Effect of the shape of the exposure-response function on estimated hospital costs in a study on non-elective pneumonia hospitalizations related to particulate matter.
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Title: Effect of the shape of the exposure-response function on estimated hospital costs in a study on non-elective pneumonia hospitalizations related to particulate matter.

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Abstract

Objective We used log-linear and log-log exposure response (E-R) functions to model the association between $PM_{2.5}$ exposure and non-elective hospitalizations for pneumonia, and estimated the attributable hospital costs by using the effect estimates obtained from both functions.

Methods We used hospital discharge data on 3519 non-elective pneumonia admissions from UZ Brussels between 2007 and 2012 and we combined a case-crossover design with distributed lag models. The annual averted pneumonia hospitalization costs for a reduction in $PM_{2.5}$ exposure from the mean (21.4 µg/m^3) to the WHO guideline for annual mean $PM_{2.5}$ (10 µg/m³) were estimated and extrapolated for Belgium.

Results Non-elective hospitalizations for pneumonia were significantly associated with $PM_{2.5}$ exposure in both models. Using a log-linear E-R function, the estimated risk reduction for pneumonia hospitalization associated with a decrease in mean $PM_{2.5}$ exposure to 10 µg/m^3 was 4.9%. The corresponding estimate for the log-log model was 10.7%. These estimates translate to an annual pneumonia hospital cost saving in Belgium of €15.5 million and almost €34 million for the log-linear and log-log E-R function, respectively.

Discussion Although further research is required to assess the shape of the association between $PM_{2.5}$ exposure and pneumonia hospitalizations, we demonstrated that estimates for health effects and associated costs heavily depend on the assumed E-R function. These results are important for policy making, as supra-linear E-R associations imply that significant health benefits may still be obtained from additional pollution control measures in areas where PM levels have already been reduced.

1   Introduction

Studies that provide estimates of the health effects of air pollution are necessary for evidence-based policy making in public health. Meaningful interpretations of air pollution effects require accurate knowledge on the shape of the exposure-response (E-R) functions linking air pollution exposures with adverse health outcomes. Traditionally, the association between air pollution and health outcomes is assumed to be linear (Atkinson et al., 2014; ExternE Project, Bickel & Friedrich, 2005). Consequently, with a rising level of pollution, the marginal harm to health will increase incrementally, implying that for a fixed change in the exposure there is a corresponding fixed change in the health outcome. As a result, current public policy often aims to clean up the most polluted regions first (Pope et al., 2015).

Leading experts in the field recently cast doubt on the linearity of the E-R function of $PM_{2.5}$ in relation to mortality (Pope et al., 2015; Smith & Peel, 2010). Recent research suggests that the E-R function between $PM_{2.5}$ exposure and mortality is likely to be supralinear (i.e. the slope of the association is steepest at the lowest levels of exposure) for wide ranges that include very high levels of exposure (Pope et al., 2015; Goodkind et al., 2014). In studies on $PM_{2.5}$ exposure from ambient air pollution, second-hand smoke and active smoking, a flattening out of the slope at very high exposure levels has been observed for cardiovascular mortality (Pope et al., 2009; Pope et al., 2011; Burnett et al., 2014). Even at relatively low ambient concentrations (<30 μg/m³) in Canada and the United States, supralinearity in the association between $PM_{2.5}$ and mortality has been suggested (Krewski et al., 2009; Crouse et al., 2012). Supralinear associations with air pollution have also been observed for health outcomes such as adverse birth outcomes (Winckelmans et al., 2015), cardiovascular morbidity (Devos et al., 2015), pneumonia among children (Yu & Chien, 2015), white blood cell DNA adducts (Lewtas et el., 1997), respiratory epithelium integrity (Provost et al., 2014), as well as for other exposures (Vineis et al., 2000; Hertz-Picciotto & Smith, 1993).

The aim of this study was to juxtapose log-linear and log-log E-R functions to model the association between $PM_{2.5}$ and non-elective hospitalizations for pneumonia. Estimates derived from these models were used to calculate hospital cost savings for pneumonia associated with a reduction in mean $PM_{2.5}$ exposure to the WHO guideline for annual mean $PM_{2.5}$ (10μg/m³). In a secondary analysis, we focused

on non-elective pneumonia hospitalizations among children (younger than 16 years), which are known

to be particularly vulnerable for air pollution.

