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Evidence of effect and exposure-response functions for PM2.5 and NO2 linked to morbidity

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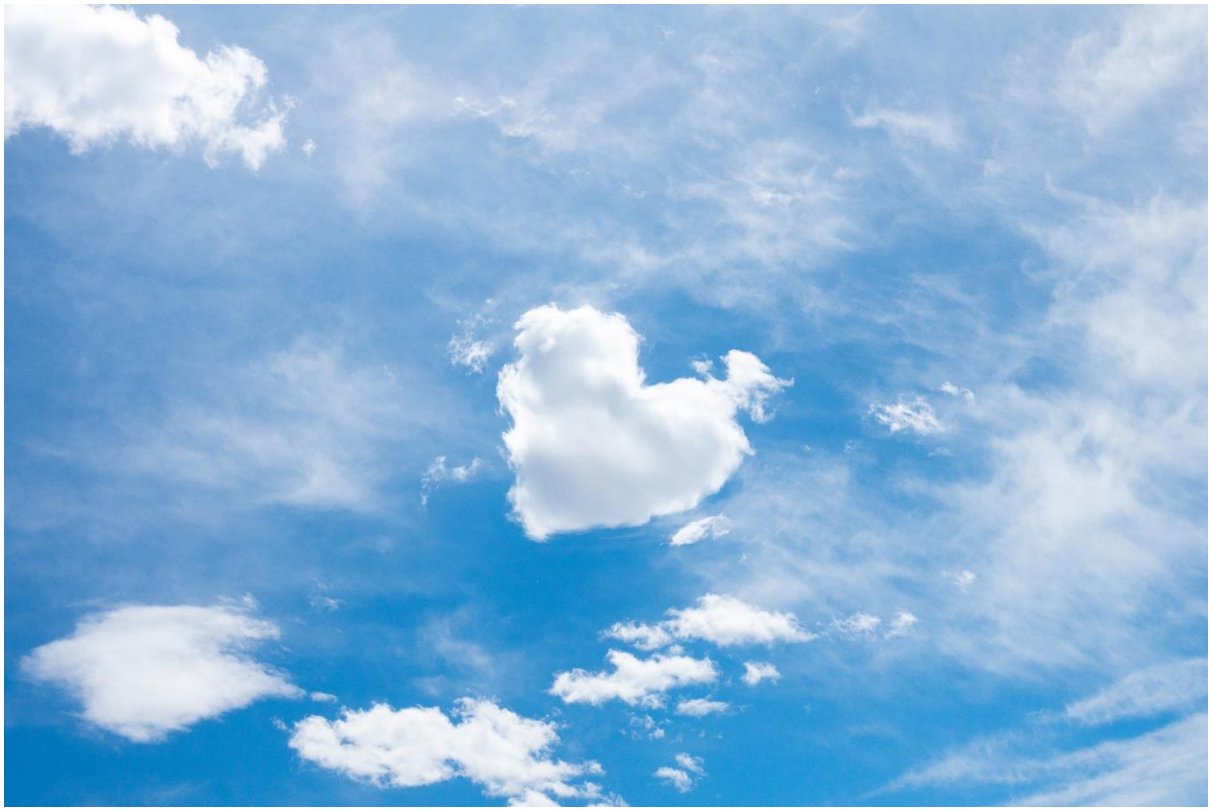

Contents

Overview

Aim

Health impact assessments (HIA) have largely focused on mortality; this report, therefore, examines and evaluates which morbidity impacts are appropriate to include in HIAs. The task was assigned by Swedish Environmental Protection Agency (EPA), and the original report (written in Swedish) was performed by Anna Oudin (AO), Erin Flanagan (EF), and Ebba Malmqvist (EM). The original report also includes a section on mortality conducted by Bertil Forsberg (BF), but this is not included here due to time constraints for translation. The outcomes to be evaluated were pre-defined by researchers AO, EM and BF during the first project meeting. Among adults, these were chronic obstructive pulmonary disease (COPD), cardiovascular diseases, including ischemic heart disease (IHD) and stroke, diabetes, dementia, cognitive decline. For outcomes during pregnancy and childhood, we included preeclampsia, gestational diabetes, low birth weight, premature births, lung function, asthma, bronchitis, infections, autism, cognition, and type 1 diabetes.

