

# Benefits of future clean air policies in Europe

## Proposed analyses of the mortality impacts of PM<sub>2.5</sub> and NO<sub>2</sub>

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### Introduction

Health impact assessments (HIA) and cost-benefit analyses (CBA) play a major role in the ongoing revision of the European Union Ambient Air Quality Directive (EU AAQD). HIAs quantify the public health impacts of the air pollution levels a population is exposed to. CBAs quantify the economic costs of achieving lower air pollution levels and the (monetized) benefits for public health that result from these lower air pollution levels. In this commentary, we consider the recent body of evidence on the effects of long-term exposure to fine particulate matter (PM<sub>2.5</sub>) and nitrogen dioxide (NO<sub>2</sub>) on total mortality from natural causes and present the rationale for conducting additional analyses within the framework of the HIA conducted for the revision of the EU AAQD, based on the recently published European “Effects of Low-Level Air Pollution: A Study in Europe” (ELAPSE) study.

The air pollution-related burden (presented as impact on mortality from natural causes) for Europe has been estimated since 2014 in the annual “Air Quality in Europe” reports published by the European Environment Agency (EEA). EEA in their HIA has used relative risk estimates from meta-analyses by Hoek and colleagues<sup>1</sup> in 2013, based on evidence published before January 2013: 1.06 (1.04, 1.08) for PM<sub>2.5</sub> and 1.05 (1.03, 1.08) for NO<sub>2</sub>, both per 10 µg/m<sup>3</sup>. The EEA, in its latest HIA for 2019, assumed no threshold for PM<sub>2.5</sub>, and a threshold of 20 µg/m<sup>3</sup> for NO<sub>2</sub>, and estimated 307,000 and 40,400 premature deaths in the EU27 associated with PM<sub>2.5</sub> and NO<sub>2</sub>, respectively.<sup>2</sup>

In support of the recent development of the 2021 World Health Organization (WHO) Air Quality Guidelines, new systematic reviews of the evidence of effects of air pollutants on mortality were published in 2020.<sup>3,4</sup> These reviews include studies conducted in all parts of the world and across a wide range of exposure levels. The linear summary estimates from these global systematic reviews are used in the current HIA and CBA informing the revision of the EU AAQD. The systematic review on PM<sub>2.5</sub> and total mortality documented a summary estimate of 1.08 per 10 µg/m<sup>3</sup> with a confidence interval of (1.06, 1.09), based on 25 studies.<sup>3</sup> The systematic review on NO<sub>2</sub> and total mortality reported a summary estimate of 1.02 per 10 µg/m<sup>3</sup> with a confidence interval of (1.01, 1.04), based on 24 studies.<sup>4</sup> This latter review has also reported an association between long-term, warm season ozone exposure and total mortality with a summary effect estimate of 1.01 (1.00, 1.02) per 10 µg/m<sup>3</sup>, which is being used to estimate the impacts of long-term warm season ozone concentrations in the revision of the EU AAQD.

These systematic reviews were published in 2020 and included studies available until September 2018. They do not include important new European studies that have been published since. We propose that additional analyses should be conducted based on these new studies to ensure that the HIA and CBA to inform the revision of the EU AAQD considers the most recent and relevant evidence. We suggest using effect estimates from recent European studies only, as these are the most relevant to estimating impacts and benefits for recent European exposure levels and populations. While studies conducted outside of Europe form an important part of the overall evidence base, when quantifying risks in Europe, it is important to use exposure-response estimates from epidemiologic studies that reflect European population demographics, air quality and exposure patterns, healthcare systems (particularly for outcomes based on administrative databases), and baseline mortality and morbidity rates. Geographical restriction for HIA and CBA purposes is common practice in many other countries, including the policy assessment for the review of National Ambient Air Quality Standards in the United States.

