Variability in the association between long-term exposure to ambient air pollution and mortality by exposure assessment method and covariate adjustment: a census-based country-wide cohort study

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Abstract

Background: Ambient air pollution exposure has been associated with higher mortality risk in numerous studies. We assessed potential variability in the magnitude of this association for non-accidental, cardiovascular disease, respiratory disease, and lung cancer mortality in a country-wide administrative cohort by exposure assessment method and by adjustment for geographic subdivisions.

Methods: We used the Belgian 2001 census linked to population and mortality register including nearly 5.5 million adults aged ≥30 (mean follow-up: 9.97 years). Annual mean concentrations for fine particulate matter ($PM_{2.5}$), nitrogen dioxide (NO_2), black carbon (BC) and ozone (O_3) were assessed at baseline residential address using two exposure methods; Europe-wide hybrid land use regression (LUR) models [100x100m], and Belgium-wide interpolation-dispersion (RIO-IFDM) models [25x25m]. We used Cox proportional hazards models with age as the underlying time scale and adjusted for various individual and area-level covariates. We further adjusted main models for two different area-levels following the European Nomenclature of Territorial Units for Statistics (NUTS); NUTS-1 (n=3), or NUTS-3 (n=43).

Results: We found no consistent differences between both exposure methods. We observed most robust associations with lung cancer mortality. Hazard Ratios (HRs) per 10 $\mu g/m^3$ increase for NO_2 were 1.060 (95%CI 1.042-1.078) [hybrid LUR] and 1.040 (95%CI 1.022-1.058) [RIO-IFDM]. Associations with non-accidental, respiratory disease and cardiovascular disease mortality were generally null in main models but were enhanced after further adjustment for NUTS-1 or NUTS-3. HRs for non-accidental mortality per 5 $\mu g/m^3$ increase for $PM_{2.5}$ for the main model using hybrid LUR exposure were 1.023 (95%CI 1.011-1.035). After including random effects HRs were 1.044 (95%CI 1.033-1.057) [NUTS-1] and 1.076 (95%CI 1.060-

1.092) [NUTS-3].

Conclusion: Long-term air pollution exposure was associated with higher lung cancer mortality risk but not consistently with the other studied causes. Magnitude of associations varied by adjustment for geographic subdivisions, area-level socio-economic covariates and less by exposure assessment method.

Keywords:
population-based
environmental hazard
exposure assessment
survival analysis
cause-specific mortality
health effects

Highlights:

Large prospective country-wide cohort study including nearly 5.5 million adults
Non-accidental and cause-specific mortality over long-term ten years follow-up
Several ambient air pollutants evaluated using two exposure assessment models
Most robust associations observed between both NO_2 or BC and lung cancer mortality
Associations varied mildly between hybrid LUR and interpolation-dispersion model
Magnitude associations differed by differential adjustment for area-level indicators

1 Introduction

Over the past few years, a relatively large number of studies on the association between long-term exposure to ambient air pollution and mortality has been published (Hoek et al., 2013; Atkinson et al., 2018; Huangfu and Atkinson, 2020; Chen and Hoek, 2020; Huang et al., 2021). The majority of studies reported increased mortality risks, although large variation has been observed in magnitude of the effect estimates both between and within countries (Hoek et al., 2013; Atkinson et al., 2018; Huangfu and Atkinson, 2020; Chen and Hoek, 2020; Huang et al., 2021). Part of this heterogeneity in air pollution epidemiological studies might be explained by methodological differences in exposure assessment method, study design or statistical data analysis approach, or by study-specific contextual differences. So far there is little evidence on how air pollution exposure assessment method affects mortality risk estimates (Yap et al., 2012; Jerrett et al., 2016; Klompmaker et al. 2020; Samoli et al., 2020; Butland et al., 2020; Gariazzo et al., 2021). Multicenter studies provide a great opportunity to investigate some of this heterogeneity. This study forms part of the Effects of Low-level Air Pollution: A Study in Europe (ELAPSE) project (www.elapseproject.eu) (Klompmaker et al., 2020; Hvidtfeldt et al., 2020), where Belgium is one of the seven participating European countries contributing to the project with large administrative cohort data. The project's central approach was to harmonize to the greatest extent possible exposure assessment, outcome and confounder definitions as well as statistical methods between different administrative cohorts. Study-specific contextual heterogeneity is likely to remain notwithstanding large harmonization efforts and may potentially affect health effect estimates in relation to long-term exposure to air pollution. Study-specific between-area variability in mortality patterns has been widely observed in several country-wide studies, including in Belgium (Deboosere and Gadeyne, 2002; Van Hemelrijck et al., 2016). Air pollution health effect estimates may be affected if broad scale air