Method

Morbidity in adults

We have used the Integrated Science Assessment (ISA) from the United States (U.S.) EPA for particulate matter (PM) (EPA 2019), ozone (O3) (EPA 2020), and nitrogen oxides/dioxide (NO2/NOx) (EPA 2016). We have also added exposure-response functions (ER-functions) from the World Health Organization's (WHO) project "Health risks of air pollution in Europe" (HRAPIE) (WHO 2013, Héroux, Anderson et al. 2015). Additionally, more recently published review articles have been included for NO2/NOx exposure since the corresponding ISA evaluation was not as recent as the other assessments. The search criteria used is specified below.

COPD and respiratory diseases
Searches: "NO2 COPD review", "NOx COPD review", "NO2 bronchitis review", "NOx bronchitis review"

Cardiovascular diseases and diabetes
Searches: "NO2 cardiovascular disease review", "NOx cardiovascular disease review", "NO2 myocardial infarction review", "NO2 stroke review"

Dementia and cognitive decline
Searches: "NO2 dementia review", "NOx cognition review"

Morbidity during pregnancy and childhood

We began by investigating if the outcome-pollutant pairs were included in WHO's HRAPIE from 2013 (WHO 2013, Héroux, Anderson et al. 2015). We also investigated which outcomes were included in the 2016 Global Burden of Disease (GBD) (World Health Organization 2016) and in the Environmental Benefits Mapping and Analysis Program (BenMap) (Sacks, Lloyd et al. 2018). If an outcome was not included in WHO HRAPIE, we looked for evidence in the U.S. EPA's ISA for PM (EPA 2019), ozone (EPA 2020) and nitrogen dioxides (EPA 2016). The first

two are more recent than the ISA for nitrogen oxides. The methods utilized in the U.S. EPA's assessments include a thorough literature review of both the current epidemiological and toxicological evidence. Additionally, a review by Perera et al. 2019 (Perera, Ashrafi et al. 2019) investigating which child health outcomes can be relevant to include in a HIA was utilized. Their methods are similar to the U.S. EPA's ISAs, but toxicological evidence is not evaluated with the same weight. Perera et al. was based on a systematic review of studies published between 2000 and 2018 concerning PM with an aerodynamic diameter of less than 2.5 μm (PM2.5), NO2, polycyclic aromatic hydrocarbons (PAH), and PM with an aerodynamic diameter of less than 10 μm (PM10) exposure and premature birth, low birth weight, asthma, autism, attention deficit hyperactivity disorder (ADHD), and cognition. If evidence was found, a meta-analysis was conducted to derive ER-functions for those missing in the existing literature. Findings from the latest GBD (Ghosh, Causey et al. 2021), published in 2021 during the writing of this report, were also incorporated; these include only PM2.5 exposure and perinatal outcomes. Finally, a search was performed to identify relevant Swedish studies or other studies in similar low-exposure settings.

Results

Morbidity in adults

COPD and respiratory diseases

PM2.5
The U.S. EPA's ISA on PM (2019) made the conclusion that there is a *likely to be causal relationship* between PM2.5 and respiratory diseases, but additional studies on COPD, specifically, are needed (EPA 2019).

No studies on PM2.5 and COPD were found in Sweden, but a study on black carbon and chronic bronchitis has demonstrated an effect (Wang, Hallberg et al. 2020).

NO2
The U.S. EPA's ISA on NO2 (2016) concluded that the evidence varies between respiratory outcomes, and uncertainty still surrounds the relationship between NO2 and COPD (EPA 2016).

A study in Sweden observed NOx exposure to be associated with diagnosis of COPD, asthma, and chronic bronchitis (Lindgren, Stroh et al. 2009). Young adults, followed since the first year of life through the BAMSE (Swedish abbreviation for C*hildren, Allergy, Milieu, Stockholm, Epidemiology*) cohort, had persistently impaired lung function in association with NOx exposure, with symptoms in line with COPD criteria for young adults (Wang, Kull et al. 2020).

Cardiovascular diseases and diabetes

PM2.5
The U.S. EPA's ISA on PM (2019) found a *causal relationship* between long-term exposure to PM2.5 and cardiovascular diseases, with increased evidence from toxicological studies and from epidemiological studies after adjusting for co-pollutants and socioeconomic factors (EPA

2019). For metabolic diseases (including diabetes), they assessed the evidence to be *suggestive of, but not sufficient to infer, a causal relationship* for long-term exposure to PM2.5.

NO2/NOx
We did not find enough evidence.