We recommend the use of the exposure-response relationship estimates from ELAPSE for these additional analyses. ELAPSE is the largest study in Europe by far, designed specifically to address the effects of exposure to low levels of air pollution—below current EU air quality limit values—and represents the latest and most relevant data for Europe. ELAPSE has estimated associations between long-term exposure to air pollution and mortality using two approaches: a pooled cohort of over 325,000 persons from eight cohorts from six EU countries, published in Strak et al.,<sup>5</sup> and analyses of 28 million people from seven large administrative nationwide (Denmark, Netherlands, Norway, United Kingdom, Switzerland, Belgium) and citywide (Rome) cohorts, published in Stafoggia et al.<sup>6</sup> The pooled cohort had access to detailed information, such as smoking, physical activity, body mass index, and alcohol intake. The very large administrative cohorts have less detailed information on lifestyle and social factors, and they used an “indirect” approach to account for those factors in the analyses. ELAPSE includes data on a very large number of participants in 11 European countries in total, almost all of whom were exposed to levels of PM<sub>2.5</sub> and NO<sub>2</sub>

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below current EU limit values.<sup>5-7</sup> Several other European studies have been published very recently as well, and we have included those results for comparison and completeness. In the absence of convincing new studies on long-term ozone and mortality for Europe, we do not propose additional analyses for ozone.

**Mortality estimates from recent European studies**

The results of the ELAPSE study for associations of PM<sub>2.5</sub> with total mortality are shown in Figure 1.<sup>7</sup> The figure includes the combined estimates from two ELAPSE analyses: a large, pooled cohort study of eight individual cohorts from six EU countries,<sup>5</sup> and seven separate very large nationwide or citywide administrative cohorts.<sup>6</sup> Importantly, all estimates adjusted for smoking and other important lifestyle and social factors. The summary effect estimate for PM<sub>2.5</sub> is 1.118 (1.060, 1.179) per 10 µg/m<sup>3</sup>, which is larger than the 1.08 (1.06, 1.09) summary effect estimate from the WHO systematic review.<sup>3</sup>

Figure 2 shows the results of ELAPSE for NO<sub>2</sub>. This figure again includes the estimates from a large, pooled cohort study including data from eight cohorts from six EU countries,<sup>5</sup> and seven separate very large administrative cohorts.<sup>6,7</sup> As for PM<sub>2.5</sub>, these estimates represent analyses adjusted for smoking and other important lifestyle and social factors. The summary estimate is 1.045 (1.026, 1.065) per 10 µg/m<sup>3</sup>, which is larger than the 1.02 (1.01, 1.04) effect estimate from the WHO systematic review.<sup>4</sup>