pollution patterns are correlated to regional mortality patterns. In recent North American cohort studies, investigators have adjusted for geographic subdivisions of the country to account for potential variability in spatial patterns (Crouse et al. 2012, 2015; Di et al. 2017). The current study presents results for the Belgian administrative cohort on the association between long-term exposure to several ambient air pollutants (fine particulate matter ($PM_{2.5}$), nitrogen dioxide (NO_2), black carbon (BC) and ozone (O_3)) and non-accidental, cardiovascular disease, respiratory disease, and lung cancer mortality during a ten-year follow-up period for about 5.5 million Belgian adults. The aim of this study was to explore and assess potential variability in mortality effect estimates by different air pollution exposure assessment methods and by additional adjustment for geographic subdivisions of the country.

2 Methods

2.1 Data design and study population

Administrative cohort data was based on the Belgian 2001 census which was linked to population, emigration and mortality follow-up data for the study period October 1, 2001-December 31, 2011 (10.25 years). Data were made available by the Belgian statistical office (Statbel) and contained individual information for the entire population officially residing in Belgium at the time of the census. Individuals were geolocated based on the XY-coordinate of their residential address at baseline, near-complete with 98.7% of individuals included. All adults aged 30 and older with complete covariate information were included in the present study. We excluded about 15% of individuals with missing data on main covariates.

Individual sociodemographic covariates were collected through a census questionnaire at baseline, and included: age, sex, marital status (single, cohabiting/married, separated/divorced and widowed), country of origin (local vs foreign), education level (no/primary, secondary and tertiary), and occupational status (employed/self-employed, unemployed, homemaker and

158 retired). Available area-level socio-economic position (SEP) covariates consisted of mean
159 income (i.e. mean household net taxable income), unemployment (i.e. percentage of working
160 age population unemployed), low education (i.e. percentage of population with no/primary
161 education), and ethnicity (i.e. percentage of non-Western migrants). All area-level SEP
162 indicators were retrieved from the Belgian 2011 census, except for ethnicity which was only
163 obtainable for the year 2001. Area-level SEP variables were available at two different area-
164 levels: 1) neighbourhood (n=6,344), i.e. geographical units having a size in between those of
165 census tracts (n=19,781) and local administrative units (LAU) (n=589); and 2) NUTS-3 (n=43),
166 i.e. as defined by the European Nomenclature of Territorial Units for Statistics (NUTS)
167 (Eurostat, 2018). Both aforementioned area-level SEP definitions and selected spatial levels
168 were based on the statistical protocol of ELAPSE (Klompmaker et al., 2020).
169

170 ## 2.2 Air pollution exposure assessment

171 Air pollution exposure assessment was done using two approaches: Europe-wide hybrid land use
172 regression (LUR) and Belgian interpolation-dispersion (RIO-IFDM) exposure models. Annual
173 mean concentrations for different ambient air pollutants ($PM_{2.5}$, NO_2, BC and O_3) for the year
174 2010 were assigned to the residential geocode at baseline (01/10/2001). The measurements for
175 O_3 were obtained by averaging warm season months from April through September. A brief
176 description of the methodologies of both models is given below and an overview of the
177 differences can be found in supplementary material (S1).
178

179 ### 2.2.1 European hybrid LUR model

180 In the framework of ELAPSE, Europe-wide air pollution exposure assessment was developed
181 and validated following a harmonised protocol, described in detail by de Hoogh et al. (2018). In
182 brief, hybrid LUR models were developed by combining air pollution monitoring data with

