

BURDEN OF DISEASE DUE TO AIR POLLUTION

Overview of the methodologies for air quality
attributable burden calculations in Belgium and its
regions

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WHO WE ARE

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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

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ABBREVIATIONS

AQG	Air Quality Guidelines
BC	Black carbon
CI	Confidence interval
COMEAP	Committee on the Medical Effects of Air Pollutants
CRA	Comparative risk assessment
CRF	Concentration-response function
DALY	Disability-adjusted life year
EC	European Commission
EEA	European Environment Agency
ELAPSE	Effects of Low-Level Air Pollution: A Study in Europe
GBD	Global Burden of Disease study
HRAPIE	Health Risks of Air Pollution In Europe
IRCEL-CELINE	Belgian Interregional Environment Agency
NO₂	Nitrogen dioxide
O₃	Ozone
PM	Particulate matter
RR	Relative risk
TMREL	Theoretical minimum risk exposure level
VITO	Vlaamse Instelling voor Technologisch Onderzoek
WHO	World Health Organisation

INTRODUCTION

In June 2023, Sciensano organised a technical workshop on the topic of air quality attributable burden of disease, inviting several research groups who are active in this domain in Belgium and its regions. One of the outcomes of this discussion was the willingness to cocreate a document that compares the methodological choices of ongoing projects that calculate the burden of mortality or morbidity attributable to air pollution.

A recent study in Germany (Tobollik et al., 2022) highlights the impact of methodological choices on the reported burden, leading to varying estimates and decreasing trust of policy makers and the general public. The main focus is on the selection of the concentration-response function, as this step has the largest impact on the final estimate. Additionally, the concentration-response function is the largest contributor the overall uncertainty on attributable burden figures, and largely explains the wide confidence interval on the central estimate.

The main purpose of this report is to act as a reference point for explaining differences in estimates published by the different institutions in Belgium and its regions. It aims to offer methodological transparency to researchers, stakeholders and the wider public as to how attributable burden figures are obtained and why estimates might differ substantially depending on the publication and the publication date. This report may also be updated at regular times seeing the constant evolution of new insights in the air pollution domain.

First, a background section provides a brief overview of the concentration-response functions available, focusing on recommendations by the WHO, and recent meta-analyses or important individual studies in the environmental epidemiologic literature. This part also covers methodological issues related to the use of concentration-response functions for attributable burden calculations, such as exposure thresholds, stratification and subgroup analyses. A detailed comparison of the available concentration-response functions for particulate matter and nitrogen dioxide, two 'classic' air pollutants, is added as an annex.

Subsequently, the varying approaches of existing research projects are outlined in a chapter on methodologies. Attention mainly goes to ongoing initiatives that routinely publish air pollution burden estimates or interactive tools to generate such estimates based on user input, with the primary objective of supporting policymakers with reliable scientific figures. This overview includes the selection of the concentration-response function and related choices, such as the inclusion of a cut-off and stratified or subgroup burden calculations.

Finally, the results of a sensitivity analysis are presented that quantify the impact of applying different concentration-response functions and the introduction of exposure thresholds. The analysis was carried out for all-cause mortality attributable particulate matter. Comparison of the results obtained under different scenario's sheds light on the extent to which estimates can differ depending on methodological choices. The sensitivity analysis demonstrated that the choice of the concentration-response function, and the implementation of an exposure threshold, have a significant impact on the final attributable burden estimate.

BACKGROUND

1. Concentration-response functions

A **concentration-response function** (CRF) is a statistical relationship that translates the pollutant concentration a population is exposed to into the risk of an associated health outcome. At any level of population exposure, the CRF of a given stressor-outcome pair returns the **relative risk** (RR) – or another effect measure like the odds ratio or hazard ratio – of the outcome occurring, which could be fatal (e.g. respiratory mortality) or non-fatal (e.g., incidence of ischaemic heart disease). The CRF can be a complex curve, but in air pollution burden of disease studies, it is common to approximate this with a relationship where the RR increases proportionally with a linear exposure increment.

In the **comparative risk assessment** (CRA) framework, selecting an exposure-response function is one of the crucial steps in calculating the burden attributable to risk factors (Plass et al., 2022). CRFs are sourced from the epidemiologic literature, where the relationship between exposure and relative risk is derived in longitudinal (e.g., cohort, case-control), cross-sectional or ecological studies. Longitudinal cohort studies are seen as the golden standard to derive CRFs. Alternatively, the CRF can be meta-analytic, meaning that it is a pooled estimate of the results of multiple data sources, either analysed in the same study or collected in a systematic review. CRA then applies the CRF to the observed population exposure to air pollution, and determines the relative contribution of the risk factor to the disease burden by comparing the actual RR to a theoretical ('counterfactual') situation resulting from a different level of population exposure.

In 2013, the WHO Regional Office for Europe coordinated the project **Health Risks of Air Pollution In Europe** (HRAPIE) to support the **European Commission** (EC) with evidence-based advice on the health aspects of air pollution (WHO Regional Office for Europe, 2013). The main purpose of the initiative was to provide recommendations for CRFs to be included in cost-benefit analyses supporting the revision of the European Union's air quality policy. Included air pollutants are **particulate matter** (PM) and **nitrogen dioxide** (NO₂) and **ozone** (O₃), for a number of mortality and morbidity effects, including all-cause mortality, ischaemic heart disease, stroke, chronic obstructive pulmonary disease and lung cancer. Pollutant-outcome pairs were divided into two groups:

- Group A: pollutant-outcome pairs for which enough data are available to enable reliable quantification of effects;
- Group B: pollutant-outcome pairs for which there is more uncertainty about the precision of the data used for quantification of effects.

HRAPIE's conclusions were supported by meta-analyses of the evidence available at the time. In addition, dedicated meta-analyses were performed within the frame of the project, as well as a causality assessment relating air pollutants to health outcomes (World Health Organization, 2013). The recommended CRFs were applied by the **European Environment Agency** (EEA) in their health risk assessments (González Ortiz et al., 2021; Soares et al., 2020, 2022) and formed the basis of the WHO's tool for health risk assessment, AirQ+. This led to HRAPIE CRFs being widely adopted by researchers and policymakers. HRAPIE was published in 2013, and cites studies dating back to 1987. However, since its publication, many new studies on the health effects of air pollution came out, meaning some risk-outcome pairs are missing, and several of the recommended CRFs are no longer up-to-date. At the time of writing, a new systematic review to support a revision of HRAPIE has started.