Dementia and cognitive decline

PM2.5
The U.S. EPA's ISA on PM (2019) determined: "There is a *likely to be causal relationship* between long-term PM2.5 exposure and nervous system effects" (EPA 2019), which includes dementia and cognitive decline in adults. The Lancet Commission (2020) also added air pollution (PM2.5) as a risk factor for dementia after finding enough convincing evidence (Livingston, Huntley et al. 2020). Additionally, a literature review calculated a meta-analysis for cognitive impairment with a RR=1.08 (95% CI: 1.03-1.13) per 5 μg/m3 increment increase in PM2.5 (Yu, Zheng et al. 2020). Another literature review found the heterogeneity between studies to be too large to calculate a meta-analysis, however (Peters, Ee et al. 2019). Thus, the effect estimate by Yu et al. 2020 should be used with caution.

NO2
Neither dementia nor cognition in adults was included in the U.S. EPA's ISA on NO2/NOx from 2016. In addition to PM2.5, the Lancet Commission's report (2020) also found support for NO2/NOx and dementia but with no clear distinction of which one drives the effect (Livingston, Huntley et al. 2020).

Morbidity effects during pregnancy and childhood

Pregnancy outcomes

PM2.5
Preeclampsia and gestational hypertension were not included in HRAPIE, as most epidemiological studies on these outcomes were published after their review (WHO 2013, Héroux, Anderson et al. 2015). The U.S. EPA's ISA for PM (2019) considered two meta-analyses demonstrating positive associations, but they found discrepancies in exposure assessments between studies included in the meta-analyses (EPA 2019).

The U.S. EPA's ISA on PM (2019) found too few studies on gestational diabetes to assess causality (EPA 2019). Studies in Sweden observed associations between PM2.5 and preeclampsia (Mandakh, Rittner et al. 2020). Additionally, particles collected from traffic and wood smoke in Sweden have been seen to have an effect on placenta cells in experimental studies (Familari, Nääv et al. 2019, Erlandsson, Lindgren et al. 2020, Nääv, Erlandsson et al. 2020).

NO2/NOx
Pregnancy outcomes were not included in HRAPIE (WHO 2013, Héroux, Anderson et al. 2015), the 2016 GBD (World Health Organization 2016), or the U.S. EPA's ISA on NO2/NOx (2016) (EPA 2016). Studies in Sweden have found an effect of NO2/NOx on such health

outcomes (Malmqvist, Jakobsson et al. 2013) (Olsson, Mogren et al. 2015) (Mandakh, Rittner et al. 2020).

Birth outcomes

PM2.5

The U.S. EPA's ISA on PM (2019) found the evidence to be *suggestive of, but not sufficient to infer, a causal relationship* for low birth weight (LBW) and PM2.5 due to some inconsistency in exposure windows, co-pollutant models, and toxicological data (EPA 2019). Perera et al., however, considered the evidence to be sufficient (Perera, Ashrafi et al. 2019). Toxicological studies supporting underlying biological mechanisms have been increasing in recent years, and the most recent GBD has included LBW in its assessments (Ghosh, Causey et al. 2021). Pooled cohort studies within the European Study of Cohorts for Air Pollution Effects (ESCAPE) project (Pedersen, Giorgis-Allemand et al. 2013) as well as studies in Stockholm, Sweden (Olsson, Johansson et al. 2020), demonstrated an effect of PM on LBW. The former also included co-pollutant model adjustment for NO2 (Pedersen, Giorgis-Allemand et al. 2013).

For exposure to PM2.5 and preterm birth (PTB), the U.S. EPA's ISA on PM (2019) also determined the evidence to be *suggestive of, but not sufficient to infer, a causal relationship* (EPA 2019). Again, the review by Perera et al. found enough evidence to include PTB (Perera, Ashrafi et al. 2019). Similar to LBW above, PTB has also been included in the most recent GBD (Ghosh, Causey et al. 2021).

NO2

Perera et al. observed some indication of causal evidence for NO2 and LBW (Perera, Ashrafi et al. 2019). The results from Swedish studies were mixed: no effects were seen in Scania for LBW but for Small for Gestational Age (SGA) (Malmqvist, Rignell-Hydbom et al. 2011), while associations were found in Stockholm (Olsson, Mogren et al. 2015) (Olsson, Ekström et al. 2012).

Lung function

PM2.5

The U.S. EPA ISA on PM (2019) found a *likely to be a causal* relationship between long-term exposure to PM2.5 and lung function (EPA 2019). The Swedish BAMSE cohort study also supports an effect as part of the ESCAPE multi-cohort studies (Gehring, Gruzieva et al. 2013).