183 predictor variables obtained from satellite derived air pollution data, chemical transport model
184 data, and land cover and road traffic data. Monitoring data for $PM_{2.5}$, NO_2 and O_3 warm season
185 were derived from Airbase version 8 routine data (EEA, 2020; de Hoogh et al., 2016). As Airbase
186 data were not available for BC, European Study of Cohorts for Air Pollution Effects (ESCAPE)
187 monitoring data were used instead (Eeftens et al., 2012a; 2012b). Models were developed at a
188 spatial resolution of 100 x 100 m for the year 2010 (annual mean). Estimates for $PM_{2.5}$, NO_2
189 and O_3 were expressed in micrograms per cubic meter ($\mu g/m^3$) and for BC in $10^{-5}m^{-1}$ (i.e. similar
190 magnitude compared to BC in $\mu g/m^3$).
191
192 **2.2.2 Belgian RIO-IFDM model**
193 Air quality model exposure predictions for the same pollutants and year were provided by the
194 Belgian Interregional Environment Agency (IRCEL-CELINE). The estimates were obtained
195 through the coupling of a spatial interpolation model (RIO) and a dispersion model (IFDM).
196 The interpolation model uses air quality measurements from fixed measuring stations and
197 CORINE Land Cover data (EEA, 2019; Hooyberghs et al., 2006). These background results
198 were combined with a dispersion receptor model using emissions from industrial point and
199 traffic line sources and meteorological data (Lefebvre and Vranckx, 2013). The results are
200 modelled on high-resolution grids of 25 x 25 m. Further details regarding the applied model
201 chain can be consulted in the following technical report by Lefebvre and Vranckx (2013). All
202 annual mean concentrations were expressed in micrograms per cubic meter ($\mu g/m^3$).
203
204 **2.3 Mortality outcomes**
205 The studied mortality outcomes were identified through the WHO International Classification
206 of Diseases, Tenth Revision codes (ICD-10) (W.H.O., 2004), based on the selection of the
207 underlying cause of death on the death certificates. We considered non-accidental (ICD-10:

A00-R99), cardiovascular disease (ICD-10: I10-I70), respiratory disease (ICD-10: J00-J99), and lung cancer mortality (ICD-10: C34.0-C34.9).

2.4 Statistical analyses

We assessed the association between the different air pollutants and mortality outcomes using Cox proportional hazard models with age as the underlying time scale. Individuals were right censored when information about their survival time was incomplete, i.e. death to another cause not under study for cause-specific outcomes, loss to follow-up due to emigration or end of follow-up (31/12/2011).

Three models with increasing degree of adjustment were defined a priori within the ELAPSE project (Klompmaker et al., 2020; Hvidtfeldt et al., 2020): model 1 (M1) stratified by sex and accounted for within-area correlations of the individuals by including a cluster term for neighbourhood (Therneau, 2015); model 2 (M2) adding to M1 with additional adjustment for individual sociodemographic covariates (marital status, country of origin, education level and occupational status), and model 3 (M3) adding to M2 with additional control for area-level SEP indicators (mean income, unemployment, low education, and ethnicity). In the analysis, area-level SEP was operationalized as the NUTS-3 area-level SEP variable and the deviation between NUTS-3 and neighbourhood area-level SEP variable. In ELAPSE we a priori decided to adjust for multiple dimensions of SEP at both a neighbourhood and regional scale to adjust for potential confounding by socio-economic indicators.

We evaluated the shape of the concentration-response curves for the relationship between the different air pollutants and mortality outcomes. We specified natural spline plots for three degrees of freedom (df) (Eisen et al., 2004) and compared the goodness of fit of these models with the models specified with a linear term (M3) using the Bayesian Information Criterion

(BIC). No clear deviation from linearity was found based on the model fit nor the splines (i.e. large uncertainty observed about the shape at low and high end of the distribution as indicated by the 95% CIs), thus exposure hazard ratios (HR) were reported as a continuous linear term (Supplementary Figure S1). For linear models, results are presented as HRs with 95% CIs using pollutant-specific increments based on the ESCAPE project: 5 $\mu g/m^3$ for $PM_{2.5}$, 10 $\mu g/m^3$ for NO_2, 0.5 $10^{-5}m^{-1}$ (hybrid LUR) or 0.5 $\mu g/m^3$ (RIO-IFDM) for BC, and 10 $\mu g/m^3$ for O_3.