2   Methods

2.1   Data

2.1.1   Health and hospital cost data

The study population was recruited from UZ Brussels (University Hospital Brussels, Belgium). Hospital discharge data on non-elective pneumonia hospitalizations (ICD-9-CM 480 - 486) from January 1st 2007 until July 1st 2012 were obtained. Non-elective hospitalizations were selected in order to focus on acute events only. For the identified patients at interest, following variables were extracted from the Minimal Clinical Dataset: length of stay, date of admission, and patient characteristics such as gender, age, and zip code of residence (municipality). Ethical approval for the study was obtained by the Ethics Committee of UZ Brussels (B.U.N.143201215726).

Hospital costs considered in this study included individual-level emergency and hospital claims. These are registered in the Minimal Financial Dataset and contain all claims charged to patients (co-payments), health insurances, and/or other insurances. Additionally, a fixed day price was added to calculate the total hospital cost of the included patients (Devos et al., 2015). For each day a patient stays in the hospital, Belgian hospitals receive an additional lump sum from the public health insurance funds to finance non-medical hospital activities such as capital expenditures and investments for housing and medico-technical facilities, hotel function, and nursing care. This day price was initially not included in the claim database. For this study the weighted average per diem price across Belgian hospitals was used (Cleemput et al., 2012). All costs were converted into 2012 euros using the Belgian health care inflation rates published by the Belgian Directorate-General Statistics and Economic information.

2.1.2   Exposure and meteorological data

Daily average $PM_{2.5}$ concentrations were obtained from the Belgian Interregional Environment Agency. In Belgium (33,990 km^2) there are 38 monitoring stations for $PM_{2.5}$. Data from monitoring stations are combined with land cover data obtained from satellite images (Corine land cover data set) in a spatial temporal interpolation method (Kriging) described by Janssen et al. (2008). This provides interpolated $PM_{2.5}$ estimates on a 4 x 4 km^2 grid, which are then used to calculate population-weighted averages per

municipality. PM$_{2.5}$ estimates are linked to hospitalization data through the postal code of the patient's residency.

Because temperature is a known confounder of the association between air pollution and health (Huynen et al., 2001; Nawrot et al., 2007), daily mean air temperature and relative humidity measured at the station in Uccle (Brussels, Belgium) provided by the Belgian Royal Meteorological Institute were considered in the models. To adjust for the potential confounding effect of influenza episodes, we obtained data on weekly consultation rates for influenza-like illnesses from the representative Belgian Sentinel General Practitioner network, coordinated by the WIV-ISP (Scientific Institute of Public Health) (Van Casteren et al., 2010). Influenza epidemics were defined as weeks (Monday to Sunday) with an incidence above the threshold of 141 cases per 100,000 inhabitants (Van Casteren et al., 2010).

2.2   *Statistical Analyses*

2.2.1   *Modelling the exposure-response associations*

The association between PM$_{2.5}$ and non-elective hospitalizations for pneumonia was investigated by using a case-crossover design, which is widely used for short-term exposures and acute outcomes (Mittleman et al., 1993; Nawrot et al.; 2011, Devos et al.; 2015). In a case-crossover design each case subject (patient with a non-elective pneumonia admission) acts as its own control (Maclure, 1991). Therefore, the study design inherently adjusts for known and unknown time-invariant confounders. The case-crossover design compares each patient's exposure in a time period just before the admission (the hazard period) with that patient's exposure in the corresponding time periods before the selected control days (the control periods). We used the bidirectional time-stratified design to avoid selection bias (Levy et al., 2001): control days were selected within the same month and year as the case day, both before and after the case day. This way, season and long-term trends are controlled for by design. Cases and controls were additionally matched by day of the week to control for any weekly patterns in pneumonia hospitalizations or pollution levels.

We combined the case-crossover design with distributed lag non-linear models (DLNM) (Gasparrini, 2014) to investigate potential non-linear and delayed effects of PM$_{2.5}$ exposure on pneumonia

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hospitalizations. The DLNM is defined through a "cross-basis" function, which allows the simultaneous estimation of a non-linear E-R association and non-linear effects across lags, the latter termed lag-response association. We used a recent extension of the DLNM methodology beyond aggregated time series data by implementing it in a conditional logistic regression model on individual-level data (Gasparrini, 2014). The maximum lag was set to 1 week, so the hazard period contains up to 6 days before the case day and each of the control periods contains up to 6 days before the control day. We fitted both log-linear and log-log E-R associations by applying linear functions to untransformed and log-transformed $PM_{2.5}$ exposures respectively. The latter can be achieved by specifying a user-defined function $[f(x) = \log(x + 1)]$ that can be used directly in the cross-basis definition (Gasparrini, 2014). The lag structure was modelled with a natural cubic spline with 3 degrees of freedom (df). The knots in the lag space were set at equally spaced values in the log scale of lags to allow more flexible lag effects at shorter delays (Gasparrini, 2011).

