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Error in air pollution exposure model determinants and bias in health estimates

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Error in air pollution exposure model determinants and bias in health estimates

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Abstract

Background

Land use regression (LUR) models are commonly used in environmental epidemiology to assign spatially resolved estimates of air pollution to study participants. In this setting estimated LUR model parameters are assumed to be transportable to a main study (the 'transportability assumption'). We provide an empirical illustration of how violation of this assumption can affect exposure predictions and bias health effect estimates.

Methods

We based our simulation on two existing LUR models, one for nitrogen dioxide, the other for particulate matter with aerodynamic diameter < 2.5 μm. We assessed the impact of error in exposure determinants used in the LUR models on resultant air pollution predictions and on bias in an exposure health-effect estimate assessed in a hypothetical cohort. We assigned error to predictors at monitoring sites (sites used to develop the LUR model) and at prediction sites (sites for which exposure predictions were needed), allowing for different error levels between site types.

Results

Realistic error in the exposure determinants of the selected LUR models did not induce large additional error in exposure predictions and resulted in only minor (<1%) bias in health effect estimates. Bias in the health-effect estimates strongly increased (up to 13.6%) when exposure determinant errors were different for monitoring sites than for prediction sites.

Conclusions

These results suggest that only modest reductions in bias in estimated exposure health-effects are to be expected from reducing error in exposure determinants. It is important to avoid heterogeneous errors in exposure determinants between monitoring sites and prediction sites to satisfy the transportability assumption and avoid bias in estimated exposure health-effects.

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Introduction

Land use regression (LUR) models are commonly used in environmental epidemiology to assign spatially resolved estimates of air pollution markers to study participants[1]. For example, in the pan-European ESCAPE project of ± 30 cohort studies including approximately 900,000 subjects, LUR derived exposure estimates[2,3] were shown to be associated with a variety of health outcomes such as birth weight, cardiovascular and respiratory disease, cancer incidence, and mortality[4–11].

Exposure prediction using LUR models proceeds in two steps. First, LUR models are estimated by regressing exposure measurement data collected at a limited number of sites (monitoring sites) on a set of geographical exposure determinants[3,12]. Second, these LUR models are used to predict exposure levels for study subjects using the same set of exposure determinants collected using the geographical location of their whereabouts (prediction sites, e.g. residence(s), work location). These predicted exposures are then used in an epidemiological analysis to assess the association between this exposure and a health outcome of interest (See Figure 1 for a graphical representation).

Usually, the locations of monitoring sites do not match the locations of the prediction sites, a situation known as spatial misalignment[13]. Spatial misalignment can induce error in the exposure estimates which in turn has an impact on the estimation of the exposure-health association.

How much error is introduced depends on the degree to which the exposure measurement error model is transportable, i.e. to which extent the measurement error model at the monitoring sites also holds true at the prediction sites[14].

Error in LUR model exposure determinants can be the result of inherent error in the source information that is used to generate a certain exposure determinant (e.g. in the database that is used to estimate the number of vehicles on the road), but can also be due to error in the measured geographical location of monitoring and prediction sites (See figure 1 for an illustration of where these errors occur).

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Following standard "errors-in-variables" theory[15], classical error in the exposure determinants at monitoring sites will bias the LUR model parameter estimates. However, there is generally little intrinsic interest in the LUR model parameters, but only in the impact of these errors on the health effect estimates that result from using a biased LUR model (i.e. a model with biased parameter estimates).

Here, using a Monte Carlo approach, we illustrate the impact of realistic error in the exposure determinants of the Netherlands/Belgium LUR models for nitrogen dioxide (NO_2) and for particulate matter with aerodynamic diameter < 2.5 μm ($PM_{2.5}$) that were developed within the ESCAPE project. We illustrate the extent to which these errors are translated into error in predicted exposures at an external set of prediction sites and into subsequent bias of exposure-health effect parameter estimates. We show the importance of balancing the error in exposure determinants at prediction sites with the error in exposure determinants at monitoring sites, the only situation that yields essentially unbiased health effect estimates. We compare the impact of error in LUR model exposure determinants in our simulation to other sources that have been reported to contribute to measurement error in LUR model estimates.

