EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Original article

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Please cite this article as: Khreis H, Cirach M, Mueller N, *et al*. Outdoor Air Pollution and the Burden of Childhood Asthma across Europe. *Eur Respir J* 2019; in press (https://doi.org/10.1183/13993003.02194-2018).

Outdoor Air Pollution and the Burden of Childhood Asthma across Europe

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Competing financial interests: The authors declare they have no competing interests.

Abstract

Background Emerging evidence suggests that air pollution may contribute to childhood asthma development. We estimated the burden of incident childhood asthma that may be attributable to outdoor NO_2, $PM_{2.5}$ and black carbon (BC) in Europe.

Methods We combined country-level childhood incidence rates and pooled exposure-response functions with children's (1-14 years) counts, and exposure estimates at 1,540,386 1 km x 1 km cells, across 18 European countries and 63,442,419 children. Annual average pollutant concentrations were obtained from a validated and harmonized European land-use regression (LUR) model. We investigated two exposure reduction scenarios. For the first, we used recommended annual World Health Organization (WHO) air quality guideline values. For the second, we used the minimum air pollution levels recorded across 41 studies in the underlying meta-analysis.

Results NO_2 ranged from 1.4 to 70.0 $\mu g/m^3$, with a mean of 11.8 $\mu g/m^3$. $PM_{2.5}$ ranged from 2.0 to 41.1 $\mu g/m^3$, with a mean of 11.6 $\mu g/m^3$. BC ranged from 0.003 to 3.7 x 10^{-5} m^{-1}, with a mean of 1.0 x 10^{-5} m^{-1}. Compliance with the NO_2 and $PM_{2.5}$ WHO guidelines, respectively, was estimated to prevent 2,434 (0.4%) and 66,567 (11%) incident cases. Meeting the minimum air pollution levels for NO_2 (1.5 $\mu g/m^3$), $PM_{2.5}$ (0.4 $\mu g/m^3$) and BC (0.4 x $10^{-5} m^{-1}$), respectively, was estimated to prevent 135,257 (23%), 191,883 (33%) and 89,191 (15%) incident cases.

Conclusions A significant proportion of childhood asthma cases may be attributable to outdoor air pollution, and these cases could be prevented. Our estimates underline an urgent need to reduce children's exposure to air pollution.

Keywords: Childhood; asthma; air pollution; exposure; burden of disease; Europe

Highlights

- We estimated the annual burden of incident childhood asthma that may be attributable to outdoor air pollution
- Our analyses covered 18 European countries and 63,442,419 children
- Compliance with the NO_2 WHO air quality guidelines was estimated to prevent 2,434 (0.4% of total cases) incident childhood asthma cases per year
- Compliance with the $PM_{2.5}$ WHO air quality guidelines was estimated to prevent 66,567 (11% of total cases) incident childhood asthma cases per year
- Meeting the minimum air pollution levels recorded in the literature prevented a much larger proportion of cases: 23% for NO_2, 33% for $PM_{2.5}$ and 15% for black carbon
- There is an urgent need to reduce children's exposure to air pollution

Abbreviations

BC: $PM_{2.5\ absorbance}$/ black carbon

BoD: Burden of disease

CI: Confidence Intervals

EFGS: European Forum for Geography and Statistics

GBD: Global Burden of Disease

GIS: Geographical information systems

LCI: Lower Confidence Interval

LUR: Land-use regression

NO_2: Nitrogen Dioxide

NO_x: Nitrogen Oxides

OR: Odds Ratio

PAF: Population attributable fraction

PM_{10}: Particulate Matter equal or less than 10 micrometers in diameter

$PM_{2.5}$: Particulate Matter equal or less than 2.5 micrometers in diameter

RR: Relative risk

TRAP: Traffic-related air pollution

UCI: Upper Confidence Interval

UK: United Kingdom

WHO: World Health Organization

1. Introduction

Asthma is a chronic disorder of the airways affecting more than 334 million people worldwide [1]. Asthma is often cited as the most common chronic disease in childhood [2-4]. The social burden of childhood asthma is considerable. It manifests in the disruption of the child's life, reduced physical abilities due to symptoms or attacks, the burden posed on the child's caregiver, and direct healthcare costs arising from consultations in primary and secondary care, hospital admissions and treatment costs [5].

The most recent systematic review and meta-analysis established statistically significant associations between long-term exposure to outdoor air pollution, specifically black carbon (BC), nitrogen dioxide (NO_2), particulate matter equal or less than 2.5 micrometers in diameter ($PM_{2.5}$) and particulate matter equal or less than 10 micrometers in diameter (PM_{10}), and the development of childhood asthma from birth to 18 years old [6]. In urban areas, these pollutants are often traffic-related, to varying extents, with NO_2 and BC being better markers of traffic sources than particulate matter [6-9]. In line with these findings, more recent primary studies also showed that exposures to outdoor air pollution and specific traffic markers were associated with asthma development in children [10-13]. Supporting these epidemiological observations, the available toxicological and clinical evidence suggest that there are documented biological mechanisms by which air pollution could plausibly induce new childhood asthma and plausibly contribute to the diagnosis of asthma in a clinical setting [14, 15].

Despite this emerging evidence, which has fundamental implications to estimating the Burden of Disease (BoD) attributable to outdoor air pollution beyond mortality endpoints [16], to date, little work has been undertaken to estimate the burden of childhood asthma attributable to outdoor air pollution. Four studies, coming from the same research group, quantified the number of prevalent asthma cases attributable to traffic-related air pollution (TRAP) as characterized by proximity to major roadways [16-19]. Three of these studies were conducted in California, in the Long Beach, Riverside and Los Angeles counties [16, 18, 19], whilst the fourth study was conducted across 10 European cities: Barcelona, Bilbao, Brussels, Granada, Ljubljana, Rome, Seville, Stockholm, Valencia and Vienna [17]. All four studies estimated the impacts of proximity to major roadways (as the TRAP exposure surrogate), on asthma prevalence in children up to 18 years old and suggested that 6% to 14% of prevalent asthma cases may be attributable to proximity to major roadways. Two more recent analyses were set in Bradford, United Kingdom (UK). The first suggested that 7% and 12% of annual incident childhood asthma cases may be attributable to traffic-related NO_2 and nitrogen oxides (NO_x) exposures, as characterized by Gaussian dispersion models [20]. The percentage of annual incident childhood asthma cases attributable to NO_2 and NO_x exposures from all sources (including industry, point sources, heating, aircrafts, rail and regional sources) was 22% and 35%, respectively [20]. The second study in Bradford suggested that 7%, 11% and 12% of annual incident childhood asthma cases may be attributable to traffic-related $PM_{2.5}$, PM_{10} and $BC/PM_{2.5}$ absorbance, respectively, as estimated by land-use regression (LUR) models [21]. The percentage of annual incident childhood asthma cases attributable to $PM_{2.5}$, PM_{10} and $BC/PM_{2.5}$ absorbance exposures from all sources was 27%, 33% and 15%, respectively [21].

As summarized above, the geographical coverage of previous studies was limited and the broadest coverage was reported in the paper by Perez, Declercq [17] which covered 10 cities in 6 European countries but used proximity to major roadways as the exposure metric. Further, all previous studies, except for Khreis, de Hoogh [20] and their follow-up work in Khreis, Ramani [22], were concerned with asthma prevalence, rather than asthma incidence/development. As such, those studies did not

take into account latest evidence associating air pollution with childhood asthma development and do not give indication of how many cases may be preventable by reducing air pollution exposures.

In this paper, we take into account recent findings showing that outdoor air pollution exposures, specifically TRAP, are associated with the development of childhood asthma, and significantly expand the geographical coverage of previous analyses. We aim to estimate the annual number of incident childhood asthma cases that may be attributable to outdoor air pollution, across 18 European countries and 63,442,419 children, exploiting recently developed and harmonized European models of outdoor air pollution concentrations. In line with previous published works, we also assume that the same risk estimates sourced from the most recent meta-analysis can be applied to both traffic-related and generic outdoor air pollution [6], keeping in mind that intra-urban variations of air pollution, specifically BC and NO_2, are mainly dominated by traffic sources [23], and that NO_2 is likely acting as a surrogate for the traffic mixture.

2. Methods

2.1. Study area and time points

The analyses presented in this paper covered 18 European countries, 16 from the European Union (EU) (Austria, Belgium, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Lithuania, the Netherlands, Portugal, Spain, Sweden, and the United Kingdom,) and two non-EU countries (Norway and Switzerland). These 18 countries were selected based on the availability of air pollution exposure data and the percentage of grid cells with complete air pollution *and* population data (≈100%). From the EU's 28 countries, we excluded the following 12, mainly due to the unavailability of air pollution exposure data: Bulgaria, Cyprus, Croatia, Czech Republic, Estonia, Latvia, Luxemburg, Malta, Poland, Romania, Slovak Republic, and Slovenia. Overall, we included 63,442,419 children in our analyses.

The years of analysis were 2010 for the air pollution exposure data [24], and 2011 and 2012 for the population data and children's proportions data, respectively. Joining the census population and air pollution exposure data, and all analyses, were undertaken at the 1 km x 1 km grid cell scale. The 1 km x 1 km grid cell scale was the finest scale at which we found population data for the 18 countries. Overall, the data presented gives a good spatial representation of Northern, Central and Southern Europe, but not Eastern Europe, due to the unavailability of air pollution exposure data from our models in that region [24]. This is a key limitation of this analysis as air pollution concentrations are known to be high in Eastern Europe.

