Original Article

The Burden of COPD Due to Ozone Exposure in Germany

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Summary

Background: The chronic effects of ozone have only rarely been investigated in disease burden studies to date. Our goal was to determine this disease burden in Germany over the period 2007–2016, with particular attention to estimation based on effect estimates adjusted for particulate matter (PM_{2.5}) and nitrogen dioxide (NO₂).

Methods: The nationwide, high-spatial-resolution (2 km × 2 km), population-based exposure to ozone in the summer months (“summer ozone”) was calculated on the basis of modeled ozone data and population counts in Germany. Next, risk estimates derived from cohort studies were used to quantify the burden of chronic obstructive pulmonary disease (COPD). Data on population counts, life expectancy, and mortality in Germany were used to reflect the situation across the country as accurately as possible.

Results: The estimates of years of life lost (YLL) due to summer ozone ranged from 18.33 per 100 000 people (95% confidence interval [14.02; 22.08]) in 2007 to 35.77 per 100 000 people [27.45; 42.98] in 2015. These findings indicate that ozone affects the COPD burden independently of other harmful components of the air. No clear secular trend in the COPD burden can be seen over the period 2007 to 2016.

Conclusion: Long-term exposure to ozone contributes to the COPD burden among the general population in Germany. As climate change may lead to a rise in the ozone concentration, more intensive research is required on the effects of ozone on health.

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The concept of disease burden was developed to describe the loss of life as well as the loss of health due to disease, injury and risk factors in the population (1–5). This concept is based on the assumption that while all people can live for a certain number of years, a certain number of healthy years of life are lost as the result of limitations of health due to disease and premature death. With the help of the concept of environmental burden of disease, in turn, the disease burden related to the effect of an environmental risk factor on human health can be quantified (1). Apart from other measures, the years lost due to premature disease-related death as the result of environmental risk factors—the Years of Life Lost (YLL)—can be calculated to describe the environmental burden of disease (6, 7).

Due to its potent chemical reactivity, ozone is an irritant, causing oxidative damage to cells and the mucous membrane of the respiratory tract and immunoinflammatory reactions in the lungs, among other effects (8). It is scientifically proven and considered a causal factor that short-term ozone exposure is associated with increased mortality due to diseases of the respiratory system and with an increased number of respiratory disease-related emergency consultations and hospitalizations (8–10). Long-term exposure to ozone—the focus of this paper—is associated with compromised pulmonary function and deterioration of lung disease (11) as well as increased mortality due to diseases of the respiratory system (12–14). A comprehensive review of the literature, published by the U.S. Environmental Protection Agency in 2020, concluded that the association between long-term ozone exposure and respiratory mortality is likely to be causal (8). Relationships are referred to as likely to be causal if there are clear indications of causality, but the published data are considered not adequate to fulfill all the criteria for causality (10).

To date, only few studies have quantified the disease burden from long-term exposure to ozone (15, 16). Just recently, the latest estimation of disease burden from long-term ozone exposure on chronic obstructive pulmonary disease (COPD) mortality has been published as a result of the Global Burden of Disease (GBD) study (17). However, this estimation is based on modelled ozone data with a spatial resolution of 11 km × 11 km. In addition, the standardized

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Population counts in the summer-ozone concentration classes in 5-µg/m³ increments for the period 2007–2016

life expectancy used in the GBD study is higher than the life expectancy documented in Germany.

The aim of this study was to determine the disease burden caused by ozone in Germany over the period 2007–2016. The calculation was based on the nationwide, high-spatial-resolution (2 km × 2 km) mean population-based exposure to ozone in the summer months (“summer ozone”) and data on population, life expectancy, and deaths in Germany to reflect the national situation as accurately as possible. In addition, further epidemiological evidence on the COPD mortality risk due to long-term exposure to ozone from the most recent cohort studies was taken into account. Another aim of this study was to estimate the disease burden from ozone after adjustment for additional air pollutants (particulate matter [PM_{2.5}], nitrogen dioxide [NO₂]).

Methods

Selection of the health endpoint

This study estimated the disease burden only for COPD, because strong evidence from epidemiological studies as well as biological plausibility from experimental studies (animal experimental and mechanistic/in vitro studies) was available for this disease. In the study on which our paper is based, a systematic search of the literature and systematic mappings were conducted to review the evidence (18).