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Methods

We conducted a Monte Carlo simulation to illustrate how realistic error in exposure determinants of a LUR model could induce error in predicted exposures and bias exposure-health effect estimates. We based our simulation on two LUR models, for NO_2 and $PM_{2.5}$, that were developed for the Netherlands and Belgium within the ESCAPE project[3,12]. The models were developed using measurement data from 80 (NO_2), and 40 ($PM_{2.5}$) monitoring sites classified as 'regional background' (RB), 'urban background' (UB), or 'street' (S)[16,17]. For each monitoring site three two-week-long measurements were available distributed over the seasons and corrected for temporal variation with the use of a reference site[16,17]. A number of geographical exposure determinants were used to predict the spatial variation in NO_2 and $PM_{2.5}$ concentrations at the monitoring sites (Table 1). For each exposure determinant included in the LUR models we estimated the error in the exposure determinant that was introduced by error in the source data (inherent error). Furthermore we estimated the error in each of the exposure determinants resulting from error in the geographical location of monitoring and prediction sites (positional error).

Inherent error in model exposure determinants

Full details of our approach to derive realistic error estimates for all exposure determinants are provided in the Supplemental Material. Briefly, error in the regional contribution of NO_2 or $PM_{2.5}$ at each site (REG) was estimated using the variation in measurement data at regional background sites across three sampling campaigns.. Error in the population density (PD) and distance to the nearest road (DTR) was estimated by calculating the standard deviation of the difference in estimates for each site from two independent data sources. Estimates for error in traffic load exposure determinants–traffic load in a 50m buffer (TL50), heavy traffic load in a 25m buffer (HTL 25), heavy traffic load in a 25m to 500m buffer (HTL500), and traffic load on major roads in a 1000m buffer (TML1000)–were taken from a study that reported relative standard deviations (RSDs) per road type for estimates of vehicle miles traveled (a quantity very similar to buffer variables used in the ESCAPE

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LUR models) from the U.S.A: 7.8 % for street sites and urban background sites and 3.0 % for regional background sites[18]. We assumed that very precise source data was available for exposure determinant road length (RL) and had no data available to reject this assumption. This exposure determinant was therefore not included in the Monte Carlo simulation.

Error in the geographical location of monitoring and prediction sites

Geographical location for prediction sites in the Netherlands and Belgium were geocoded In the ESCAPE study using individual building matching techniques based upon cadastral data. The accuracy of cadastral data is high. For example, in the Address Coordinates Netherlands database 93.5% of all coordinates are located at the centroid of the correct building, 6.0% located at the centroid of the correct parcel, and only 0.5% not located in the correct building or parcel[19]. For the simulations we assume that the average geographical location error in residential addresses in the Netherlands and Belgium was 4 meters, based on the average width and depth of a home in NL/BE[20]. We contrast this situation with that where the average error is 30 meters, which has been reported for settings where sub-optimal spatial interpolation techniques have been used[21].

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Monte Carlo simulation

The design of the simulation is described in detail in the Supplemental Material. Linking GIS data to the geographical coordinates is a time-consuming operation, and we therefore restricted the simulated study size to include 200 prediction sites (randomly sampled from residential locations of participants in the PIAMA birth cohort[22]), and 68 (NO_2 model) respectively 34 ($PM_{2.5}$ model) monitoring sites. To avoid introducing unnecessary additional Monte Carlo error, we used a fully deterministic model for the outcome Y (i.e. the sampling varianceσ_y^2 was set to 0).

For the true parameters of the exposure-health model we used an arbitrary intercept (β_0) of 1.8, and a slope (β_1) of -5. This slope resembles the percentage decrease in FEV1 in children with a roughly 20 µg/m3 increase in NO_2 or a 5 µg/m3 increase in $PM_{2.5}$ in the PIAMA study[23].

For each simulation, we sampled exposure determinant data contaminated with non-differential measurement error from a multivariate normal distribution based on mean zero (all variables were standardized) and the covariance matrix of the original exposure determinants at monitoring and prediction sites. This matrix was then used in all subsequent simulations to draw multivariate normal errors. We calculated the average β_1 across the simulations. To improve coverage we estimated 95% confidence intervals using a parametric bootstrap.