Based on the single pollutant main model (M3), we specified two-pollutant models where pollutants within the same exposure model (i.e. hybrid LUR and RIO-IFDM) were simultaneously entered in the model to assess potential co-pollutant confounding.

In additional analyses, we specified two alternative mixed-effect Cox models with random intercept. Both included additional levels of spatial correlation to account for potential differences in mortality rate between geographical areas not accounted for in the main model. The first model adjusted for both neighbourhood and large geographical NUTS-1 area-level (n=3), whereas the second model adjusted for both neighbourhood and NUTS-3 area-level (n=43). To explore potential effect modification, we included multiplicative interaction terms into our main model between each of the pollutants and age (<65 years or $\geq$65 years), and education level (no/primary education, secondary education or tertiary education). We evaluated the goodness of fit of models with and without interaction term using the Wald test.

As sensitivity analyses, we repeated M1 with the full population sample (i.e. complete cases analysis using only M1 covariates) and compared these with the reduced sample of the main model (i.e. complete cases after including M3 covariates). We further evaluated the consistency of our effect estimates to area-level SEP adjustment in our main model (M3) by specifying models where each of the four available area-level SEP indicator was adjusted for separately instead of combined. Additionally, we indirectly adjusted main model HRs to account for important missing health-related behavioral indicators in the census in relation to mortality risk.

We used the method proposed by Shin et al. (2014) to apply indirect adjustment for both smoking status (current, former or never) and body mass index (BMI) (underweight <18.5, normal 18.5-24.9, overweight 25-29.9 or obese ≥30). In brief, the indirect adjustment method extracts ancillary information on these health-related behavioral indicators from a dataset representative of the study population. We obtained the Belgian 2001 Health Interview Survey (HIS) (http://www.healthsurvey.be) matching with the baseline year of the administrative cohort. The HIS also included the same individual and area-level covariates as in our main model, with the exception of marital status which was not available. We assigned identical exposure models to the HIS participants, following the same procedure as previously described in section 2.2. We then ran multivariate linear regression models with the harmonized HIS data to retrieve the estimates based on the association between the air pollutants and the available health-related behavioral indicators. The indirect adjustment method also uses estimates based on the association between the health-related behavioral indicators and the different mortality outcomes under study, which have been retrieved from ELAPSE pooled cohort analysis. More information on the applied indirect adjustment method (Shin et al., 2014) or the ELAPSE pooled dataset (Brunekreef et al., 2021) can be found elsewhere.

Statistical significance was set at p-value < 0.05. Statistical analyses and exposure data linkages were performed in R version 3.4.0 (R Core Team 2019) and RStudio (RStudio Team, 2019) using the following packages: survival (Therneau, 2015), coxme (Therneau, 2018), ggplot2 (Wickham, 2009), data.table (Dowle and Srinivasan, 2017), gdalUtils (Greenberg and Mattiuzzi, 2015), raster (Hijmans, 2016), rgdal (Bivand et al., 2017), and base and dependency packages.

3 Results

3.1 Study population and air pollution exposure

The included study population consisted of 5,474,470 adults, with a total of 54,574,471 person-years and mean follow-up period of 9.97 years (Table 1). The number of men and women was nearly equal with a mean age at baseline of 52.6 years. The majority of subjects were born in Belgium (96.6%), were cohabiting/married (68.3%), had obtained secondary education level or higher (76.3%), and were employed (53.3%) at the time of the census. We observed 707,138 individuals who died from non-accidental causes of which 33.2% from cardiovascular disease, 11.6% from respiratory disease, and 7.4% from lung cancer mortality.

