[FHI, KM] [2]

Institution: Norwegian Institute of Public Health (FHI/NIPH)
Administrative unit: Division of Climate and Environmental Health
Title of case study: Improved knowledge of health effects of low levels of air pollution and its contribution to guidelines and regulations
Period when the underpinning research was undertaken: 2012 - 2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2012-2022
Period when the impact occurred: 2012-2022

3. Summary of the impact

Air pollution is the number one environmental contributor to the burden of disease in Europe, and the fourth most important risk factor for premature death and disability worldwide according to the Global Burden of Disease Study 2019. Combining epidemiology and experimental research, our department contributes to a mechanistic and holistic understanding of the impact of air pollution on health. Our research has helped elucidating the main contributors and the mode of action for the health effects observed, as well as contributed new knowledge about health impacts of low levels of air pollution, ultimately underpinning changed air quality recommendations both nationally and internationally. Our research within this field has had an impact on national and international advisory and policy making to improve public health. More specifically, our research has contributed to newly updated air quality criteria in Norway.

2. Underpinning research

The research and knowledge of health effects of air pollution is based on both epidemiological and experimental studies. In our department we have both types of expertise. The department conducted large scale epidemiological studies in collaboration with leading research centers in Europe, and provided data, verified data, conducted statistical analysis, contributed to scientific discussions and critical review of manuscripts. Prior to the EU funded ESCAPE (European Study of Cohorts of Air pollution Effects) project, most studies providing evidence on exposure – response relationships were from North America. ESCAPE used refined assessments of residential long-term air pollution exposure linked to data from European cohorts and contributed new knowledge on exposure – response relationships and thresholds for health impacts. Our department provided data from the HUBRO cohort, contributing to the lowest exposure levels of air pollution. Although there were indications of adverse health effects below existing recommended limits in previous studies, knowledge of effects including the shape of exposure-response association at low exposure levels was still limited and uncertain. Studies were generally lacking sufficient data at the lower end of the exposure continuum. Further building on ESCAPE, ELAPSE (Effects of Low-level Air Pollution: A Study in Europe) aimed at contributing new knowledge of health effects at low levels of air pollution. Since Norway has low air pollution levels compared to most other countries, the department's contributions were crucial. The department established a national administrative cohort, NORCOHORT, composed of extensive registry data linked with improved air pollution exposures calculated for the individual home addresses of 2.6 million Norwegian citizens. Statistical analyses including adjustment for age, sex, and both individual and area level of socioeconomic factors provided exposure – response relationships showing health impacts below existing air pollution guidelines and limits. Results from several administrative cohorts across Europe were combined by means of meta-analysis, producing final results showing increased risk of mortality even at low levels of air pollution.

Since epidemiological studies show associations between air pollution and health effects, experimental studies have been used to support a possible causal relationship. To approach this challenge, our department explored the mechanisms of different air pollutants to study which of the components are the most critical. We have received three projects from the Norwegian

Research Council and one EU-project to elucidate this. The projects have mainly been focusing on PM (particulate matter) and the different chemical components attached, in addition to the relative contribution of different PM-sources and its impact on health. We have used animal- and clinical studies, but mostly cell models in monocultures and in advanced co-cultures exposed to different air pollutants. The mutual interactions between respiratory (epithelial and macrophages) and cardiovascular cells (endothelial, cardiomyocytes and fibroblasts) have been examined, with emphasis on cytotoxicity, inflammatory responses, cellular receptors and inter- and intracellular mediators involved.

We have studied the role of different particle sizes, traffic-related sources (exhaust particles and road abrasion particles), wood combustion particles and also several nanoparticles (NPs) as models for ultrafine particles. In particular, silica NPs and crystalline silica particles were compared, and cellular signaling pathways like involvement of inflammasome activation have been demonstrated. In addition, inflammatory processes induced by the PM-components like different minerals, metals, polycyclic aromatic hydrocarbons (PAH) and endotoxins have been studied regarding reactive oxygen species (ROS), CYP-enzymes and aryl hydrocarbon receptor (AhR) linked-mechanisms. Furthermore, effects of PM on other secondary organs than the cardiovascular system like nervous system, blood cells and liver have also been explored. A benefit was to develop advanced culture models to examine different air pollutants to complement and replace animal studies.

The breadth of research in the department with both epidemiological and experimental expertise is important for elucidating health effects of air pollution. Such knowledge and studies will complement each other with regard to dose-response relationships, causality and point out important sources and components inducing health effects.

The underpinning research was carried out throughout the whole evaluation period. Research output was numerous peer reviewed papers, news letters, and in communication in advisory work. The impact was a continuous process over the period, finally leading to the last revision of the Air Quality Criteria, starting 2022 and finalized 2023.

