Harmonized confounder model analyses in MAPLE, ELAPSE and Medicare cohorts

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Background. Long-term exposure to fine particles (PM$_{2.5}$) has been consistently associated with increased mortality risks around the world with variations in the magnitude of effect estimates. Investigators have speculated that the differences in effect estimates could be due to differences in the study population, components of PM$_{2.5}$ mixture, exposure assessment methodology, or statistical models. We aimed to further understand the influential factors on mortality effect estimates related to long-term PM$_{2.5}$ exposure, by harmonizing the exposure assessment and statistical modeling approaches in three large projects in Europe and North America.

Methods. The study populations include all Medicare enrollees from 2000 to 2016 (N = 73 million), census-based Canadian cohorts (“stacked” [1991, 1996, 2001] CanCHEC, N=7.1 million), and six European administrative cohorts from 2000 to 2016 (N = 26 million). Exposure to annual average PM$_{2.5}$ concentrations was assessed at a 1x1 km spatial resolution using the MAPLE methodology primarily based upon satellite AOD and linked to participants’ residential addresses. We applied Cox proportional hazard models incorporating PM$_{2.5}$ as time-varying exposure (the Medicare cohort applied an equivalent Poisson additive model). For comparison, we assessed associations between PM$_{2.5}$ exposure with all-cause mortality in a population 65 and older. Additional analyses were performed in MAPLE and ELAPSE investigating associations with non-accidental mortality and in populations ages 25+ (MAPLE) or 30+ (ELAPSE). We harmonize confounder models as much as possible, acknowledging different definitions and covariate availability across cohorts. We specified four models with increasing adjustment for potential confounders: Model 1 included age, sex, calendar years/year of enrollment; Model 2 further adjusted for individual level socioeconomic status (SES) and ethnicity; Model 3 further adjusted for area-level SES; Model 4 added indicators for geographic regions.

Results. Overall we observed positive associations between PM$_{2.5}$ exposure and all-cause mortality in those ≥ 65 years of age (Hazard Ratios (HRs) ranged from 1.009 to 1.095 per 5 µg/m$^3$ increase in PM$_{2.5}$). Increasing control for potential confounders changed PM$_{2.5}$ effect estimates in different directions: HRs increased in the Canadian CanCHEC study, Medicare, and the European Norwegian and Swiss cohorts; HRs did not change in the Dutch and Roman cohorts; HRs attenuated slightly in the Danish cohort. HRs for non-accidental mortality were very close to HRs for all-cause mortality. HRs in the full population were generally similar or higher than HRs in the population aged 65 and above.

Conclusions. Adjustment for potential confounders changed PM$_{2.5}$ effect estimates in different directions because of the different correlations between PM$_{2.5}$ and potential confounders in the three studies. These new analyses did not change any of the previous conclusions based on published studies in these populations.
Harmonized Abstracts: Assessing Health Effects of Long-Term Exposure to Low Levels of Ambient Air Pollution

The shape of the PM$_{2.5}$-mortality exposure-response relationship in the MAPLE, ELAPSE and Medicare cohorts. What have we learned from the studies of exposure to low levels?

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Background. With widespread evidence of the mortality risk associated with long-term exposure to PM$_{2.5}$ there is urgency to reduce ambient concentrations. Evaluating the benefits of reductions in concentrations depends upon understanding both the magnitude of the PM$_{2.5}$ mortality risk and the shape of this relationship. We present results on the shape of the relationship between PM$_{2.5}$ and all-cause mortality based on harmonized exposure assessment and statistical modeling approaches applied to three large projects in Europe and North America.

Methods. The study populations include all Medicare enrollees from 2000 to 2016 (N = 73 million), census-based Canadian cohorts (“stacked” 1991, 1996, 2001 CanCHEC, N =7.1 million), and six European administrative cohorts followed up from 2000 to 2016 (N = 26 million). Satellite-based estimates of annual average PM$_{2.5}$ concentrations were linked to participants’ residential addresses. Cox proportional hazard models incorporating PM$_{2.5}$ as time-varying exposure (the Medicare cohort applied an equivalent Poisson additive model) estimated all-cause mortality risk for those ages 65+ with harmonized covariates (age, sex, calendar years/year of enrollment; individual and area level socioeconomic status and ethnicity, regions). Exposure-response relationships were evaluated by 1) restricting analyses to person-years with concentrations below 5, 7.5, 10 and 12 µg/m$^3$ 2) applying the extended Shape-Constrained Health Impact Function (eSCHIF) which relates risk to concentration in a form suitable for quantitative benefits analysis.

