristics (e.g., study design, study period, study location), population characteristics (sampling of the study population, number of participants, response and attrition rate, gender, age, exposure assessment and health outcome assessment, and the results of the study	Information extracted on smoking status, smoking intensity, alcohol consumption, and leisure-time physical activity, weight and height, educational level, marital status, area-level mean income, air pollution.
Reliability	Based on adult population. No subgroup analyses for this outcome.	Based on adult population. No subgroup analyses for this outcome.	Based on adult population. Subgroup analyses available for age, sex, marital status, BMI, physical activity, smoking status, educational level, calendar year, $PM_{2.5}$, and NO_2.

	Outcome derived from mortality register or by self-reporting, clinical interview or healthcare registration, defined by ICD codes. Varying adjustment for confounders (smoking, air pollution, SES). Exposure assessment mostly by noise models, some by measurement. No clear evidence of statistical heterogeneity.	Outcome derived by self-reporting, clinical interview or healthcare registration, defined by ICD codes. Varying adjustment for confounders (smoking, air pollution, SES). Exposure assessment mostly by noise models, some by measurement. Evidence of statistical heterogeneity.	No distinction between mortality or morbidity of the outcome. Main model adjusted for age, cohort, sex, calendar year, educational status, marital status, area-level income, and other transportation noise sources. All cohorts modeled road traffic and railway noise using the Nordic Prediction Method or an update of this method, Nord2000.
Evidence	GRADE: Very low quality. Review includes studies 2000-2015.	Low Risk of Bias. Review includes all studies until February 2019.	The analysis relied on a large Scandinavian pooled cohort study, with a total of 132,801 participants (22,459 events).
Relevance	The results of the meta-analysis are relevant in terms of exposure assessment (annual average sound level in dB LDEN), outcome definition (specified in ICD codes), geographical extent (all but one study from Europe), population characteristics and observed exposure range.	The results of the meta-analysis are relevant in terms of exposure assessment (annual average sound level in dB LDEN), outcome definition (specified in ICD codes), geographical extent (all but one study from Europe), population characteristics and observed exposure range.	The results of the study are relevant in terms of exposure assessment (annual average sound level in dB LDEN) and outcome definition (specified in ICD codes). The results are not necessarily relevant when regarding geographical extent, population characteristics and observed exposure range, as the study is based exclusively on Scandinavian data.

Table . Dose-response function evaluation grid for long-term exposure to railway traffic noise and stroke.

	WHO 2018	WHO 2018 (update)	NordSOUND
Value	/ Morbidity: 1.07 (0.92–1.25) per 10 dB	/	Mortality + morbidity: 0.96 (0.91, 1.01) per 10 dB
Accessibility	Log-linear RR with confidence interval, available from article text.	/	Log-linear HR with confidence interval, available from article text
Transparency	Meta-analysis: Inclusion of 1 study for stroke. Data extracted on general study characteristics (e.g., study design, study period, study	/	Information extracted on smoking status, smoking intensity, alcohol consumption, and leisure-time physical activity, weight and

	location), population characteristics (sampling of the study population, number of participants, response and attrition rate, gender, age, exposure assessment and health outcome assessment, and the results of the study.		height, educational level, marital status, area-level mean income, air pollution.
Reliability	Based on adult population. No subgroup analyses for this outcome. Outcome derived from mortality register or by self-reporting, clinical interview or healthcare registration, defined by ICD codes. Varying adjustment for confounders (smoking, air pollution, SES). Exposure assessment mostly by noise models, some by measurement. No clear evidence of statistical heterogeneity.	/	Based on adult population. Subgroup analyses available for age, sex, marital status, BMI, physical activity, smoking status, educational level, calendar year, $PM_{2.5}$, and NO_2. No distinction between mortality or morbidity of the outcome. Main model adjusted for age, cohort, sex, calendar year, educational status, marital status, area-level income, and other transportation noise sources. All cohorts modeled road traffic and railway noise using the Nordic Prediction Method or an update of this method, Nord2000.
Evidence	GRADE: Very low quality. Review includes studies 2000-2015.	/	The analysis relied on a large Scandinavian pooled cohort study, with a total of 135,951 participants (11,056 events).
Relevance	The results of the meta-analysis are relevant in terms of exposure assessment (annual average sound level in dB LDEN), outcome definition (specified in ICD codes), geographical extent (all studies from Europe), population characteristics and observed exposure range.	/	The results of the study are relevant in terms of exposure assessment (annual average sound level in dB LDEN) and outcome definition (specified in ICD codes). The results are not necessarily relevant when regarding geographical extent, population characteristics and observed exposure range, as the study is based exclusively on Scandinavian data.