The supplementary material includes full description of the methods and the datasets underlying our analyses. Next, we only briefly describe the various steps.

2.2. Census data

The total population count at the 1 km x 1 km grid cell unit was extracted from the GEOSTAT 2011 population grid (V2.0.1) database (Eurostat EFGS, 2011). The GEOSTAT database did not specifically include childhood population counts. To calculate the children's count in each grid, which was our population of interest, the percentage of people aged 1 to 14 years old was extracted from the NUTS 3 dataset (Nomenclature of Territorial Units for Statistics, Eurostat, European Commission, version 2010) at the regional scale, which are the smallest available regions for statistical purposes. We multiplied the percentage of people aged 1 to 14 from each region by the total population count, as extracted from the GEOSTAT population grid database, and calculated the childhood population count at the 1 km x 1 km grid cell scale. The older childhood group (>14 to 18 years old) was mixed with adults (15-29), and as such we performed our analysis exclusively for children aged 1 to 14. We

stratified our analysis by age and present results for young children between 1 and 4 years old and children aged 5-14 years old, as shown in the supplementary material.

2.3. Exposure assessment model and data

Childhood exposures to NO_2, $PM_{2.5}$ and BC were assessed at the 1 km x 1 km scale using a validated hybrid LUR model, which is briefly described next and fully described in the supplementary material and in de Hoogh, Chen [24].

LUR modeling is an empirical air pollution modeling technique which uses predictor variables such as land-use, geographic, road and traffic characteristics to explain spatial variations of measured air pollution concentrations at multiple sites across the study area [25]. The set of LUR models we use comes from work reported in de Hoogh, Chen [24], where the authors modeled NO_2, $PM_{2.5}$ and BC 2010 annual mean exposures at the 100 m x 100 m grid cell scale, incorporating chemical transport model estimates (NO_2, $PM_{2.5}$, BC) and satellite derived data ($PM_{2.5}$, BC), together with fine scale local predictors in a geostatistical framework allowing to refine the spatial scale from the otherwise coarse chemical transport model and satellite data (~10x10km). We used these LUR models to estimate exposures in this study area due to the availability of the models, their harmonization across all included countries and their refinement in the most recent work reported in de Hoogh, Chen [24]. *For NO_2*, the final model adopted had an adjusted R^2 of 0.59 whilst the hold-out-validation R^2 was 0.58. *For $PM_{2.5}$*, the final model adopted had an adjusted R^2 of 0.72 whilst the hold-out-validation R^2 equaled 0.66. *For BC*, the final model adopted had an adjusted R^2 of 0.54 whilst the hold-out-validation R^2 was 0.51. In addition, for $PM_{2.5}$ and NO_2, the authors performed an independent validation using monitoring sites not used in model development, which explained 0.65 and 0.49 of spatial variation in the measured concentrations, respectively [24].

2.4. Matching of census and exposure data

To match the childhood population data with the exposure estimates, the NO_2, $PM_{2.5}$ and BC exposure estimates from the LUR model (section 2.3) were averaged up from the 100 m x 100 m grid cell to the 1 km x 1 km grid cell, as this was the finest scale at which census population data was available. The average exposure estimate was then assigned to all children who lived within that 1 km x 1 km grid cell. There were 1,540,386 1 km x 1 km grid cells across the 18 included countries which had complete data, and which we included in our analysis. The exposure and population characteristics in these 1 km x 1 km grid cells are shown in Table S1 in the supplementary material.

2.5. Burden of disease assessment

We followed standard procedures to assess the childhood asthma BoD in association with the three pollutants: NO_2, $PM_{2.5}$ and BC (section 2.3) [18, 26], by:

- Defining the exposure measures (section 2.3)
- Defining the baseline incidence rate of asthma amongst the exposed children (section 2.5.1)
- Selecting exposure-response functions to quantify the association between the exposures and the development of childhood asthma between birth and 18 years old (section 2.5.2)
- Combining exposures data with population data and scaled exposure-response functions to quantify the attributable burden of incident childhood asthma cases (section 2.5.3. and 2.5.4).

2.5.1. Baseline childhood asthma incidence rates

The incidence rates of asthma in children (newly diagnosed cases) from 1-4 and 5-14 years old were extracted from the Global Burden of Disease (GBD) study database (Table S2) [27]. Incidence rates were extracted at the country level for the year 2016, which, at the time of this analysis, was the latest

and theoretically the best assessment as more input data became available in recent years. The GBD data uses public and official health data records reported from health surveys and clinical records. Between year 2010 (the year of the air pollution exposure assessment) and year 2016, the average childhood asthma incidence rate across the 18 included countries decreased by 2% (Global Burden of Disease Collaborative Network, 2016). Additional information can be found at GHDx (http://ghdx.healthdata.org/gbd-results-tool). Incident cases in the age group 1 to 14 years old for the different countries were estimated using the GBD 2016 data, by combining incident cases in the age groups 1-4 and 5-14, which were directly available through the GBD datasets. We used the age-specific incidence rates in the age groups 1-4 and 5-14 and also stratified our analysis in these two groups. We report the age-specific results in the supplementary materials.

2.5.2. Exposure-response functions

Exposure-response functions for the association between the exposures to NO_2, $PM_{2.5}$ and BC and the subsequent development of childhood asthma from birth to 18 years old were extracted from random effects meta-analyses reported in Khreis, Kelly [6]. The NO_2 exposure-response function was based on 20 studies and equaled OR= 1.05 (95% CI, 1.02 - 1.07) per the exposure to 4 $\mu g/m^3$. The $PM_{2.5}$ exposure-response function was based on 10 studies and equaled OR=1.03 (95% CI, 1.01 - 1.05), per the exposure to 1 $\mu g/m^3$ $PM_{2.5.}$ The BC exposure-response function was based on eight studies and equaled OR=1.08 (95% CI, 1.03 - 1.14), per the exposure to 0.5 x 10^{-5} m^{-1} BC. Detailed information on the derivation of these exposure-response functions, the underlying studies and asthma definitions used can be found in the original paper [6]. However, a key point worth emphasizing is that studies included in this meta-analyses *did not* adjust for co-pollutants. As such, the number of incident asthma cases attributable to NO_2, $PM_{2.5}$ and BC should *not* be added up but viewed as independent estimates of the potential impact of outdoor air pollution.

2.5.3. Estimation of the impact of exposure reduction scenarios

We assessed the impacts of two plausible exposure reduction scenarios on the burden of incident childhood asthma:

1) where in exceedance, the reduction of air pollution levels to comply with the World Health Organization (WHO) air quality guideline values [28]. This scenario was applicable to NO_2 and $PM_{2.5}$ only, as BC has no guideline value.
2) And where in exceedance, the reduction of air pollution levels to meet the minimum air pollution levels recorded in any of the 41 studies synthesized in the underlying systematic review from which we sourced our exposure-response functions [6] (see supplementary material for further details on the exact air pollution levels in both scenarios).

The number of preventable incident childhood asthma cases which may be attributable to these scenarios was estimated. These estimates are only indicative as there is no evidence that asthma's risk does not increase under these "thresholds" [6, 29], and policy efforts should aim at reducing air pollution as much as possible.

2.5.4. Estimation of population attributable fraction and attributable number of cases

Using the exposure-response functions above (section 2.5.2), the risk estimates for asthma development in association with the three pollutants were scaled to the difference in exposure level between the two counterfactual scenarios (section 2.5.3) and the reference scenario (current exposures as estimated from the LUR model, see section 2.3). Each analysis was undertaken for each pollutant and scenario separately and at the 1 km x 1 km grid cell. To scale the risk estimate from the exposure-response functions' concentration unit to the exposure difference between the reference and the two

counterfactual scenarios, standard methods, as described in the supplementary material, were used [30].

The population attributable fraction (PAF) was then calculated, also for each 1 km x 1 km grid cell, pollutant and scenario. PAF defines the proportional reduction in morbidity that would occur if the specific exposure, to outdoor air pollution in this case, was reduced to the counterfactual exposure scenario(s). Finally, the number of incident childhood asthma cases attributable to the excess exposure compared to the counterfactual exposure scenarios was calculated, separately for each cell, pollutant and scenario. All calculations are shown in full in the supplementary material.

3. Results

Figure 1 shows the spatial distribution of NO_2, $PM_{2.5}$ and BC across the 18 included countries. As shown in Table S1, at the 1 km x 1 km grid cells, NO_2 ranged from 1.4 to 70.0 $\mu g/m^3$, with an estimated mean of 11.8 $\mu g/m^3$. $PM_{2.5}$ ranged from 2.0 to 41.1 $\mu g/m^3$, with an estimated mean of 11.6 $\mu g/m^3$. Finally, BC ranged from 0.003 to 3.7 $x10^{-5}$ m^{-1}, with an estimated mean of 1.0 $x10^{-5}$ m^{-1}. The correlation between the three pollutants was moderate to high and ranged from 0.67 (between NO_2 and BC) to 0.81 (between $PM_{2.5}$ and BC). The summary statistics for exposures in each of the 18 included countries are shown in Table S3.

