A proposal for sensitivity analyses of the health impacts of $PM_{2.5}$ and NO_2 in Europe, in support of the revision of the EU ambient Air Quality Standards for these pollutants

Authors: Bert Brunekreef[1], Zorana J Andersen[2], Francesco Forastiere[3], Barbara Hoffmann[4], Hanna Boogaard[5]

[1] Environmental Epidemiology IRAS, University of Utrecht

[2] Department of Public Health, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, European Respiratory Society (ERS)

[3] School of Public Health, Imperial College, London

[4] Institute for Occupational, Social and Environmental Medicine, Medical Faculty, University of Düsseldorf, European Respiratory Society (ERS)

[5] Health Effects Institute, Boston, the US, International Society for Environmental Epidemiology (ISEE)

Summary

To estimate the potential benefit of air pollutant reductions adequately, health impact assessment (HIA) and cost-benefit analyses (CBA) need to include the latest and most relevant information on the relationships between air pollutants and health outcomes. Effect estimates from the ELAPSE (Effects of Low-Level Air Pollution: A Study in Europe) study represent the largest and most relevant data for Europe to date.

We recommend the following sensitivity analyses for inclusion in the HIA and CBA to inform the revision of the EU Ambient Air Quality Directive:

All-cause mortality for long-term $PM_{2.5}$ and NO_2 using the pooled ELAPSE results

- **summary estimate for $PM_{2.5}$ 1.118 (1.060 – 1.179) per 10 μg/m^3**
- **summary estimate for NO_2 1.045 (1.026 – 1.065) per 10 μg/m^3**

Rationale

Health impact assessment (HIA) and cost-benefit analyses (CBA) play a major role in the revision of the EU Ambient Air Quality Directive (AAQD), as they quantify the health benefits of pollutant reductions. In this note, we consider the recent body of evidence on the effects of long-term exposure to fine particulate matter ($PM_{2.5}$) and nitrogen dioxide (NO_2) on total mortality (natural causes). We discuss the rationale for conducting sensitivity analyses of the EU HIA using a different exposure-response estimate for $PM_{2.5}$ and NO_2 with mortality, based on the ELAPSE study.

Mortality impacts for Europe, calculated since 2014 in the annual 'Air Quality in Europe' reports published by the European Environment Agency (EEA), have used relative risk estimates published by (Hoek et al., 2013). These estimates are based on evidence published before 2011. The summary estimates were 1.06 (1.04 – 1.08) for $PM_{2.5}$ and 1.05 (1.03 – 1.08) for NO_2, both per 10 μg/m^3. The EEA, in its 2021 HIA, assumed no threshold for $PM_{2.5}$, and a threshold of 20 μg/m^3 for NO_2. Based on these premises, the premature mortality in the EU27 due to $PM_{2.5}$ and due to NO_2 in 2019 in the EU was 307,000 and 40,400 deaths, respectively (EEA 2021).

In support of the recent development of the 2021 WHO Air Quality Guidelines, new systematic reviews of the evidence of effects of air pollutants on mortality (Chen & Hoek, 2020) (Huangfu & Atkinson, 2020) were published in 2020. 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 $PM_{2.5}$ and total mortality documented a summary estimate of 1.08 per 10 µg/m^3 with a confidence interval of (1.06 – 1.09), based on 25 studies (Chen & Hoek, 2020). The systematic review on NO_2 and total mortality reported a summary estimate of 1.02 per 10 µg/m^3 with a confidence interval of (1.01 – 1.04), based on 24 studies (Huangfu & Atkinson, 2020).

These systematic reviews were published in 2020 and included studies available until September 2018. Since then, important new European studies have been published. We propose that a sensitivity analysis should be conducted based on these new studies to ensure that the HIA to inform the revision of the AAQD considers the most recent and relevant evidence. In particular, we recommend the use of the exposure-response estimate from ELAPSE (Effects of Low-Level Air Pollution: A Study in Europe). ELAPSE is the largest study in Europe by far, and represents the latest and most relevant data for Europe. It includes data from studies on about 30 million participants in 11 EU countries, almost all of whom were exposed to levels of $PM_{2.5}$ and NO_2 below current EU limit values (Strak et al., 2021) (Stafoggia et al., 2022) (Brunekreef et al., 2021). Several other European studies have been published in recent years as well, and we have included those results as well for comparison and completeness.