Table . Dose-response function evaluation grid for long-term exposure to railway traffic noise and diabetes.

	WHO 2018	WHO 2018 (update)	NordSOUND
Value	Mortality: /	Mortality: /	/
	Morbidity: 0.97 (0.89, 1.05) per 10 dB	Morbidity: 0.99 (0.94, 1.04) per 10 dB	

Accessibility	Log-linear RR with confidence interval, available from article text	Log-linear RR with confidence interval, available from article text	/
Transparency	Meta-analysis: Inclusion of 1 study for diabetes. Data extracted on general study characteristics (e.g., study design, study period, study location), population characteristics (sampling of the study population, number of participants, response and attrition rate, gender, age, exposure assessment and health outcome assessment, and the results of the study.	Meta-analysis: Inclusion of 2 studies for diabetes. Data extracted on general study characteristics (e.g., study design, study period, study location), population characteristics (sampling of the study population, number of participants, response and attrition rate, gender, age, exposure assessment and health outcome assessment, and the results of the study	/
Reliability	Based on adult population. No subgroup analyses for this outcome. Outcome derived from mortality register or by self-reporting, clinical interview or healthcare registration, defined by ICD codes. Varying adjustment for confounders (smoking, air pollution, SES). Exposure assessment mostly by noise models, some by measurement. No clear evidence of statistical heterogeneity.	Based on adult population. No subgroup analyses for this outcome. Outcome derived from mortality register or by self-reporting, clinical interview or healthcare registration, defined by ICD codes. Varying adjustment for confounders (smoking, air pollution, SES). Exposure assessment mostly by noise models, some by measurement. Evidence of statistical heterogeneity.	/
Evidence	GRADE: Moderate quality of evidence Review includes studies 2000-2015.	Low Risk of Bias. Review includes all studies until February 2019.	/
Relevance	The results of the meta-analysis are relevant in terms of exposure assessment (annual average sound level in dB LDEN), outcome definition (specified in ICD codes), geographical extent (all studies from Europe), population characteristics and observed exposure range.	The results of the meta-analysis are relevant in terms of exposure assessment (annual average sound level in dB LDEN), outcome definition (specified in ICD codes), geographical extent (all but one study from Europe), population characteristics and observed exposure range.	/

3.2.3. Aircraft traffic noise

Table . Dose-response function evaluation grid for long-term exposure to aircraft traffic noise and IHD.