Since HRAPIE, several new CRFs based on more actualised evidence became available. One example are the air pollution CRFs used in the **Global Burden of Disease Study 2019** (GBD 2019). The Global Burden of disease initiative 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 most recent iteration of the study (Murray et al., 2020) examines 87 behavioral, environmental/occupational and metabolic risk factors, among which are indoor and ambient PM_{2.5} and ambient O₃ pollution. For these pollutants, the GBD derives its own CRFs by fitting a non-linear function using cubic splines on data from studies collected in a review. For PM_{2.5}, multiple outcomes are quantified, many of which overlap with those included in HRAPIE. Included in the PM_{2.5} model are RR estimates (for both ambient and indoor air pollution) from 200 studies with data from 40 countries. For O₃, only COPD mortality is considered, with a model fit to results from 5 studies from 3 countries.

In 2021, the WHO published a revision of the global **Air Quality Guidelines** (AQGs), aimed at protecting and improving public health by providing quantitative health-based recommendations for air quality management (World Health Organization, 2021). These levels are derived for each risk-outcome pair that is deemed critical by the guideline development group, composed of experts and stakeholders, with the help of CRFs. The CRFs are linear RRs resulting from meta-analyses commissioned by the WHO for among others long-term exposure to PM (Chen & Hoek, 2020), NO₂ and O₃ (Huangfu & Atkinson, 2020) related to all-cause and cause specific mortality. The study for PM extracted data from 107 articles and the study on NO₂ and O₃ relied on data from 46 papers. The EEA, in their latest air pollution health impact assessment (Soares et al., 2022) adopted the AQG CRFs to quantify premature mortality due to PM_{2.5}, NO₂, and O₃ exposure. The new CRFs are also being utilized in EU policy research, including the Clean Air Outlook (Zbigniew et al., 2022) and the research supporting the proposal for the new Ambient Air Quality Directive (European Commission. Directorate General for Environment., 2022).

A final significant initiative concerns the **Effects of Low-Level Air Pollution: A Study in Europe** (ELAPSE), funded by the Health Effects Institute (Brunekreef et al., 2021). The research examines health effects at low exposure levels, which makes it especially relevant in high-income countries where concentrations are generally lower. In addition, the air pollution mixture in Europe may also differ compared to other regions. ELAPSE investigates various mortality and morbidity outcomes related to PM_{2.5}, BC, NO₂, and O₃ in 22 European cohorts. Although it is a single study, ELAPSE can draw from an extensive database:

- 7 administrative cohorts: 325,367 participants (47,131 deaths). This includes a Belgian cohort.
- 15 conventional cohorts: 28,153,138 participants (3,593,741 deaths)

The administrative cohorts are obtained by linking different administrative databases including a census, a population registry, and death registries. The conventional cohorts are those of the ESCAPE study (European Study of Cohorts for Air Pollution Effects). Both cohorts are studied independently because of their qualitative and quantitative differences. Relying on CRFs from a single study offers advantages over the results of a meta-analysis:

- As population exposure and outcome definition are performed uniformly, there is less heterogeneity on the effect estimate
- The shape of CRF is available, instead of just a linear approximation
- Co-pollutant models can be included, that estimate the health effect of one pollutant taking into account the influence of one or multiple other pollutants

As ELAPSE was published in the same year as the WHO's AQGs, the results are not integrated in the derivation of the AQG values. In a proposal issued in the year subsequent to the publication of ELAPSE, some of its authors argue to integrate the results for PM_{2.5} and NO₂ into the health impact assessments and cost-benefit analyses that aim to inform the revision of the EU Ambient Air Quality Directive

(Brunekreef et al., 2022). They recommend to use CRFs resulting from the pooling of the administrative and conventional cohorts.

A more detailed discussion on the methodological differences between HRAPIE, WHO AQGs and ELAPSE for NO₂ and PM_{2.5} CRFs is provided in the annex.

2. Exposure cut-off

An exposure cut-off corresponds to a pollution threshold below which no health effects are expected to occur on a population level. As observations generally become more scarce at the extremes of the exposure spectrum, the uncertainty on the effect size is substantial for low pollutant concentrations. The questions on the existence and value of a 'safe' pollution level are thus not settled, and the implementation of a cut-off exposure in attributable burden calculations is therefore debated.

In the CRA framework, setting the exposure cut-off is closely related to defining the **theoretical minimum risk exposure level** (TMREL), the level of population exposure that corresponds to no increased risk (i.e., a RR equal to 1). If an exposure threshold is adopted in the derivation of the attributable burden, the TMREL can be defined as lying anywhere between zero concentration and the value of the cut-off. If no threshold is adopted, the TMREL is set at zero concentration, and effects are attributed all the way down to the lowest values of exposure. As the discussion is limited to long-term effects, the thresholds are expressed in terms of annual mean concentrations (except O₃, see below).

Given the lack of a definite answer to the exposure threshold question, two types of reasoning are possible with regard to a cut-off in burden calculations. The first type says that, since there is at present no evidence for a threshold, no cut-off value should be implemented. In doing so you are not accounting for health effects below a certain pollution level, and as such part of the disease burden might not be included in the attribution. 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).

A second possible reasoning says that, because of the lack of evidence of harmful effects at low concentrations, extrapolating the risk function down to zero exposure brings additional uncertainty to the burden estimate. Therefore, it is advised to instate a lower boundary in the concentration range and only attribute effects above this level of population exposure. The result can be viewed as a conservative estimate. A common choice for the cut-off value is the minimum, or a percentile in the low exposure extreme, of the concentrations measured in the study where the CRF is sourced from.

In HRAPIE, no threshold is recommended for the quantification of the burden attributable to long-term PM_{2.5} exposure. For long-term NO₂ mortality, approached death from all causes, a cut-off at 20 µg/m³ is advised. The reason is that in the studies considered at the time to derive the CRF, no statistically significant relationship was found below this level. Given the current evidence of adverse effects well below 20 µg/m³ of NO₂, this cut-off should be considered outdated. For long-term O₃ respiratory mortality, 35 ppb (70 µg/m³) is recommended as counterfactual concentration. The rationale here is that the O₃ exposure is measured as the peak season (April–September) average of daily maximum 8-hour mean O₃ concentration, which rarely drops below 35 ppb in value.

The GBD 2019 uses exposure thresholds in their calculations, but instead of a fixed cut-off, a random value is drawn from a distribution to reflect the uncertainty surrounding the level at which the scientific evidence is consistent with adverse effects. The distribution is defined as uniform with bounds equal to the minimum and 5th percentile concentrations observed in the underlying study (or the means thereof in case multiple studies are considered). For PM_{2.5}, the counterfactual concentration ranges from 2.4 to 5.9 µg/m³, and for O₃ from 29.1 to 35.7 in ppb.

Another option is to use the WHO's AQGs as counterfactual concentrations. A long-term AQG level is defined as the lowest exposure level above which the guideline development group is confident that there is an increase in adverse health effects, which makes it an obvious choice for the cut-off value. As there still might be harmful effects at concentrations below the recommended levels, that have as of yet remained undetected, a cut-off equal to half the AQG value is sometimes chosen by means of compromise.