Results. In the Medicare cohort, positive associations between PM$_{2.5}$ exposure and all-cause mortality were observed in all restricted cohort analyses. Using the eSCHIF the shape was slightly supralinear, with an increase at the lowest concentrations, a plateau between 4-7 µg/m$^3$ and another increase at higher concentrations. In MAPLE, positive associations were observed in the full cohort and when restricting to person-years <12 µg/m$^3$. Using the eSCHIF there was a steep supralinear relationship from 2 – 5 µg/m$^3$, a flat relationship to ~8 µg/m$^3$ and a near linear increase at higher concentrations. Within ELAPSE there were consistent positive associations only in the full Swiss cohort, in analyses excluding person-years > 7.5 µg/m$^3$ and >5 µg/m$^3$ in the Danish and Norwegian cohorts, respectively. eSCHIF shapes indicated supralinear relationships in the Danish cohort, sub-linear relationships in the Norwegian and Rome cohorts and flat and somewhat protective relationships in the Swiss cohort.

Conclusions. There was evidence of associations between PM$_{2.5}$ and all-cause mortality even after restricting analyses to person-years exposed to < 5 µg/m$^3$, although results differed between cohorts.
Harmonized causal inference analyses in MAPLE, ELAPSE and Medicare cohorts

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Background. Ideally when studying the health effects of air pollution on mortality one would randomize individuals to low/high air pollution, but this is not feasible in practice. Observational studies, such as the three large projects conducted in Europe and North America to study the effects of long-term exposure to PM₂.⁵ on mortality (the MAPLE, ELAPSE, and the Harvard Medicare study), have limitations due to lack of randomization. Factors that are associated both with both exposures and health outcomes (e.g. socioeconomic status (SES)-related factors) may confound exposure comparisons. Traditionally potential confounders are included as covariates in a regression model, but this does not allow for the evaluation of covariate balance, which can indicate the quality of causal inference for recovering randomized experiments. Here, we apply an innovative causal inference based approach, based on Generalized Propensity Score (GPS) matching, to evaluate the effect of long-term exposure to PM₂.⁵ on mortality.

Methods. The study populations include all Medicare enrollees from 2000 to 2016 (N = 73 million), three census-based Canadian cohorts (1991, 1996 and 2001 “stacked” CanCHEC, N =7.1 million), and six European administrative cohorts followed up from 2000 to 2016 (N = 26 million). Exposure to annual average PM₂.⁵ concentrations was assessed at a 1x1 km spatial resolution using satellite-derived estimates and linked to participants’ residential addresses. GPS matching was applied using the CausalGPS R package (https://fasrc.github.io/CausalGPS/). The GPS model was fit conditioning PM₂.⁵ on the potential confounders, and a matched pseudo population was generated by matching on the GPS and exposures. Covariate balance was assessed by estimating the absolute correlations between the PM₂.⁵ exposure and the potential confounders. Cox proportional hazards models were applied to the matched dataset (the Medicare cohort applied an equivalent Poisson additive model).

Results. In the MAPLE study, the hazard ratio (HR) between PM₂.⁵ exposure and non-accidental mortality was 1.004 (95% CI: 1.000, 1.009) per 5 µg/m³ increase in PM₂.⁵. In the Harvard Medicare study the HR between PM₂.⁵ exposure and all cause mortality was 1.036 (95% CI: 1.019, 1.053) per 5 µg/m³ increase in PM₂.⁵. The mean absolute correlation between PM₂.⁵ exposure and the potential confounders was 0.0379 in the MAPLE study and 0.052 in the Harvard Medicare study, indicating good covariate balance.

Conclusions. The Harvard Medicare study showed robust and reproducible evidence on a causal link between PM₂.⁵ exposure and all cause mortality. The MAPLE study also showed evidence of a causal link but with a reduced magnitude HR compared to the non-GPS cox models. Future work includes applying GPS matching in the European ELAPSE study.