NO2

Not enough evidence has been found to assess causality, but an association was seen between NO2/NOx and lung function in the multi-centre studies of the ESCAPE project (Gehring, Gruzieva et al. 2013) as well as in the BAMSE cohort in Sweden (Nordling, Berglind et al. 2008) (Schultz, Hallberg et al. 2016).

Asthma

PM2.5

The U.S. EPA ISA on PM (2019) found a *likely to be causal relationship* between long-term exposure to PM2.5 and asthma (EPA 2019). Perera et al. observed enough evidence for this exposure and asthma incidence (Perera, Ashrafi et al. 2019). A study of four cohorts, including a Swedish one, did find (non-significant) evidence for PM2.5 absorbance and asthma development, especially during longer follow-up when asthma diagnosis becomes more certain (Gehring, Wijga et al. 2015). An effect was not seen in the multi-centre ESCAPE project, where the follow-up period was shorter (Mölter, Simpson et al. 2015). The Respiratory Health in Northern Europe, Spain and Australia (RHINESSA) generation study found an association between gestational exposure to PM2.5 and asthma development (Kuiper, Markevych et al. 2020).

NO2/NOx

Perera et al. found enough evidence to include long-term exposure to NO2 and asthma development in their assessment (Perera, Ashrafi et al. 2019). When the longer follow-up period was used, a multi-cohort study in Europe also supports an association (Gehring, Wijga et al. 2015), as does a national Swedish study (Oudin, Bråbäck et al. 2017). The multi-centre ESCAPE project, investigating a shorter follow-up period, did not observe evidence of an association, however (Mölter, Simpson et al. 2015).

Bronchitis

NO2/NOx

In its assessment, HRAPIE concluded that enough evidence exists for exposure to NO2 and bronchitis among asthmatic children (5–14 years old); based on a co-pollutants study, authors found the prevalence of bronchitis symptoms to be 1.021 (0.990–1.060) per 1 μg/m3 increment increase in NO2 as an annual mean (WHO 2013, Héroux, Anderson et al. 2015).

Infections

PM2.5

The U.S. EPA's ISA on PM (2019) designated the relationship between long-term exposure to PM2.5 and respiratory infections in children as *likely to be causal* (EPA 2019). In the multi-centre ESCAPE project, an association between PM2.5 and pneumonia was observed (MacIntyre, Gehring et al. 2014).

NO2/NOx

Acute lower respiratory infections are often included in the GBD but may primarily refer to low- and middle-income countries. Exposure to NO2 and NOx was associated with pneumonia in the multi-centre ESCAPE project, and an association between NO2 only and otitis media was also documented (MacIntyre, Gehring et al. 2014).

Autism

PM2.5

Autism was not included in HRAPIE (WHO 2013, Héroux, Anderson et al. 2015), and the study of this health outcome in connection to air pollution exposure is a relatively new field. Still, the U.S. EPA's ISA on PM (2019) found consistent epidemiological evidence; however, some studies did not adjusted for co-pollutants and exposure windows differed somewhat (EPA 2019). Animal studies also supported an association according to the U.S. EPA's assessment (EPA 2019). Perera et al.'s evaluation determined the evidence to be sufficient (Perera, Ashrafi et al. 2019). The only Swedish study that could be identified investigating PM2.5 exposure and autism only considered parental reported autistic traits and found no effect (Guxens, Ghassabian et al. 2016).

NO2/NOx

Again, the effect of NO2/NOx on autism was not included in HRAPIE (WHO 2013, Héroux, Anderson et al. 2015). Perera et al. conclude that more studies might be needed to warrant the inclusion of this pollutant-outcome pair in HIAs (Perera, Ashrafi et al. 2019). The multi-centre ESCAPE project did not find any associations between NO2/NOx exposure and autistic traits (Guxens, Ghassabian et al. 2016). Swedish studies show conflicting results, with effects seen in southern Sweden (Oudin, Frondelius et al. 2019) but not in Stockholm (Gong, Dalman et al. 2017) (Gong, Almqvist et al. 2014). Additionally, a Danish study observed an association between NO2 exposure and autism (Ritz, Liew et al. 2018).

Cognition and type 1 diabetes

Not enough evidence could be found for either PM2.5 or NO2/NOx exposure and cognition. The same conclusion stands for type 1 diabetes.