	WHO 2018	WHO 2018 (update)	NordSOUND
Value	Mortality: 1.04 (0.98, 1.11) per 10 dB	Mortality: /	Mortality + morbidity: 0.95 (0.83, 1.09) per 10 dB
	Morbidity: 1.07 (0.94, 1.23) per 10 dB	Morbidity: 1.03 (0.98, 1.09) per 10 dB	
Accessibility	Log-linear RR with confidence interval, available from article text.	Log-linear RR with confidence interval, available from article text.	Log-linear HR with confidence interval, available from article text.
Transparency	Meta-analysis: Inclusion of 1 study for morality and 2 studies for morbidity of IHD, myocardial infarction and angina pectoris. Data extracted on general study characteristics (e.g., study design, study period, study location), population characteristics (sampling of the study population, number of participants, response and attrition rate, gender, age, exposure assessment and health outcome assessment, and the results of the study	Meta-analysis: Inclusion of 5 studies for IHD, myocardial infarction and angina pectoris. Data extracted on general study characteristics (e.g., study design, study period, study location), population characteristics (sampling of the study population, number of participants, response and attrition rate, gender, age, exposure assessment and health outcome assessment, and the results of the study	Information extracted on smoking status, smoking intensity, alcohol consumption, and leisure-time physical activity, weight and height, educational level, marital status, area-level mean income, air pollution.
Reliability	Based on adult population. No subgroup analyses for this outcome. Outcome derived from mortality register or by self-reporting, clinical interview or healthcare registration, defined by ICD codes. Varying adjustment for confounders (smoking, air pollution, SES). Exposure assessment mostly by noise models, some by measurement. No clear evidence of statistical heterogeneity.	Based on adult population. No subgroup analyses for this outcome. Outcome derived by self-reporting, clinical interview or healthcare registration, defined by ICD codes. Varying adjustment for confounders (smoking, air pollution, SES). Exposure assessment mostly by noise models, some by measurement. Evidence of statistical heterogeneity.	Based on adult population. Subgroup analyses available for age, sex, marital status, BMI, physical activity, smoking status, educational level, calendar year, $PM_{2.5}$, and NO_2. No distinction between mortality or morbidity of the outcome. Main model adjusted for age, cohort, sex, calendar year, educational status, marital status, area-level income, and other transportation noise sources. All cohorts modeled road traffic and railway noise using the Nordic Prediction Method or an update of this method, Nord2000.

Evidence	GRADE: Low quality for mortality, very low quality for morbidity. Review includes studies 2000-2015.	High Risk of Bias. Review includes all studies until February 2019.	The analysis relied on a large Scandinavian pooled cohort study, with a total of 132,801 participants (22,459 events).
Relevance	The results of the meta-analysis are relevant in terms of exposure assessment (annual average sound level in dB LDEN), outcome definition (specified in ICD codes), geographical extent (all but one study from Europe), population characteristics and observed exposure range.	The results of the meta-analysis are relevant in terms of exposure assessment (annual average sound level in dB LDEN), outcome definition (specified in ICD codes), geographical extent (all but one study from Europe), population characteristics and observed exposure range.	The results of the study are relevant in terms of exposure assessment (annual average sound level in dB LDEN) and outcome definition (specified in ICD codes). The results are not necessarily relevant when regarding geographical extent, population characteristics and observed exposure range, as the study is based exclusively on Scandinavian data.

Table . Dose-response function evaluation grid for long-term exposure to aircraft traffic noise and stroke.

	WHO 2018	WHO 2018 (update)	NordSOUND
Value	Mortality: 0.99 (0.94–1.04) per 10 dB Morbidity: 1.02 (0.80, 1.28) per 10 dB	/	Mortality + morbidity: 0.94 (0.79, 1.11) per 10 dB
Accessibility	Log-linear RR with confidence interval, available from article text	/	Log-linear HR with confidence interval, available from article text
Transparency	Meta-analysis: Inclusion of 1 study for morality and 2 studies for morbidity of stroke. Data extracted on general study characteristics (e.g., study design, study period, study location), population characteristics (sampling of the study population, number of participants, response and attrition rate, gender, age, exposure assessment and health outcome assessment, and the results of the study.	/	Information extracted on smoking status, smoking intensity, alcohol consumption, and leisure-time physical activity, weight and height, educational level, marital status, area-level mean income, air pollution.
Reliability	Based on adult population. No subgroup analyses for this outcome. Outcome derived from mortality register or by self-reporting, clinical interview or healthcare registration, defined by ICD codes.	/	Based on adult population. Subgroup analyses available for age, sex, marital status, BMI, physical activity, smoking status, educational level, calendar year, $PM_{2.5}$, and NO_2.