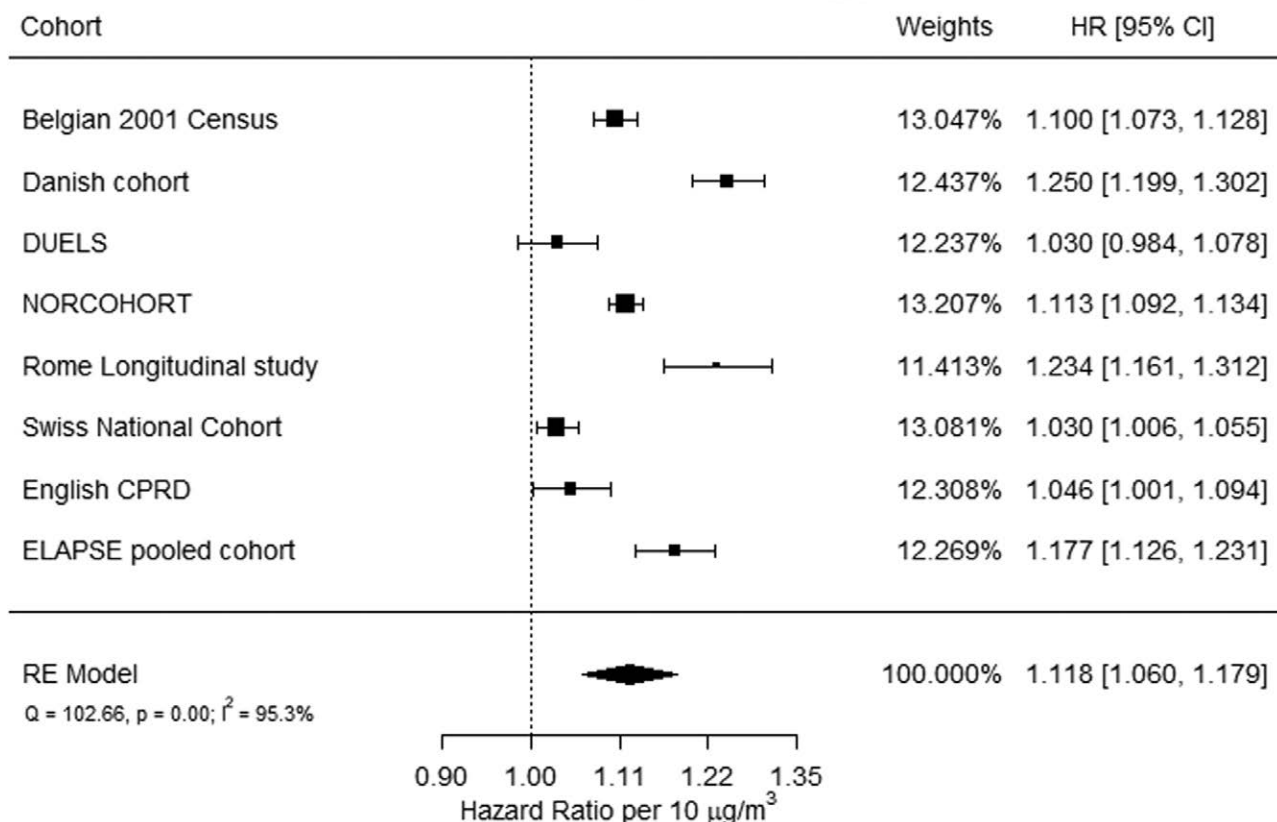
Figures 3 and 4 show the mortality results of other recent European studies for long-term PM<sub>2.5</sub><sup>8-15</sup> and NO<sub>2</sub><sup>11-19</sup> respectively, which were published after the closing dates of the WHO systematic reviews. The results from these studies are compared

with the summary estimates from the WHO systematic reviews (red vertical line) and the summary estimate from the ELAPSE study. The findings corroborate the ELAPSE findings, namely that the PM<sub>2.5</sub> and NO<sub>2</sub> effects on mortality in Europe are generally larger than the estimates of the global WHO systematic reviews. This is due in part to the supra-linear form of the exposure-response function.

**Additional considerations: larger associations at lowest concentrations**

Recent studies have documented a supra-linear form of the exposure-response relationship between long-term exposure to PM<sub>2.5</sub> and NO<sub>2</sub> with multiple health outcomes, “supra-linear” to be understood as higher effect estimates per additional microgram of exposure at low pollutant concentrations than at high concentrations (see, for instance, Burnett and colleagues<sup>20</sup>). The ELAPSE study made a systematic effort to estimate associations in subpopulations exposed to concentrations below certain cut-points in Europe. Those results are summarized in tables 7 and 20 of the main report.<sup>7</sup> They show that in the pooled cohort of eight cohorts from six EU countries, the effect estimate for PM<sub>2.5</sub> was about twice higher in the subpopulation exposed to concentrations below 15 µg/m<sup>3</sup> than in the full population. This subpopulation contained about half of all study participants. For NO<sub>2</sub>, the effect estimate was about 30% higher in the subpopulation exposed to concentrations below 30 µg/m<sup>3</sup> than in the full population. This subpopulation contained about 75% of all study participants. Analyses of the shape of the exposure-response functions based on the full population in the pooled cohort supported this finding, showing a supra-linear curve (Figure 5).

**Total mortality and PM<sub>2.5</sub>**



**Figure 1.** Total mortality and long-term PM<sub>2.5</sub> from ELAPSE.<sup>7</sup> \*Effect estimates were indirectly adjusted for smoking and BMI for six of the administrative cohorts. The English CPRD cohort adjusted for smoking and BMI directly. The pooled cohort adjusted for smoking and BMI as well, and the time varying effect estimate was extracted. BMI indicates body mass index; CI, confidence interval; HR, hazard ratio.