A more detailed summary can be found in table 4 and 5 in Appendix 1.

Assessing which outcomes to use in HIA

For consistency and harmonization between this report and a similar project in Sweden, we have also incorporated the findings from the ASEK (Swedish abbreviation for *Analytical methods and socioeconomic cost/benefit calculations*) project (Trafikverket 2019) here. In ASEK, the assessment of societal costs of air pollution from traffic (ASEK, 2019) are based on old assessments from WHO projects: HRAPIE (WHO 2013, Héroux, Anderson et al. 2015) and "Review of evidence on health aspects of air pollution" (REVIHAAP) (WHO 2013b); an American Thoracic Society (ATS)/European Respiratory Society (ERS) statement (Thurston, Kipen et al. 2017); a health cost assessment for Public Health England in the United Kingdom (UK) (Pimpin et al., 2018); and the U.S. EPA's ISA on PM (EPA 2019). Regarding sick days, ASEK follows recommendations from WHO HRAPIE (WHO 2013, Héroux, Anderson et al. 2015) and REVIHAAP (WHO 2013b), but the ER-function is quite old and based on U.S. evidence (Ostro 1987); therefore, new studies are needed. The ASEK review concluded that mortality, myocardial infarction (MI; incidence), stroke (incidence), COPD (incidence), type 2 diabetes (incidence), childhood asthma (incidence), preterm birth, and sick days were relevant health outcomes to include for PM2.5.

ASEK's reasoning behind excluding some outcomes included in, for example, Thurston et al. 2018 is based on the need for the selected outcomes to have reliable data on health calculations and economic calculations as well as to avoid the double counting of effects. We have chosen a similar approach; see Tables 1 and 2. These tables should be read as a sieve: an outcome will only move to the next column to the right if it is supported by the present column statement.

The main differences between our report and ASEK are that we included some health outcomes related to NO2 exposure, added gestational hypertension, and excluded sick days. Concerning the differences between our report and the health cost assessment for Public Health England (Pimpin, Retat et al. 2018), authors chose to include low birth weight, whereas we included preterm birth instead (applicable to both PM2.5 and NO2). The weight of evidence for both of these birth outcomes is similar. Because they are linked to each other, however, including both LBW and PTB could result in double counting. Still, the risk of double counting can be avoided if only low birth weight at term is used. Additionally, the UK assessment includes dementia (emphasizing caution); here, we include gestational hypertension (emphazising caution). Finally, in the UK assessment, type 2 diabetes is included for NO2, which is not the case for the present report. Overall, ER-functions in this report vary slightly from those included in both ASEK and the UK assessment

It should also be noted that since our review there has been an updated version of US EPA ISA for PM with increased evidence of long term PM2.5 effects for lung cancer (from suggestive to likely to be causal), and neurvous system effects (likely to be causal), with strongest evidence for cognitive effects in older adults (EPA. 2021). Given this information, we would likely have included dementia and PM2.5 in this assessment. In line with this it is important to note that the choice of outcomes should not be seen as static as it is an expanding knowledge.

Table 1. PM2.5 and outcomes, in a sieve table going from effects to evaluate, enough evidence, enough economic reasons, reliable indata for a HIA, and without risk of double counting. Outcomes in italic should be interpreted with more caution.

Effects to evaluate	**Effects with enough evidence**	**Effects of value to evaluate from economic standpoint**	**Effects that can be included in HIA based on reliable indata**	**Effects that can be included without risk of double counting**
Lung cancer	Lung cancer	Lung cancer	Lung cancer	Lung cancer
Mental health	Autism Dementia	Autism Dementia		
Cardiovascular diseases	Cardiovascular diseases	Cardiovascular diseases	*Myocardial infarction* *Stroke*	*Myocardial infarction* *Stroke*
Respiratory diseases	COPD Lung function Asthma	COPD Lung function Asthma	*COPD*	*COPD*
Metabolic	Type 2 diabetes	Type 2 diabetes	*Type 2 diabetes*	Type 2 diabetes
Gestational complications and birth outcomes	Preeclampsia/ Gestational hypertension Low birth weight Preterm birth	Preeclampsia/ Gestational hypertension Low birth weight Preterm birth	Preeclampsia/ Gestational hypertension Low birth weight Preterm birth	Gestational hypertension Preterm birth *Low birth weight (at term)*

Table 2. NO2 and outcomes, in a sieve table going from effects to evaluate, enough evidence, enough economic reasons, reliable indata for a HIA, and without risk of double counting. Outcomes in italic should be interpreted with more caution.