Exposure estimation

The population-based exposure to ozone across Germany was estimated based on nationwide data on the spatial distribution of ozone concentrations in ambient air (19). The calculation used data from the period 2007–2016, reflecting the pollution levels in both rural and urban backgrounds in a spatial resolution of approximately 2 km × 2 km (ozone grid cell). Using

the chemical transport model REM/CALGRID, the data were generated and then combined with ozone measurement data of the nationwide air monitoring network of the German federal states and the Federal Environment Agency, using the optimal interpolation technique (20).

As an ozone exposure indicator, the summer ozone concentrations (in µg/m³) for each year were calculated as the mean over the daily maxima of the 8-hour moving averages from April to September for each ozone grid cell (19). These ozone data were combined with spatial population data for Germany of the 2011 census (German Federal and State Statistical Offices—version 1; 23 April 2015); then the population-weighted summer ozone exposure was calculated for each year of the period 2007–2016.

Quantification of the disease burden from ozone

Input data

For the quantification of the disease burden attributable to ozone, data on population counts, life expectancy, and mortality in Germany were used to reflect the situation across the country as accurately as possible. For a detailed description of the input data, refer to the *eMethods* section.

Estimation of the disease burden from ozone

Only risk estimates from cohort studies on long-term exposure (annual mean of summer ozone concentrations) were used to calculate the burden of disease from summer ozone exposure. If multiple robust effect estimates for the exposure–response relationship were available from different studies, these were pooled in a first step by performing a meta-analysis with random effects (21) (*eMethods*).

The population-weighted ozone exposure in Germany and the combined effect estimates were then

used to calculate the so-called attributable fraction (3, 22)—the proportion of the COPD burden that can be attributed to the risk factor ozone.

In a further step, the number of years of life lost (YLL) due to premature mortality related to COPD were determined (7). These were calculated by multiplying the number of COPD-related deaths per year by the statistical residual life expectancy of the German population (1, 7) (*eMethods*). Finally, the ozone-related burden for COPD was estimated by multiplying the attributable fraction by the number of years of life lost (YLL) due to COPD mortality.

The uncertainty about whether the burden of disease can actually be attributed to a single pollutant (single pollutant effect estimate) is a fundamental problem of studies on pollutant-related burden of disease, since air pollutants always occur as a mixture of pollutants which often originate from the same sources. Thus, our study paid particular attention to the estimation of the disease burden from summer ozone based on effect estimates adjusted for particulate matter (PM_{2.5}) and nitrogen dioxide (NO₂).

Sensitivity analyses

In a sensitivity analysis, an exposure–response relationship after adjustment for PM_{2.5}, NO₂ and, additionally, temperature (12) was used as an alternative approach to calculate the attributable fraction and the YLL related to COPD burden.

Results

The majority of the German population (mean 95.3%; minimum: 79.6% in 2015, maximum 99.0% in 2013) were exposed to summer ozone concentrations of 75–95 µg/m³ in the period 2007–2016 (*Figure*). On average, 1.1% of people lived in the least polluted regions with summer ozone concentrations below 75 µg/m³, from 0.0% in 2015 to 3.4% in 2007. On average, 3.6% of people lived in regions with summer ozone concentrations higher than 95 µg/m³.

COPD burden from long-term exposure to summer ozone

The results for COPD burden (based on deaths coded with J40–J44, ICD-10) due to long-term exposure to summer ozone in the period 2007–2016 are presented in *Table 1*. Based on the age range for the study populations, the age range was set at 30 years and older. An important point to note when interpreting these results is that the years of life lost are not equally distributed among all residents, but rather some residents lose more years of life than others.

Overall, no clear trend can be identified in the period 2007–2016; during the 10-year observation period, the disease burden varied by more than one-third from year to year. Moreover, variations in disease burden are caused by variations in COPD mortality. The highest attributable fraction and also the highest number of YLL was observed in 2015, reflecting the very high ozone concentrations recorded in that year.