Similar findings were observed in the analysis of the seven administrative cohorts within ELAPSE. The effect estimate for PM<sub>2.5</sub> was about 80% higher in the subpopulation exposed to concentrations below 12 µg/m<sup>3</sup> than in the full population. This subpopulation contained about 4.5 million study subjects. For NO<sub>2</sub>, the effect estimate was about 40% higher in the subpopulation exposed to concentrations below 20 µg/m<sup>3</sup> than in the full population. This subpopulation contained about 6 million study participants. Analyses of the exposure-response function supported this finding, showing supra-linear curves in the meta-analysis of the seven administrative cohorts and for most of the individual cohorts.<sup>6</sup> As the administrative cohorts were very large, precise and statistically significant effect estimates could still be obtained from those subgroup analyses.

Because those subgroup analyses are not usually conducted in other studies, we do not propose to use these even higher effect estimates in the additional analyses, in part because of the smaller sample sizes, and because of the importance of

generalizability for use in HIA and CBA. However, they do support the use of the ELAPSE effect estimates as shown in Figures 1 and 2 as additional analyses.

**Additional considerations: air pollution and morbidity**

The above considerations are restricted to effects on mortality only, which contribute to the years of life lost due to air pollution. They do not cover morbidity outcomes, which translate into years lived with disability, which is the second major component of the burden of disease. Recent reviews document that air pollution is associated with a growing list of various diseases (e.g., Thurston and colleagues<sup>21</sup>). ELAPSE also documented clear associations between long-term exposure to PM<sub>2.5</sub> and/or NO<sub>2</sub> and the incidence of lung cancer,<sup>22</sup> cerebrovascular events,<sup>23</sup> chronic obstructive pulmonary disease (COPD),<sup>24</sup> asthma,<sup>25</sup> and liver cancer.<sup>26</sup> Furthermore, long-term NO<sub>2</sub> exposure in urban areas was associated with asthma onset in children.<sup>27</sup> In addition, emerging evidence reports a likely association of air pollution with diabetes, low birth weight, preterm births, cognitive decline and dementia, Parkinson’s diseases, impaired cognitive development in children, and mental health outcomes.<sup>21</sup> These associations may lead to sick days, doctor visits, need for medication and hospital care, and to huge costs related to health care, loss in productivity, and reducing quality of life.