To capture (potentially delayed) effects of heat and cold on non-elective pneumonia hospitalizations, we also included a cross-basis for mean temperature in the model with a maximum lag of 25 days. We used a natural cubic spline with 5 df for the temperature–response function and a natural cubic spline with 6 df (with knots at equally spaced values in the log scale) for the lag-response function. Spline knots for temperature were placed at equally spaced values of the actual temperature range to allow enough flexibility in the two ends of the temperature distribution. Models were additionally adjusted for same-day (lag 0) humidity, using a natural cubic spline with 3 df, and for indicator variables for public holidays and influenza epidemics. Model fit was assessed based on the Akaike Information Criterion (AIC). We estimated relative risks (RR) of pneumonia hospitalizations associated with $PM_{2.5}$ exposure using the WHO guideline for annual mean $PM_{2.5}$ (10 µg/m³) as reference value (RR=1). Cumulative effects were computed by summing the log RRs over the lags of interest. Final estimates are presented as the percent change in pneumonia hospitalizations for a decrease in $PM_{2.5}$ from the mean exposure among patients (21.4 µg/m³) to the value of 10 µg/m³ [100*(1–RR)]. DLNM analyses were performed with the statistical software R (R Foundation for Statistical Computing, Vienna, Austria) using the "dlnm" package (Gasparrini, 2011).

In a secondary analysis, we investigated effect modification by age. We ran separate models for three age categories: 0-15 years, 16-60 years, and >60 years old. We further examined the E-R shape as well by using a piecewise linear DLNM model, allowing for a change in slope above a certain breakpoint. We searched for the breakpoint that minimized the AIC of the model by testing all integers of the $PM_{2.5}$ range.

2.2.2 *Hospital cost calculation*

A bottom-up cost calculation was used to estimate the average cost of non-elective hospitalizations for pneumonia. Because of the skewness of the cost data, non-parametric bootstrapping was used to generate 95% bias-corrected confidence intervals (95% CI BC) of the mean costs (Barber & Thompson, 2000; Nixon et al., 2010). Cost analyses were conducted using Stata/MP (version 12.1). Results were expressed as the hospital cost averted for non-elective pneumonia hospitalizations associated with a reduction in mean $PM_{2.5}$ exposure to 10µg/m³.

We extrapolated the hospital costs to the total Belgian population (11 million inhabitants) based on the national number of non-elective hospitalizations with pneumonia as main diagnosis in 2011 (N=33,695) provided by the Belgian Federal Public Service Health, Food Chain Safety and Environment (FPS Health). In the secondary analyses by age group, the extrapolation was based on the national number of pneumonia hospitalizations in the age groups 0-15 years (N=6,931), 16-60 years (N=7,275), and >60 years (N=19,489).

3 Results

3.1 Data description

3,553 patients with non-elective hospitalizations for pneumonia were identified in the database of UZ Brussels. 20 patients with an extreme length of stay of more than 100 days and 14 patients with an invalid or missing ZIP code were excluded, so the final study population consisted of 3,519 patients. The catchment area for UZ Brussel was widely spread over Belgium, with included patients living in different Belgian regions.

Table 1 provides a brief overview of the demographic characteristics of the included patients and their hospital costs. Women and men were almost equally affected and their hospital costs were similar. The majority of patients were either children (younger than 16 years) or elderly (76 years or older), representing 39% and 32% of the study population respectively. Persons of 45 years or younger had the lowest mean hospital cost (<8000 €), whereas the age group 61-75 years old generated the highest mean hospital cost (12,535 €, 95% CI BC: 11,519 € – 13,631 €). The average cost of a non-elective pneumonia hospitalization in our study population was 9,404 € (95% CI BC 9,122 € - 9,743 €).