TABLE 1

COPD burden (people aged 30 years and older) from long-term exposure to summer ozone in Germany for the period 2007–2016*

Year	Attributable fraction in percent [95% CI]	Years of Life Lost (YLL) [95% CI]	YLL per 100 000 people [95% CI]
2007	6.15 [4.70; 7.40]	15 078 [11 535; 18 162]	18.33 [14.02; 22.08]
2008	6.46 [4.94; 7.78]	16 097 [12 323; 19 380]	19.60 [15.01; 23.60]
2009	6.81 [5.22; 8.20]	19 076 [14 612; 22 953]	23.30 [17.85; 28.03]
2010	6.58 [5.04; 7.92]	18 763 [14 369; 22 583]	22.95 [17.57; 27.62]
2011	7.37 [5.65; 8.87]	21 243 [16 285; 25 543]	26.46 [20.29; 31.82]
2012	6.58 [5.04; 7.92]	19 006 [14 549; 22 881]	23.63 [18.09; 28.45]
2013	6.11 [4.68; 7.36]	19 751 [15 116; 23 784]	24.49 [18.74; 29.49]
2014	6.23 [4.76; 7.50]	18 828 [14 408; 22 673]	23.25 [17.79; 28.00]
2015	8.29 [6.36; 9.96]	29 222 [22 421; 35 111]	35.77 [27.45; 42.98]
2016	6.71 [5.14; 8.07]	22 993 [17 609; 27 672]	27.92 [21.38; 33.60]

* Counterfactual value of 65 µg/m³

Pooled effect estimate of the cohort studies Lim et al. 2019 (12).

Kazemparkouhi et al. 2020 (14) and Turner et al. 2016 (13): 1.037 (95% CI: [1.028; 1.045]) per 10 µg/m³ (This effect estimate is used as an exposure–response relationship between COPD and long-term exposure to summer ozone to calculate the attributable fraction.)

COPD, chronic obstructive pulmonary disease; 95% CI, 95% confidence interval

Disease burden from ozone after adjustment for other air pollutants

Table 2 shows the results for the disease burden from long-term exposure to summer ozone after adjustment for PM_{2.5} and NO₂. Compared to the results in *Table 1*, the disease burden of COPD is even higher after adjustment for PM_{2.5} and NO₂. These findings indicate that ozone affects the COPD burden independent of other pollutants.

Sensitivity analyses

The use of the exposure–response relationship after adjustment for particulate matter, nitrogen dioxide and, in addition, temperature is illustrated in *Table 3* for 2016 as an example. A corresponding effect estimate is available from one study only (12). For this reason, disease burden estimates based on single-pollutant effect estimates and after adjustment for particulate matter and NO₂ are presented in *Table 3* to enhance comparability. While no significant changes in the attributable fraction and the YLL were observed, it was found that the confidence intervals were very wide. All in all, the results are indicative of an independent effect of summer ozone on COPD burden, even after adjustment for temperature.

Discussion

Long-term exposure to ozone contributes to the disease burden among the general population in Germany. For the COPD burden, the estimates of years of life lost ranged from 18.33 per 100 000 people (95% confidence interval [14.02; 22.08]) (year 2007) to 35.77 per

TABLE 2

COPD burden (people aged 30 years and older) from long-term exposure to summer ozone in Germany for the period 2007–2016*

Year	Attributable fraction in percent [95% CI]	Years of Life Lost (YLL) [95% CI]	YLL per 100 000 people [95% CI]
2007	6.78 [6.46; 7.25]	16 627 [15 854; 17 780]	20.21 [19.27; 21.61]
2008	7.12 [6.79; 7.61]	17 747 [16 924; 18 974]	21.61 [20.61; 23.10]
2009	7.51 [7.16; 8.03]	21 025 [20 053; 22 473]	25.68 [24.49; 27.45]
2010	7.25 [6.92; 7.75]	20 683 [19 726; 22 110]	25.30 [24.13; 27.04]
2011	8.12 [7.75; 8.68]	23 405 [22 327; 25 011]	29.16 [27.81; 31.16]
2012	7.25 [6.92; 7.76]	20 953 [19 982; 22 401]	26.05 [24.85; 27.85]
2013	6.74 [6.43; 7.21]	21 777 [20 767; 23 284]	27.00 [25.75; 28.87]
2014	6.86 [6.55; 7.34]	20 760 [19 796; 22 197]	25.64 [24.45; 27.41]
2015	9.13 [8.71; 9.76]	32 185 [30 708; 34 383]	39.40 [37.59; 42.09]
2016	7.40 [7.05; 7.91]	25 345 [24 172; 27 093]	30.78 [29.35; 32.90]