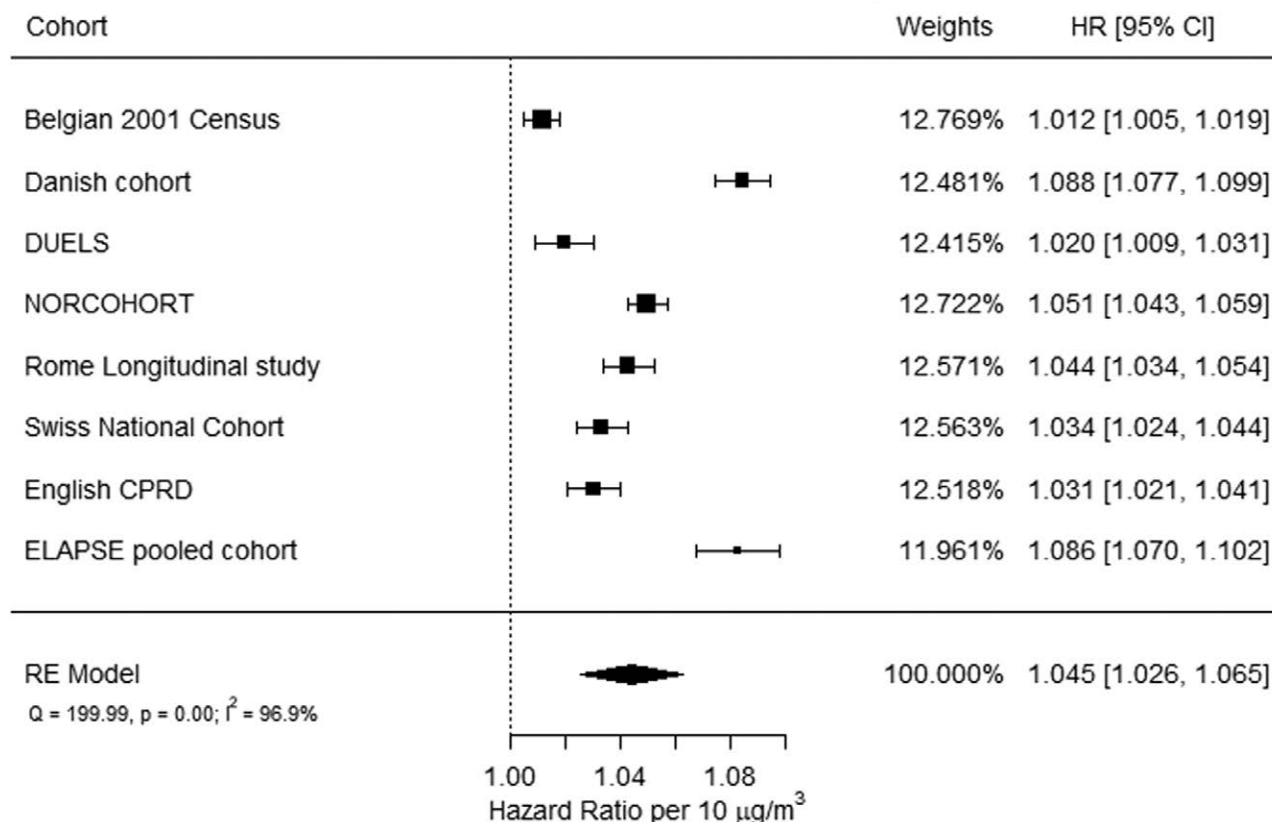
Several systematic reviews have been conducted recently on which a comprehensive impact assessment of the years lived with disability due to PM<sub>2.5</sub> and NO<sub>2</sub> could be based. For example, the United Kingdom has undertaken a comprehensive

**Table 1.** Single and multiple pollutant HRs from a Canadian study on air pollution and all-cause mortality<sup>30</sup>