Mortality estimates from recent European studies

The results of the ELAPSE study for associations of $PM_{2.5}$ with total mortality is shown in Figure 1 (Brunekreef et al., 2021). The figure includes the estimates from a large pooled cohort study of eight individual cohorts from six EU countries, and 7 separate very large nationwide or citywide administrative cohorts. Importantly, all estimates adjusted for smoking and other important lifestyle and social factors. The summary estimate for $PM_{2.5}$ is 1.118 (1.060 – 1.179) per 10 µg/m^3, which is larger than the 1.08 summary estimate from the WHO systematic review (Chen & Hoek, 2020).

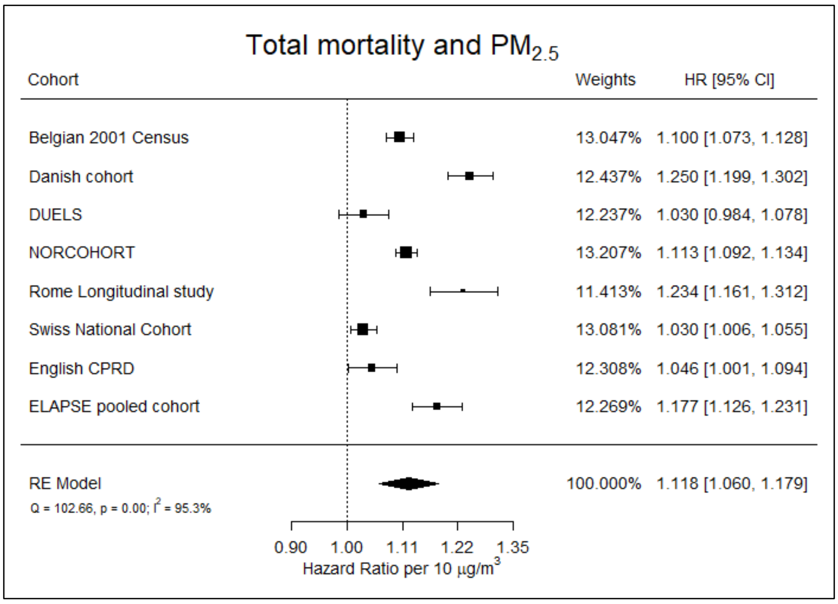

Figure 1: Total mortality and long-term $PM_{2.5}$ from ELAPSE (Brunekreef et al., 2021).*

*indirectly adjusted estimates for smoking for the 6 administrative cohorts (Table 22). The English CPRD cohort adjusted for smoking directly (Figure 14). The pooled cohort adjusted for smoking as well, and the time varying effect estimate was extracted (Table 10).

Figure 2 shows the results of ELAPSE for NO_2. This figure again includes the estimates from a large pooled cohort study including data from eight cohorts from six EU countries , and 7 separate very large administrative cohorts (Brunekreef et al., 2021). As for $PM_{2.5}$, 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^3, which is larger than the 1.02 effect estimate from the WHO systematic review (Huangfu & Atkinson, 2020).