As a sensitivity analysis, we sampled exposure determinant data setting all off-diagonal values of the covariance matrix to zero (removing covariance between the exposure determinants).Similarly, we conducted analyses using the original covariance matrix of the error in the exposure determinants, and by setting all off-diagonal values to zero (removing covariance between the errors in the exposure determinants).

REG was included in the ESCAPE LUR models to capture regional variability in $PM_{2.5}$ and NO_2. REG is unlikely to change as a result of relatively small positional errors in the estimated geographical

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location of the monitoring and prediction sites, and we therefore only assessed the impact of error in the source information for this determinant.

Within the ESCAPE project all exposure determinants at the prediction sites were constrained to be within the range of values that were observed at the monitoring sites. We applied the same approach in our simulation, but assessed the sensitivity of our results to removing this constraint.

Code availability: Computing code required to replicate the results reported in this submission are available upon request from the corresponding author.

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Results

Table 1 presents an overview of the exposure determinants that were included in the Netherlands/Belgium $PM_{2.5}$ and NO_2 LUR models developed within the ESCAPE project. We report the parameter estimates and the change in R^2 due to removal of the exposure determinant from the regression model (ΔR^2). The overall R^2 was 86.5% for the NO_2 model, and 66.6% for the $PM_{2.5}$ model which is higher than the summed ΔR^2 for each individual exposure determinant because of correlations between exposure determinants. In Tables S1 and S2 we report the error variance that we assigned to exposure determinants in the LUR models and in Figures S1–S8 we show the simulated error distribution of the exposure determinants at the monitoring sites.

Exposure simulation

Boxplots in Figure 2 show the impact on exposure predictions of either inherent error in the source data of the geographical exposure determinants (either adding error to all model exposure determinants simultaneously or adding error to one of the exposure determinants while retaining the original values for the remaining exposure determinants) and of positional error introduced in all exposure determinants simultaneously as a result of error in the recorded geographical location of prediction sites (using either a 4 or 30 meter error radius).

When applied simultaneously, realistic error in the exposure determinants of the NO_2 model resulted in median RSDs of the predicted NO_2 concentrations of 6.6%, 4.1%, and 3.2% at regional background (RB), urban background (UB), and street (S) locations, respectively. Error in NO_2 predictions due to inherent error in exposure determinant sources was primarily due to error in DTR, PD, REG, while error in TL50, HTL25, and HTL500 had only minor impact. An error radius of 4 meter in the geographical location of the monitoring sites resulted in median RSDs of 2.0%, 1.8%, and 1.8%, at RB, UB, and S sites, respectively, while a 30m error radius resulted in much larger mean RSDs of 9.5%, 5.8%, and 10.2%.

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Combined error in exposure determinant sources resulted in median RSDs of predicted $PM_{2.5}$ concentrations of 1.5%, 1.4%, and 1.2% at RB, UB, and S locations, respectively. The error in these predictions was primarily the result of error in REG. Error in traffic on a major road in a 1000m buffer (TML1000) contributed to some (<0.5%) error at S and UB sites, but not at RB sites. Positional error within a 4 meter radius in the geographical location had very little impact on predicted $PM_{2.5}$ concentrations (RSD <0.2%), regardless of site type. Impact of positional error in a 30 meter radius was restricted almost completely to street sites (median RSD 1.7%). In Figures S9 and S10 we show the impact of positional error within a 4m and 30m radius on the variance of the standardized exposure determinants at both monitoring and exposure determinant sites.

Health simulation

For each simulation we calculated as a reference the results from a two-stage analysis where the true (i.e. error-free) exposure determinants were available at both monitoring and prediction sites (first column with estimates in Tables 2 and 3). The results indicate that the slope estimates (β_1) from this analysis are slightly biased downwards (ranging from -4.85 to -4.95), probably due to error in the LUR model parameter estimates. Average β_1 for the $PM_{2.5}$ -health model were generally slightly lower than the average β_1 for the NO_2-health model, reflecting the lower coefficient of determination (R^2 66.6%) of the $PM_{2.5}$ exposure model. Coverage of the parametric bootstrap derived confidence intervals varied around 95% (deviations due to the limited number of simulations).