Per Everhard Schwarze, Department director, from 2015 to 2017
Bente Margaret Oftedal, Scientist (2012-2014) Senior Scientist (2014-)
Marit Låg, Senior Scientist (2012-)
Johan Øvrevik Scientist (2012-2013), Senior Scientist (2013-2016), Department Director (2017-2021)
Magne Refsnes, Senior Scientist (2012-2022)
Vegard Grytting Sæter, PhD (2017-2021), Scientist (2021-2022) Post doc (2022-)
Jørn Holme, Senior Scientist (2012 -2022)

4. References to the research

1. Author(s): Stafoggia M, **Oftedal B,** Chen J, Rodopoulou S, Renzi M, Atkinson RW et al.
- Title: 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
- Year of publication: 2022
- Lancet Planetary health, 6: e9-18. DOI: https://doi.org/10.1016/S2542-5196(21)00277-1

Evidence about the quality of the research: This paper was awarded the prize for "Best Environmental Epidemiology Paper (BEEP) published in 2022 at the ISEE (International Society for Environmental Epidemiology) conference the following year, with this rationale according to the Awards committee: "*The article makes an outstanding contribution to the knowledge of environmental epidemiology and was selected because of its quality, originality, importance and*

expected impact, particularly through its novel application of methodology."
(https://iseepi.org/beep.php)
Citations: 140
2. Author(s): Sophia Rodopoulou, Massimo Stafoggia, Jie Chen, Kees de Hoogh, Mariska Bauwelinck, Amar J. Mehta, Jochem O. Klompmaker, **Bente Oftedal** et al.
- Title: Long-term exposure to fine particle elemental components and mortality in Europe: Results from six European administrative cohorts within the ELAPSE project
- Year of publication: 2022
- Sci Total Environ 2022 Feb 25:809:152205. DOI: 10.1016/j.scitotenv.2021.152205.
Citations: 12
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- Title: Effects of long-term exposure to air pollution on natural-cause mortality: an analysis of 22 European cohorts within the multicentre ESCAPE project
- Year of publication: 2014
- Lancet 2014 Mar 1;383(9919):785-95. DOI:10.1016/S0140-6736(13)62158-3.
Citations: 1476
4. Authors: **Øvrevik J, Refsnes M, Låg M, Holme JA, Schwarze PE**.
-Title: Activation of Proinflammatory Responses in Cells of the Airway Mucosa by Particulate Matter: Oxidant- and Non-Oxidant-Mediated Triggering Mechanisms. Review
-Year of publication: 2015
- Journal: Biomolecules 5, Jul 2; 5 (3):1399-440
Citations: 221
5. Authors: **Låg M**, **Øvrevik J**, **Refsnes M**, **Holme JA.**
- Title: Potential role of polycyclic aromatic hydrocarbons in air pollution-induced non-malignant respiratory diseases Review
-Year of publication: 2020
-Journal: Respir Res.Nov 13;21(1):299. doi: 10.1186/s12931-020-01563-1.
-*Citations: 107*
6. Authors: **Skuland T, Låg M**, Gutleb AC, **Brinchmann BC**, Serchi T, **Øvrevik J, Holme JA, Refsnes M**
-Title: (2020). Pro-inflammatory effects of crystalline- and nano-sized non-crystalline silica particles in a 3D alveolar model.
-Year of publication: 2020
-Journal: Part Fibre Toxicol. Apr 21;17(1):13.
-*Citations: 42*

4. Details of the impact

Air pollution is a major threat to global health and prosperity, responsible for more than 6.5 million deaths each year globally (The Lancet Planetary Health, 2022). Air pollution can affect lung development and is implicated in the development of emphysema, asthma, and other respiratory diseases, such as chronic obstructive pulmonary disease (COPD). Increases in asthma prevalence and severity are linked to urbanization and outdoor air pollution. Other health effects from air pollution have been described such as cardiovascular diseases, diabetes, adverse birth outcomes and possibly neurological defects such as dementia and disturbed neurodevelopment in children.

Studying the health effects of air pollution in Norway and the Nordic countries has been an important contribution to help us understanding the impact on health even at low concentrations. These epidemiological studies together with experimental studies also help us identifying the different emission sources and chemical components of particulate matter, which pollutants are most harmful and develop strategies to reduce exposure to these harmful components. Norway

and Nordic countries have different emission sources of air pollution in different seasons of the year. The winter season contributes to high levels of particulate matter (PM10) from the use of spiked tires on icy roads and high levels of PM 2,5 from wood burning. Moreover, high air pollution levels can be measured in the cities with temperature inversions during cold temperature shifts. For the planning of healthy urban environments and the best measures, it is important to understand how other outdoor exposures possibly interact with and influence effects of air pollution. The department has expertise on all major outdoor exposures, and data on both noise and surrounding greenness are included in all recent studies (e.g. ELAPSE). The department's holistic research approach contributes to a broader understanding and improved knowledge of the health burden ascribed to air pollution and the most harmful components. Over the last years, the department has studied surrounding greenness, nature-based solutions and urbanisation (HELIX, Athlete, ELAPSE) and how climate change with emphasis on extreme temperatures may impact both exposure and vulnerability to air pollution (EXHAUSTION).