	Varying adjustment for confounders (smoking, air pollution, SES). Exposure assessment mostly by noise models, some by measurement. No clear evidence of statistical heterogeneity.		No distinction between mortality or morbidity of the outcome. Main model adjusted for age, cohort, sex, calendar year, educational status, marital status, area-level income, and other transportation noise sources. All cohorts modeled road traffic and railway noise using the Nordic Prediction Method or an update of this method, Nord2000.
Evidence	GRADE: Moderate quality for mortality, very low quality for morbidity. Review includes studies 2000-2015.	/	The analysis relied on a large Scandinavian pooled cohort study, with a total of 135,951 participants (11,056 events).
Relevance	The results of the meta-analysis are relevant in terms of exposure assessment (annual average sound level in dB LDEN), outcome definition (specified in ICD codes), geographical extent (all studies from Europe), population characteristics and observed exposure range.	/	The results of the study are relevant in terms of exposure assessment (annual average sound level in dB LDEN) and outcome definition (specified in ICD codes). The results are not necessarily relevant when regarding geographical extent, population characteristics and observed exposure range, as the study is based exclusively on Scandinavian data.

Table . Dose-response function evaluation grid for long-term exposure to aircraft traffic noise and diabetes.

	WHO 2018	WHO 2018 (update)	NordSOUND
Value	Mortality: /	Mortality: /	/
	Morbidity: 0.99 (0.47, 2.09) per 10 dB	Morbidity: 1.20 (0.88, 1.63) per 10 dB	
Accessibility	Log-linear RR with confidence interval, available from article text	Log-linear RR with confidence interval, available from article text	/
Transparency	Meta-analysis: Inclusion of 1 study for diabetes. Data extracted on general study characteristics (e.g., study design, study period, study location), population characteristics (sampling of the study population, number of participants, response and attrition rate, gender, age,	Meta-analysis: Inclusion of 3 studies for diabetes. Data extracted on general study characteristics (e.g., study design, study period, study location), population characteristics (sampling of the study population, number of participants,	/

	exposure assessment and health outcome assessment, and the results of the study.	response and attrition rate, gender, age, exposure assessment and health outcome assessment, and the results of the study	
Reliability	Based on adult population. No subgroup analyses for this outcome. Outcome derived from mortality register or by self-reporting, clinical interview or healthcare registration, defined by ICD codes. Varying adjustment for confounders (smoking, air pollution, SES). Exposure assessment mostly by noise models, some by measurement. No clear evidence of statistical heterogeneity.	Based on adult population. No subgroup analyses for this outcome. Outcome derived from mortality register or by self-reporting, clinical interview or healthcare registration, defined by ICD codes. Varying adjustment for confounders (smoking, air pollution, SES). Exposure assessment mostly by noise models, some by measurement. Evidence of statistical heterogeneity.	/
Evidence	GRADE: Low quality of evidence Review includes studies 2000-2015.	Low Risk of Bias. Review includes all studies until February 2019.	/
Relevance	The results of the meta-analysis are relevant in terms of exposure assessment (annual average sound level in dB LDEN), outcome definition (specified in ICD codes), geographical extent (all studies from Europe), population characteristics and observed exposure range.	The results of the meta-analysis are relevant in terms of exposure assessment (annual average sound level in dB LDEN), outcome definition (specified in ICD codes), geographical extent (all but one study from Europe), population characteristics and observed exposure range.	/

CONTACT

Arno Pauwels • T+32 2 642 51 15 • arno.pauwels@sciensano.be

MORE INFORMATION

—

Visit our website
www.sciensano.be

Sciensano • Rue Juliette Wytsmanstraat 14 • Brussels • Belgium • T + 32 2 642 51 11 • T press + 32 2 642 54 20 • info@sciensano.be • www.sciensano.be

Responsible editor: Christian Leonard, Managing director • Rue Juliette Wytsmanstraat 14 • Brussels • Belgium • D/2024.14.440/32