One of the conclusions of ELAPSE is that the study shows no evidence for a level of exposure below which no association with the health outcomes is found. It is stated that a possible explanation is the large difference in individual sensitivity within the population and the absence of a sharp threshold within individuals.

3. Stratification and subgroups

Stratification refers to dividing the population into regular segments and performing exposure assessment and burden calculations separately, with a CRF specific for each segment. The underlying rationale is that risk factors can differentially impact health, based on the structure of the population. The most typical stratifications are those based on age (e.g., 5 year intervals starting at age 0) and sex (i.e., male versus female). Aside from regular stratification, a subgroup analysis is also a common approach. In this case, the included population is limited to a certain demographic depending on the outcome considered (e.g., low birth weight is limited to newborns, testicular cancer is limited to adult males). In the context research into the health effects of air pollution, stratification is rarely applied, while subgroup analyses are mostly related to age limits.

In HRAPIE, for the quantification of all-cause mortality due to long-term PM_{2.5} exposure only the adult population (30+ years of age) is included, as most of the epidemiologic studies considered focus on this subgroup. For ischaemic heart disease and stroke mortality, HRAPIE recommends to make both general and age-specific calculations, as their review of the evidence showed that the risk of these outcomes declines with the logarithm of age. For long-term PM₁₀, there are some age-specific outcomes:

- Post-neonatal mortality: infants aged between 1 and 12 months
- Prevalence of bronchitis in children: age 6–12 (or 6–18) years
- Incidence of chronic bronchitis in adults: age 18+ years

As for all-cause and cause-specific mortality due to long-term NO₂, the CRFs in HRAPIE are only applicable to the adult population, and this for the same reason as PM_{2.5}. For respiratory mortality due to long-term O₃, again only adults (30+ years) are considered.

Congruent with HRAPIE, the GBD 2019 issues age group-stratified PM_{2.5} CRFs for stroke and ischaemic heart disease to account for evidence showing that relative risk of cardiovascular diseases decreases with age. For O₃, a single CRF is used to quantify COPD mortality for the general population. However, the next iteration of the GBD will not have subgroup-specific CRFs for the air pollutants. In case there are no significant age differences in the RR, it is warranted to use the general population CRF for separate age groups to obtain stratified estimates.

The WHO AQGs do not provide stratified CRFs, but do state that “differences in the population structure (age, health status), climate (temperature and humidity) and geography (altitude, different ecosystems) can have an impact on the prevalence, frequency and severity of effects and may modify the concentration–response relationships provided in these guidelines in their application to a particular population.”

The conventional and administrative cohorts studied in ELAPSE differ severely in age and sex structure, and only include adult subjects. ELAPSE examined effect modification due to age by subdividing the population into the elderly ($65 \geq$ years) and the rest (<65 years) and performing the analysis of health effects separately for the conventional cohorts. For natural mortality, they found the hazard ratio to be higher in the elderly population for $PM_{2.5}$ and lower for NO_2 , although the confidence intervals of $PM_{2.5}$ overlap. The only other significant age-related differences are found for $PM_{2.5}$ vs. acute coronary heart disease incidence and stroke incidence (higher risk for the elderly), contradicting the evidence cited by HRAPIE and GBD 2019 on cardiovascular risk decreasing with age.

RESEARCH PROJECTS

1. IRCEL-CELINE

At the behest of the Vlaamse Milieumaatschappij, the **Belgian Interregional Environment Agency** (IRCEL-CELINE) assesses population exposure to air pollution and resulting premature mortality in Flanders, Brussels and the Walloon Region. Estimates for the year 2021 -2023 are available for PM_{2.5}, NO₂ and O₃ ; the results are published online in the form of factsheets containing infographics (Vlaamse Milieumaatschappij, 2023). The CRFs used are the linear RRs used in the derivation of the WHO's AQGs, resulting from the systematic review and meta-analysis by (Chen & Hoek, 2020) and (Huangfu & Atkinson, 2020). In the calculation, an exposure threshold is used, equal to half of the AQG value for the pollutant: 2.5 µg/m³ for PM_{2.5}, 5 µg/m³ for NO₂ and 30 µg/m³ for O₃.

Table 1: The CRFs used by IRCEL-CELINE.

Pollutant	Outcome	CRF*	Threshold	Age	Source
PM2.5	All-cause mortality	1.08 (1.06 - 1.09)	2.5 µg/m ³	≥30	WHO AQGs
NO2	All-cause mortality	1.02 (1.01 - 1.04)	5 µg/m ³	≥30	WHO AQGs
O3	All-cause mortality	1.01 (1.00 - 1.02)	30 µg/m ³	≥30	WHO AQGs

* RR (95% CI) per increase of 10 µg/m³ in annual mean concentration for PM_{2.5} and NO₂, and in peak-season average of daily maximum 8-hour mean concentration for O₃.

2. VITO

2.1. HEALTHY LIFE YEARS LOST DUE TO PM

As part of a series on indicators related to the environment, Departement Omgeving publishes **disability-adjusted life years** (DALYs) for particulate matter (PM_{2.5} and PM₁₀), based on calculations performed by VITO (Departement Omgeving, 2023). The estimates receive annual updates, and the results (both DALYs and premature deaths) are visualised as a time series currently stretching from 2005 to 2021. For the most recent reference year, there is a breakdown of the DALYs into long-term versus short-term exposure, and for premature mortality (all cause years of life lost (YLLs)) versus various morbidity outcomes. Premature deaths and YLLs for PM_{2.5} are calculated for all causes, based on the relative risk from ELAPSE 2013 (pooled or admin) with an exposure threshold equal to half the AQG level. The CRFs for the non-fatal outcomes are to a large part sourced from HRAPIE, extended with relationships from more recent studies.

Table 2: The CRFs used by VITO for Departement Omgeving.