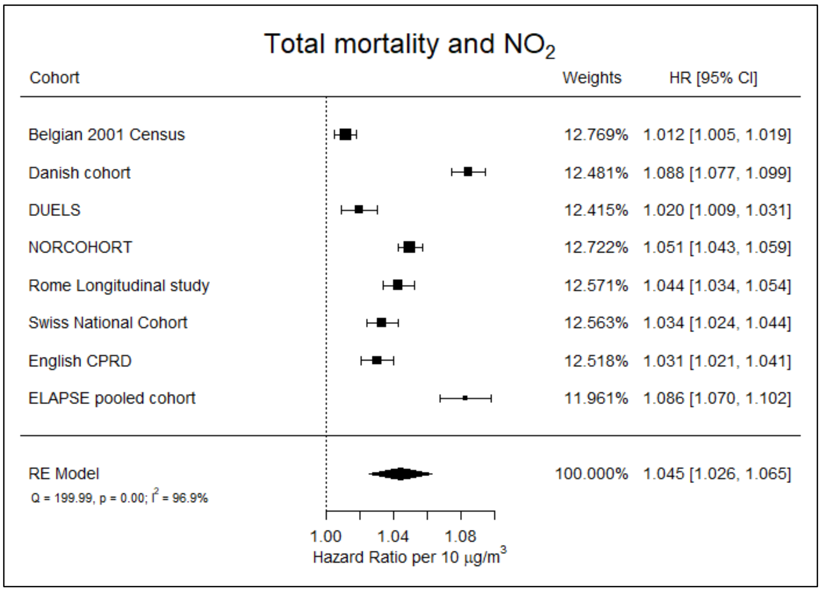

Figure 2. Total mortality and long-term NO_2 from ELAPSE (Brunekreef et al., 2021).*

*indirectly adjusted estimates for smoking for the 6 administrative cohorts (Table 22). The English CPRD cohort adjusted for smoking directly (Figure 14). The pooled cohort adjusted for smoking as well, and the main exposure effect estimate was extracted since no difference with time-varying exposure estimate (Table 9).

Figures 3 and 4 show the mortality results of other recent European studies for long-term $PM_{2.5}$ and NO_2, respectively, which were published after the deadline of the WHO systematic reviews. The results from these studies are compared to the summary estimates from the WHO systematic reviews (red vertical line) and the summary estimate from the ELAPSE study. The findings corroborate the conclusions drawn from the ELAPSE study, namely that the $PM_{2.5}$ and NO_2 effects on mortality in Europe are larger than the estimates of the global WHO systematic reviews.