*Based on effect estimates after adjustment for particulate matter (PM_{2.5}) and nitrogen dioxide (NO₂) and with a counterfactual value of 65 µg/m³. Pooled effect estimate of the cohort studies Lim et al. 2019 (12), Kazemiparkouhi et al. 2020 (14) and Turner et al. 2016 (13): 1.041 [95%-KI: 1.039; 1.044] per 10 µg/m³ (This effect estimate is used as an exposure–response relationship between COPD and long-term exposure to summer ozone to calculate the attributable fraction.) COPD, chronic obstructive pulmonary disease; 95% CI, 95% confidence interval

100 000 people [27.45; 42.98] (year 2015). Overall, no clear temporal trend can be identified in the disease burden over the period 2007–2016; during the 10-year observation period, the relative disease burden varied by more than one-third from year to year. After additional adjustment of the effect estimate for PM_{2.5} and NO₂, the COPD burden attributable to ozone was slightly higher compared to the unadjusted results.

To date, there are only few studies that have quantified the disease burden from long-term exposure to ozone (15, 16). Just recently, the latest estimation of disease burden from long-term ozone exposure on COPD mortality has been published as a result of the Global Burden of Disease (GBD) study (17). Unlike previous burden of disease studies, this latest estimation was based on a risk estimate averaged from three cohort studies. For the year 2016, 43.05 ozone-related YLL per 100 000 people [18.14; 74.06] were published for Germany. This figure is higher than the estimate of 27.92 YLL [21.38; 33.60] for 2016 calculated in our study. However, it should be noted that the estimation of the GBD study is based on modeled ozone data with a spatial resolution of 11 km × 11 km, while we used a high resolution of 2 km × 2 km in our study. In addition, the standardized life expectancy used in the GBD study is higher than the life expectancy documented in Germany. Furthermore, in the GBD study the disease burden was estimated for all age groups 25 years and older, while our study set the lower age limit at age 30 years.

With regard to the biological plausibility of a link between long-term ozone exposure and COPD

mortality, there is evidence from experimental studies (animal experimental and mechanistic/in vitro studies), indicating that chronic exposure to ozone can trigger pathophysiological processes similar to those seen with COPD (8, 11). These include persistent inflammatory processes, oxidative stress as well as airway damage and structural remodeling, resulting in irreversible changes, including fibrotic and emphysematous changes of the lung (8).

Of special interest are the estimates of COPD burden from ozone which were calculated using effect estimates adjusted for other air pollutants (PM_{2.5} and NO₂) and are presented for the first time. These results suggest that the effect of ozone on COPD burden is largely independent of other air pollutants. However, it should be noted that the level of ozone concentrations and the mix of pollutants in the United States (all studies covered were US studies) are not necessarily comparable with those in Germany, mainly due to differences in the structure of the emitters, the climatic conditions and, consequently, the atmospheric transformation processes.

Any comparisons of disease burden estimates in this paper with estimates for particulate matter (23, 24) and NO₂ (25) should take into account the complexity of the data and methods underlying these estimates. First, there are considerable differences in the health endpoints investigated and the risk estimates used. Further differences also arise for the time periods considered and the spatial resolutions of the nationwide exposure data. Despite all this uncertainty, and when the results of the GBD study are also included (17), a clear gradation of disease burdens appears to be emerging for the three air pollutants studied. Long-term ozone exposure shows the lowest disease burden, presumably followed by NO₂ and PM_{2.5} with the by far highest burden of disease.

Strengths and limitations

This study has a number of strengths. For example, the 2 km × 2 km grid size resolution of the spatial ozone concentration data used in this study is higher than any of the resolutions used in other comparable studies. The use of the current effect estimates in studies of the American Cancer Society (ACS) (13) and the Canadian Census Health and Environment Cohort (CanCHEC) (26) as well as other effect estimates published for the first time is considered an additional strength of this study. Effect estimates adjusted for particulate matter, NO₂ and, additionally, temperature were used to estimate the disease burden due to ozone in further analyses. This is of special importance since the use of estimates derived from single-pollutant models has been criticized for years (27), in many cases, however, without remedying this shortcoming.