	Eindpunt	Leeftijd	blootstelling-effect	source
PM2.5	Mortaliteit	>30	RR 1.118 per 10 µg/m ³ en drempel 2.5 µg/m ³	ELAPSE
	Dagen verminderde activiteit	15-64j	RR 1.047 per µg/m ³	HRAPIE 2013
	Absenteïsme werk	15-64j	RR 1.046 per 10 µg/m ³	HRAPIE 2013
	Hospitalisaties ademhalingsproblemen	Gehele	RR 1.019 per 10 µg/m ³	HRAPIE 2013
	Hospitalisaties hartproblemen	Gehele	RR 1.0091 per 10 µg/m ³	HRAPIE 2013
	astma kinderen, incidentie	0-18j	RR 1.03 per µg/m ³	Khreis et al. 2017
	vroeggeboorte	borelingen	RR 1.14 per 10 µg/m ³	Lamichhane et al., 2015
	diabetes mellitus type 2, incidentie	>19j	RR 1.10 per 10 µg/m ³	Yang et al. 2020
	longkanker incidentie	<29j	RR 1.08 per 10 µg/m ³	Huang et al. 2017
	COPD	30-99j	RR 1.18 per 10 µg/m ³	Park et al. 2021
	Myocardinfarct	30-99	RR 1.08 per 10 µg/m ³	Alexeef et al. 2012
	beroerte	30-99j	RR 1.13 per 10 µg/m ³	Alexeef et al. 2012
PM10	Mortaliteit baby's	1 maand-1 jaar	RR 1.04 per 10 µg/m ³	HRAPIE 2013
	Chronische bronchitis, incidentie	>18j	RR 1.12 per 10 µg/m ³	HRAPIE 2013
	bronchitis, prevalentie	6-12/18 jaar	RR 1.08 per 10 µg/m ³	HRAPIE 2013
	hypertensie, incidentie	>29j	RR 1.21 per 10 µg/m ³	Zhao et al. 2022
	dagen met astmasymptomen bij astmatische kinderen	5-14j	RR 1.028 per 10 µg/m ³	HRAPIE 2013
	dagen met astmasymptomen bij astmatische volwassenen	>20j	RR 1.028 per 10 µg/m ³	HRAPIE 2013

2.2. ENVIRONMENT HEALTH IMPACT SIMULATOR

As commissioned by Departement Zorg, VITO maps the health effects and related costs of air pollution and environmental noise at the local level. The results are disseminated through an online interactive dashboard: the Environment Health Impact Simulator (E-HIS) (Departement Zorg, n.d.). The air pollutants considered are PM₁₀, PM_{2.5}, NO₂ and O₃. For mortality, the outcomes are presented in attributable deaths and YLLs. The CRFs used for PM_{2.5} and O₃ and all-cause mortality are from HRAPIE 2013, and for NO₂ mortality estimates are made available for both HRAPIE 2013 and COMEAP 2018 (Committee on the Medical Effects of Air Pollutants, 2018). An exposure threshold is included for NO₂, with a value of 10 µg/m³ for the CRF from HRAPIE and 5 µg/m³ for COMEAP. For the morbidity effects, E-HIS relies on CRFs from various meta-analyses identified in a systematic review. No cut-offs are used to quantify the morbidity impacts (Hooyberghs et al., 2021).

The CRFs used in E-HIS are currently being updated. Relative risks are taken from the most recent review of the WHO, while the counterfactual value will be set to the updated WHO guidelines. In the near future, also the CRFs for morbidity will be updated.

Table 3: Risk-outcome pairs included in E-HIS*.

	Gezondheidseffect	Doelgroep	Polluent	Type
Ademhalings-systeem	Astma	Volwassenen 30 - 75 jaar	NO ₂ + PM	primair
	Astma	Kinderen 0-18 jaar	NO ₂ + PM	primair
	Longontsteking	Kinderen 0-3 jaar	NO ₂ +PM	secundair
	Middenoorontsteking	Kinderen 0-3 jaar	NO ₂	secundair
	COPD	Volwassenen	NO ₂	primair
	Lage luchtweginfecties	Kinderen 0-2 jaar	PM	primair
	Bronchitis	Kinderen 6-12/18 jaar	PM	secundair
	Chronische bronchitis	Volwassenen (> 18 jaar)	PM	secundair
Cardiovasculair systeem	Hypertensie	Volwassenen ≥ 30jaar	NO ₂ +PM	secundair / primair
	Hartfalen	Volwassenen 40-89 jaar	NO ₂	primair
	Beroerte	Volwassenen 40-89 jaar	NO ₂ + PM	secundair / primair
Geboorte en ontwikkeling	Myocardinfarct	Volwassenen	PM	primair
	Parkinson	Volwassenen	NO ₂	secundair
	Laag geboortegewicht	Pasgeborenen	NO ₂ + PM	primair
Kanker	Vroeggeboorte	Borelingen	PM	primair
	Longkanker	Volwassenen	NO ₂ + PM	secundair / primair
Diabetes	Diabetes mellitus type 2	Volwassenen	NO ₂ + PM	primair

* The full list of all CRFs reviewed in the frame of the E-HIS is extensive and can be consulted in Hooyberghs et al. (2021).

3. Sciensano

In partnership with Departement Zorg, Sciensano started 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 CRA, where the disease burden is quantified as DALYs. As in the E-HIS, estimates are rendered at the local level of the statistical sector. Given the extensive list of potential environmental risk-outcome pairs, a set of priorities was defined in terms of environmental stressors and health outcomes. The risk factors that will be studied first 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.

With regard to air quality, EBoD-FL estimates the burden of PM_{2.5}, PM₁₀, NO₂ and O₃ using the linear RRs by (Chen & Hoek, 2020) and (Huangfu & Atkinson, 2020), cited in the WHO's AQGs. CRFs recommended by the WHO can be seen as reflecting an international consensus, and are likely to be widely adopted by researchers. It was decided not to introduce exposure thresholds in the calculations, following the first type of reasoning outlined in part 2 of the background section. Stratified estimates are obtained by applying the general RRs to the sex and age subgroups.

Table 4: CRFs used by Sciensano in EBoD-FL.

Pollutant	Outcome	CRF*	Threshold	Age	Source
PM _{2.5}	All-cause mortality	1.08 (1.06, 1.09)	None	All	WHO AQG
PM _{2.5}	Ischemic heart disease mortality	1.16 (1.10, 1.21)	None	All	WHO AQG
PM _{2.5}	Stroke mortality	1.11 (1.04, 1.18)	None	All	WHO AQG
PM _{2.5}	Chronic obstructive pulmonary disease mortality	1.11 (1.05, 1.17)	None	All	WHO AQG
PM _{2.5}	Acute lower respiratory infection mortality	1.16 (1.01, 1.34)	None	All	WHO AQG
NO ₂	All-cause mortality	1.02 (1.01, 1.04)	None	All	WHO AQG
NO ₂	Chronic obstructive pulmonary disease mortality	1.03 (1.01, 1.04)	None	All	WHO AQG
NO ₂	Acute lower respiratory infection mortality	1.06 (1.02, 1.10)	None	All	WHO AQG
O ₃	All-cause mortality	1.01 (1.00, 1.02)	None	All	WHO AQG

* RR (95% CI) per increase of 10 µg/m³ in annual mean concentration for PM_{2.5} and NO₂, and in peak-season average of daily maximum 8-hour mean concentration for O₃.

SENSITIVITY ANALYSIS

1. Method

As an illustration of the impact of methodological choices on the final attributable burden estimate, all-cause mortality due to long-term exposure to fine particulate matter (PM_{2.5}) in Belgium was calculated under different scenario's. The purpose is to demonstrate the effect of selecting a CRF and of implementing an exposure cut-off on the estimated attributable mortality. The used data are from the year 2021:

- Exposure is calculated as a population-weighted average concentration based on the RIO air quality model provided by IRCEL-CELINE (IRCEL-CELINE, n.d.), and population by Belgian statistical sector provided by Statbel (Statbel, n.d.).
- Total mortality in Belgium (112,291 deaths) was used as baseline burden, as reported by Statbel.