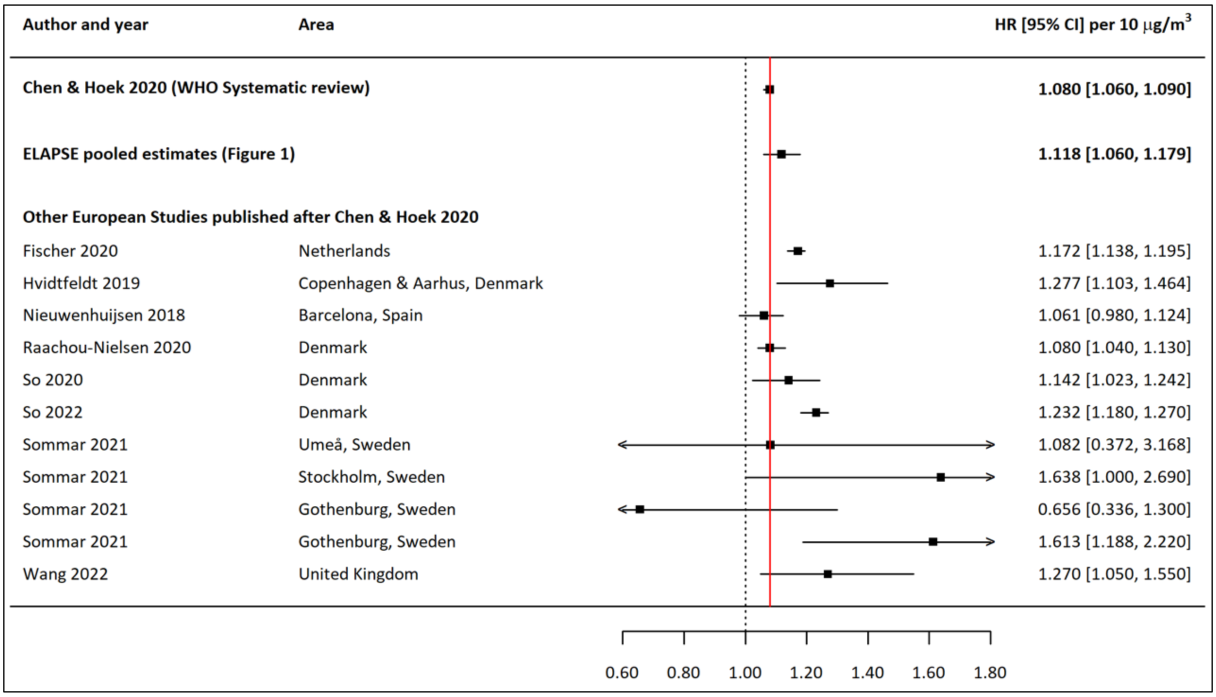

Figure 3. Total mortality and long-term $PM_{2.5}$ from other European studies published since the WHO systematic review by Chen & Hoek (2020).*

*Red line indicates the summary estimate from the systematic review by Chen & Hoek (2020). Range of mean $PM_{2.5}$ exposure in European studies from 5.8 to 20.5 μg/m^3.

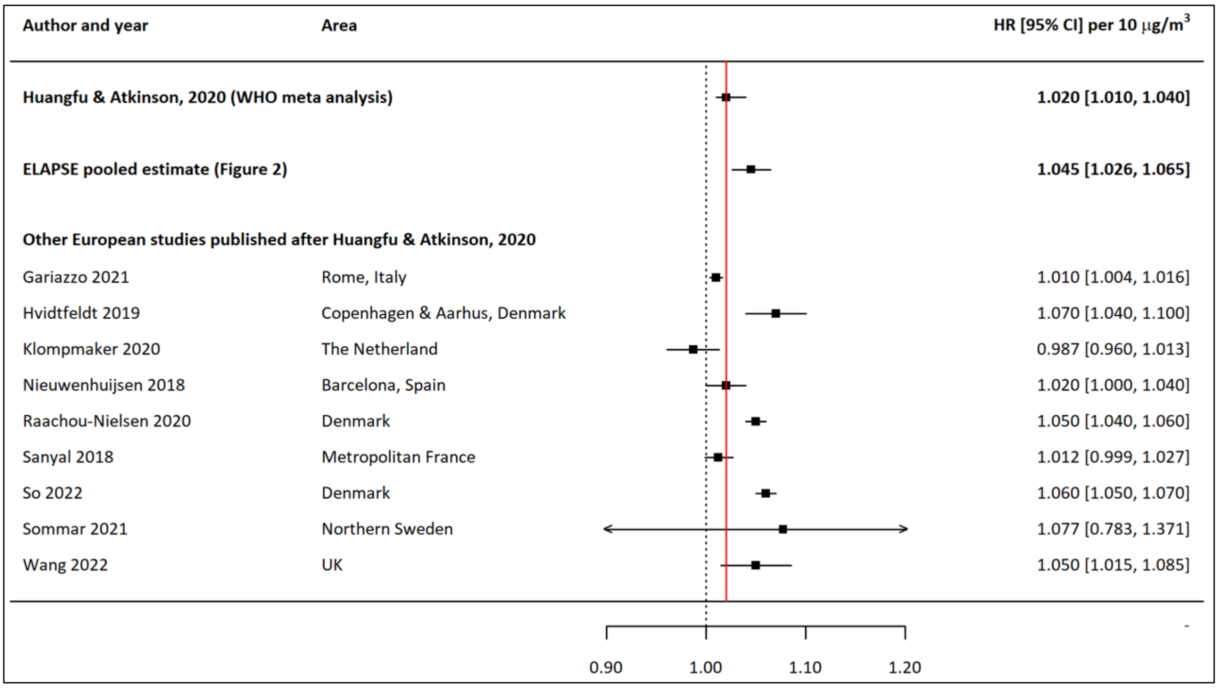

Figure 4. Total mortality and long-term NO_2 from other European published since the WHO systematic review by Huangfu & Atkinson (2020).*

*Red line indicates the summary estimate from the systematic review by Huangfu & Atkinson (2020). Range of mean NO_2 exposure in European studies from 7.1 to 53.4 µg/m^3.