Compared to the reference scenario, we observed only limited additional bias in slopes for the scenario where we added the same degree of error to exposure determinants at both monitoring and prediction sites. For inherent error (Table 2) mean additional bias was < 0.8% for the NO_2 model and < 1.0% for the $PM_{2.5}$ model. For positional error (Table 3) the mean additional bias was between -0.2% and -0.6% for the NO_2 model and between 0.2% and -1.0% for the $PM_{2.5}$ model. For both pollutants constraining of the exposure determinants had a small but unpredictable (both up- and downwards) impact on the mean additional bias. Mean additional bias increased with increasing

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error in estimated geographical location of the prediction sites (4m vs. 30m). Coverage of 95% confidence intervals was generally unaffected for all settings.

Considerable additional negative bias (compared to the reference scenario) was observed in the scenario where we added error to the exposure determinants at prediction sites, but not at monitoring sites. For inherent error (Table 2) the additional biases were -10.5% and -13.6% for the NO_2 model and -7.3% (twice) for the $PM_{2.5}$ model. For positional error (Table 3) large additional mean bias was observed for the NO_2 model when exposure determinants were not constrained (-80.8% for 4m error and -96.0% for 30m). Average bias was restricted when exposure determinants were constrained (-0.8% (4m) and -9.3% (30m)). For the $PM_{2.5}$ model, mean bias ranged between 0.0% and -6.0%, increased with increasing positional error of the prediction sites (4m vs. 30m) and was restricted when exposure determinants were constrained. Coverage of the 95% confidence intervals changed in parallel to the bias induced in β_1.

Considerable additional positive bias (compared to the reference scenario) was observed in the scenario where we added error to the exposure determinants on the monitoring sites, but not on the exposure determinant sites (mean additional bias ranging from +0.4% to +2.6% for the NO_2 model and from +0% to +5.6% for the $PM_{2.5}$ model). Mean bias increased with increasing positional error of the prediction sites, while constraining of the exposure determinants had minimal impact. Coverage of the 95% confidence intervals changed in parallel to the bias induced in β_1.

Results in Tables S3-S6 indicate that removing the covariance between exposure determinants resulted in stronger bias in all scenarios were exposure determinants were affected by error. Removing the covariance between the errors of the exposure determinants had only negligible impact under all scenarios.

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Discussion

Impact of error in determinants on exposure predictions

Our analysis demonstrates that, perhaps with the exception of the regional contribution of NO2 or PM2.5 at each site (REG), added error in the exposure determinants that were used in our LUR models did not induce large error in exposure predictions. Realistic error in exposure determinant REG had the largest influence on error in predictions of both NO_2 and the $PM_{2.5}$. Based on its large contribution to the coefficient of determination of the LUR models used in this exercise this was expected, and it shows that accurate measurement of this exposure determinant is important. Within the ESCAPE study this was done by conducting three two-week sampling campaigns at 20 sites (10 for $PM_{2.5}$) to estimate the long-term average regional contribution to ambient air pollution levels[3,12]. An approach to reduce the influence of the error in the REG would be to further increase the number of measurements per measurement site to reduce the error in the average. Alternatively, the REG could be better characterized by utilizing additional data to represent regional variation in ambient air pollution such as satellite data or modelled regional background levels from chemical transport models.

In our simulation the impact on exposure predictions of realistic error in model exposure determinants on monitoring and exposure determinant sites was higher for the NO_2 model than for the $PM_{2.5}$ model. As the LUR models primarily captured small scale spatial variability in ambient air pollution, these observations correspond to the notion that spatial variability in NO_2 concentrations, for which local traffic is a primary source, occurs on a smaller scale than spatial variability in $PM_{2.5}$ concentrations, to which many sources contribute in addition to local traffic[24]. This is also reflected in the higher number of exposure determinants of small scale variation that is included in the NO_2 model compared to the $PM_{2.5}$ model.