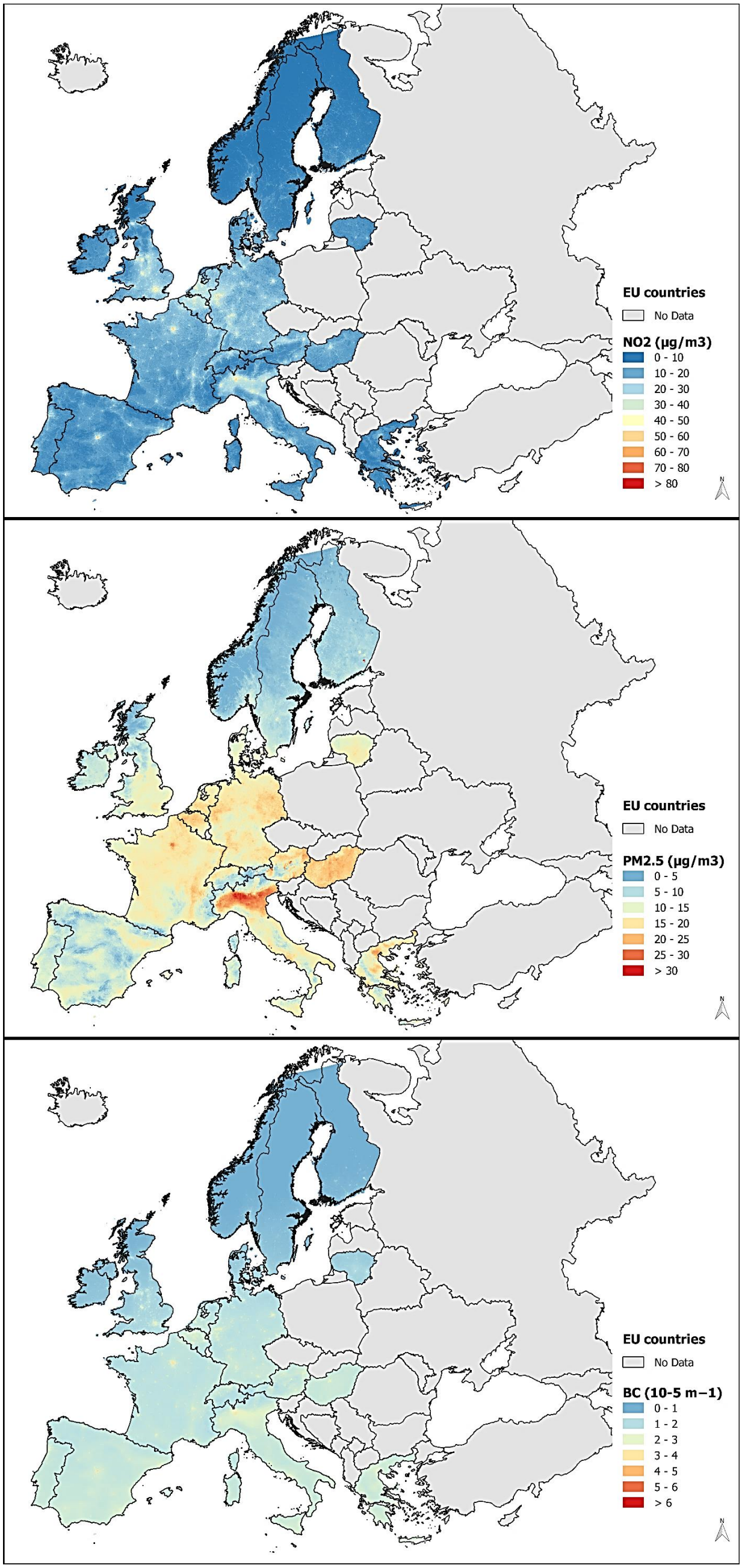

Figure 1: NO_2, $PM_{2.5}$ and BC levels in the study area as estimated from at the original 100 m x 100 m grid resolution. NO_2: Nitrogen Dioxide; $PM_{2.5}$: Particulate Matter equal or less than 2.5 micrometers in diameter; BC: $PM_{2.5}$ absorbance/ black carbon

Table 1 shows the BoD estimates in association with the first exposure reduction scenario: the reduction of air pollution levels to comply with the WHO air quality guideline values, when in exceedance. Overall, compliance with the NO_2 WHO annual guideline value was estimated to prevent 2,434 new cases of childhood asthma a year (95% CI, 1,020 – 3,307) or 0.4% of all annual cases of childhood asthma. Compliance with the $PM_{2.5}$ WHO annual guideline value was estimated to prevent 66,567 new cases of childhood asthma a year (95% CI, 32,213 – 108,617) or 11% of all annual cases of childhood asthma. The variations in the BoD estimates between the countries was also notable as shown in Table 1. Depending on the percentage of attributable cases, Spain was estimated to benefit the most from complying with the WHO NO_2 air quality guideline value, potentially preventing 1.6% of all its annual cases of childhood asthma. On the other hand, Finland, Hungary, Ireland, Lithuania, and Norway had no grid cells exceeding the WHO NO_2 air quality guideline. In terms of compliance with the $PM_{2.5}$ WHO air quality guideline value, Hungary was estimated to benefit the most from complying, potentially preventing 24% of all its annual cases of childhood asthma, whilst Finland was estimated to benefit the least, potentially preventing 0.2% of all its annual cases.

Stratifying the results by age group for young children between 1 and 4 years old and children aged 5-14 years old yielded similar results, as shown in Tables S4 and S5.

For young children between 1 and 4 years old (17,528,813 kids), compliance with the NO_2 WHO annual guideline value was estimated to prevent 1,288 new cases of childhood asthma a year (95% CI, 540 – 1,750), or 0.4% of all annual cases of childhood asthma, whilst compliance with the $PM_{2.5}$ WHO annual guideline value was estimated to prevent 36,471 new cases of childhood asthma a year (95% CI, 13,147 – 56,465), or almost 12% of all annual cases of childhood asthma. On the other hand, for children aged 5-14 years old (45,913,606 kids), compliance with the NO_2 WHO annual guideline value was estimated to prevent 1,146 new cases of childhood asthma a year (95% CI, 480 – 1,557), or 0.4% of all annual cases of childhood asthma, whilst compliance with the $PM_{2.5}$ WHO annual guideline value was estimated to prevent 30,095 new cases of childhood asthma a year (95% CI, 19,056 – 52,152), or 11% of all annual cases of childhood asthma. The variations in the BoD estimates between the countries was similar to the overall analysis.

Table 2, on the other hand, shows the BoD estimates in association with the second exposure reduction scenario: meeting the minimum air pollution levels recorded in any of the 41 studies synthesized in the most recent systematic review on TRAP and risk of incident childhood asthma [6]. Overall, meeting the minimum air pollution level for NO_2 was estimated to prevent 135,257 new cases of childhood asthma a year (95% CI, 60,187 – 177,093), or 23% of all annual cases of childhood asthma. Meeting the minimum air pollution level for $PM_{2.5}$ was estimated to prevent 191,883 new cases of childhood asthma a year (95% CI, 74,198 – 278,802), or 33% of all annual cases of childhood asthma. Meeting the minimum air pollution level for BC was estimated to prevent 89,191 new cases of childhood asthma a year (95% CI, 36,461 – 141,764), or 15% of all annual cases of childhood asthma. The variations in the BoD estimates between the countries was also notable as shown in Table 2 and depended on the pollutant selected in the analysis. For example, Belgium and the Netherlands are the countries that would benefit the most from the absolute reduction of NO_2 levels (29% of all annual cases of childhood asthma may be prevented), whilst for $PM_{2.5}$ and BC, respectively, the countries that would benefit the most were Hungary (43%) and Greece (23%).

Stratifying the results by age group for young children between 1 and 4 years old and children aged 5-14 years old yielded similar results, as shown in Tables S6 and S7.

For young children between 1 and 4 years old (17,528,813 kids), meeting the minimum air pollution level for NO_2 was estimated to prevent 72,497 new cases of childhood asthma a year (95% CI, 32,265 – 94,910), or 23% of all annual cases of childhood asthma, whilst meeting the minimum air pollution level for $PM_{2.5}$ and BC was estimated to prevent 101,792 new cases of childhood asthma a year (95% CI, 39,307 - 148,074), or 33% of all annual cases of childhood asthma and 47,139 new cases of childhood asthma a year (95% CI, 19,262 - 74,962), or 15% of all annual cases of childhood asthma, respectively. The percentage of attributable cases was also similar in the older age group. The variations in the BoD estimates between the countries was similar to the overall analysis.