Table 1: Demographic characteristics of the study population

Characteristic	N (%)	Mean hospital cost, € (P5 – P95)	95% CI BC, €
Gender			
Male	1,868 (53)	9,402 (2,243 – 27,812)	8,977 – 9,817
Female	1651 (47)	9,407 (2,189 – 27,802)	8,964 – 9,870
Age category			
0-15 years	1,357 (39)	6,529 (2,588 – 17,625)	6,193 - 6,886
16-30 years	94 (3)	6,812 (1,251 – 21,434)	5,660 – 8,585
31-45 years	186 (5)	7,738 (2,189 – 26,479)	6,506 – 9,061
46-60 years	280 (8)	11,725 (2,583 – 36,666)	10,428 – 13,092
61-75 years	473 (13)	12,535 (2,636 – 33,705)	11,519 – 13,631
76-90 years	973 (28)	11,689 (2,206 – 31,090)	11,081 – 12,300
>90 years	156 (4)	10,052 (1,379 – 28,936)	8,654 – 11,899

Total	3,519	9,404 (2,303 – 27,812)	9,122 - 9,743

Abbreviations: P5 = 5th percentile; P95= 95th percentile; 95% CI BC = 95% bias-corrected confidence interval

The mean (range) PM$_{2.5}$ exposure of patients on the day of the hospitalization (lag 0) was 21.4 µg/m³ (3.4 – 99.7 µg/m^3). The 5th, 25th, 75th, and 95th percentiles of the PM$_{2.5}$ distribution were 7.3, 11.9, 27.1, and 48.6 µg/m³, respectively. We used the mean PM$_{2.5}$ exposure of all patients (21.4 µg/m³) to calculate RRs in both the main and the secondary analyses, as the mean (range) exposure in subpopulations was very similar, e.g. 21.6 µg/m^3 (3.9 – 97.7 µg/m^3) for children younger than 16 years.

3.2   Main analysis

Both the log-linear and log-log DLNM model showed increased RRs of pneumonia hospitalizations associated with same-day (lag 0) and previous-day (lag 1) PM$_{2.5}$ exposure (Figure 1). Because RRs were close to 1 at later lags, the cumulative lag 0–1 estimates were used in further analyses.

Figure 1. Exposure-lag-response surfaces for the association between pneumonia hospital admissions and PM$_{2.5}$ exposure (µg/m^3), estimated by DLNM models with a log-linear (left panel) and a log-log (right panel) E-R function. RRs are relative to the reference value of 10 µg/m^3 (WHO guideline for annual mean PM$_{2.5}$; bold line).
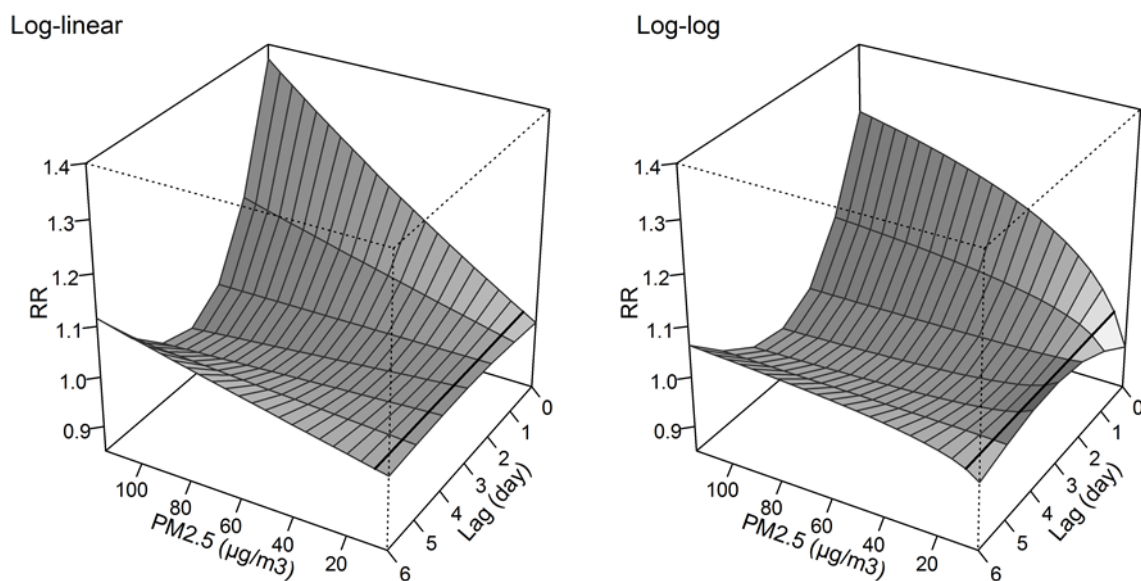
Figure 2 shows the log-linear and log-log E-R shapes for the cumulative lag 0–1 effect. RRs from the log-log model were higher than those from the log-linear model for $PM_{2.5}$ levels between 10 µg/m^3 and 75 µg/m^3, roughly corresponding to the 25th and 99th percentiles of the observed $PM_{2.5}$ range. The AIC of the log-linear model was equal to 10,407, whereas the AIC of the log-log model was equal to 10,404.