The framework for calculating attributable burden used in the sensitivity analysis is CRA. In CRA, the population attributable fraction (PAF) is calculated based on an estimate of population exposure to the risk factor, in this case particulate matter air pollution. In a first step, the relative risk (RR) of the outcome (here all-cause mortality) is calculated with a concentration-response function:

$$RR(C) = \exp(\ln(RR_{10})/10 \times (C - TH)) \quad (\text{eq. 1})$$

In equation 1, C is the population-weighted average concentration, RR_{10} is the increase in relative risk per 10 $\mu\text{g}/\text{m}^3$ increase in concentration, and TH is the concentration threshold. Based on the value of $RR(C)$, the population attributable fraction can be calculated:

$$PAF = \frac{RR(C) - 1}{RR(C)} \quad (\text{eq. 2})$$

The attributable burden is then calculated by multiplying the PAF with the baseline burden (here total mortality).

In the sensitivity analysis, the burden attributable to PM_{2.5} is calculated according to 9 different scenarios (Table 5). The PAF is calculated with the CRFs of HRAPIE, the WHO's AQGs and ELAPSE. For each CRF, the PAF is calculated with no exposure threshold, with a threshold set to half value of the WHO's AQG for PM_{2.5} (2.5 $\mu\text{g}/\text{m}^3$) and set to the full value of the AQG (5 $\mu\text{g}/\text{m}^3$). The sensitivity of the calculation under the different scenarios is visualised in a bar plot, showing central estimates as well as 95% confidence intervals.

Table 5: Scenarios of PM_{2.5}-attributable burden calculation used in the sensitivity analysis.

Scenario	RR (95% CI) per 10 µg/m ³	Exposure threshold
HRAPIE	1.062 (1.040 - 1.083)	0 µg/m ³
HRAPIE>2.5	1.062 (1.040 - 1.083)	2.5 µg/m ³
HRAPIE>5.0	1.062 (1.040 - 1.083)	5.0 µg/m ³
WHO AQG	1.080 (1.060 - 1.090)	0 µg/m ³
WHO AQG>2.5	1.080 (1.060 - 1.090)	2.5 µg/m ³
WHO AQG>5.0	1.080 (1.060 - 1.090)	5.0 µg/m ³
ELAPSE	1.118 (1.060 - 1.179)	0 µg/m ³
ELAPSE>2.5	1.118 (1.060 - 1.179)	2.5 µg/m ³
ELAPSE>5.0	1.118 (1.060 - 1.179)	5.0 µg/m ³

2. Results

The population-weighted average concentration is estimated at 10.19 µg/m³. Figure 1 visualises the number of deaths attributable to particulate matter under the different scenarios. The choice of the CRF (represented by the colours of the bars) has a large impact on the number of attributable deaths. Comparing estimates where no exposure cut-off was instated, the CRF recommended by HRAPIE attributes 6679 (95% CI: 4401 - 8767) deaths to PM_{2.5}. The CRF from the WHO's AQGs leads to an estimate of 8473 (95% CI: 6476 - 9444) deaths, more than a quarter higher compared to the HRAPIE estimate. Using the CRF from ELAPSE, the attributable number of deaths is estimated at 12,070 (95% CI: 6476 - 17,353), an increase of 80% compared to HRAPIE. As the RR in the WHO's AQGs is higher compared to HRAPIE, and still higher in ELAPSE, this increase in attributable deaths was to be expected. A higher RR means that the risk increases steeper with exposure, and as a result leads to a higher estimate of the PAF. Although the difference in RR across the sources appears limited (in the order of 2 to 6 percentage points), the estimated attributable deaths increases sharply. This indicates that the final estimate is highly sensitive to the choice of the CRF.

Aside from the CRF choice, the impact of setting an exposure threshold can be examined as well in Figure 1. Implementing an exposure cut-off leads to lower estimates, in a way that is proportional to the value of the threshold. This is to be expected, given that adverse health effects are attributed in excess of the cut-off value, and a higher value means that a given exposure level is considered less harmful. The impact of instating an exposure cut-off is remarkable: regardless of the CRF applied, a threshold equal to half the AQG value leads to approximately a quarter fewer attributable deaths, while a threshold equal to the AQG value almost halves the number of attributable deaths. As was the case for the CRF choice, the final estimate is highly sensitive to the value of the exposure threshold, with no clear indication as to which methodological choice has the largest impact.

To put the sensitivity of the estimates to the CRF and exposure threshold into perspective, the 95% confidence intervals are included in Figure 1. For all estimates, the CI can be considered wide relative to the central value. This is especially the case for ELAPSE: although the estimated attributable burden is highest using this CRF, the estimates are also the most imprecise because of the wide CI on the corresponding RR. Although the CRF choice appears to have a large impact on the attributable burden, the difference is insignificant in the sense that the CIs of corresponding (same exposure threshold) estimates overlap. In the case of HRAPIE and ELAPSE, the same is true for the effect of an exposure threshold. For the WHO CRF on the other hand, the estimates are more precise, leading to a significant decrease in estimated attributable mortality when instating an 5 µg/m³ exposure cut-off compared to no threshold.