The exposure distribution and pairwise correlations for the different pollutants are summarised in Table 2, Supplementary Table S1 and Supplementary Figures S2-S3. For all four pollutants, median values were higher in hybrid LUR compared to RIO-IFDM exposure models, whereas the interquartile range (IQR) was moderately lower in hybrid LUR models (Table 2). Lower variability of the hybrid LUR model is particularly reflected in the lowest and highest percentiles of the distributions, whereas the range of observed concentrations was wider for all different pollutants in the RIO-IFDM model (Supplementary Figure S2). The broad spatial patterns of exposure distributions agreed quite well between both exposure models for all pollutants (Supplementary Figure S3).

Pearson correlations between hybrid LUR and RIO-IFDM models were 0.64, 0.86, 0.82 and 0.76 for $PM_{2.5}$, NO_2, BC and O_3, respectively (Supplementary Table S1). Generally, correlations between pollutants were stronger in the RIO-IFDM compared to hybrid LUR exposure model (e.g. 0.83 vs 0.62 between $PM_{2.5}$ and NO_2, respectively). Correlations between different pollutants were moderate to high, especially between NO_2 and BC. Also, expectedly, O_3 was negatively correlated with all other pollutants.

3.2 Association between air pollution and mortality

3.2.1 Main analyses

Hazard ratios (HRs) from single-pollutant models with increasing confounder adjustment for different mortality outcomes under study are presented in Figure 1 and Supplementary Table S2. HRs were sensitive to incremental adjustment for potential confounders. Overall, hazard ratios increased after individual level covariate adjustment (M2) for $PM_{2.5}$, NO_2 and BC. After area-level SEP covariate adjustment (M3), HRs mostly attenuated, except for associations with $PM_{2.5}$ where HRs generally increased. In single pollutant main models (M3), we found small HRs both above and below unity with differing patterns depending on the studied outcome. Main model HRs ranged between 0.975 and 1.060 (Figure 1 and Supplementary Table S2). For non-accidental mortality we only found a significant association for $PM_{2.5}$ with the hybrid LUR model (HR: 1.023, 95%CI 1.011-1.035). Observed HRs for cardiovascular mortality were mostly below unity, except for O_3 where HRs were above unity. For both respiratory and lung cancer mortality, HRs were mainly larger than unity, with strongest HRs observed with NO_2 and BC. HRs between hybrid LUR versus RIO-IFDM exposure models generally agreed for the different outcomes, although stronger estimates were mainly found in hybrid LUR models (Supplementary Table S3 with M3 HRs per IQR increase). The difference in HRs between the hybrid LUR and RIO-IFDM model exposures was larger in the fully adjusted model (M3) than in the age and sex only model (M1).

Our main results were relatively robust after further adjustment in two-pollutant models (Table 3). However, interpretation of these estimates must be with caution due to potential multicollinearity, especially between NO_2 and BC. The association between non-accidental mortality and $PM_{2.5}$ remained and became slightly stronger after adjustment for NO_2, BC or O_3. Associations with NO_2 became stronger after adjustment for O_3. Associations with O_3 became larger than unity and significant after adjustment for the other pollutants with the hybrid LUR exposure model. For cardiovascular mortality, negative associations with O_3

remained significant only after adjustment for $PM_{2.5}$ in hybrid LUR and BC in RIO-IFDM exposure models. The significant inverse associations in single pollutant models approached unity after adjustment for O_3. Associations with lung cancer mortality remained in both hybrid LUR and RIO-IFDM exposure models for NO_2 and BC after adjustment for other pollutants, except for BC after NO_2 adjustment. Associations in two-pollutant models were most notable in both respiratory and lung cancer mortality where HRs generally were stronger after adjustment for O_3, in addition to higher estimates for O_3.

3.2.2 Additional analyses

In additional analysis, we further accounted for between-area variability by including a random intercept in our main models for neighbourhood and NUTS-1 (n=3) or neighbourhood and NUTS-3 area-level (n=43) (Figure 1 and Supplementary Table S4). Specification of random effects with NUTS-1 area-level only mildly affected HRs, with the exception of non-accidental mortality where associations between $PM_{2.5}$, NO_2 and BC became larger than unity and statistically significant, albeit with small HRs. Estimates were influenced more when allowing for random effects with the spatially more detailed level of NUTS-3, and generally resulted in substantially larger HRs, mainly for associations with $PM_{2.5}$. Overall, most HRs that were above unity in our main model (M3) became stronger for $PM_{2.5}$, NO_2 and BC. HRs in models with aforementioned pollutants that were lower than unity lost statistical significance or became larger than unity with increasing degree of area-level adjustment. HRs for associations with O_3 became inversely statistically significant with increasing area-control for non-accidental, respiratory and lung cancer mortality. Associations with O_3 and cardiovascular mortality did not retain statistical significance. Also, differences in effect estimates between the two exposure assessment methods became smaller and more stable when introducing random effects with NUTS-1 or more pronouncedly including the spatially more refined NUTS-3 area-level.