Figure 2. Cumulative (lag 0–1) log-linear (red) and log-log (blue) E-R functions for the association between pneumonia hospitalizations and $PM_{2.5}$ exposure (µg/m^3). Relative risks (RR) are relative to the reference value of 10 µg/m^3 (WHO guideline for annual mean $PM_{2.5}$).The vertical dotted line represents the 99th percentile of the $PM_{2.5}$ distribution of our study population (76.3 µg/m³).
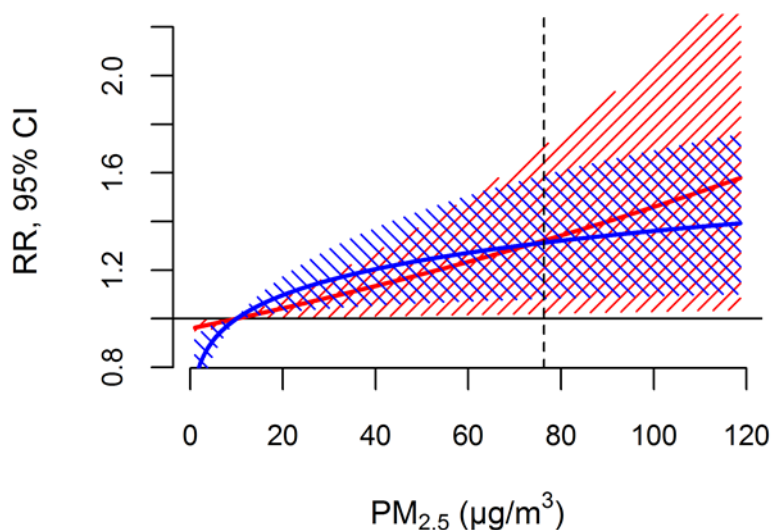
For a decrease in $PM_{2.5}$ exposure from 24.1 µg/m^3 (mean exposure of patients) to 10 µg/m³, the 2-day (lag 0–1) decrease in pneumonia hospitalizations estimated by the log-linear model was 4.9% (95% CI: 0.4% - 9.6%), whereas the corresponding estimate from the log-log model was 10.7% (95% CI: 3.0% - 19.0%) (Table 2). This corresponded to a total of 172 and 377 averted cases in our study population for the log-linear and log-log model, respectively. With a mean cost of 9,404 € per hospital stay, the estimate from the log-linear model translated to a pneumonia related hospital cost saving of 1,617,488 € and the estimate from the log-log model translated to a pneumonia related hospital cost saving of 3,545,308 €. Extrapolated to the 33,695 non-elective pneumonia hospitalizations in Belgium in 2011, the estimates

from the log-linear and log-log models corresponded to 1,651 and 3,605 avoided hospitalizations and a

pneumonia related hospital cost saving of 15,526,004 € and 33,901,420 €, respectively.

Table 2: Percent change in pneumonia hospitalizations attributable to a reduction in lag 0–1 $PM_{2.5}$ exposure from 24.1 µg/m³ to 10 µg/m³ and the associated costs averted within the study population and extrapolated for Belgium.

	Log-Linear E-R function	Log-Log E-R function
% Change in hospitalizations (95 % CI)	-4.9% (- 9.6% ; -0.4)	-10.7% (- 19.0% ; -3.0%;)
Akaike Information Criterion	10,407	10,404
Mean cost per hospitalization (95% BC CI)	9,404 € (9,122 € ; 9,743 €)	9,404 € (9,122 € ; 9,743 €)
Study Population		
Number of hospitalizations averted	172	377
Averted costs (95% BC CI)	1,617,488 €	3,545,308 €
	(1,568,984 € ; 1,675,796 €)	(3,438,994 € ; 3,673,111€)
Belgium		
Number of hospitalizations averted	1,651	3,605
Annual averted costs (95% BC CI)	15,526,004 €	33,901,420 €
	(15,060,422 € ; 16,085,693€)	(32,884,810 € ; 35,123,51€)

3.3   Secondary analyses

The analysis by age group showed a trend of decreasing health effect estimates for increasing age, with

no evidence for an effect among elderly (>60 years). The decrease in pneumonia hospitalizations for a

reduction in mean $PM_{2.5}$ to 10 µg/m³ estimated by the log-linear model was 10.7% (95% CI: 3.0% to

18.9%), 9.2% (95% CI: -2.6% to 22.4%), and -0.3% (95% CI: -6.6% to 6.5%) for the age groups <16,

16-60, and >60 years, respectively (Supplementary Table S1). Corresponding estimates from the log-

log model were 23.1% (95% CI: 9.6% to 38.2%), 19.5% (95% CI: -0.9% to 44.1%), and -1.0% (95%

CI: -11.0% to 10.1%), respectively. The AIC showed a better fit for the log-log model than for the log-

linear model in the age groups <16 years (4,027 *vs.* 4,032) and 16-60 years (1,683 *vs.* 1,686), whereas

the AIC of both models was nearly identical in the age group >60 years (4,758).