On the other hand, our study has some limitations. With regard to the calculation of ozone exposure, it must be clearly stated that these ozone concentrations are only modeled concentrations in a specific

TABLE 3

COPD burden (people aged 30 years and older) due to long-term exposure to summer ozone in Germany for 2016; comparison of the disease burden based on single-pollutant and multi-pollutant effect estimates (ERF) (Lim et al. 2019 [12])

	Single pollutant ERF ^{*1}	ERF after adjustment for PM _{2.5} and NO ₂ ^{*2}	ERF after adjustment for PM _{2.5} , NO ₂ and temperature ^{*3}
Attributable fraction in percent [95% CI]	4.61 [1.88; 7.05]	6.19 [2.80; 9.58]	5.49 [0.95; 10.23]
Years of Life Lost (YLL) [95% CI]	15 786 [6 443; 24 172]	21 213 [9 600; 32 819]	18 817 [3 244; 35 068]
YLL per 100 000 people [95% CI]	19.17 [7.82; 29.35]	25.76 [11.66; 39.85]	22.85 [3.94; 42.58]

^{*1}1.025 ((95% CI: 1.010; 1.039)) per 10 µg/m³; ^{*2}1.034 [1.015; 1.054] per 10 µg/m³; ^{*3}1.030 [1.005; 1.058] per 10 µg/m³
ERF, exposure–response function; 95% CI, 95% confidence interval.

(small-scale) polygon across Germany. Although this is a common approach to estimate exposure, it is a greatly simplified method, especially because the length of stay differs between people. Furthermore, there is potential for misclassification of exposure because movements of people in and out of an area are not or only incompletely taken into account; this applies especially to migrants where the COPD rate can be particularly high as the result of the situation in their home countries (28).

In addition, it is important to mention that COPD is a disease with progression over decades. The development or rather the cause underlying the development of COPD predates the exposure years assessed in this study. Apart from ozone, other factors are known to contribute to the development of COPD (e.g., smoking, genetic disposition, occupational inhalation of dust, respiratory tract infections in childhood, and prematurity).

As with all environmental burden of disease studies, the results of this study are to be used exclusively to draw conclusions on the population level. Information about the health status of specific individuals cannot be derived from it (29). Furthermore, these estimates are based on calculations. In order to perform these calculations, various assumptions must be made, such as, for example, assumptions about the exposure–response relationship or the residual life expectancy at the time of death. The effect estimates used in this study are from large North American studies. Their applicability to German conditions is to be understood as a necessary, pragmatic approach, reflecting the lack of pertinent German or European data.

The ranges of uncertainty of the estimates of disease burden from ozone are large, as shown, for example, by the confidence intervals. Therefore, we explicitly warn against an uncritical use of the point estimate without stating the confidence interval.

Conclusion

Long-term exposure to ozone contributes to disease burden among the general population in Germany. Since climate change may lead to a rise in ozone concentrations (30, 31), more intensive research is required

on the effects of ozone on health and on the disease burden attributable to ozone. This means that more cohort studies on the long-term effects of ozone in Europe and especially in Germany are generally needed. Moreover, the fact that regulated air pollutants, such as particulate matter, NO₂ and ozone, always occur as a mixture of pollutants has not been adequately taken into account to date. Furthermore, the health effects of interactions between long-term ozone exposure on the one hand and temperature, volatile organic compounds, ultrafine particles and green spaces on the other hand have not yet been studied sufficiently.

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Conflict of interest statement

The authors declare that no conflict of interest exists.

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► Supplementary material

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eMETHODS**Quantification of the disease burden from ozone****Input data**

For the quantification of the disease burden caused by ozone, data on population counts, life expectancy, and causes of death in Germany were used to reflect the situation across the country as accurately as possible.

The annual average population data were obtained from the Federal Health Monitoring System. Data for the period 2007–2010 were based on the 1987 census (1990 census for East Germany [GDR]) and its update (e1), while data for the period 2011–2016 were taken from the 2011 census and its update (e2).

Annual data on the life expectancy of the German population were taken as three-year moving averages from the period life tables for Germany for the periods 2006/2008–2015/2017 and aggregated into five-year age groups.