Impact of error in exposure determinants on bias in health effect estimates

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Using a simulation framework we showed that realistic (non-differential) error in the exposure determinants of the ESCAPE LUR models introduced bias in health effect estimates when there was an imbalance in the degree of error between exposure determinants at the monitoring sites and exposure determinants at the prediction sites.

We explain this observation as follows: error in the exposure determinants of the exposure model results in a wider distribution of the measured exposure determinant values compared to the true exposure determinant values at the monitoring sites. Consequently, parameter estimates for the measured exposure determinants derived from a linear regression model will be biased. When these biased parameter estimates are used on a new set of exposure determinants at the exposure determinant sites that are equally affected by error (have a similar error structure) the resulting predicted exposure distribution will approach the true exposure distribution and health effect estimates will be largely unbiased. However, when exposure determinants at the monitoring sites are not affected by error and exposure determinants at the prediction sites are, parameter estimates for the measured exposure determinants will not be biased, but the exposure distribution predicted for the prediction sites will be wider than the true exposure distribution and health effect estimates will be biased downwards. Furthermore, in the (admittedly unrealistic) situation of exposure determinants at the monitoring sites are affected by error, but exposure determinants at the prediction sites being unaffected, the exposure distribution predicted for the prediction sites will be narrower than the true exposure distribution and health effect estimates will be biased upwards.

Our observation contributes to the realization that one sided investments in improving the quality of exposure determinants at monitoring sites while similar improvements cannot be made at the prediction sites will introduce bias in health effect estimates. An example of such a situation would be the location of the monitoring sites being determined using higher quality information (e.g. using Global Positioning System equipment) and therefore measured with less error than the locations of the prediction sites (e.g. only determined with 'building matching techniques'). In this example bias

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in health effect estimates will be reduced when similar techniques are used on both monitoring and prediction sites.

Results from our simulation are also consistent with patterns that have been observed in studies that assessed the impact of the quality of geocoding techniques on the magnitude of the association between exposure to air pollution and (simulated) health outcomes. In these studies the strength of the relationship between air pollution and disease decreased with decreasing geocoding accuracy[21,25].

Figures S9 and S10 illustrate that in this simulation a similar degree of error in the location of a site had a differential effect on the error in the model exposure determinants between monitoring and prediction sites. This phenomenon occurred because there was a difference in the distribution of site characteristics between monitoring and prediction (e.g. on average more monitoring than prediction sites in an urban area or vice versa) and highlights the importance of the exposure determinants at monitoring sites having the same distribution as the exposure determinants at prediction sites (no misspecification)[26], a situation that is not necessarily reached when monitoring sites are selected to achieve highest contrast in exposure determinants (as was done in ESCAPE and other studies)[1]. A weighting approach (using weights representing exposure determinant distributions from the study population in the LUR development phase) might be a viable approach to correct for this source of bias.

A number of other sources of measurement error in modeled exposure estimates have been described in air pollution epidemiology studies using LUR models[14,27–30]. For example, Basagaña et al. showed that the number of monitoring sites, the number of available exposure determinants for model selection, and the amount of explainable variability in the true exposure had a large impact on the estimated LUR model parameters and assigned air pollution exposure, and consequently substantially attenuated health effect estimates (up to 78% in the worst case scenario)[31]. Alexeeff et al demonstrated the impact of model mis-specification, showing that a LUR models with low R-

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squared sometimes yielded biases ranging from 60% upward bias to 70% downward in the health effect estimates[32]. The degree of bias we report here is much smaller than what has been reported in these two studies, thereby suggesting that error in model exposure determinants is not a major contributor to bias in air pollution epidemiology studies based on LUR models.

Several methods have been developed to correct health effect estimates for the bias and error introduced by the use of a model that does not account for all sources of the 'true' exposure (model mis-specification) or from error in estimating exposure model parameters (see refs[26,29,30] for some examples). However, the bias due to imbalance in error in the model exposure determinants described here cannot be corrected for by these methods.

One limitation of our simulation was a necessarily limited number of iterations (n=200) that was possible in each scenario. Using a *t*-test we compared the distributions of the generated health effect estimates in each scenario (Tables S3 and S4). We observed that, with the exception of the scenario in which 4m positional error was introduced, sufficient statistical power was obtained in all other scenarios.