Effect modification analyses by age indicated stronger associations for all mortality outcomes under study with $PM_{2.5}$, NO_2 and BC in younger age (<65 years), and with O_3 in older age (≥65 years) (Supplementary Table S5). Observed effect modification patterns by education level were overall suggestive of stronger associations for $PM_{2.5}$, NO_2 and BC among individuals with tertiary education (Supplementary Table S5).

3.2.3 Sensitivity analyses

Effect estimates for M1 including the full population sample (i.e. individuals without any missing value for air pollution exposure, age and sex) were almost identical for non-accidental and cardiovascular mortality and slightly stronger for respiratory and lung cancer mortality, although very similar compared to the reduced sample (i.e. with no missing additional covariates) used in the main models (Supplementary Table S6).

HRs were sensitive to the inclusion of different area-level SEP covariates (Supplementary Table S7). When adjusting separately for each area-level SEP variable, HRs differed in both directions from M2 and the main model (M3; i.e. all available area-level SEP indicators combined). For example, for non-accidental and respiratory mortality in model SEP3, effects were downward for $PM_{2.5}$ and upward for NO_2 compared to the main model. The observed sensitivity was less for lung cancer mortality where HRs were larger. No substantial differences were observed between the different exposure models.

Study population characteristics between cohort and survey data were fairly similar (Supplementary Table S8), suggesting the use of the survey for the retrieval of ancillary information to be adequate.

Indirect adjusted HRs for smoking status and BMI were generally higher in all mortality outcomes and for both exposure models. Strongest effect estimates were consistently observed in mortality associations with $PM_{2.5}$ (Supplementary Table S9).

4 Discussion

We observed associations between long-term exposure to ambient air pollution and mortality risk for natural and cause-specific mortality outcomes. Effect estimates were sensitive to exposure assessment method, additional adjustment for geographical subdivisions (NUTS-1 or NUTS-3) of the country and differential adjustment for area-level socio-economic covariates. Mortality risk in relation to ambient air pollution was suggested to be highest among individuals younger than 65 years at baseline or with tertiary education. Overall, we observed most robust associations with lung cancer and both NO_2 or BC for both exposure methods, independently of alternative model specifications. Observed consistency of aforementioned results among exposure methods is an important finding, as each method may incorporate different degrees of measurement error. These potentially introduce bias to health effect estimates of which magnitude and direction is hard to quantify.

To our knowledge, only four other studies systematically compared potential heterogeneity in effect estimates using different exposure assessment methods when evaluating the association between long-term exposure to ambient air pollution and various mortality outcomes using cohort data (Yap et al. 2012; Jerrett et al., 2016; Klompmaker et al. 2020; Gariazzo et al., 2021). All four aforementioned studies also detected variation in the effect estimates in terms of magnitude, direction or statistical significance depending on the applied exposure assessment method. In our study, observed variation in effect estimates only seemed to differ to a small degree between exposure models and might be explained by methodological differences (supplementary material S1). Although both models were of similar fine-scale spatial resolution, we generally found somewhat stronger associations with lowest compared with highest resolution models (100 x 100 m for hybrid LUR and 25 x 25 m for RIO-IFDM, respectively). These findings agree with those recently obtained by Gariazzo et al. (2021) for associations between both coarse PM or NO_2 and non-accidental, respiratory disease and

406 cardiovascular disease mortality.