Effects to evaluate	**Effects with enough evidence**	**Effects of value to evaluate from economic standpoint**	**Effects that can be included in HIA based on reliable indata**	**Effects that can be included without risk of double counting**
Gestational complications and birth outcomes	Low birth weight Preterm birth	Low birth weight Preterm birth	Low birth weight Preterm birth	*Low birth weight (at term)* Preterm birth
Lung cancer	Lung cancer	Lung cancer	Lung cancer	Lung cancer
Respiratory diseases	Asthma Bronchitis	Asthma Bronchitis	*Asthma*	*Asthma*

Exposure-response functions

In Table 3 we give examples of Exposure -response functions that can be used for the different outcomes and air pollutant pairs.

Table 3. Exposure-response functions for various air pollutants and multiple health outcomes along with their sources.

Health outcome	**PM2.5**	Source	**NO2**	Source
Total mortality, age ≥30 years	**A)** 1.08 per 10 µg/m3 **B)** 1.26 per 10 µg/m3	**A)** (Chen and Hoek 2020) [1] **B)** (Turner, Jerrett et al. 2016) [2]	1.05 per 10 ppb	(Stieb, Berjawi et al. 2021) [3]
Myocardial infarction, age ≥30 years	1.13 per 5 µg/m3	(Cesaroni, Forastiere et al. 2014) [1]	Evidence lacking	
Stroke, age ≥30 years	1.10 per 5 µg/m3	(Wolf, Hoffmann et al. 2021) [5]	1.08 per 10 µg/m3	(Wolf, Hoffmann et al. 2021) [5]
Chronic obstructive pulmonary disease (COPD), age ≥50 years	1.18 per 10 µg/m3	(Park, Kim et al. 2021) [6]	1.07 per 10 µg/m3	(Park, Kim et al. 2021) [6]
Lung cancer, age ≥35 years	1.11 per 10 µg/m3	(Ciabattini, Rizzello et al. 2021) [7]	1.04 per 10 µg/m3	(Hamra, Laden et al. 2015) [8]
Type 2 diabetes, age ≥15 years	1.25 per 10 µg/m3	(He, Wu et al. 2017) [9]	Evidence lacking	
Childhood asthma, age 2-18 years (with prescription medication)	1.03 per 1 µg/m3	(Khreis, Kelly et al. 2017) [10]	1.05 per 4 µg/m3	(Khreis, Kelly et al. 2017) [10]
Preterm birth (≤36 weeks of gestation)	1.24 per 10 µg/m3	(Klepac, Locatelli et al. 2018) [11]	1.09 per 10 µg/m3	(Klepac, Locatelli et al. 2018) [11]
Hypertensive disorders of pregnancy	1.32 per 10 µg/m3	(Yu, Yin et al. 2020) [12]	Evidence lacking	

[1.] Review of 104 cohort studies. [2.] Cohort study from U.S. [3.] Review of 47 cohort studies. [5.] Review of 12 cohort studies for PM2.5 < 15 µg/m3 and 12 cohorts for NO2. [6.] Review of 7 cohort studies. [7.] Review of 4 cohort studies for PM2.5 (incidence) and 7 cohort studies for PM10 (incidence and mortality). [8.] Review of 20 studies (incidence and mortality). [9.] Review of 8 cohort studies. [10.] Review of 41 cohort studies. [11.] Review of 48 cohort studies (both cross-sectional and longitudinal). [12.] Review of 9 studies. Ppb = parts per billion.

Appendix 1. Evidence of association summary

Tables 4 and 5 below summarize the current state of evidence for associations between PM2.5 and NO2, respectively, and multiple health outcomes according to various sources.

Table 4. Weight of evidence for causal determination of select health outcomes and long-term and short-term exposure to PM2.5.