Additional considerations: larger associations at lowest concentrations

Recent studies have documented the supra-linear form of the exposure-response relationship between long-term exposure to $PM_{2.5}$ and NO_2 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 et al., 2018)). The ELAPSE study made a systematic effort to estimate associations in sub-populations exposed to concentrations below certain cut-points in Europe. Those results are summarized in tables 7 and 20 of the main report (Brunekreef et al., 2021). They show that in the pooled cohort of eight cohorts from six EU countries, the effect estimate for $PM_{2.5}$ was about twice higher in the sub-population exposed to concentrations below 15 µg/m^3 than in the full population. The sub-population contained about half of all study participants. For NO_2, the effect estimate was about 30% higher in the sub-population exposed to concentrations below 30 µg/m^3 than in the full population. The sub-population contained about 75% of all study participants. Analyses of the exposure-response function supported this finding, showing a supra-linear curve (Figure 5).

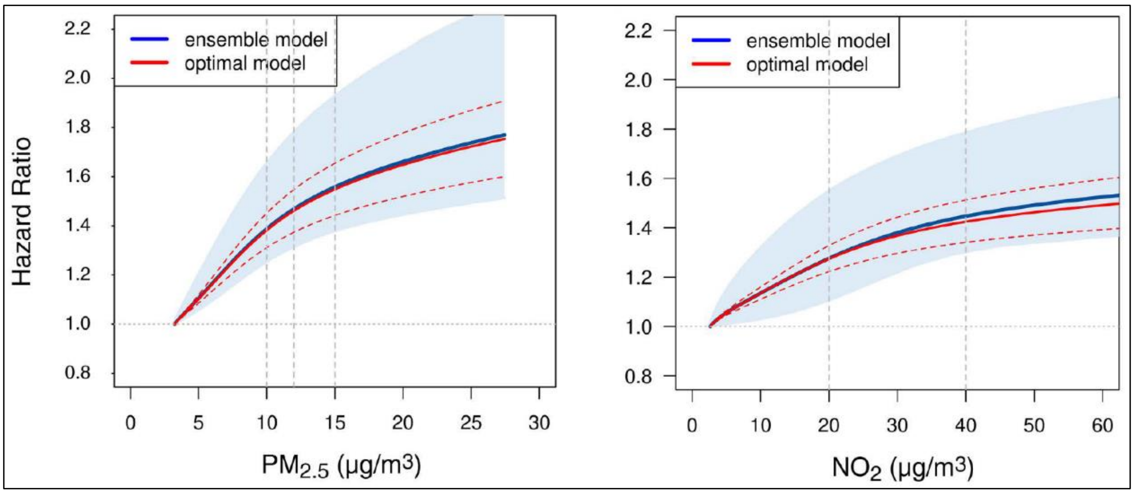

Figure 5: Exposure-response function for $PM_{2.5}$ and NO_2 and total mortality from the ELAPSE pooled cohort (Brunekreef et al., 2021).