Table 1: burden of disease results with WHO air quality guidelines scenario – children between 1 and 14 years old

Country	Children population assessed (#)	NO_2 – WHO guideline value*				$PM_{2.5}$ – WHO guideline value**			
		Percentage of total cases attributable to the exposure scenario (%)	Attributable expected cases	LCI	UCI	Percentage of total cases attributable to the exposure scenario (%)	Attributable expected cases	LCI	UCI
Austria	1,165,734	0.10	9	4	13	21.74	2,083	765	3,167
Belgium	1,788,001	0.72	99	41	135	21.31	2,924	1,067	4,468
Denmark	899,709	0.01	0.47	0.19	0.65	5.81	537	186	862
Finland	840,626	0.00	0	0	0	0.19	14	5	23
France	11,234,118	0.62	632	264	860	16.67	16,860	6,114	25,950
Germany	10,459,150	0.10	70	29	96	10.95	7,815	10,982	17,841
Greece	1,413,106	0.81	90	37	123	18.32	2,036	739	3,130
Hungary	1,319,551	0.00	0	0	0	24.61	2,801	1,034	4,234
Ireland	966,048	0.00	0	0	0	0.46	50	17	82
Italy	7,791,095	0.56	295	124	400	20.84	11,001	4,119	16,471
Lithuania	390,930	0.00	0	0	0	10.79	426	150	673
Netherlands	2,625,237	0.42	80	33	109	18.01	3,456	1,245	5,347
Norway	873,491	0.00	0	0	0	0.83	99	34	161
Portugal	1,388,377	0.08	12	5	17	4.39	714	247	1,147
Spain	6,579,656	1.60	736	312	993	7.85	3,603	1,266	5,710
Sweden	1,628,914	0.00	0.09	0.04	0.12	1.10	214	74	345
Switzerland	1,172,805	0.02	2	1	3	14.17	1,523	544	2,374
United Kingdom	10,905,872	0.27	408	170	558	6.81	10,409	3,624	16,633
Total	63,442,419	0.42	2,434	1,020	3,307	11.49	66,567	32,213	108,617

* NO_2 reduced to 40 µg/m^3 (annual average), where in exceedance

** $PM_{2.5}$ reduced to 10 µg/m^3 (annual average), where in exceedance

Abbreviations: NO_2: Nitrogen Dioxide; $PM_{2.5}$: Particulate Matter equal or less than 2.5 micrometers in diameter; WHO: World Health Organization; LCI: Lower Confidence Interval; UCI: Upper Confidence Interval

Table 2: burden of disease results with minimum air pollution levels scenario – children between 1 to 14 years old

Country	Children population assessed (#)	NO_2*				$PM_{2.5}$**				BC***			
		Percentage of total cases attributable to the exposure scenario (%)	Attributable expected cases	LCI	UCI	Percentage of total cases attributable to the exposure scenario (%)	Attributable expected cases	LCI	UCI	Percentage of total cases attributable to the exposure scenario (%)	Attributable expected cases	LCI	UCI
Austria	1,165,734	23	2,159	955	2,837	39	3,755	1,490	5,333	19	1,824	751	2,876
Belgium	1,788,001	29	3,931	1,770	5,108	41	5,591	2,220	7,928	19	2,646	1,088	4,178
Denmark	899,709	19	1,763	770	2,334	29	2,680	1,008	3,985	9	815	325	1,331
Finland	840,626	14	1,077	463	1,440	18	1,377	497	2,126	3	217	86	360
France	11,234,118	23	22,879	10,179	29,966	37	37,638	14,754	54,009	18	17,921	7,361	28,341
Germany	10,459,150	24	16,897	7,474	22,199	37	26,287	10,256	37,854	16	11,231	4,561	17,975
Greece	1,413,106	22	2,409	1,082	3,138	38	4,269	1,680	6,101	23	2,553	1,067	3,963
Hungary	1,319,551	18	2,021	876	2,688	43	4,920	1,977	6,907	18	2,019	824	3,212
Ireland	966,048	14	1,500	645	2,006	22	2,373	866	3,627	5	558	221	917
Italy	7,791,095	24	12,518	5,579	16,376	40	21,289	8,538	30,003	20	10,820	4,470	16,996
Lithuania	390,930	14	551	235	739	33	1,296	496	1,898	9	366	146	599
Netherlands	2,625,237	29	5,654	2,551	7,338	38	7,343	2,880	10,524	16	3,129	1,273	4,999
Norway	873,491	15	1,740	752	2,319	19	2,323	846	3,559	3	373	147	615
Portugal	1,388,377	21	3,362	1,480	4,430	27	4,387	1,640	6,563	19	3,113	1,280	4,915
Spain	6,579,656	25	11,356	5,116	14,765	30	13,768	5,220	20,339	21	9,721	4,031	15,211
Sweden	1,628,914	16	3,035	1,314	4,041	20	3,908	1,425	5,982	5	892	352	1,472
Switzerland	1,172,805	22	2,317	1,018	3,056	35	3,783	1,466	5,479	17	1,855	757	2,951
United Kingdom	10,905,872	26	40,088	17,927	52,314	29	44,895	16,939	66,585	13	19,139	7,721	30,855
Total	63,442,419	23	135,257	60,187	177,093	33	191,883	74,198	278,802	15	89,191	36,461	141,764

* NO_2 reduced to 1.5 µg/m^3 (annual average) as recorded in Oftedal et al, (2009), where in exceedance

** $PM_{2.5}$ reduced to 0.4 µg/m^3 (annual average) as recorded in Fuertes et al, (2013), where in exceedance

*** BC reduced to 0.4 x $10^{-5}m^{-1}$ (annual average) as recorded in Gehring et al, (2015), where in exceedance

Abbreviations: NO_2: Nitrogen Dioxide; $PM_{2.5}$: Particulate Matter equal or less than 2.5 micrometers in diameter; BC: $PM_{2.5}$ absorbance/ black carbon; WHO: World Health Organization; LCI: Lower Confidence Interval; UCI: Upper Confidence Interval

4. Discussion

4.1. Summary and Comparison to other Studies

In this study, we estimated that up to 33% of all childhood asthma cases could be attributed to air pollution exposures ($PM_{2.5}$) in 18 European countries and 63,442,419 children from 1 to 14 years old. These cases are potentially preventable. We also found that the attributable percentage of cases varies according to the pollutant studied (23% for NO_2 and 15% for BC), and the exposure reduction scenario investigated. The attributable percentage of cases was not sensitive to the use of age-specific asthma incidence rates as shown in our stratified analysis for the age groups 1-4 and 5-14 years old.

This study significantly expands on the coverage of previous similar BoD assessments and offers wider estimates. It also highlights the variations in air pollution exposures and associated BoD across 18 European countries, using harmonized LUR models. Our analysis suggested that compliance with the NO_2 WHO air quality guideline value could prevent 2,434 (or 0.4% of all) childhood asthma cases from developing, per year. Compliance with the $PM_{2.5}$ WHO air quality guideline value, however, had a larger impact with an estimated 66,567 (or 11%) preventable incident childhood asthma cases, per year. We, however, believe that the current WHO air quality guideline values are outdated and require update and lowering, which is currently underway. Using lower thresholds in the future may therefore result in an even larger burden.

Further, whilst we believe that the WHO air quality guideline values for both pollutants (NO_2 and $PM_{2.5}$) offer useful policy references and compliance scenarios, there is in fact no evidence that the risk of developing childhood asthma does not increase under these "thresholds" [6, 29]. Instead, policy efforts should aim at reducing air pollution levels as much as possible. As such, we also tested the impacts of reducing the air pollution levels to meet the minimum levels recorded in any of the 41 studies synthesized in the most recent systematic review on TRAP and the risk of incident childhood asthma, from which we sourced our exposure-response functions [6]. The analysis of this scenario suggested that meeting minimum levels as recorded in the literature for NO_2, $PM_{2.5}$ and BC, respectively, can prevent 135,257 (or 23%), 191,883 (or 33%) and 89,191 (or 15% of all) childhood asthma cases from developing, per year.

These estimates are in line with two previous English studies which found that the percentage of annual incident childhood asthma attributable to all NO_2 (i.e. exposure elimination scenario) was 22% [20], whilst the percentage of annual incident childhood asthma attributable to eliminating all $PM_{2.5}$ and BC was 27% and 15%, respectively [22]. The only European-focused analysis previously published on this topic [17], estimated that exposure to roads with high vehicle traffic, a proxy for near road traffic-related air pollution, accounted for 14% of all asthma *prevalent* cases. As such, our study's BoD estimates were higher than the only previous European analysis, which may be explained by the different exposure models we used and the fact that our LUR model's air pollution estimates incorporate air pollution from sources beyond traffic. Interestingly, however, the BC's BoD estimates in this study (15%) were very comparable to the BoD estimates in association with proximity to roads with high traffic in the previous European analysis (14%) [17]. BC is indeed a relatively specific marker for traffic in urban Europe [31], especially truck traffic [32], and these similar estimates might reflect traffic as a common source of air pollution and the attributable burden. Further, during the write-up of this paper, two more recent BoD analyses were also published. The first, which was conducted for the contiguous United States across 48 states and the District of Columbia, attributed 18% of all childhood asthma cases in 2010 to NO_2, a fairly

specific marker of TRAP [23]. The second, which was conducted for 194 countries across the world, attributed 13% of *global* incidence to NO_2, whilst the European analysis subset reported in the same paper estimated that 17% of the burden in Western Europe, 14% in Central Europe and 17% in Eastern Europe were attributable to NO_2 [33]. All of the above estimates, which have mostly emerged in the past two years, are similar and strengthen the case from different research teams that air pollution is contributing substantially to the burden of childhood asthma.

4.2. Strengths and limitations

Thus far, our study offers one of the widest coverages of the burden of incident childhood asthma attributable to outdoor air pollution, with a specific focus on Europe. It is the first study that investigates the childhood asthma BoD in association to three common air pollutants which have been associated with increased risk of onset childhood asthma, given that the most relevant pollutant to be included in the analysis remains unknown. Our analysis allows for comparison across 18 European countries, using harmonized air quality assessment models. We also used a validated set of LUR models to assess exposure to three ubiquitous air pollutants (NO_2, $PM_{2.5}$ and BC), and showed that the BoD estimates vary across the different pollutants but are comparable to previous similar studies. We used pooled exposure-response functions of continuous pollutant exposures [6], as opposed to an exposure-response function from a single study relying on a traffic proximity exposure measure [34], as has been done in the past European assessment [17]. In the absence of location-specific and population-specific exposure-response functions, we believe that using a pooled exposure-response function is more appropriate when extrapolating risk estimates to different locations and diverse populations.