Among children younger than 16 years, a reduction in $PM_{2.5}$ to 10 μg/m^3 would result in a national-level pneumonia-related hospital cost saving of €4.8 million within the log-linear scenario and €10.5 million within the log-log scenario.

Table 3: Percent change in pneumonia hospitalizations among children (<16 years old) attributable to a reduction in lag 0–1 $PM_{2.5}$ exposure from 24.1 μg/m³ to 10 μg/m³ and the associated costs averted within the study population and extrapolated for Belgium.

	Log-Linear E-R function	Log-Log E-R function
% Change in hospitalizations (95 % CI)	-10.7% (- 18.9% ; -3.0%;)	-23.1% (-38.2% ; -9.6%;)
Akaike Information Criterion	4,032	4,027
Mean cost per hospitalization (95% BC CI) (95% BC CI)	6,529 € (6,193 € ; 6,886 €)	6.529 € (6,193 € ; 6,886 €)
Study population		
Number of hospitalizations averted	145	313
Averted costs (95% BC CI)	946,705 €	2,043,577 €
	(897,985 € ; 998,470 €)	(1,938,409 € ; 2,155,318 €)
Belgium		
Number of hospitalizations averted	742	1601
Annual averted costs (95% BC CI)	4,844,518 €	10,452,929 €
	(4,595,206 € ; 5,109,412 €)	(9,914,993 €; 11,024,486 €)

The breakpoint producing the best fit in the piecewise linear model was 15 μg/m^3, with (despite the higher number of model parameters) a slightly lower AIC (10,406.9) compared to the log-linear model (10,407.2). At $PM_{2.5}$ concentrations below 15 μg/m^3, the estimated increase in the risk of pneumonia hospitalization for each unit increase in $PM_{2.5}$ was 2.7% (95% CI: 0.8% to 4.6%), with no evidence for a further increase in risk at $PM_{2.5}$ levels above 15 μg/m^3 (0.2%, 95% CI: -0.3 to 0.6 for each unit increase). The estimate for the decrease in pneumonia hospitalizations associated with a reduction in mean $PM_{2.5}$ to 10 μg/m^3 (15.6%, 95% CI: 4.8% to 27.6%) was higher than those from the log-linear and log-log model.

4 Discussion

Recent research disclosed a discussion on the shape of the association between fine particulate matter exposure and adverse health effects. In this study we used log-linear and log-log E-R functions to estimate the reduction in pneumonia hospitalizations associated with a decrease in two-day (lag 0-1) $PM_{2.5}$ exposure from the mean (21.4 $\mu g/m^3$) to the WHO guideline for annual mean (10 $\mu g/m^3$). The impact of the used E-R function was substantial: the estimated reduction in pneumonia hospitalizations was 4.9% for the log-linear function and 10.7% for the log-log function. This corresponds to an estimated hospital cost saving for pneumonia in Belgium of almost €15.5 million per year (1.42 € per inhabitant) for the log-linear function, whereas the estimate obtained from the log-log model was more than double this amount, i.e. more than €33.9 million (3.10 € per inhabitant).