In the 7 administrative cohorts within ELAPSE, the effect estimate for $PM_{2.5}$ was about 80% higher in the sub-population exposed to concentrations below 12 µg/m^3 than in the full population. The sub-population contained about 4.5 Million study participants. For NO_2, the effect estimate was about 40% higher in the sub-population exposed to concentrations below 20 µg/m^3 than in the full population. The sub-population contained about 6 million study participants. Analyses of the exposure-response function supported this finding, showing supra-linear curves for most of the cohorts (Stafoggia et al., 2022). 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 sensitivity analyses, in part because of the smaller sample sizes, and the importance of generalizability for use in HIA. They support the use of the ELAPSE effect estimates as shown in Figures 1 and 2 as an additional sensitivity 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, 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 et al., 2017). ELAPSE also documented clear associations between long-term exposure to $PM_{2.5}$ and/or NO_2 and the incidence of lung cancer (Hvidtfeldt et al., 2021), coronary and cerebrovascular events (Wolf et al., 2021), COPD (Liu et al., 2021a), asthma (Liu et al., 2021b), and liver cancer (So et al., 2021). Furthermore, long-term NO_2 exposure in urban areas was associated with asthma onset in children (Anenberg et al., 2022). In addition, new 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 throughout lifetime (Thurston et al., 2017). These associations may lead to in sick days, doctor visits, need for medication and hospital care, and accumulating 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 $PM_{2.5}$ and NO_2 could be based. For example, the UK has undertaken a comprehensive assessment of morbidity outcomes, including stroke incidence, asthma incidence in children, and lung cancer incidence (Public Health England, 2018). The Swedish EPA has recently published a report (in Swedish only, but it will be translated in English shortly) assessing which morbidity impacts of air pollution can be included in HIA. A similar effort has been undertaken in France (ANSES, 2019). 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 want to emphasize that the WHO systematic reviews have – only due to lack of resources – ignored the effects of long-term exposure of air pollution on morbidity. The current HIA is underestimating the health benefits of air pollution reductions by not quantifying the various morbidity outcomes.

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 document to provide a review of joint effect estimates for the purpose of HIA. In general, 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.

Conclusions

We propose using the summary estimates for $PM_{2.5}$ and NO_2 for mortality from ELAPSE in the HIA and CBA conducted for the revision of the EU AAQD. They represent the largest and most relevant evidence on health effects currently available for Europe. The following sensitivity analyses of mortality for long-term $PM_{2.5}$ and NO_2 are recommended: summary estimate for $PM_{2.5}$ of 1.118 (1.060 – 1.179) per 10 µg/m^3 and summary estimate for NO_2 of 1.045 (1.026 – 1.065) per 10 µg/m^3.

References

Anenberg, S. C., Mohegh, A., Goldberg, D. L., Kerr, G. H., Brauer, M., Burkart, K., . . . Lamsal, L. (2022). Long-term trends in urban NO2 concentrations and associated paediatric asthma incidence: estimates from global datasets. *Lancet Planet Health, 6*(1), e49-e58. doi:10.1016/S2542-5196(21)00255-2

ANSES. (2019). *Particulate matter in ambient air. Health effects according to components, sources and particle size*. Retrieved from France:

Brunekreef, B., Strak, M., Chen, J., Andersen, Z. J., Atkinson, R., Bauwelinck, M., . . . Hoek, G. (2021). *Mortality and Morbidity Effects of Long-Term Exposure to Low-Level PM2.5, BC, NO2, and O3: An Analysis of European Cohorts in the ELAPSE Project*. Retrieved from

Burnett, R., Chen, H., Szyszkowicz, M., Fann, N., Hubbell, B., Pope, C. A., 3rd, . . . Spadaro, J. V. (2018). Global estimates of mortality associated with long-term exposure to outdoor fine particulate matter. *Proc Natl Acad Sci U S A, 115*(38), 9592-9597. doi:10.1073/pnas.1803222115

Chen, J., & Hoek, G. (2020). Long-term exposure to PM and all-cause and cause-specific mortality: A systematic review and meta-analysis. *Environ Int, 143*, 105974. doi:10.1016/j.envint.2020.105974

European Environment Agency (2021). Health impacts of air pollution in Europe, 2021. https://www.eea.europa.eu/publications/air-quality-in-europe-2021/health-impacts-of-air-pollution. Last accessed Apr 29, 2022.