Although individual studies included in the pooled exposure-response function underlying our analysis adjusted for major confounders that can also increase the risk of childhood asthma onset (e.g. socioeconomic status, smoking, parental atopy) [6], there were no specific exposure-response functions based on these variables (e.g. an exposure-response function for low versus high median household income), and as such we could not account for this in our analysis. This is a persistent limitation in BoD studies which generally rely on published epidemiological literature to source appropriate exposure-response functions. So far, the assessment of exposure-response functions has been done in an aggregate manner that does not consider sub-populations or stratify by potential effect modifiers, such as socioeconomic factors, and this is especially true in the case of childhood asthma onset in association to air pollution [6]. The pooled exposure-response functions we used were pollutant-specific and as such were better suited to capture the impact of the spatial variability of pollutants; allowing us to investigate the different impacts attributable to the different pollutants. The most suitable pollutant to be used in future BoD exercises, however, is unclear, may depend on the source of air pollution of interest and should be considered in the context of the wider literature and toxicological evidence. Finally, the BoD estimates we present in this paper offer new basis for the monetization of health impacts associated with outdoor air pollution in Europe.

On the other hand, a key limitation of this analysis is the use of exposure estimates at the 1 km x 1 km grid cell scale. Unfortunately, the total population counts were available at the 1 km x 1 km grid cell scale. As such, we conducted our exposure assessment at the same spatial resolution. Currently, the impact of averaging exposures at this coarser geographical scale on the BoD estimates is unknown and warrants further investigation. However, in the context of the literature, this analysis advances previous efforts and better accounts for the spatial distribution of air pollution, across a range of three ubiquitous

air pollutants [17], which have not been systematically included in previous BoD assessments. We also only assigned exposures at the 1 km x 1 km grid cell scale in which residential locations/addresses fell. There is well-established spatiotemporal variability in air pollution exposures at the indoor, outdoor and personal levels [35, 36], including for children who spend several hours at schools where the exposure can differ from their residential addresses. However, the currently available data did not allow us to consider activity patterns in the assessment of children's exposure to the three pollutants, and the attributable health impacts, partly due to the large sample size of this analysis (> 63 million children). This is a common limitation in large burden of disease assessments. Despite not being able to account for children's activity patterns in our analysis, the pooled exposure-response functions we used were predominantly based on residential locations and long-term/annual average air pollution concentrations [6], and as such, support the use of the grid cell scale in which residential locations fell in this instance. Further, there is evidence in the literature that the associations between new onset asthma and modeled air pollution exposures are slightly stronger at home than at school, although strongest when both home and school exposures are combined [37]. Our analysis also generally gives a good spatial representation of Northern, Central and Southern Europe, but not Eastern Europe. Eastern Europe was not included in the analyses due to the unavailability of the three pollutants' exposure data in that region. This is a key data gap which future research should aim to fill, especially that air pollution concentrations are known to be high in Eastern Europe.

Other limitations relate to uncertainty in the underlying asthma incidence rates, the exposure-response functions and the assumption that outdoor air pollution is causally associated with the development of childhood asthma.

First, asthma is a complex and heterogeneous disease with a challenging diagnosis and challenges in the data collection and harmonization due to the use of different tools (health surveys and records) between, and within, countries, and even among local health structures. The variations of asthma incidence rates across Europe cannot be solely explained by variations in air pollution levels. This could be due to the differences in country's asthma incidence rates which may be strongly influenced by the structure of national health services and diagnosis practices that are known to vary by country. Also, it is well-established that the risk of asthma incidence is impacted by a wide variety of factors beyond air pollution, which have been generally associated with larger risk estimates, but which we could not directly account for in our BoD. These factors include a family history of asthma as there is a strong familial clustering of the disease, a family history of allergic conditions such as atopic dermatitis, rhinitis, and food allergy, early-life upper and lower respiratory tract infections, exposures to indoor allergens, and others. Variations in these factors may better explain variations in incidence rates across Europe. Incidence rates also are influenced by other factors, including the structure of national health services and heterogeneities among local health structures. This study provides a national level assessment, using national incidence rates from the Global Burden of Disease project to each unit of analysis (1 km x 1 km grid cell scale). For this reason, we were not able to provide the expected subnational geographical variability in asthma incidence rates, that could be expected from heterogeneity in national, regional and local health structures. Finally, the three pollutants we used in our analysis might be surrogates for the true putative agents in the air pollution mixture, which remain unknown and unmeasured, and may better explain variations in incidence.

Asthma diagnosis also differs by age. To address this latter point, we re-ran all our analyses using age-specific asthma incidence rate, stratifying the results in two age groups indexed in the GBD datasets: 1-4

and 5-14 years old. The age-specific analysis yielded similar results to the overall aggregate analysis. Second, there is statistical uncertainty associated with the risk estimates that were sourced from the pooled exposure-response functions. We, however, have provided a range of this uncertainty by using the lower and upper confidence intervals and estimating a range for the BoD associated with each central estimate. Further, the individual studies included in the underlying meta-analyses did not adjust for co-pollutants. Therefore, the incident asthma cases attributable to NO_2, $PM_{2.5}$ and BC should not be added up, but instead viewed as independent estimates of the potential impact of outdoor air pollution on childhood asthma burden. Indeed, the correlation between the three pollutants we investigated was moderate to high, ranging from 0.67 (between NO_2 and BC) to 0.81 (between $PM_{2.5}$ and BC).

Another important question that remains open is which are the putative agents in the air pollution mixture? Our analysis is underlined by the assumption that outdoor air pollution is associated with the onset of childhood asthma. Although we believe that there is sufficient evidence now to support an association between the exposure to TRAP and the development of childhood asthma, the evidence is less clear for generic outdoor air pollution (i.e. air pollution not associated with traffic sources) [6, 38], and is better established in relation to exposures during early life, specifically the first 3 years of life [6]. As such, the smaller BoD estimates in association with NO_2 and BC, despite potentially not being the putative agents, could be a better representation of the true burden, as these pollutants are more specific markers for traffic than $PM_{2.5}$ [39-41]. This, however, is an open question. Whether pollutants act in single or multiple causal pathways leading to the development of asthma is unknown. Although the assumption underlying our analyses and the exposure-response functions we used is that childhood and early-life in particular represent the most critical exposure windows, it can be that exposures in later life also contribute to the development of asthma. Studies systematically investigating associations with multiple windows of exposures are few and more research to establish these associations, and how later-life exposures might impact the risk of asthma onset differently, is needed.

4.3. Research and policy recommendations

Future research can usefully develop and match population and exposure maps at a finer spatial resolution and assess the impacts of averaging exposures at the 1 km x 1 km scale on final BoD estimates. There is currently little knowledge on the impact of the exposure assessment's spatial resolution on BoD estimates. The potential future availability of population and underlying baseline asthma rates at smaller geographical scale can advance current knowledge. Similarly, a more accurate representation of mobility and resulting exposure patterns is under-investigated in BoD assessment studies overall, likely owning to the large coverage of such analyses which typically include hundreds of thousands to millions of people. The exposure assessment method we used in this study did not allow us to trace certain proportions of the BoD back to the air pollution sources responsible. The use of dispersion models, for example, which can specify the contribution of traffic to the overall air pollution and asthma burden can provide further insights, but again such models have not been typically used in large BoD studies and they require severe data, software and expertise demands [42]. Future work should also investigate the differential effects of air pollution exposure on childhood asthma development, by different susceptibility factors, for example, ethnicity, socio-economic status, age and sex. The populations included this analysis are likely to have very different underlying susceptibility factors. Yet, these factors and the resulting differential burden cannot be considered given the current lack of subgroup specific exposure-response functions. Future work would also benefit from exposure-response functions adjusted by other pollutants. At present, a distinction of pollutant-specific effects is not possible.

Our results suggest that compliance with the NO_2 WHO air quality guideline value may prevent 2,434 (or 0.4% of all) childhood asthma cases from developing, per year, whilst compliance with the $PM_{2.5}$ WHO air quality guideline value may prevent 66,567 (or 11%) incident childhood asthma cases, per year. There is no evidence that the risk of developing childhood asthma does not increase under these "thresholds" [6, 29], and policy efforts should reduce exposure levels as much as possible.

The attribution of incident asthma cases to air pollution has substantial implications for the burden of asthma-related exacerbations as well. As air pollution increases the risk of developing new asthma cases, all future acute exacerbations of these cases, regardless of subsequent (immediate) causes of the exacerbations, should be again attributed to air pollution. This conceptual model has been previously followed in the literature where the BoD estimates attributable to air pollution were revised to account not only for asthma symptoms that are directly triggered by air pollution; but also for asthma symptoms triggered by other causes in children who developed asthma because of air pollution. The result was a significantly higher BoD estimate and perhaps a more realistic picture of the societal and economic impact of air pollution [16, 43]. Largely, these impacts are preventable and there are numerous transport and land-use policy measures at the city level which can reduce the ambient levels of and exposures to outdoor air pollution [44].

