

## Publication

Comparison of traditional cox regression and causal modeling to investigate the association between long-term air pollution exposure and natural-cause mortality within European cohorts

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Most studies investigating the health effects of long-term exposure to air pollution used traditional regression models, although causal inference approaches have been proposed as alternative. However, few studies have applied causal models and comparisons with traditional methods are sparse. We therefore compared the associations between natural-cause mortality and exposure to fine particulate matter (PM(2.5)) and nitrogen dioxide (NO(2)) using traditional Cox and causal models in a large multicenter cohort setting. We analyzed data from eight well-characterized cohorts (pooled cohort) and seven administrative cohorts from eleven European countries. Annual mean PM(2.5) and NO(2) from Europe-wide models were assigned to baseline residential addresses and dichotomized at selected cut-off values (PM(2.5): 10, 12, 15 µg/m(3); NO(2): 20, 40 µg/m(3)). For each pollutant, we estimated the propensity score as the conditional likelihood of exposure given available covariates, and derived corresponding inverse-probability weights (IPW). We applied Cox proportional hazards models i) adjusting for all covariates ("traditional Cox") and ii) weighting by IPW ("causal model"). Of 325,367 and 28,063,809 participants in the pooled and administrative cohorts, 47,131 and 3,580,264 died from natural causes, respectively. For PM(2.5) above vs. below 12 µg/m(3), the hazard ratios (HRs) of natural-cause mortality were 1.17 (95% CI 1.13-1.21) and 1.15 (1.11-1.19) for the traditional and causal models in the pooled cohort, and 1.03 (1.01-1.06) and 1.02 (0.97-1.09) in the administrative cohorts. For NO(2) above vs. below 20 µg/m(3), the HRs were 1.12 (1.09-1.14) and 1.07 (1.05-1.09) for the pooled and 1.06 (95% CI 1.03-1.08) and 1.05 (1.02-1.07) for the administrative cohorts. In conclusion, we observed mostly consistent associations between long-term air pollution exposure and natural-cause mortality with both approaches, though estimates partly differed in individual cohorts with no systematic pattern. The application of multiple modelling methods might help to improve causal inference. 299 of 300 words.

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