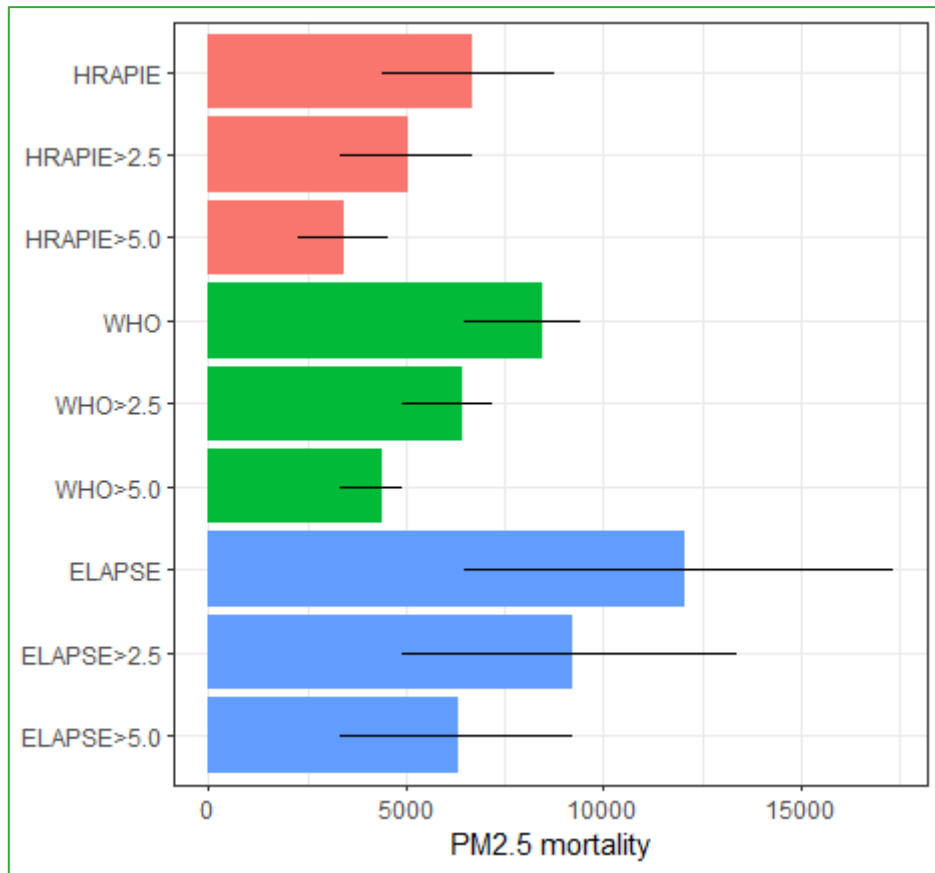


Figure 1: The number of all-cause deaths attributable to particulate matter (PM_{2.5}) in Belgium in 2021, calculated under different scenarios.

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ANNEXES

DETAILED COMPARISON OF CONCENTRATION-RESPONSE FUNCTIONS

1. Introduction

To choose from multiple available concentration-response functions for air pollutants such as PM_{2.5} and NO₂, ensuring a robust scientific comparison of estimates requires a thorough consideration of several critical aspects. These encompass the resolution and quality of exposure assessment, which have significantly evolved over time. While initial estimates employed air quality models with resolutions like 4 x 4 km or 1 x 1 km, often focused on background concentrations and not considering locally elevated concentrations, recent advancements have yielded high-resolution models that offer more detailed and accurate exposure estimations. Past models often underestimated pollution near sources like transportation due to their focus on background concentrations, omitting local emissions. Moreover, the characteristics of study participants, ranging from representative populations to specific patient cohorts, exert a substantial influence on the results' generalizability. The geographical scope of the study also holds significance, given the diverse sources of PM_{2.5} and NO₂ across regions. For instance, variations in chemical composition dictate dose-response relationships, particularly for PM_{2.5}. Additionally, the temporal dimension matters; a rapid surge in studies during the last decade underscores the dynamic landscape of research, compared to earlier periods. The consideration of adjustments for multi-pollutant exposures, the linearity of dose-response relationships, and other methodological nuances further contribute to the comprehensive evaluation of exposure-response functions. By addressing these multifaceted elements, the accuracy and applicability of estimates for informed policy decisions and public health interventions can be enhanced.

Table 6: NO₂: comparative characteristics of the three main meta-analysis used.

HRAPIE, 2013	COMEAP, 2018 - Huangfu & Atkinson, 2020	ELAPSE 2021
1.055 [1.031 - 1.080] per 10 µg/m ³ (from 20 µg/m ³) NO ₂	1.02 [1.01 - 1.03] per 10 µg/m ³ NO ₂	1.045 [1.026 - 1.065] per 10 µg/m ³ NO ₂

Table 7: PM_{2.5}: comparative characteristics of the three main meta-analysis used.

HRAPIE, 2013	Chen & Hoek, 2020	ELAPSE 2021
1.062 [1.040 - 1.083] per 10 µg/m ³ PM _{2.5}	1.08 [1.06 - 1.09] per 10 µg/m ³	1.118 [1.060 - 1.179] per 10 µg/m ³ NO ₂

2. Exposure assessment

Initial estimations utilised air quality models with resolutions such as 4 x 4 km or 1 x 1 km, often concentrating on background concentrations and disregarding locally heightened levels. However, recent progress has led to the development of high-resolution models that provide more detailed and precise exposure assessments. Earlier models frequently underestimated pollution near sources like transportation due to their exclusive focus on background concentrations, neglecting emissions from local sources.

In this context, the study by Huangfu & Atkinson (2020) and COMEAP (2018) may introduce certain concerns, given the inconsistent and diverse exposure assessments across the studies included in their

analysis. For instance, Abbey et al. (1999) is encompassed in the pooled estimate, where exposure assessment relies on interpolations from a limited number of measurement stations, located up to 50 km away from individuals' residences. Additionally, this interpolation lacks the utilisation of Land Use Regression, resulting in unreliable and unsatisfactory exposure evaluations. Notably, Abbey et al.'s (1999) study holds substantial weight in the pooled estimate, raising questions about the validity of exposure estimates in the Huangfu & Atkinson (2020) and COMEAP (2018) meta-analysis. Presently, Land Use Regression interpolation is a common practice in air pollution modelling, markedly improving accuracy compared to the methods employed in the Abbey et al. (1999) study. Furthermore, this approach primarily addresses background concentrations and fails to account for local hotspots, primarily associated with traffic-related emissions. Contemporary advancements, exemplified by models like the Belgian ATMO-STREET, encompass emissions and street canyon modelling, yielding significant enhancements in exposure assessment. Given the current evidence, the exposure assessment utilised in Abbey et al. (1999) is deemed inappropriate. Notably, while the Huangfu & Atkinson (2020) and COMEAP (2018) review has a more recent cut-off date (2015 vs. 2011) in comparison to the earlier HRAPIE study, certain studies included in the former analysis are older than any in the latter, due to different inclusion criteria.

The other studies for NO₂ (HRAPIE and ELAPSE) and all meta-analyses for PM_{2.5} also contain some level of heterogeneity in the exposure assessment techniques, however problematic outliers such as found in Huangfu & Atkinson, 2020 - COMEAP, 2018 are not found in those studies.

Table 8: NO₂: comparative characteristics of exposure assessment in the three main meta-analysis used.

HRAPIE, 2013	COMEAP, 2018 Huangfu & Atkinson, 2020	ELAPSE, 2021
Some heterogeneity, quality of exposure assessment considered as criteria to give weights to the different studies	High heterogeneity of exposure assessment. Varies from 50km interpolation (without land-use regression) to 100 meter resolution. Some studies with highly problematic exposure assessment receive high weights in the pooled calculation	Some heterogeneity. More recent studies included often have 100 or at least 1000m resolution. Overall higher resolution compared to earlier meta-analysis.

Table 9: PM_{2.5}: comparative characteristics of exposure assessment in the three main meta-analysis used.

HRAPIE, 2013	Chen & Hoek 2020	ELAPSE, 2021
Some heterogeneity, quality of exposure assessment considered as criteria to give weights to the different studies	Some heterogeneity, quality of exposure assessment considered as criteria to give weights to the different studies	Some heterogeneity. More recent studies included often have 100 or at least 1000m resolution. Overall higher resolution compared to earlier meta-analysis.