5. Conclusions

In conclusion, we estimated that, per year, 0.4% and 11% of all incident childhood asthma cases across 18 European countries may be prevented by complying with the WHO air quality guideline values for NO_2 and $PM_{2.5}$, respectively. These results suggest that the current NO_2 air quality guideline provides less protection than the $PM_{2.5}$ guideline, in light of the most recent evidence that there is no threshold for these pollutants under which no health effects occur. Both values may require update and lowering to be better suited for protecting children's health. A much larger proportion of incident childhood asthma cases (15% - 33%) could be prevented by lowering NO_2, $PM_{2.5}$ and BC levels to minimum levels recorded in the literature; a relevant issue given the lack of evidence that a safe air pollution threshold exists. Our estimates are larger than previous documentation and underline the urgent need to reduce children's air pollution exposure across Europe. We also showed that the selection of pollutant in the BoD assessment makes a measurable impact on final estimates. The most suitable pollutant to be used in future BoD exercises, however, is unclear, may depend on the source of air pollution of most interest and should be considered in the context of the available toxicological evidence and biological plausibility. In summary, there is an urgent need to reduce children's exposure to air pollution.

Tables

Figures

Supplementary Material - Datasets and Methods

Census data

The total population count at the 1 km x 1 km grid cell unit was extracted from the GEOSTAT 2011 population grid (V2.0.1) database (Eurostat EFGS, 2011). This database was a joint initiative between Eurostat and European Forum for Geography and Statistics (EFGS), which contains national population grid information for European countries. The GEOSTAT database did not specifically include childhood population counts. To calculate the childhood population count in each grid, which was our population of interest, the percentage of people aged 1 to 14 years old was extracted from the NUTS 3 dataset (Nomenclature of Territorial Units for Statistics, Eurostat, European Commission, version 2010) at the regional scale, which are the smallest available regions for statistical purposes. The NUTS classification is a hierarchical system for dividing the economic territory of the European Union for different purposes. NUTS 3 level contains 1,566 regions within European countries and represents the regional unit for socio-economic statistics. We multiplied the percentage of people aged 1 to 14 from each region by the total population count, as extracted from the GEOSTAT population grid database, to calculate the childhood population count at the 1 km x 1 km grid cell scale. Unfortunately, at the 1 km x 1 km scale of our analysis, we had no source of data on childhood population count from age 0 to 18 years old. The older childhood group (>14 to 18 years old) was mixed with adults (15-29), and as such we performed our analysis exclusively for the age group 1 to 14 years old. We also stratified our analysis by age and present results for young children under 5 years old and children aged 5-14 years old.

Exposure assessment model and data

Childhood exposures to NO_2, $PM_{2.5}$ and BC were assessed at the 1 km x 1 km scale using a validated LUR model, which is described next. LUR modeling is an increasingly popular empirical air pollution modeling technique which uses predictor variables such as land-use, geographic, road and traffic characteristics to explain spatial variations of measured air pollution concentrations at multiple sites across the study area [25].

The set of LUR models we use comes from work reported in de Hoogh, Chen [24], where the authors modeled NO_2, $PM_{2.5}$ and BC annual mean 2010 exposures at the 100 m x 100 m grid cell scale. The LUR models were developed on the full monitoring data set (100%) and a robust validation was performed by developing five hold-out-validation models (on 80% of sites) and comparing the measured concentrations against the predictions at the five (20% each) hold-out samples. Another difference with the original founding LUR models reported in previous work by de Hoogh, Gulliver [45] was the additional step in the $PM_{2.5}$ model's development to explain the residual spatial variation at urban and rural background sites only, using ordinary kriging.

For NO_2, the final model adopted included the following predictor variables: chemical transport model estimates, all roads (50, 300 and 2000m), major roads (100m), natural area (400m), ports (700m) and residential area (300m). The adjusted R^2 of this model equaled 0.59 whilst the hold-out-validation R^2 equaled 0.58. *For $PM_{2.5}$*, the final model adopted included the following predictor variables: satellite and chemical transport model estimates, all roads (100m), natural area (50m), ports (800m), residential area (200m) and altitude and additional ordinary kriging was applied to the residuals. The adjusted R^2 of this model equaled 0.72 (0.62 before kriging) whilst the hold-out-validation R^2 equaled 0.66 (0.59 before kriging). *For BC*, the final model adopted included the following predictor variables: satellite and chemical transport model estimates, length of major roads within 100m, all roads (50 and 700m), residential area (3000m), urban green (1000m) and latitude.

The adjusted R^2 of this model equaled 0.54 whilst the hold-out-validation R^2 equaled 0.51. Full detail on these models' development and performance/validation can be found in de Hoogh, Chen [24]. All three models were used to estimate NO_2, $PM_{2.5}$ exposures (in $\mu g/m^3$), and BC (in 10^{-5} m^{-1}), at the 100 m x 100 m grid cell scale, across the 18 countries in our study area (section 2.1).

Matching of census and exposure data

To match the childhood population data with the exposure estimates, the NO_2, $PM_{2.5}$ and BC exposure estimates from the LUR model (section 2.3) were averaged up from the 100 m x 100 m grid cell to the 1 km x 1 km grid cell, as this was the finest scale at which census population data was available. Therefore, for each 1 km x 1 km grid cell across our study area, an average exposure estimate was calculated, based on all the 100 m x 100 m grid cells contained within each 1 km x 1 km grid cell. This average exposure estimate was then assigned to all children who lived within that 1 km x 1 km grid cell. There were 1,540,386 1 km x 1 km grid cells across the 18 included countries which had complete data, and which we included in our analysis. The exposure and population characteristics in these 1 km x 1 km grid cells are shown in Table S1, below.

Table S1 Population and exposure characteristics at the 1 km x 1 km grid cells across the 18 selected countries

Population characteristics		
Number of total 1 km x 1 km grid cells across the 18 selected countries (with complete population and air pollution data)	1,540,386	
Total number of children in all included 1 km x 1 km grid cells (1 – 14y.o.)	63,4 M	
Average number of children in all included 1 km x 1 km grid cells (1 – 14 y.o.)	43	
Minimum number of children in any included 1 km x 1 km grid cell (1 – 14 y.o.)	1	
Maximum number of children in any included 1 km x 1 km grid cell (1 – 14 y.o.)	8,141	
Exposure characteristics		
NO_2 ($\mu g/m^3$)	Mean (sd)	11.8 (6.7)
	Minimum	1.4
	25^{th} percentile	7.0
	Median	10.6
	75^{th} percentile	15.4
	Maximum	70.0
$PM_{2.5}$ ($\mu g/m^3$)	Mean (sd)	11.6 (4.6)
	Minimum	2.0
	25^{th} percentile	8.2
	Median	12.1
	75^{th} percentile	14.5
	Maximum	41.1
BC (10^{-5} m^{-1})	Mean (sd)	1.0 (0.5)
	Minimum	0.003
	25^{th} percentile	0.7
	Median	1.2
	75^{th} percentile	1.4
	Maximum	3.7

Abbreviations: NO_2: Nitrogen Dioxide; $PM_{2.5}$: Particulate Matter equal or less than 2.5 micrometers in diameter; BC: $PM_{2.5}$ absorbance/ black carbon; km: kilometers; y.o.: years old; sd: standard deviation

Baseline childhood asthma incidence rates

Incidence rates were extracted at the country level for the year 2016, which, at the time of this analysis, was the latest and theoretically the best available assessment as more input data became available in recent years. The GBD data uses public and official health data records reported from health surveys and clinical records. Between year 2010 (the year of the air pollution exposure assessment) and year 2016 (the year of the asthma incidence rates assessment), the average childhood asthma incidence rate across the 18 included countries decreased by 2% (Global Burden of Disease Collaborative Network, 2016). Additional information can be found at GHDx (http://ghdx.healthdata.org/gbd-results-tool).

Incidence rates in the age group 1-4 and 5-14 years old, were directly provided by the GBD, and no further analysis was required to establish the baseline asthma incidence rates used in the age-stratified analyses. For the wider age group 1-14 years old, the GBD did not directly provide the incidence rate for this specific group. Instead, we estimated the number of cases in the 1-4 and 5-14 years old age groups and summed these cases to represent the burden in the age group 1-14 years old.