		Causal relationship	Likely to be a causal relationship	Suggestive of, but not sufficient to infer, a causal relationship	Inadequate to infer a causal relationship	Not likely to be a causal relationship
Adult health outcomes						
Cardiovascular effects		Short-term[2] Long-term[2] Short-term[4]				
	Myocardial infarction	Long-term[1] ("ischemic heart disease")				
	Stroke	Long-term[1]				
Respiratory effects		Short-term[4]	Short-term[2] Long-term[2]			
	Bronchitis Asthma					
	COPD	Long-term[1]				
Metabolic effects				Short-term[2] Long-term[2]		
	Diabetes					
Nervous system effects			Long-term[2]	Short-term[2]		
	Cognitive decline Dementia					
Other adult effects						
	Restricted activity days		Long-term[4,†]			
Pregnancy, birth and child health outcomes						

Pregnancy outcomes				Long-term[2]
	Preeclampsia Gestational diabetes			
Birth outcomes				Long-term[2]
	Low birth weight	Entire pregnancy[3,5]	Entire pregnancy[3,5]	
	Preterm birth	Entire pregnancy[3,5]	Entire pregnancy[3,5]	
Nervous system effects*,**			Long-term[2]	
	Cognition Autism	Entire pregnancy[3]	Entire pregnancy[3]	
Respiratory effects**			Long-term[2]	
	Respiratory disease Lung capacity			
	Asthma	Entire pregnancy[3]	Entire pregnancy[3]	
	Bronchitis	Long-term[1] ("acute lower respiratory disease")		
	Infections			
Metabolic effects				Short-term[2] Long-term[2]
	Type I diabetes ***			

[1] WHO. Ambient air pollution: A global assessment of exposure and burden of disease. (World Health Organization 2016) "Health outcomes, for which there is enough epidemiological evidence to be included in the analysis, comprise acute lower respiratory, chronic obstructive pulmonary disease, stroke, ischeamic heart disease and lung cancer. Many other diseases have been associated with air pollution, but are not included in this assessment because the evidence was not considered sufficiently robust… excludes health impacts where evidence is still limited (e.g. pre-term birth or low birth weight)."

[2] U.S. EPA. Integrated Science Assessment (ISA) for Particulate Matter (EPA 2019). * "Positive associations between long-term exposure to PM2.5 during the prenatal period and autism spectrum disorder (ASD) were consistently observed across multiple epidemiologic studies (Section 8.2.7.2). However, several studies of performance on tests of cognitive function provided little support for an association." Limitations: "lack of control for potential confounding by co-pollutants, the small number

of studies, and uncertainty regarding critical exposure windows. An animal study indicates initial evidence of biologically plausible pathway of PM2.5 to ASD." ** Section 9.1.5.3 Developmental Outcomes: "There is recent evidence from both epidemiologic and toxicological studies supporting a relationship between prenatal and childhood PM2.5 exposure and effects on postnatal development, including effects on the respiratory, nervous, and cardiovascular systems (Table 9-7)." *** Took same evidence conclusion as adult metabolic effects, short-term PM2.5: no study on childhood diabetes (7.1.2.1 Epidemiologic Studies), long-term PM2.5: three epi studies on children, specifically glucose homeostasis (7.2.3.1 Epidemiologic Studies). Section 7.2.6 Age of Onset of Type 1 Diabetes: "Overall, evidence to inform a proposed pathway for TID is not available and the limited epidemiologic studies do not provide evidence that is associated with the incidence of T1D. Findings from an epidemiologic study examining the association of PM with T1D age of onset were not replicated."

[3] (Perera, Ashrafi et al. 2019). Authors state, "We present C-R functions for endpoints having a causal or likely causal relationship with the pollutants that we believe can be incorporated into a primary analysis as well as those having a suggestive relationship with the pollutants that are eligible for a secondary analysis." Therefore, pollutant-outcome pairs included in their primary analysis are marked as both "causal" and "likely to be causal" in the table above, as their differentiation could not be determined.

[4] (Héroux, Anderson et al. 2015). The authors write, "Each of the pollutant–outcome pairs recommended for cost–benefit analysis was classified into two categories: Group A: pollutant–outcome pairs for which enough data are available to enable quantification of effects; Group B: pollutant–outcome pairs for which there is more uncertainty about the data used for quantification of effects. [However,] …there is sufficient evidence of a causal relationship for pollutant–outcome pairs in both groups." Therefore, pollutant-outcome pairs in Group A were considered to be "causal" and pollutant-outcome pairs in Group B were categorized as "likely to be causal". Outcome details: Hospital admissions: CVDs (including stroke), all ages. Hospital admissions: respiratory diseases, all ages. Restricted activity days (RADs), all ages. [†] For RADs, 2-week average converted to PM2.5 annual average.