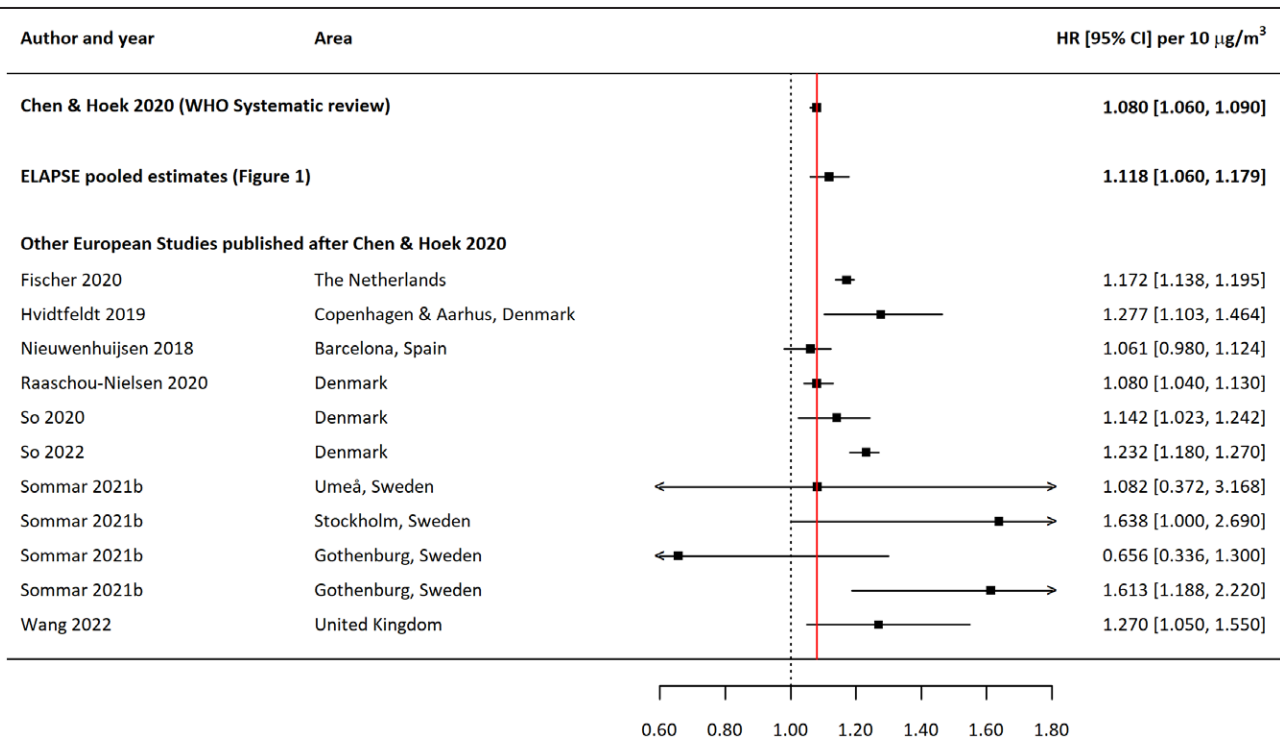
Pollutant	Per mean-5th percentile	Single pollutant HR	Three-pollutant HR
PM <sub>2.5</sub>	5.0 µg/m <sup>3</sup>	1.035 (1.029, 1.041)	1.011 (1.003, 1.020)
O <sub>3</sub>	9.5 ppb	1.031 (1.025, 1.036)	1.018 (1.010, 1.026)
NO <sub>2</sub>	8.1 ppb	1.052 (1.045, 1.059)	1.045 (1.037, 1.052)
Cumulative	NA	1.123 (NA)	1.075 (1.064, 1.082)

Cumulative HRs are derived by multiplying the three individual pollutant HRs. HR indicates hazard ratio; NA, not applicable.