Table S2 Baseline childhood asthma incidence rates by country, source: (Global Burden of Disease Collaborative Network, 2016)

Country	**Childhood asthma incidence rate 1-4 years old** **Year 2016 (cases per 100,000 person-years)**
Austria	1592
Belgium	1488
Denmark	2017
Finland	1776
France	1730
Germany	1244
Greece	1554
Hungary	1570
Ireland	2293
Italy	1128
Lithuania	1681
Netherlands	1459
Norway	2780
Portugal	2487
Spain	1382
Sweden	2160
Switzerland	1766
United Kingdom	2820
Country	**Childhood asthma incidence rate 5-14 years old** **Year 2016 (cases per 100,000 person-years)**
Austria	514
Belgium	479
Denmark	676
Finland	569
France	583
Germany	470
Greece	514
Hungary	598
Ireland	677

Italy	513
Lithuania	722
Netherlands	464
Norway	821
Portugal	744
Spain	447
Sweden	809
Switzerland	561
United Kingdom	823

Estimation of the impact of exposure reduction scenarios

We assessed the impacts of two plausible scenarios on the burden of incident childhood asthma:

1. Where in exceedance, the reduction of air pollution levels to comply with the World Health Organization (WHO) air quality guideline values [28]. This scenario was applicable to two of the three studied pollutants, as BC has no air quality guideline value:
    a. **NO_2 reduced to 40 µg/m^3** (annual average), where in exceedance;
    b. **$PM_{2.5}$ reduced to 10 µg/m^3** (annual average), where in exceedance.
2. Where in exceedance, the reduction of air pollution levels to meet the minimum air pollution levels recorded across any of the 41 studies synthesized in the underlying systematic review from which we sourced our exposure-response functions [6]:
    a. **NO_2 reduced to 1.5 µg/m^3** (annual average) as recorded in Oftedal, Nystad [46], where in exceedance;
    b. **$PM_{2.5}$ reduced to 0.4 µg/m^3** (annual average) as recorded in Fuertes, Standl [47], where in exceedance.
    c. **BC reduced to 0.4 x 10^{-5} m^{-1}** (annual average) as recorded in Gehring, Wijga [48], where in exceedance;

Estimation of population attributable fraction and attributable number of cases

Using the exposure-response functions shown in section 2.5.2, the risk estimates for asthma development in association with the three investigated pollutants were scaled to the difference in exposure level between the two counterfactual scenarios (section 2.5.3) and the reference scenario (current exposure as estimated from the LUR model). Each analysis was undertaken for each pollutant separately and at the 1 km x 1 km grid cell. To scale the risk estimate from the exposure-response functions' concentration unit to the exposure difference between the reference and the two counterfactual scenarios, standard methods were used [30], where:

$$RR_{exposure\_difference} = e^{\left(\left(\frac{\ln RR}{E_{RR\_unit}}\right)\times E_{exposure\_difference}\right)}$$

Where *RR* is the relative risk obtained from the exposure-response function for each pollutant (section 2.5.2.);

E_{RR_unit} is the exposure unit that corresponds to the RR obtained from the exposure-response function for each pollutant (section 2.5.2.);

$E_{exposure\_difference}$ is the difference in the exposure level between the counterfactual scenario (section 2.5.3.) and the reference scenario (current exposure);

$RR_{exposure\_difference}$ is the scaled relative risk that corresponds to the difference in exposure level between the counterfactual (section 2.5.3.) and reference (current exposure) scenarios.

Next, the population attributable fraction (PAF) was calculated, also for each 1 km x 1 km grid cell, pollutant and scenario. The PAF is an epidemiological measure that is widely used in BoD and health impact assessments to identify the fraction of all cases of a particular health outcome in a population that is attributable to a specific exposure [49]. As such, it defines the proportional reduction in morbidity that would occur if the specific exposure, to outdoor air pollution in this case, was reduced to the counterfactual exposure scenario(s):

$$PAF = \frac{\sum_{i=1}^{n} P\,(RR_{exposure\_difference} - 1)}{\sum_{i=1}^{n} P\,(RR_{exposure\ difference} - 1) + 1}$$

Where P is the proportion of the exposed population (100% assumed);

$RR_{exposure\_difference}$ is the previously scaled RR that corresponds to the difference in the exposure level between the counterfactual scenario (section 2.5.3.) and the reference scenario (current exposure);

n is the number of exposure levels (1 in this case).

Finally, the number of incident childhood asthma cases attributable to the excess exposure compared to the counterfactual exposure scenarios was calculated as follows, separately for each cell, pollutant and scenario:

$$Attributable\ number\ of\ asthma\ cases = PAF * expected\ asthma\ cases\ due\ to\ all\ causes$$

Where:

$$Expected\ asthma\ cases\ due\ to\ all\ causes$$
$$= childhood\ population * baseline\ childhood\ asthma\ incidence\ rate$$

The confidence intervals around the central values were estimated using the confidence intervals around the exposure-response functions, as provided by the underlying meta-analysis (Khreis et al. 2017). Confidence intervals were estimated for each cell, pollutant and scenario, and then added to estimate the total country values, as done for the central estimate.

Supplementary Material – Results

Table S3: summary statistics for exposures in each of the 18 included countries

	NO_2 ($\mu g/m^3$)					$PM_{2.5}$ ($\mu g/m^3$)					BC (10^{-5} m^{-1})				
Country	Mean	sd	min	max	median	mean	sd	min	max	median	mean	sd	min	max	median
Austria	13.86	4.98	2.34	44	13.62	14.72	3.86	2.05	41.1	15.14	1.42	0.2	0.75	2.84	1.42
Belgium	21.5	5.72	7.6	56.36	21.47	16.42	2.32	8.52	22.29	17.05	1.48	0.23	0.98	2.97	1.46
Denmark	10.33	3.35	3.68	42.76	9.69	10.61	1.25	5.87	19.13	10.57	0.67	0.16	0.15	2.3	0.66
Finland	4.6	3.02	1.4	36.66	3.86	4.53	1.53	2.05	31.74	4.37	0.1	0.14	0	1.67	0.05
France	11.34	4.58	1.4	58.42	10.51	13.17	2.26	2.05	28.01	13.32	1.21	0.18	0.81	3.39	1.18
Germany	16.53	5.01	3.7	50.99	15.65	14.33	2.15	2.76	23.46	14.28	1.24	0.22	0.65	2.74	1.23
Greece	8.6	5.39	1.4	60.89	7.6	14.14	3.03	3.13	23.26	14.27	1.64	0.19	1.28	3.48	1.62
Hungary	11.52	3.74	3.57	39.39	10.69	18.4	1.37	11.58	23.75	18.42	1.47	0.13	1.19	2.66	1.44
Ireland	6.48	2.64	1.4	37.71	6.37	7.12	1.11	2.38	13.16	7.32	0.43	0.11	0.14	1.92	0.43
Italy	14.49	7.23	1.4	63.96	12.74	15.34	5.24	2.05	31.15	14.01	1.56	0.24	0.82	3.33	1.51
Lithuania	7.17	2.11	2.1	28.29	6.97	11.9	1.59	6.98	17.29	11.91	0.73	0.12	0.48	1.89	0.73
Netherlands	21.19	6.06	7.27	51.99	20.84	15.37	1.6	8.22	22.35	15.53	1.24	0.23	0.67	2.75	1.22
Norway	5.37	3.84	1.4	39.2	4.3	4.6	2.06	2.05	12.98	4.19	0.14	0.17	0	1.81	0.08
Portugal	9.98	4.98	1.61	45.47	8.68	8.36	1.98	2.05	15.75	8.38	1.41	0.18	1.06	3.11	1.38
Spain	11.45	6.5	1.4	69.98	9.81	9.28	2.78	2.05	19.8	9.24	1.45	0.26	0.99	3.74	1.4
Sweden	5.14	3.58	1.4	41.18	4.24	5.37	2.2	2.05	21.06	5.24	0.29	0.22	0	1.86	0.29
Switzerland	13.47	5.57	1.78	47.29	13.22	12.55	3.05	2.05	25.34	13.02	1.33	0.22	0.83	2.7	1.32
United Kingdom	15.37	7.04	1.4	55.45	14.74	9.99	2.34	2.05	18.32	10.47	0.8	0.32	0	2.46	0.81

Abbreviations: NO_2: Nitrogen Dioxide; $PM_{2.5}$: Particulate Matter equal or less than 2.5 micrometers in diameter; BC: $PM_{2.5}$ absorbance/ black carbon

Table S4: burden of disease results with WHO air quality guidelines scenario – young children between 1 and 4 years old

Country	Children population assessed (#)	NO_2 – WHO guideline value*				$PM_{2.5}$ – WHO guideline value**			
		Percentage of total cases attributable to the exposure scenario (%)	Attributable expected cases	LCI	UCI	Percentage of total cases attributable to the exposure scenario (%)	Attributable expected cases	LCI	UCI
Austria	332,715	0.09	5	2	6	19.66	1,041	383	1,584
Belgium	510,857	0.72	55	23	75	21.31	1,620	591	2,476
Denmark	236,198	0.01	0.24	0.10	0.33	5.81	277	96	444
Finland	234,472	0.00	0.00	0.00	0.00	0.19	8	3	13
France	3,106,577	0.62	336	140	457	16.67	8,959	3,249	13,789
Germany	2,870,930	0.10	35	15	48	16.11	5,750	2,066	8,920
Greece	369,993	0.81	46	19	63	18.32	1,053	382	1,619
Hungary	358,812	0.00	0.00	0.00	0.00	24.61	1,387	512	2,097
Ireland	275,872	0.00	0.00	0.00	0.00	0.46	29	10	47
Italy	2,084,242	0.56	131	55	178	20.84	4,898	1,834	7,333
Lithuania	117,734	0.00	0.00	0.00	0.00	10.79	214	75	337
Netherlands	704,472	0.42	43	18	59	18.01	1,851	667	2,863
Norway	245,074	0.00	0.00	0.00	0.00	0.83	56	19	92
Portugal	340,041	0.08	6	3	9	4.39	371	129	597
Spain	1,764,634	1.60	391	166	527	7.85	1,915	673	3,035
Sweden	472,059	0.00	0.05	0.02	0.06	1.10	112	39	180
Switzerland	345,719	0.02	1.3	0.5	1.8	14.17	865	309	1,349
United Kingdom	3,158,411	0.27	238	99	325	6.81	6,066	2,112	9,693
Total	17,528,813	0.42	1,288	540	1,750	11.77	36,471	13,147	56,465