[5] (Ghosh, Causey et al. 2021). While an official causal determination assessment was not conducted by the authors, this source represents a recent global burden of disease meta-regression for perinatal outcomes. Authors state, "Ambient and household PM2.5 were associated with reduced birth weight and [gestational age]". Specifically, "Pooled estimates indicated 22 grams (95% UI: 12, 32) lower **birth weight**, 11% greater risk of **LBW** (1.11, 95% UI: 1.07, 1.16), and 12% greater risk of **PTB** (1.12, 95% UI: 1.06, 1.19), per 10 μg/m3 increment in ambient PM2.5. We estimated a global population–weighted mean lowering of 89 grams (95% UI: 88, 89) of **birth weight** and 3.4 weeks (95% UI: 3.4, 3.4) of **GA** in 2019, attributable to total PM2.5. Globally, an estimated 15.6% (95% UI: 15.6, 15.7) of all **LBW** and 35.7% (95% UI: 35.6, 35.9) of all **PTB** infants were attributable to total PM2.5, equivalent to 2,761,720 (95% UI: 2,746,713 to 2,776,722) and 5,870,103 (95% UI: 5,848,046 to 5,892,166) infants in 2019, respectively." Importantly, this source was marked as both "causal" and "likely to be a causal relationship" in the table above, as it was not a causal determination assessment.

Table 5. Weight of evidence for causal determination of select health outcomes and long-term and short-term exposure to NO2.

		Causal relationship	Likely to be a causal relationship	Suggestive of, but not sufficient to infer, a causal relationship	Inadequate to infer a causal relationship	Not likely to be a causal relationship
Adult health outcomes						
Cardiovascular effects	Myocardial infarction Stroke			Short-term[1] Long-term[1]		
Respiratory effects*	Bronchitis Asthma COPD	Short-term[1] Short-term[3, †]	Long-term[1]			
Metabolic effects	Diabetes			Long-term[1]		
Nervous system effects**	Cognitive decline Dementia					
Other adult effects	Restricted activity days					
Pregnancy, birth and child health outcomes						
Pregnancy outcomes	Preeclampsia Gestational diabetes				Long-term[1]	
Birth outcomes				Long-term[1]		

	Low birth weight Preterm birth				
Nervous system effects					Long-term[1]
	Cognition Autism				
Respiratory effects* **		Short-term[1]	Long-term[1]		
	Respiratory disease Lung capacity				
	Asthma	Long-term[2]	Long-term[2]		
	Bronchitis		Long-term[3]		
	Infections				
Metabolic effects** **				Short-term[1]	
	Type 1 diabetes				

[1] U.S. EPA. Integrated Science Assessment for Oxides of Nitrogen- Health Criteria (EPA 2016). * Short-term: "There is some support for NO2-related exacerbation of respiratory allergy and COPD, respiratory infection, respiratory mortality, and respiratory effects in healthy populations. However, because of inconsistency among lines of evidence and consequent uncertainty about the effects of NO2 exposure, evidence for these other non-asthma respiratory effects does not strongly contribute to the determination of a causal relationship". Long-term: "There is more uncertainty in relationships with lung function and partially irreversible decrements in lung development in children, respiratory disease severity, chronic bronchitis/asthma incidence in adults, COPD hospital admissions, and respiratory infection.". ** No mention of dementia, Alzheimer's, cognitive decline for adults (searched the document using ctrl + f). *** Took same evidence conclusion from adult respiratory outcomes (see * above). **** Evidence on focusing on insulin resistance as opposed to type 1 diabetes explicitly.

[2] (Perera, Ashrafi et al. 2019). Authors state, "We present C-R functions for endpoints having a causal or likely causal relationship with the pollutants that we believe can be incorporated into a primary analysis as well as those having a suggestive relationship with the pollutants that are eligible for a secondary analysis." Therefore, pollutant-outcome pairs included in their primary analysis are marked as both "causal" and "likely to be causal" in the table above, as their differentiation could not be determined.

[3] (Héroux, Anderson et al. 2015). The authors write, "Each of the pollutant–outcome pairs recommended for cost–benefit analysis was classified into two categories: Group A: pollutant–outcome pairs for which enough data are available to enable quantification of effects; Group B: pollutant–outcome pairs for which there is more uncertainty about the data used for quantification of effects. [However,] …there is sufficient evidence of a causal relationship for pollutant–outcome pairs in both groups." Outcome details: Prevalence of bronchitic symptoms in asthmatic children aged 5–14 years. Hospital admissions, respiratory diseases, all ages. [†] Short-term as both NO_2, daily maximum 1-h mean and NO_2, 24-h mean.

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