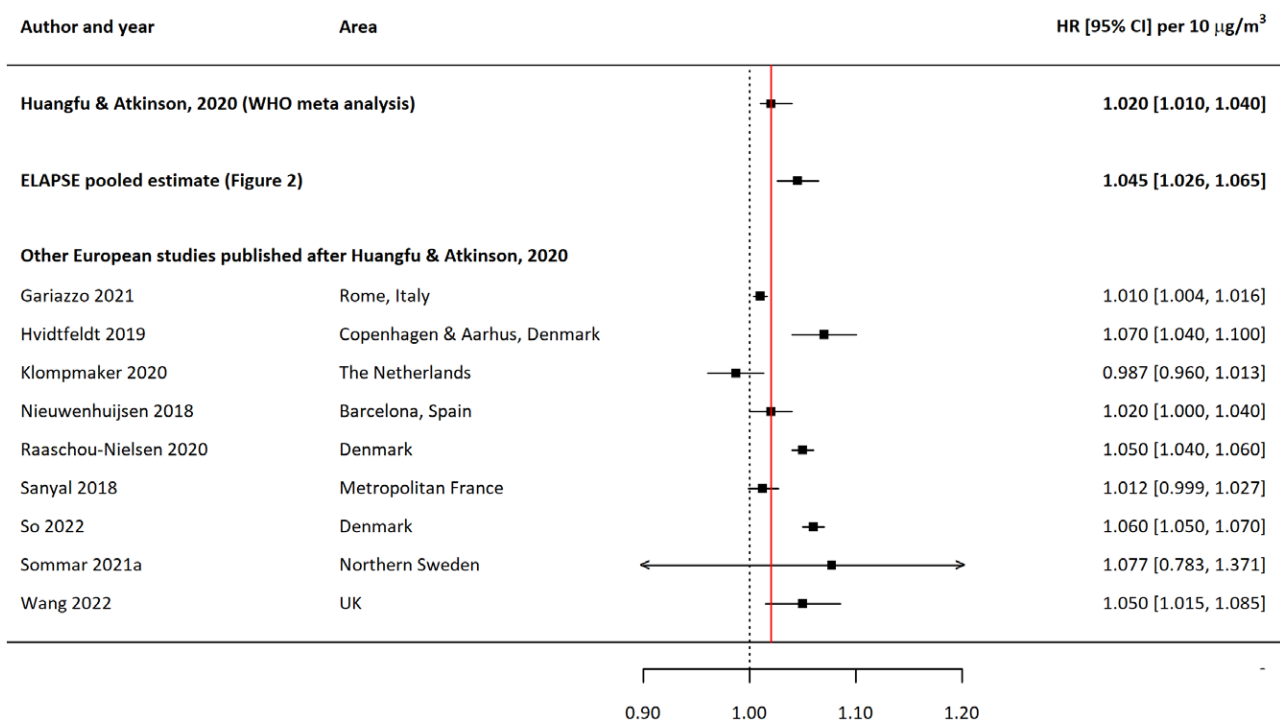
**Total mortality and NO<sub>2</sub>**



**Figure 2.** Total mortality and long-term NO<sub>2</sub> from ELAPSE.<sup>7</sup> \*Effect estimates were indirectly adjusted for smoking and BMI for six of the administrative cohorts. The English CPRD cohort adjusted for smoking and BMI directly. The pooled cohort adjusted for smoking as well, and the main exposure effect estimate was extracted since no difference with time-varying exposure estimate. BMI indicates body mass index; CI, confidence interval; CPRD, clinical practice research datalink; DUELS = The dutch environmental longitudinal study; HR, hazard ratio; NORCOHORT = norwegian cohort; RE = random effects.



**Figure 3.** Total mortality and long-term  $\text{PM}_{2.5}$  from other European studies published since the WHO systematic review by Chen and Hoek.<sup>3</sup> \*Red line indicates the summary estimate from the systematic review by Chen and Hoek.<sup>3</sup> Mean  $\text{PM}_{2.5}$  exposure in European studies range from 5.8 to 20.5  $\mu\text{g}/\text{m}^3$ . CI indicates confidence interval; HR, hazard ratio.



**Figure 4.** Total mortality and long-term  $\text{NO}_2$  from other European published since the WHO systematic review by Huangfu and Atkinson.<sup>4</sup> \*Red line indicates the summary estimate from the systematic review by Huangfu and Atkinson.<sup>4</sup> Mean  $\text{NO}_2$  exposure in European studies range from 7.1 to 53.4  $\mu\text{g}/\text{m}^3$ . CI indicates confidence interval; HR, hazard ratio.

assessment of morbidity outcomes, including stroke incidence, asthma incidence in children, and lung cancer incidence.<sup>28</sup> A similar effort has been undertaken in France.<sup>29</sup> At WHO, multiple efforts are underway to inform exposure-response estimates for morbidity outcomes for use in HIA, such as the

Estimation of Morbidity from Air Pollution and its Economic Costs project (EMAPEC), and an active Global Air Pollution and Health-Technical Advisory Group (GAPH-TAG). We propose to include morbidity outcomes in future HIAs and CBAs that will be conducted for informing policy making.