* NO_2 reduced to 40 µg/m^3 (annual average), where in exceedance

** $PM_{2.5}$ reduced to 10 µg/m^3 (annual average), where in exceedance

Abbreviations: NO_2: Nitrogen Dioxide; $PM_{2.5}$: Particulate Matter equal or less than 2.5 micrometers in diameter; WHO: World Health Organization; LCI: Lower Confidence Interval; UCI: Upper Confidence Interval

Table S5: burden of disease results with WHO air quality guidelines scenario – children between 5 and 14 years old

Country	Children population assessed (#)	NO_2 – WHO guideline value*				$PM_{2.5}$ – WHO guideline value**			
		Percentage of total cases attributable to the exposure scenario (%)	Attributable expected cases	LCI	UCI	Percentage of total cases attributable to the exposure scenario (%)	Attributable expected cases	LCI	UCI
Austria	833,019	0.11	5	2	6	24.32	1,041	383	1,584
Belgium	1,277,143	0.72	44	18	60	21.31	1,304	476	1,993
Denmark	663,511	0.01	0.23	0.09	0.31	5.81	261	90	418
Finland	606,154	0.00	0.00	0.00	0.00	0.19	6	2	10
France	8,127,540	0.62	296	124	403	16.67	7,902	2,865	12,162
Germany	7,588,220	0.10	35	15	48	5.79	2,065	8,916	8,920
Greece	1,043,113	0.81	43	18	59	18.32	983	357	1,511
Hungary	960,739	0.00	0.00	0.00	0.00	24.61	1,414	522	2,138
Ireland	690,175	0.00	0.00	0.00	0.00	0.46	21	7	35
Italy	5,706,853	0.56	163	69	222	20.84	6,103	2,285	9,137
Lithuania	273,196	0.00	0.00	0.00	0.00	10.79	213	75	336
Netherlands	1,920,765	0.42	37	15	51	18.01	1,605	578	2,484
Norway	628,416	0.00	0.00	0.00	0.00	0.83	43	15	69
Portugal	1,048,336	0.08	6	2	8	4.39	342	119	550
Spain	4,815,022	1.60	345	146	465	7.85	1,688	593	2,676
Sweden	1,156,855	0.00	0.04	0.02	0.06	1.10	103	36	165
Switzerland	827,086	0.02	0.98	0.40	1.35	14.17	657	235	1,025
United Kingdom	7,747,461	0.27	170	71	233	6.81	4,343	1,512	6,940
Total	45,913,606	0.43	1,146	480	1,557	11.16	30,095	19,065	52,152

* NO_2 reduced to 40 µg/m^3 (annual average), where in exceedance

** $PM_{2.5}$ reduced to 10 µg/m^3 (annual average), where in exceedance

Abbreviations: NO_2: Nitrogen Dioxide; $PM_{2.5}$: Particulate Matter equal or less than 2.5 micrometers in diameter; WHO: World Health Organization; LCI: Lower Confidence Interval; UCI: Upper Confidence Interval

Table S6: burden of disease results with minimum air pollution levels scenario – young children between 1 and 4 years old

Country	Children population assessed (#)	NO_2*				$PM_{2.5}$**				BC***			
		Percentage of total cases attributable to the exposure scenario (%)	Attributable expected cases	LCI	UCI	Percentage of total cases attributable to the exposure scenario (%)	Attributable expected cases	LCI	UCI	Percentage of total cases attributable to the exposure scenario (%)	Attributable expected cases	LCI	UCI
Austria	332,715	23	1,194	528	1,569	39	2,076	824	2,949	19	1,008	415	1,590
Belgium	510,857	29	2,178	981	2,830	41	3,098	1,230	4,392	19	1,466	603	2,315
Denmark	236,198	19	908	397	1,202	29	1,380	519	2,052	9	420	167	685
Finland	234,472	14	589	253	787	18	753	272	1,162	3	119	47	197
France	3,106,577	23	12,157	5,408	15,922	37	19,999	7,839	28,697	18	9,522	3,911	15,059
Germany	2,870,930	24	8,451	3,738	11,102	37	13,147	5,129	18,932	16	5,617	2,281	8,990
Greece	369,993	22	1,246	560	1,623	38	2,208	869	3,156	23	1,321	552	2,050
Hungary	358,812	18	1,001	434	1,331	43	2,436	979	3,420	18	1,000	408	1,590
Ireland	275,872	14	863	371	1,154	22	1,365	498	2,086	5	321	127	527
Italy	2,084,242	24	5,574	2,484	7,291	40	9,479	3,802	13,358	20	4,817	1,990	7,567
Lithuania	117,734	14	276	118	370	33	649	249	950	9	183	73	300
Netherlands	704,472	29	3,028	1,366	3,929	38	3,932	1,542	5,636	16	1,676	682	2,677
Norway	245,074	15	990	428	1,319	19	1,322	481	2,025	3	212	84	350
Portugal	340,041	21	1,749	770	2,305	27	2,282	853	3,415	19	1,619	666	2,557
Spain	1,764,634	25	6,035	2,719	7,846	30	7,317	2,774	10,808	21	5,166	2,142	8,083
Sweden	472,059	16	1,582	685	2,107	20	2,038	743	3,119	5	465	184	768
Switzerland	345,719	22	1,316	579	1,736	35	2,150	833	3,114	17	1,054	430	1,677
United Kingdom	3,158,411	26	23,361	10,447	30,486	29	26,163	9,871	38,803	13	11,153	4,499	17,981
Total	17,528,813	23	72,497	32,265	94,910	33	101,792	39,307	148,074	15	47,139	19,262	74,962

* NO_2 reduced to 1.5 µg/m^3 (annual average) as recorded in Oftedal et al, (2009), where in exceedance

** $PM_{2.5}$ reduced to 0.4 µg/m^3 (annual average) as recorded in Fuertes et al, (2013), where in exceedance

*** BC reduced to 0.4 x $10^{-5}m^{-1}$ (annual average) as recorded in Gehring et al, (2015), where in exceedance

Abbreviations: NO_2: Nitrogen Dioxide; $PM_{2.5}$: Particulate Matter equal or less than 2.5 micrometers in diameter; BC: $PM_{2.5}$ absorbance/ black carbon**;** WHO: World Health Organization; LCI: Lower Confidence Interval; UCI: Upper Confidence Interval

Table S7: burden of disease results with minimum air pollution levels scenario – children between 5 and 14 years old

Country	Children population assessed (#)	NO_2*				$PM_{2.5}$**				BC***			
		Percentage of total cases attributable to the exposure scenario (%)	Attributable expected cases	LCI	UCI	Percentage of total cases attributable to the exposure scenario (%)	Attributable expected cases	LCI	UCI	Percentage of total cases attributable to the exposure scenario (%)	Attributable expected cases	LCI	UCI
Austria	833,019	23	965	427	1,268	39	1,679	666	2,384	19	815	336	1,286
Belgium	1,277,143	29	1,753	789	2,278	41	2,493	990	3,535	19	1,180	485	1,863
Denmark	663,511	19	855	374	1,132	29	1,300	489	1,933	9	395	158	646
Finland	606,154	14	488	210	653	18	624	225	964	3	99	39	163
France	8,127,540	23	10,723	4,770	14,044	37	17,639	6,914	25,311	18	8,399	3,450	13,282
Germany	7,588,220	24	8,447	3,736	11,097	37	13,140	5,127	18,922	16	5,614	2,280	8,985
Greece	1,043,113	22	1,163	522	1,515	38	2,060	811	2,945	23	1,232	515	1,913
Hungary	960,739	18	1,020	442	1,357	43	2,484	998	3,487	18	1,019	416	1,622
Ireland	690,175	14	637	274	852	22	1,008	368	1,541	5	237	94	389
Italy	5,706,853	24	6,945	3,095	9,085	40	11,811	4,737	16,645	20	6,002	2,480	9,429
Lithuania	273,196	14	275	117	369	33	647	248	947	9	183	73	299
Netherlands	1,920,765	29	2,627	1,185	3,408	38	3,411	1,338	4,889	16	1,454	591	2,322
Norway	628,416	15	750	324	1,000	19	1,001	365	1,534	3	161	64	265
Portugal	1,048,336	21	1,613	710	2,125	27	2,105	787	3,149	19	1,493	614	2,358
Spain	4,815,022	25	5,321	2,398	6,919	30	6,452	2,446	9,531	21	4,555	1,889	7,128
Sweden	1,156,855	16	1,453	629	1,934	20	1,871	682	2,863	5	427	169	705
Switzerland	827,086	22	1,000	440	1,319	35	1,633	633	2,366	17	801	327	1,274
United Kingdom	7,747,461	26	16,727	7,480	21,828	29	18,732	7,068	27,783	13	7,986	3,221	12,874
Total	45,913,606	23	62,761	27,923	82,183	33	90,091	34,891	130,728	16	42,052	17,200	66,802

* NO_2 reduced to 1.5 µg/m^3 (annual average) as recorded in Oftedal et al, (2009), where in exceedance

** $PM_{2.5}$ reduced to 0.4 µg/m^3 (annual average) as recorded in Fuertes et al, (2013), where in exceedance

*** BC reduced to 0.4 x $10^{-5}m^{-1}$ (annual average) as recorded in Gehring et al, (2015), where in exceedance

Abbreviations: NO_2: Nitrogen Dioxide; $PM_{2.5}$: Particulate Matter equal or less than 2.5 micrometers in diameter; BC: $PM_{2.5}$ absorbance/ black carbon**;** WHO: World Health Organization; LCI: Lower Confidence Interval; UCI: Upper Confidence Interval

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