407 The study of Klompmaker et al. (2020), using Dutch administrative cohort data, was also part
408 of the ELAPSE project. In line with expectations, our study similarly found moderate
409 correlations for $PM_{2.5}$ and relatively strong correlations for NO_2 and BC between different
410 exposure methods (Klompmaker et al. 2020). Comparably, differences in HRs for both NO_2
411 and BC between exposure models were smaller in minimally adjusted models (M1; i.e.
412 including age and sex) versus fully adjusted models (M3), reflecting differential correlation
413 patterns between pollutants and area-level SEP. Further, comparison of effect estimates based
414 on the same hybrid LUR exposure model and non-accidental mortality were almost identical
415 for associations between non-accidental mortality and $PM_{2.5}$ [HR 1.023 (95%CI 1.011-1.035)
416 for the current (Belgian) and HR 1.030 (95%CI 1.019-1.041) for the Dutch administrative
417 cohort (Klompmaker et al. 2020)]. Overall observed patterns with hybrid LUR exposure
418 methods were similar in both the Belgian and Dutch administrative cohort, where strongest
419 associations were observed for lung cancer and weakest for cardiovascular mortality
420 (Klompmaker et al. 2020).

421 When study-specific between-area variability was additionally accounted for, associations in
422 our study between $PM_{2.5}$, NO_2 and BC and mortality became stronger; hence, indicating that
423 potential residual confounding does not necessarily lead to effect estimates biased upwards.
424 This finding is consistent with a review reporting that more complete adjustment for area-level
425 indicators tended to increase air pollution effect estimates rather than decrease (Vodonos et al.,
426 2018). In Canadian cohort studies (Crouse et al., 2012 and 2015), HRs also increased after
427 adjustment for large geographical area of the country. Additional adjustment for geographical
428 subdivisions (neighbourhood in addition to NUTS-1 or NUTS-3), reflected broad-scale spatial
429 variation in health due to factors other than air pollution or included socio-economic covariates
430 at individual and area-level. Previous research on spatial variability in mortality patterns in

Belgium identified a clear north-south gradient across the country, where mortality rates generally are highest in the south and in former industrial areas (Deboosere and Gadeyne, 2002; Van Hemelrijck et al., 2016). Other possible explanations for this geographic variation in health status have been proposed, such as differences in diagnostic and therapeutic practices, cultural and health-related behaviours and historical context (Deboosere and Gadeyne, 2002; Van Hemelrijck et al., 2016). Although we aimed to maximise the number of available relevant covariates in our study, no data on these specific factors was available for linkage to the Belgian administrative cohort. Therefore, we recognise that some important unobserved residual confounding may remain. With regard to country-wide spatial trends of air pollution, the aforementioned north-south gradient is inverse: observed pollutant levels are highest in the north and decrease towards the south of the country (Supplementary Figure S3). In consequence, additional adjustment for between-area variability as random effects in our main model might have accentuated the generally small exposure contrasts between different area-levels (neighbourhood in addition to NUTS-1 or NUTS-3).

Consistent with the majority of prior research evaluating effect modification by age in the association of long-term exposure to air pollution (Huangfu and Atkinson, 2020; Chen and Hoek, 2020), our study confirmed earlier findings showing higher mortality risk in younger individuals (<65 years) with $PM_{2.5}$, NO_2 and BC. Current evidence on potential effect modification by education level with these pollutants is still limited and inconclusive. Two other participating administrative cohorts in the ELAPSE project evaluated effect modification by education level (Brunekreef et al., 2021). In accordance with our study findings, the Swiss cohort also detected strongest associations among higher educated compared to lower educated with $PM_{2.5}$, NO_2 and BC. Contrarily, the observed pattern was opposite in the Norwegian cohort. Exposure distributions of studied pollutants were nearly identical between different population subgroups by age or education level. Health and mortality risks are known to be