The change in pneumonia hospitalizations estimated by the log-linear E-R function (4.9% for an increase in $PM_{2.5}$ of 14.1 $\mu g/m^3$) is in line with that from previous studies assuming a log-linear association. For an increase in $PM_{2.5}$ of 17.2 $\mu g/m^3$ in Boston (USA), Zanobetti et al. (2006) reported a same-day increase in pneumonia hospital admissions of 6.5%. Estimates from a study in Shijiazhuang (China) were smaller: a 10 $\mu g/m^3$ increase in $PM_{2.5}$ was associated with a same-day increase in pneumonia hospitalizations of 1.1% (Duan et al., 2015). Also our estimate for children (10.7% for an increase in $PM_{2.5}$ of 14.1 $\mu g/m^3$) is similar to that from other studies. In Santiago (Chili), the estimated change in pneumonia emergency visits among children younger than 15 years was 12.5% for an increase in weekly mean $PM_{2.5}$ of 13.1 $\mu g/m^3$ during warm months, and 7.0% for an increase in weekly mean $PM_{2.5}$ of 30.6 $\mu g/m^3$ during cold months (Ilabaca et al., 1999). The estimated increase in hospital admissions for pneumonia among children up to the age of 18 years in California was smaller: 4.9% for an increase in previous-day $PM_{2.5}$ of 14.6 $\mu g/m^3$ (Ostro et al., 2009). To the best of our knowledge, only one previous study allowed for a nonlinear association between $PM_{2.5}$ and pneumonia. Yu and Chien (2015) found an association between $PM_{2.5}$ and same-day clinic visits for pneumonia and influenza among school children (6-14 years) in Taipei (Taiwan): health risks increased with increasing $PM_{2.5}$ at relatively low concentrations up to 7.5 $\mu g/m^3$, but not at higher levels (except at extremely high concentrations above 90 $\mu g/m^3$). Contrary to findings from a study in Michigan (Detroit) (Ito et al., 2003), we did not find

evidence for an association between $PM_{2.5}$ and pneumonia hospitalizations among elderly. As has been observed for other health outcomes (Schwartz, 2004), effect estimates were highest for children, which may be due to higher exposure levels as well as a higher susceptibility. Children spend more time being active outside than adults and they breathe more rapidly. Previous research also demonstrated that particles are likely to hamper the ability of children's immature immune system to clear bacteria and other pathogens from the lung, which makes them at a higher risk to develop severe pneumonia requiring hospitalization (Dietert et al., 2000). Furthermore, Gauderman et al. (2004) showed that $PM_{2.5}$ is strongly associated with decreased lung function attainment in school children resulting in compromised lung development.

Deciding on the true shape of association between $PM_{2.5}$ and pneumonia hospitalizations was outside the scope of this study and requires further research in different study populations. The AIC suggested that the log-log model fitted the data slightly better than the log-linear model, but the difference in AIC was small. Although it may be difficult to pick up non-linearity by comparing models based on AIC (Roberts & Martin, 2006), a comparison of AIC values suggested that the shape of the association between $PM_{2.5}$ and pneumonia hospital admissions was concave-downward. Supralinearity was confirmed in analyses by age group and is further supported by results from the piecewise-linear model. The latter suggested a steep increase in the risk of pneumonia hospitalizations at $PM_{2.5}$ levels below 15 $\mu g/m^3$, corresponding to the 40th percentile of the $PM_{2.5}$ distribution of patients, but no further increase in risk at higher concentrations. A levelling-off of relative risks at high exposure levels may reflect different underlying mechanisms, including exposure misclassification at higher concentrations, competing risks between diseases, and saturation of underlying biochemical and cellular processes (Vineis et al., 2000; Smith & Peel 2010; Amrose & Barua, 2004). Attenuation of E-R functions at high concentrations has also been observed in studies on occupational exposures (Stayner et al., 2003). Saturation of enzyme activity, or induction of DNA repair processes or detoxification enzymes at high doses have been suggested as potential mechanisms for a supralinear association between polycyclic aromatic hydrocarbon exposure and DNA adducts in white blood cells and lung tissue (Lewtas et al., 1997). Using serum lung club cell secretory protein (Clara) as a biomarker for respiratory epithelium

integrity, a recent study suggests that short-term exposure to particulate matter may lead to increased epithelial barrier permeability in the lungs of adolescents. Interestingly, the authors observed a flattening out of the slope at weekly mean PM_{10} levels above 37 μg/m^3 (Provost et al., 2014).

It should be stressed that research endeavors to determine a the shape of the association between $PM_{2.5}$ and adverse health effects remain highly important from a policy perspective. A supralinear E-R function implies that a given reduction in $PM_{2.5}$ would yield a greater per capita health gain as the initial baseline becomes cleaner, providing an incentive to further clean places that already have relatively low pollution levels. However, the relationship between emission reductions and subsequent changes in exposure and health impact also depends on factors such as population density, urban form, meteorology, and atmospheric chemistry. Whereas the per capita health risk reduction may be greater in clean areas, the aggregate health benefit will be highest in more populated locations, which typically have higher pollution levels. Moreover, policy makers should also take into account the marginal costs of air pollution reduction. The marginal cost of air pollution reduction considered here are the costs related to each additional unit of decrease of air pollution exposure. It is reasonable that a further reduction of exposure in the low-polluted regions is extremely expensive (due to for example complex technology) compared to cleaning up the high-polluted regions. In conclusion, assuming a log-log E-R function, policy makers could prioritize to clean up the low-polluted regions, but only given that the higher marginal cost of cleaning up the low polluted metropolitan region is not overcompensating the higher health gains.