In conclusion, our results suggest that modest reductions in bias in estimated effects of LUR modeled air pollutants on health outcomes are to be expected from reducing error in model exposure determinants. To minimize bias in health effect estimates it is important that (errors in) exposure determinants at monitoring sites and at prediction sites have a similar distribution thereby adhering to the assumption of transportability.

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Conflict of interest

The authors declare no potential conflicts of interest.

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Table 1. Exposure determinants included in ESCAPE LUR models for the Netherlands and Belgium.

Exposure determinant	NO_2 model β[a] (s.e)	ΔR^2 [b]	$PM_{2.5}$ model β[a] (s.e)	ΔR^2 [b]
Intercept	-7.80 (4.18)		9.46 (2.65)	
Inverse distance to the nearest road (DTR)	$1.22*10^{1}$ (4.59)	1.3%		
Regional estimate (REG)[c]	1.18 ($2.02*10^{-1}$)	6.4%	$4.25*10^{-1}$ ($1.66*10^{-1}$)	6.1%
Population density[d] in a 5000m buffer (PD)	$2.30*10^{-5}$ ($6.32*10^{-6}$)	2.5%		
Traffic load[e] in a 50m buffer (TL50)	$2.47*10^{-6}$ ($6.65*10^{-7}$)	2.6%		
Road length of all roads in a 1000m buffer (RL1000)	$1.06*10^{-4}$ ($3.30*10^{-5}$)	2.0%		
Heavy traffic load[e] in a 25m buffer (HTL 25)	$9.84*10^{-5}$ ($3.78*10^{-5}$)	1.3%		
Heavy traffic load[e] in a 25m to 500m buffer (HTL500)	$4.47*10^{-7}$ ($1.92*10^{-7}$)	1.0%		
Road length of all major roads in a 50m buffer (MRL50)			$1.37*10^{-2}$ ($2.35*10^{-3}$)	3.1%
Traffic load[e] on major roads in a 1000m buffer (TML1000)			$2.28*10^{-9}$ ($1.04*10^{-9}$)	4.5%
R^2	**86.5%**		**66.6%**	

[a] Coefficient (and standard error) of the exposure determinant included in the original model.
[b] Change in R^2 due to removal of the exposure determinant from the regression model (does not add up to total R^2 due to correlation between the exposure determinants).
[c] Inverse distance weighted regional background concentration based on 10 regional background sites.
[d] Number of inhabitants in a buffer.
[e] Sum of the length of a road segment * the traffic intensity on that road segment for all road segments. in a buffer. Calculated for total traffic and heavy traffic, and for all roads and major.

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Table 2. Impact on β_1[a] and coverage of its bootstrapped confidence intervals[b] of inherent error in exposure determinants at monitoring (Pm) and prediction (Pp) sites of two land use regression models (NO_2 and $PM_{2.5}$). True beta is -5.00[a]

Model	Exposure determinants constrained[c]	No error on P_m, no error on P_p[a,b,d]	Error on P_m, error on P_p[a,b,d]	Error on P_p, no error on P_m[a,b,d]	error on P_m, no error on P_p[a,b,d]
NO_2	yes	-4.94 (-5.33, -4.61) *92.5%*	-4.90 (-5.39, -4.45) *92.5%*	-4.42 (-4.84, -3.94) *44.5%*	-5.03 (-5.50, -4.59) *94.5%*
NO_2	no	-4.94 (-5.34, -4.56) *99.5%*	-4.93 (-5.37, -4.47) *93.0%*	-4.27 (-4.79, -3.75) *35.5%*	-5.06 (-5.57, -4.61) *97.0%*
$PM_{2.5}$	Yes	-4.94 (-6.13 , -4.03) *91.5%*	-4.89 (-6.06 , -4.05) *93.0%*	-4.58 (-5.83 , -3.71) *80.0%*	-5.11 (-6.28 , -4.19) *94.5%*
$PM_{2.5}$	No	-4.92 (-6.07, -4.10) 89.5%	-4.93 (-6.07, -4.09) 92.5%	-4.56 (-5.54, -3.75) 79.5%	-5.14 (-6.42, -4.17) 95.5%

[a] mean, 5th and 95th percentile of β_1 estimated in 200 simulations. True beta is -5.00. Parameter reflects a realistic estimate in percentage decrease in FEV1 in children for a roughly 5 µg/m3 increase in PM2.5 and a 20 µg/m3 increase in NO2 reported in the PIAMA cohort.