With this holistic view, we give knowledge-based advice to authorities and contribute to air quality criteria/guidelines and limit values, impacting policy regulations. Through international collaborating projects like ESCAPE and ELAPSE, our research has contributed with critical data and analyses to improve concentration response functions (CRFs) for low-level air pollution and health. The ELAPSE CRFs was used by the European Commission and contributed towards the EU Parliament voting for stricter regulation of air quality fully aligning with the WHO Air Quality Guidelines by 2035. The justifications for the WHO Air Quality Guidelines 2021 have been critically evaluated by our team and taking into account our own and others research from Norway and Nordic countries (ELAPSE, NordicWelfAir). In evaluating Norwegian requirements, we have in close collaboration with the Environmental Directorate published the Air Quality Criteria for Norway. Norwegian air quality criteria were revised in 2013, 2016, 2020 and during 2022 until 2023. The last ten years, these guidelines have been using Norwegian and Nordic cohort data. The criteria are regularly updated based on the departments' research and knowledge (see ref 5). These criteria are used as national targets for reduction of air pollution. Furthermore, the guidelines are used in forecasting by the Norwegian Meteorological Institute (YR.no, https://www.yr.no/en/other-conditions/1-72837/Norway/Oslo/Oslo/Oslo), and Air Quality in Norway (https://luftkvalitet.miljodirektoratet.no/) to classify air pollution levels of different components according to risk of possible health hazard. Vulnerable groups are specified in the health recommendations. In addition, the air quality criteria are used in Planning Guidelines for the municipalities' Agency for Planning and Building Services. In the revision of the Norwegian limit values for particular matter (PM10 and PM2.5), burden of disease and cost estimated by our department together with the cost of the measures were included in a cost-benefit analysis. A socioeconomic gain favored the restriction of the legally binding national limit values for both PM10 and PM2.5 in 2022.

Through regular meeting seminars called "Luftsamarbeidet" ["Air quality cooperation"] with the Environmental Directorate, Health Directorate, Norwegian Public Roads Administration and The Norwegian Meteorological Institute, held at different levels of authority (from researchers and advisors to senior management) we discuss and agree on efficient regulations and measures to bring forward to the ministry, and ways of communicating to the public on air quality and possible health impact. The aim is to take care of life, health, and environment through reducing emissions to the air and exposure to local air pollution. A report of the work accomplished is published yearly. This cooperation between important actors in knowledge and regulation of air pollution has been important for the large reduction of air pollution levels observed in Norway during the last 10-15 years (https://miljostatus.miljodirektoratet.no/tema/forurensning/lokal-luftforurensning/)

IMPACT of the research: The revision and restriction of important Air Quality Criteria (PM2,5 and NO_2) that are used as national targets for reduction of air pollution, in the health recommendation in forecasting of air pollution and in area planning.

5. Sources to corroborate the impact

1. Fuller et al. Pollution and health: a progress update. The Lancet Planetary Health 2022 June; 6(6):e535-e547. DOI: https://doi.org/10.1016/S2542-5196(22)00090-0.(https://www.thelancet.com/journals/lanplh/article/PIIS2542-5196(22)00090-0/fulltext)
2. Wolf K, Hoffmann B, Andersen ZJ, Atkinson RW, Bauwelinck M, Bellander T ::: **Oftedal B**, ::: Schwarze P, :::, Ljungman PLS. 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 Plan Health 2021;5:e620-32. https://www.thelancet.com/action/showPdf?pii=S2542-5196%2821%2900195-9
3.
4. About the EXHAUSTION project, examining air pollution in the context of climate change: https://www.exhaustion.eu/
5. Berit Granum, **Bente Oftedal**, Lydiane Agier, Valerie Siroux, Philippa Bird, Maribel Casas, Charline Warembourg ::: Martine Vrijheid. Multiple environmental exposures in early-life and allergy-related outcomes in childhood. Eviron Int 2020 Nov; 144:106038. DOI: 10.1016/j.envint.2020.106038. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8768577/
6. Outdoor Air Handbook - Air Quality Criteria: https://www.fhi.no/en/cl/air-pollution/outdoor-air-handbook---air-quality-criteria/?term=
7. Clarsen B, Nylenna M, Klitkou ST, Vollset SE, Baravelli CM, **Bølling AK, Aasvang GM, :::** Knudsen AKS. Changes in life expectancy and disease burden in Norway, 1990-2019: an analysis of the Global Burden of Disease Study 2019. Lancet Public Health 2022 Jul;7(7): e593-e605. DOI: 10.1016/S2468-2667(22)00092-5. https://pubmed.ncbi.nlm.nih.gov/35779543/
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