Fischer, P. H., Marra, M., Ameling, C. B., Velders, G. J. M., Hoogerbrugge, R., de Vries, W., . . . Houthuijs, D. (2020). Particulate air pollution from different sources and mortality in 7.5 million adults - The Dutch Environmental Longitudinal Study (DUELS). Sci Total Environ, 705, 135778. doi:10.1016/j.scitotenv.2019.135778

Gariazzo, C., Carlino, G., Silibello, C., Tinarelli, G., Renzi, M., Finardi, S., . . . Group, B. C. (2021). Impact of different exposure models and spatial resolution on the long-term effects of air pollution. *Environ Res, 192*, 110351. doi:10.1016/j.envres.2020.110351

Hoek, G., Krishnan, R. M., Beelen, R., Peters, A., Ostro, B., Brunekreef, B., & Kaufman, J. D. (2013). Long-term air pollution exposure and cardio- respiratory mortality: a review. *Environ Health, 12*(1), 43. doi:10.1186/1476-069X-12-43

Huangfu, P., & Atkinson, R. (2020). Long-term exposure to NO2 and O3 and all-cause and respiratory mortality: A systematic review and meta-analysis. *Environ Int, 144*, 105998. doi:10.1016/j.envint.2020.105998

Hvidtfeldt, U. A., Severi, G., Andersen, Z. J., Atkinson, R., Bauwelinck, M., Bellander, T., . . . Fecht, D. (2021). Long-term low-level ambient air pollution exposure and risk of lung cancer - A pooled analysis of 7 European cohorts. *Environ Int, 146*, 106249. doi:10.1016/j.envint.2020.106249

Hvidtfeldt, U. A., Sorensen, M., Geels, C., Ketzel, M., Khan, J., Tjonneland, A., . . . Raaschou-Nielsen, O. (2019). Long-term residential exposure to PM2.5, PM10, black carbon, NO2, and ozone and mortality in a Danish cohort. *Environ Int, 123*, 265-272. doi:10.1016/j.envint.2018.12.010

Klompmaker, J. O., Hoek, G., Bloemsma, L. D., Marra, M., Wijga, A. H., van den Brink, C., . . . Janssen, N. A. H. (2020). Surrounding green, air pollution, traffic noise exposure and non-accidental and cause-specific mortality. *Environ Int, 134*, 105341. doi:10.1016/j.envint.2019.105341

Liu, S., Jorgensen, J. T., Ljungman, P., Pershagen, G., Bellander, T., Leander, K., . . . Andersen, Z. J. (2021a). Long-term exposure to low-level air pollution and incidence of chronic obstructive pulmonary disease: The ELAPSE project. *Environ Int, 146*, 106267. doi:10.1016/j.envint.2020.106267

Liu, S., Jorgensen, J. T., Ljungman, P., Pershagen, G., Bellander, T., Leander, K., . . . Andersen, Z. J. (2021b). Long-term exposure to low-level air pollution and incidence of asthma: the ELAPSE project. *Eur Respir J, 57*(6). doi:10.1183/13993003.03099-2020

Nieuwenhuijsen, M. J., Gascon, M., Martinez, D., Ponjoan, A., Blanch, J., Garcia-Gil, M. D. M., . . . Basagana, X. (2018). Air Pollution, Noise, Blue Space, and Green Space and Premature Mortality in Barcelona: A Mega Cohort. *Int J Environ Res Public Health, 15*(11). doi:10.3390/ijerph15112405

Public Health England (2018). Air pollution: a tool to estimate healthcare costs. A tool to help local authorities estimate the burden of air pollution on the health care system. https://www.gov.uk/government/publications/air-pollution-a-tool-to-estimate-healthcare-costs. Last accessed April 29, 2022.