3. Geographical area

3.1. LINEARITY OF THE DOSE-RESPONSE RELATIONSHIP

Due to a dearth of studies examining the health ramifications of NO₂ levels below 20 µg/m³, an initial decision was made in 2013 by HRAPIE to utilise a 20 µg/m³ threshold for assessing the health consequences of NO₂ exposure. However, this approach was subsequently critiqued by Héroux et al. (2015). Their work highlighted that this threshold lacks scientific validity. Newer evidence, such as findings from the ELAPSE study – the largest investigation of low-level air pollution's effects in Europe

thus far – indicates that a significant correlation between NO₂ and mortality exists even at low concentrations. Interestingly, this association might even be more pronounced with lower concentrations, gradually diminishing as concentrations rise.

Furthermore, this underscores the hazard of employing meta-analyses that amalgamate various cohort studies from non-European regions. This is due to substantial differences in air pollutant concentrations and sources across these regions. For instance, the research by Abbey et al. (1999), included in COMEAP 2018, and the work by Huangfu and Atkinson (2020) encompassed areas with NO₂ annual mean concentrations exceeding 100 µg/m³ – a level far surpassing any observed average NO₂ concentration in Europe.

For PM_{2.5}, no thresholds were used in any meta-analysis.

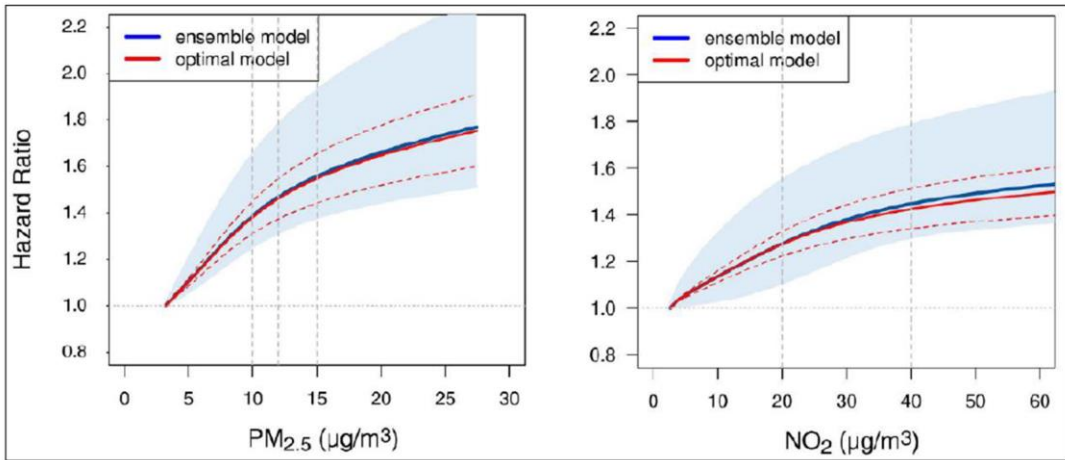


Figure 5: Exposure-response function for PM_{2.5} and NO₂ and total mortality from the ELAPSE pooled cohort (Brunekreef et al., 2021).

Table 10: NO₂: comparative characteristics of exposure assessment in the three main meta-analysis used.

HRAPIE, 2013	COMEAP, 2018 Huangfu & atkinson, 2020	ELAPSE, 2021
20 µg/m ³ NO ₂ threshold	no threshold	no threshold
	several studies contain unrealistic NO ₂ concentrations not observed in the Europe region, affecting dose-response relations	Focus on low levels of air pollution, ideally suited for the Europe region.

Table 11: PM_{2.5}: comparative characteristics of exposure assessment in the three main meta-analysis used.

HRAPIE, 2013	Chen & Hoek, 2020	ELAPSE, 2021
No threshold	No threshold	No threshold
	Several studies (especially from Asia - China) contain unrealistic NO ₂ concentrations not observed in the Europe region, affecting dose-response relations	

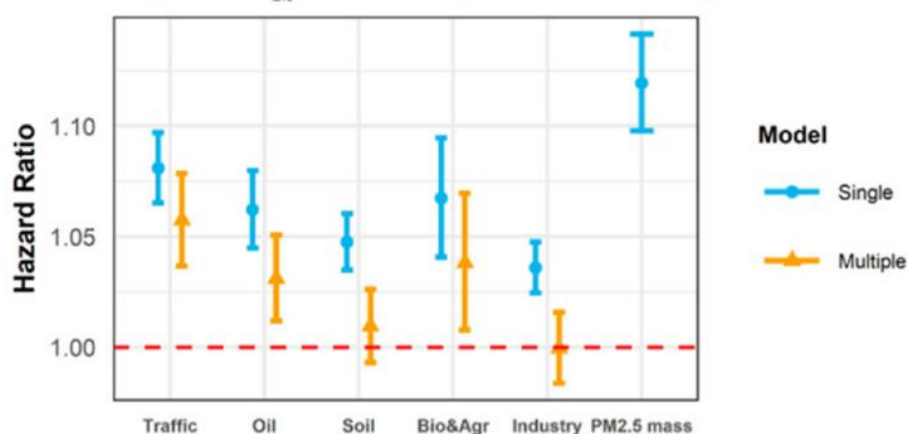
3.2. CHEMICAL COMPOSITION OF THE DIFFERENT POLLUTANTS IN DIFFERENT PARTS OF THE WORLD

The composition of particulate matter stands as a pivotal determinant in shaping its associated health effects. Notably, the heightened relative risk linked to traffic-related PM_{2.5} underscores this relationship, driven in part by constituents like Black carbon—a hazardous component prominently found within PM_{2.5} emissions from traffic sources. This phenomenon is highlighted in a study conducted by Chen et al. (2022), which reveals the increased relative risk associated with traffic-related PM_{2.5} due to the presence of Black carbon and other detrimental components. Notably, this bears vital implications, particularly within the European context. The ELAPSE meta-analysis (Hoffmann et al., 2022), with its specific focus on the Europe Region and low-level air pollution, underscores the region-specific dynamics. A salient example is the distinctive nature of PM_{2.5} in Europe compared to other regions like Africa. Europe's PM_{2.5} levels differ significantly in magnitude and composition, with a relatively higher share of traffic-related PM_{2.5} and a lesser proportion attributed to industrial sources. This divergence in chemical composition underscores the importance of considering regional nuances when assessing the health implications of PM_{2.5} exposure.

Abstract

Go to: ▶

Hazard ratios and 95% confidence intervals per IQR increase in source-specific PM_{2.5} concentrations and natural mortality



Study: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9261290/#!po=30.1020>

Table 12: NO₂: comparative characteristics of exposure assessment in the three main meta-analysis used.