Data on mortality were taken from the cause of death statistics for Germany (e4–e6). The following ICD-10 codes were included: J40–J44 for mortality due to chronic obstructive pulmonary disease (COPD).

Estimation of the disease burden from ozone

Only risk estimates from (cohort) studies on long-term exposure (annual average of summer ozone concentrations) were used to calculate the burden of disease attributable to summer ozone exposure. When multiple robust effect estimates for each exposure–response relationship were available from long-term studies, these were pooled in a first step by performing a meta-analysis. Given that some heterogeneity between studies was to be expected, random-effects meta-analyses were used (21). As suggested by the Cochrane Collaboration, the calculations were performed using the Knapp-Hartung method (in the literature also referred to as Hartung-Knapp-Sidik-Jonkman method) with the Paule-Mandel estimate for the heterogeneity parameter (21).

Using the annual population-weighted ozone exposure in Germany and the pooled effect estimates, the attributable fraction was calculated for each year in the study period 2007–2016 (3, 22). In our study, this is the proportion of the COPD burden that can be attributed to the risk factor ozone, using statistical methods. The annual population-weighted summer ozone exposure was grouped in $2\text{-}\mu\text{g}/\text{m}^3$ concentration classes ($\leq 65\text{ }\mu\text{g}/\text{m}^3$, $\leq 67\text{ }\mu\text{g}/\text{m}^3$, ..., $\leq 105\text{ }\mu\text{g}/\text{m}^3$, $> 105\text{ }\mu\text{g}/\text{m}^3$). In addition, various assumptions had to be made. A counterfactual value had to be defined which is compared to the actual exposure value in the calculation. The counterfactual value describes the concentration level below which, according to the current body of evidence, no health effect can be demonstrated with sufficient evidence, i.e. no additional risk can be assumed. (16, 25). In this project, we used a counterfactual value of $65\text{ }\mu\text{g}/\text{m}^3$ ozone. This value was chosen based on epidemiological studies (13) and the GBD study (17). For example, $65\text{ }\mu\text{g}/\text{m}^3$ ozone corresponds to about the 5th percentile and 2.5th percentile of ozone exposure and summer ozone exposure, respectively, in the American Cancer Society study (13). Moreover, this value corresponds approximately to the

expected value/median of the uniform distribution, which is assumed as the theoretical minimum in the GBD study (17). In addition, it was assumed that the relationship between ozone and the health endpoints considered is linear, i.e., represented by a linear exposure-response relationship (e7). Assuming that there is no additional risk below the counterfactual value, the attributable proportion is defined as follows (3, 22):

$$PAF = \frac{\sum P_i RR_i - 1}{\sum P_i RR_i}$$

where

- RR_i represents the relative risk in ozone concentration class i compared to the counterfactual value, and
- P_i represents the proportion of the population in ozone concentration class i ; this includes the population allocated to an ozone exposure below the counterfactual value – this population is assigned an RR of 1 (22).

In a further step, the number of years of life lost (YLL) due to premature mortality related to COPD were determined (7). For this purpose, the statistical residual life expectancy was used which expresses the mean years of life remaining at the time of death of the individuals (e3). The number of years of life lost to COPD was calculated by multiplying the sum of deaths due to COPD in a given age group, separately by sex, by the residual life expectancy in that age group; then the total across all sex and age groups was calculated (1, 7). The Excel spreadsheet template for calculating YLL provided by the World Health Organization (WHO) (www.who.int/healthinfo/global_burden_disease/tools_national/en/) was used as a starting point and adapted for our project. Instead of a global standard life expectancy, as used in the Global Burden of Disease (GBD) study and by the WHO, we used the maximum age-specific life expectancy for Germany based on the life tables 2006/2008–2015/2017 to reflect the situation across the country as accurately as possible. The mean population counts of the period 2007–2016 were used as the reference population. Following the recommendations of the EBDreview (EBD, environmental burden of disease) research project (e8), neither different weighting of years of life lost in specific age groups nor discounting of years of life lost in the future (years of life lost in the future are weighted lower compared to years of life lost currently [1]) was applied. This also corresponds to the current recommendations of the GBD study of the Institute of Health Metrics and Evaluation (IHME) (e9).

Finally, the COPD burden due to ozone was estimated by multiplying the attributable fraction by the number of years of life lost due to premature COPD-related mortality.