Raaschou-Nielsen, O., Thorsteinson, E., Antonsen, S., Holst, G. J., Sigsgaard, T., Geels, C., . . . Hvidtfeldt, U. A. (2020). Long-term exposure to air pollution and mortality in the Danish population a nationwide study. *EClinicalMedicine, 28*, 100605. doi:10.1016/j.eclinm.2020.100605

Sanyal, S., Rochereau, T., Maesano, C. N., Com-Ruelle, L., & Annesi-Maesano, I. (2018). Long-Term Effect of Outdoor Air Pollution on Mortality and Morbidity: A 12-Year Follow-Up Study for Metropolitan France. *Int J Environ Res Public Health, 15*(11). doi:10.3390/ijerph15112487

So, R., Jorgensen, J. T., Lim, Y. H., Mehta, A. J., Amini, H., Mortensen, L. H., . . . Andersen, Z. J. (2020). Long-term exposure to low levels of air pollution and mortality adjusting for road traffic noise: A Danish Nurse Cohort study. Environ Int, 143, 105983. doi:10.1016/j.envint.2020.105983

So, R., Andersen, Z. J., Chen, J., Stafoggia, M., de Hoogh, K., Katsouyanni, K., . . . Mehta, A. J. (2022). Long-term exposure to air pollution and mortality in a Danish nationwide administrative cohort study: beyond mortality from cardiopulmonary disease and lung cancer. *Environment International*, 107241. doi:https://doi.org/10.1016/j.envint.2022.107241

So, R., Chen, J., Mehta, A. J., Liu, S., Strak, M., Wolf, K., . . . Andersen, Z. J. (2021). Long-term exposure to air pollution and liver cancer incidence in six European cohorts. *Int J Cancer, 149*(11), 1887-1897. doi:10.1002/ijc.33743

Sommar, J.N., Andersson, E. M., Andersson, N., Sallsten, G., Stockfelt, L., Ljungman, P. L., . . . Forsberg, B. (2021a). Long-term exposure to particulate air pollution and black carbon in relation to natural and cause-specific mortality: a multicohort study in Sweden. BMJ Open, 11(9), e046040. doi:10.1136/bmjopen-2020-046040

Sommar, J. N., Hvidtfeldt, U. A., Geels, C., Frohn, L. M., Brandt, J., Christensen, J. H., . . . Forsberg, B. (2021b). Long-Term Residential Exposure to Particulate Matter and Its Components, Nitrogen Dioxide and Ozone-A Northern Sweden Cohort Study on Mortality. *Int J Environ Res Public Health, 18*(16). doi:10.3390/ijerph18168476

Stafoggia, M., Oftedal, B., Chen, J., Rodopoulou, S., Renzi, M., Atkinson, R. W., . . . Janssen, N. A. H. (2022). Long-term exposure to low ambient air pollution concentrations and mortality among 28 million people: results from seven large European cohorts within the ELAPSE project. *Lancet Planet Health, 6*(1), e9-e18. doi:10.1016/S2542-5196(21)00277-1

Strak, M., Weinmayr, G., Rodopoulou, S., Chen, J., de Hoogh, K., Andersen, Z. J., . . . Samoli, E. (2021). Long term exposure to low level air pollution and mortality in eight European cohorts within the ELAPSE project: pooled analysis. *BMJ, 374*, n1904. doi:10.1136/bmj.n1904

Thurston, G. D., Kipen, H., Annesi-Maesano, I., Balmes, J., Brook, R. D., Cromar, K., . . . Brunekreef, B. (2017). A joint ERS/ATS policy statement: what constitutes an adverse health effect of air pollution? An analytical framework. *Eur Respir J, 49*(1). doi:10.1183/13993003.00419-2016

Wang, M., Zhou, T., Song, Q., Ma, H., Hu, Y., Heianza, Y., & Qi, L. (2022). Ambient air pollution, healthy diet and vegetable intakes, and mortality: a prospective UK Biobank study. *Int J Epidemiol*. doi:10.1093/ije/dyac022

Wolf, K., Hoffmann, B., Andersen, Z. J., Atkinson, R. W., Bauwelinck, M., Bellander, T., . . . Ljungman, P. L. S. (2021). Long-term exposure to low-level ambient air pollution and incidence of stroke and coronary heart disease: a pooled analysis of six European cohorts within the ELAPSE project. *Lancet Planet Health, 5*(9), e620-e632. doi:10.1016/S2542-5196(21)00195-9