Wiener (2004) indicated that the shape of the E-R function is not only important for setting priorities, but also in selecting policy instruments to regulate air pollution reduction. According to welfare economics, the existence of externalities such as air pollution from human activities result in a non-Pareto optimal allocation. It presents a source of market failure, because in that case market prices do not reflect marginal social costs or marginal social benefits, and profitability from an individual's point of view does not necessarily reflect net social benefits (Schmidtchen et al., 2009). Consequently, government intervention in the domain of air pollution control could yield considerable societal benefits by implementing command-and-control approaches (e.g. environmental norms for vehicles) or market-

based policy instruments inspired by the economic theoretical concept of marginal social cost pricing (e.g. emissions taxes or tradable emissions allowances). A first example to regulate pollutants by policy are (fixed) emissions taxes. These should be based on marginal costs and in an ideal world, the tax amount should be set there were marginal benefits equal marginal abatement costs, i.c. the social optimum. However, the social optimal point will differ depending on the assumed shape of the E-R function, demonstrating the importance to unravel the E-R function that approximates reality most. Wiener himself (2004) gave the example of tradable emission allowances. He demonstrated that under a linear E-R function bunching (buying of allowances and thus creating higher emissions in certain locations) and draining (selling of allowances and thus lowering emissions in certain locations) would not increase the total harm to the population (under the assumption of identical exposure rates for all locations). However, with a log-log E-R function, trading could be beneficial if buying (bunching) and selling (draining) deviate from the average. This way, draining should occur where the E-R function is rising steeply and bunching should occur where the E-R function is flattening out. However, trading would be harmful if buyers and sellers converge towards the average of the log-log E-R function, i.e. when buying occurs where the E-R function is rising steeply and draining occurs where the E-R function is flattening out. This demonstrates that, in case of tradable emissions, wrong assumptions on the shape of the E-R function could result in undesirable and adverse effects.

There are several limitations in this study. Firstly, we used local pollutant concentrations at municipality level that might not be representative for personal exposure. However, the majority of the study population were school children (39% under 16 years old) and retired persons (45% older than 60 years). For these age groups we expect that they spend most time at school in their municipalities, or at home. A second limitation is the simplified extrapolation of estimates for one Brussels hospital to the total of Belgium. Although the study population included patients from different (urban and rural) locations in Belgium, the magnitude of the estimated effect on averted hospitalizations based on the E-R function may not be generalizable to the total country because of differences in $PM_{2.5}$ concentration and/or composition, as well as differences in patient characteristics (Supplementary Table S1). Compared to the national-level hospitalizations for pneumonia in 2011, children below the age of 16 were

overrepresented in our study population, resulting in a potential overestimation of hospital cost savings in this age category. As third limitation, only the hospitalizations costs for one disease and for one air pollutant ($PM_{2.5}$) were estimated, as a demonstration to quantify differences in averted hospitalizations and costs when using different E-R functions. We discussed with this simple example on pneumonia hospitalizations the important role of E-R functions for policy-decision making regarding marginal costs, the social optimum, air pollution control measures, and setting priorities among different regions. It should be acknowledged that in this study we did not aim to calculate the total burden of air pollution related pneumonia hospitalizations. Long-term medical care use of pneumonia patients are not considered in our calculations, neither are productivity losses or intangible costs (common costs in health economic evaluations). Including these costs could have resulted in a more complete picture of the total economic burden of air pollution related pneumonia hospitalizations, but the ratio of the effects when comparing log-linear vs. log-log E-R functions would remain the same.

In this study, we demonstrated that public health is affected by outdoor $PM_{2.5}$ air pollution, even well below the actual EU air quality guidelines (annual mean of 25 $\mu g/m^3$). Furthermore, we showed that the use of log-linear and log-log E-R functions to model the association between $PM_{2.5}$ exposure and pneumonia hospitalizations resulted in substantial differences in estimated health effects and associated averted hospital costs, indicating that special precaution is required when specific E-R functions are used in policy making. As long as there is no unanimity of a given E-R association, health effect estimates of different E-R functions should be compared and presented in a sensitivity analysis.

5   Acknowledgement

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