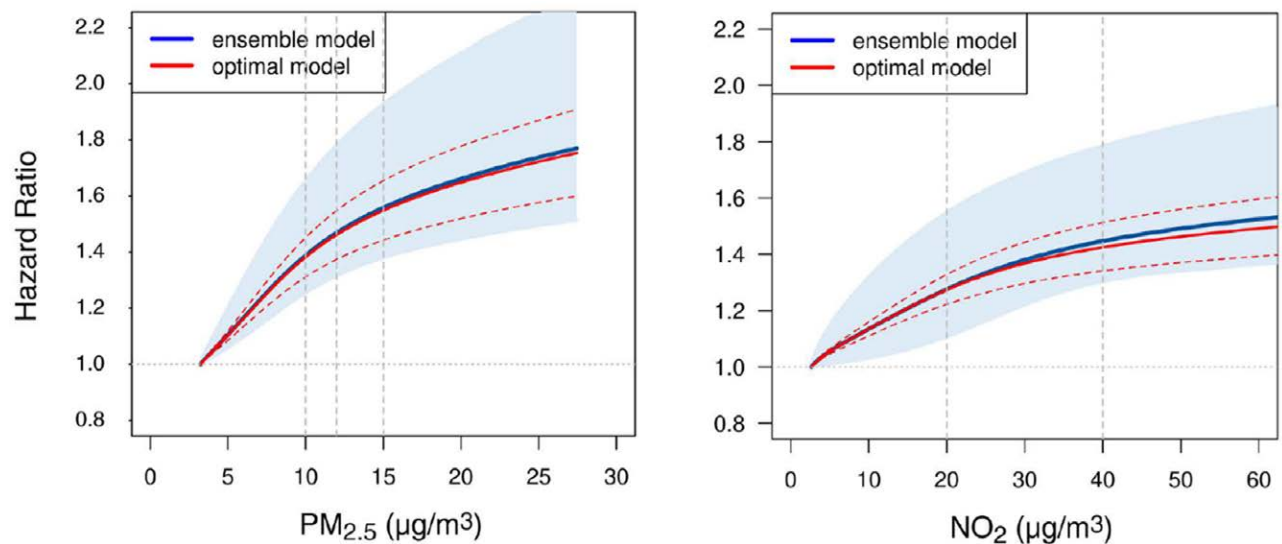


Figure 5. Exposure-response function for  $PM_{2.5}$  and  $NO_2$  and total mortality from the ELAPSE pooled cohort.<sup>7</sup>

### Additional considerations: overlap of effects from $PM_{2.5}$ and $NO_2$

$PM_{2.5}$  and  $NO_2$  are typically positively correlated and calculating the overall health impacts needs to take this into account. It is beyond the scope of this commentary to provide a review of joint effect estimates for the purpose of HIA. In general, the use of one or the other of the single pollutant model results, alone, would underestimate the total effect of the air pollution mixture to some degree, but summing effects predicted on the basis of the unadjusted coefficients would over-estimate the effects of a pollutant mixture. The joint effect estimates will depend on the relative pollutant concentrations and on the extent to which the single-pollutant effect estimates are being reduced by adjustment for the second pollutant.

Table 1 provides an example of a cumulative risk index from a three-pollutant model, estimating the joint effects of  $PM_{2.5}$ ,  $NO_2$ , and  $O_3$  in Canada.<sup>30</sup> It shows that the cumulative risk from co-pollutant adjusted hazard ratios is 1.075, which is less than the cumulative risk from the unadjusted, single-pollutant hazard ratios, which is 1.123. At the same time, the adjusted cumulative risk of 1.075 is about 50% higher than the highest single-pollutant effect estimate of 1.052 for  $NO_2$ . There is a clear need for additional deliberations on this complex issue to avoid underestimating the total air pollution effect on the one hand, and of “double counting” in HIA and CBA on the other hand.

### Conclusions

To estimate the potential benefit of air pollutant reductions as accurately as possible, HIA and CBA need to include the latest and most relevant information on the relation between air pollutants and adverse health outcomes. Effect estimates from ELAPSE represent the largest and most relevant data for Europe to date.

We recommend analyses using ELAPSE for inclusion in the HIA and CBA to inform the revision of the EU AAQD that is currently ongoing. Specifically, we suggest analyses for total mortality and long-term  $PM_{2.5}$  and  $NO_2$  using a summary estimate of 1.118 (1.060, 1.179) for  $PM_{2.5}$  and 1.045 (1.026, 1.065) for  $NO_2$ , both per 10  $\mu g/m^3$ .

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### Conflicts of interest statement

The authors declare that they have no conflicts of interest with regard to the content of this commentary.

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