HRAPIE, 2013	COMEAP, 2018 Huangfu & atkinson, 2020	ELAPSE, 2021
Europe & North-America	Europe, America, Asia	Europe

Table 13: PM_{2.5}: comparative characteristics of exposure assessment in the three main meta-analysis used.

HRAPIE, 2013	Chen & Hoek, 2020	ELAPSE, 2021
Europe, North-America	Europe, North-America, Asia	Europe

4. Population covered

Including studies focusing on patient cohorts when establishing dose-response relationships between PM_{2.5}, NO₂, and mortality/morbidity poses limitations due to potential confounding factors arising from the pre-existing health conditions of the participants. In an already sick population, the intricate interplay between disease status and exposure can obscure the true association between air pollutants and

health outcomes. Health conditions may influence individual susceptibility and modify the response to pollutants, leading to biased or non-representative estimates of the exposure-response relationship. To derive more accurate and generalizable insights, it is essential to prioritise healthy or representative populations in such studies. This is also discussed in the meta-analysis of Chen & Hoek (2020) PM_{2.5} which also concluded patient groups are very different from the general population and therefore unsuitable to include in the main meta-analysis.

In this regard, the Huangfu & Atkinson, 2020 - COMEAP 2018 review is concerning as this study includes several studies in their meta-analysis that contain a patient cohort instead of a healthy or representative population. The appendix analysis (appendix figure B.2.) of the Huangfu & Atkinson (2020) meta-analysis also demonstrate the different dose-response relationships differing between patient groups and healthy cohorts, with the patient cohorts having a pooled RR of 1.01 (95% CI: 0.98 - 1.04) and the healthy cohorts an RR of 1.02 (95% CI: 1.01 - 1.04) per 10 µg/m³ increase in NO₂. The HRAPIE, 2013 meta-review contained one patient cohort. The ELAPSE meta-analysis for both PM_{2.5} and NO₂ and the Chen & Hoek (2020) meta-analyses for PM_{2.5} only contained healthy or representative cohorts.

Table 14: NO₂: comparative characteristics of exposure assessment in the three main meta-analysis used.

HRAPIE, 2013		COMEAP, 2018 Huangfu & Atkinson, 2020	ELAPSE, 2021
1 patient cohort		Several patient cohorts	Only healthy or representative
Other studies: Healthy	/	included in the study.	cohorts
Representative		About 1/3th of the	
		included studies are	
		patient cohorts.	

Table 15: PM_{2.5}: comparative characteristics of exposure assessment in the three main meta-analysis used.

HRAPIE, 2013		CHEN & HOEK, 2020	ELAPSE, 2021
1 patient cohort		Only healthy or representative	Only healthy or representative
Other studies: Healthy	/	cohorts	cohorts
Representative			

5. Correction for covariates and confounding factors

Air pollution and confounding factors can be correlated. In Urban areas, hotspots of pollution tend more often to coincide with people living in deprived (low income, suboptimal housing) conditions (Milojevic et al., 2017). Similarly, Cities and urban areas, which are often characterised by a high burden of air pollution, have on average also younger and more highly educated residents, who tend to have a lower smoking prevalence compared to the general population, potentially offsetting the increase in all-cause mortality from environmental factors. In 2018, daily smoking prevalence in people without an educational degree was 29% while it was only 9% in people who followed tertiary education (Sciensano, n.d.; Theughels et al., 2021). Those matters show the importance of correcting for confounding factors in epidemiological studies.

In conclusion: For both NO₂ and PM_{2.5}, ELAPSE 2021 is the only meta-analysis rigorously adjusting for socio-economic factors, smoking and other confounders, as this was an inclusion criteria to include studies in the analysis (Hoffman et al, 2022).

Table 16: NO₂: comparative characteristics of exposure assessment in the three main meta-analysis used.

HRAPIE, 2013		COMEAP, 2018 Huangfu & atkinson, 2020	ELAPSE, 2021
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Contains several studies without adjustment for confounders such as smoking and socio-economic characteristics	Contains several studies without adjustment for confounders such as smoking and socio-economic characteristics	All estimates are adjusted for smoking and other important lifestyle and social factors.
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Table 17: PM_{2.5}: comparative characteristics of exposure assessment in the three main meta-analysis used.

HRAPIE, 2013	Chen & Hoek, 2020	ELAPSE, 2021
Contains several studies without adjustment for confounders such as smoking and socio-economic characteristics	Contains several studies without adjustment for confounders such as smoking and socio-economic characteristics	All estimates are adjusted for smoking and other important lifestyle and social factors.

6. Multi-pollutant models and adjusting for overlap between pollutants

Adjustments for other pollutants remains a difficult challenge and estimates on the percentage overlap between for example NO₂ and PM_{2.5} vary greatly from study to study, and there is no consensus estimate available.

Looking to cause-specific mortality, there are some recent advancements with many studies of the ELAPSE project diving into cause-specific mortality and morbidity including dose-response relationships where the different air pollutants including NO₂, PM_{2.5}, BC and O₃ are corrected for each other. For example, estimates of PM_{2.5} for cardiovascular mortality and adult asthma incidence were largely attenuated after correcting for NO₂, while inversely NO₂ estimates remained high and consistent after PM_{2.5} correction (Liu et al., 2021; Wolf et al., 2021).

Table 18: NO₂: comparative characteristics of exposure assessment in the three main meta-analysis used.

HRAPIE, 2013	COMEAP, 2018 Huangfu & atkinson, 2020	ELAPSE, 2021
All-cause mortality Suggest 0-33% reduction in NO ₂ effect to correct for overlap. Choice to reduce NO ₂ effect and leave PM _{2.5} intact is a bit arbitrary	All-cause mortality Limited overlap between NO ₂ and PM _{2.5} found in this study	All-cause mortality No formal correction in the meta-analysis. The 8 cohorts of the ELAPSE study itself contain both estimates for single-pollutant models and multiple-pollutants models where the pollutants are corrected for each other. Cause-specific mortality and morbidity: several recent studies contain both single-pollutant and adjusted multi-pollutant estimates

Table 19: PM_{2.5}: comparative characteristics of exposure assessment in the three main meta-analysis used.

HRAPIE, 2013	Chen & Hoek 2020	ELAPSE, 2021
All-cause mortality Suggest 0-33% reduction in NO ₂ effect to correct for overlap. Choice to reduce NO ₂ effect and leave PM _{2.5} intact is a	Not discussed? PM 2.5 not adjusted	All-cause mortality No formal correction in the meta-analysis. The 8 cohorts of the ELAPSE study itself contain both

bit arbitrary

estimates for single-pollutant models and multiple-pollutants models where the pollutants are corrected for each other.

Cause-specific mortality and morbidity:

several recent studies contain both single-pollutant and adjusted multi-pollutant estimates

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