456 generally higher among individuals with lower versus higher education levels, which is often
457 referred to as the social gradient in health (Wilkinson and Marmot, 2003). This is also true for
458 our study, where we found relative mortality risks to increase two- to three- fold between each
459 category of education level. The social gradient among population subgroups has been
460 attributed to several underlying health determinants, such as differences in health-related
461 behaviors (e.g. tobacco and alcohol use, dietary habits or physical activity) or differential access
462 to important resources (e.g. access to health care or basic housing conditions). While in our
463 study we only observed higher mortality risks among younger or higher educated individuals,
464 presumed mortality risks among older or lower educated individuals in relation to long-term
465 exposure to air pollution may also be detected if other, potentially more influential health
466 determinants could be mitigated. We speculate that the absence of such determinants in our data
467 might partially explain observed null-trends for cardiovascular mortality in our main model.
468 When disentangling sensitivity of various area-level SEP indicators into separate models, we
469 observed heterogeneity of patterns in effect estimates for different pollutants and mortality
470 outcomes. This finding points to the multiplicity of the construct of (area-level) SEP, as well as
471 its complex interplay with different air pollutants. Consequently, comprehensive explanation is
472 not straightforward and deserves to be addressed further in future studies focussing on health
473 and environmental inequalities.
474 Previous studies on the health effects of air pollution emphasised the importance of adjustment
475 for SEP indicators at both individual and area-level since associations with health outcomes
476 seemed to be independent (Roux, 2007; Temam et al., 2017; Vodonos et al., 2018).
477 Additionally, it has been argued that adjustment for area-level SEP complementary to
478 individual SEP might be of particular interest in studies where individuals' geographic location
479 is important (Galobardes et al., 2007). Also, the inclusion of various SEP indicators to represent
480 its different dimensions was suggested to be important (Galobardes et al., 2007; Pinault et al.,

2016). Given the complexity of SEP and in order to reduce confounding as much as possible, our main model (M3), as has been defined a priori within the ELAPSE project, adjusted for as many individual and area-level SEP indicators as available. Although concerns for potential over-adjustment might be valid, a recent meta-analytic review on associations between $PM_{2.5}$ and several mortality outcomes observed that additional adjustment for area-level SEP unlikely results in upward bias (Vodonos et al., 2018). These findings are in line with our study, where effect estimates for $PM_{2.5}$ increased after area-level SEP adjustment with non-accidental (hybrid LUR), respiratory disease (hybrid LUR and RIO-IFDM) and lung cancer mortality (RIO-IFDM). However, we did not observe a similar pattern for the other pollutants under study. Our study includes a number of limitations. First, and potentially most important, our study lacked individual information on health-related behaviors, such as tobacco and alcohol use, dietary habits or physical activity, as these have been identified as important determinants of mortality risk. However, we addressed this limitation, as far as possible, by indirectly adjusting our main models with information on smoking status and BMI using a survey representative of the study population. Such adjustment resulted mainly in stronger mortality associations with $PM_{2.5}$ for studied outcomes. Lack of adjustment for smoking status and BMI could not further explain observed weaker findings for cardiovascular mortality, nor could it explain apparent stronger findings for lung cancer mortality. A recent meta-analysis of cohort studies by Atkinson et al. (2018) also reported strongest associations with NO_2 and lung cancer. Another limitation of our study is that only time-fixed exposure for the year 2010 could be obtained for both exposure models. Although a decreasing trend in air pollution levels has been observed across Europe over the last years, we assumed its spatial distribution remained relatively stable over the follow-up period. Higher air pollution levels presumably result in larger exposure contrasts towards baseline. As such, using exposure for prior follow-up years may attenuate observed HRs, although this could not be evaluated. Additionally, individual and area-level covariates were not available for different time points over the follow-up

period, which is a common limitation in most administrative cohorts. Furthermore, updates on residential history were not obtainable either.

5 Conclusion

Long-term term exposure to ambient air pollution was associated with higher mortality risk among nearly 5.5 million Belgian adults. We observed variability in the strength of our effect estimates by additional adjustment for geographic subdivisions of the country, area-level SEP covariates and to a limited extent exposure assessment method. Most robust and consistent associations were found between both NO_2 or BC and lung cancer mortality. Future studies should apply caution and carefully evaluate analytic strategies as exposure assessment method, different model specifications and covariate availability might influence both magnitude and direction of health effect estimates related to long-term air pollution exposure.

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8 Data statement

The research data is confidential.

9 Competing Financial Interests

The authors declare they have no actual or potential competing financial interests.

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