[b] In italic: percentage of 95% confidence intervals of β_1, calculated during each simulation, that contains the true beta.

[c] 'yes': exposure determinants of the land use regression (LUR) model were constrained within the minimum and maximum values that were observed during the monitoring campaign, 'no': exposure determinants were not constrained.

[d] Pm: monitoring sites, P_p: prediction sites.

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Table 3. Impact on β_1[a] and coverage of its bootstrapped confidence intervals[b] of positional error on monitor(P_m) and prediction(P_p) sites of two land use regression models (NO_2 and $PM_{2.5}$).

Model	Positional error[c]	Exposure determinants constrained[d]	No error on P_m, no error on P_p[a,b,e]	Error on P_m, error on P_p[a,b,e]	Error on P_p, no error on P_m[a,b,e]	error on P_m, no error on P_p[a,b,e]
NO_2	4m	Yes	-4.92 (-5.31, -4.54) *91.0%*	-4.92 (-5.30, -4.54) *92.5%*	-4.88 (-5.28, -4.50) *91.5%*	-4.94 (-5.32, -4.57) *93.0%*
NO_2	4m	No	-4.95 (-5.36, -4.60) *95.5%*	-4.94 (-5.36, -4.55) *92.0%*	-0.95 (-3.12, -0.21) *8.0%*	-4.98 (-5.41, -4.57) *95.5%*
NO_2	30m	Yes	-4.92 (-5.31, -4.54) *91.0%*	-4.91 (-5.38, -4.45) *92.5%*	-4.46 (-4.91, -4.00) *55.0%*	-5.02 (-5.49, -4.54) *93.5%*
NO_2	30m	No	-4.95 (-5.36, -4.60) *95.5%*	-4.92 (-5.36, -4.54) *93.5%*	-0.20 (-0.46, 0.01) *1.5%*	-5.02 (-5.46, -4.61) *96.5%*
$PM_{2.5}$	4m	Yes	-4.90 (-6.42 , -3.77) *91.0%*	-4.90 (-6.38 , -3.78) *90.5%*	-4.90 (-6.41 , -3.76) *91.5%*	-4.90 (-6.39 , -3.79) *91.5%*
$PM_{2.5}$	4m	No	-4.85 (-6.38 , -3.80) *91.5%*	-4.85 (-6.41 , -3.83) *90.5%*	-4.84 (-6.37 , -3.80) *91.5%*	-4.85 (-6.42 , -3.83) *92.0%*
$PM_{2.5}$	30m	Yes	-4.85 (-6.42 , -3.70) *86.0%*	-4.83 (-6.56 , -3.62) *85.5%*	-4.57 (-5.96 , -3.43) *82.0%*	-5.10 (-7.06 , -3.84) *93.5%*
$PM_{2.5}$	30m	No	-4.85 (-6.38 , -3.80) *91.5%*	-4.83 (-6.57 , -3.66) *91.5%*	-4.56 (-6.15 , -3.58) *80.5%*	-5.10 (-6.87 , -3.85) *95.5%*

[a] Mean, 5th and 95th percentile of β_1 estimated in 200 simulations. True beta is -5.00. Parameter reflects a realistic estimate in percentage decrease in FEV1 in children for a roughly 5 µg/m3 increase in PM2.5 and a 20 µg/m3 increase in NO2 reported in the PIAMA cohort.

[b] In italic: percentage of 95% confidence intervals of β_1, calculated during each simulation, that contains the true beta.

[c] Error (in meters) in the geographical location of monitoring sites (P_m) and prediction sites (P_p).

[d] 'yes': exposure determinants of the land use regression (LUR) model were constrained within the minimum and maximum values that were observed during the monitoring campaign, 'no': exposure determinants were not constrained.

[e] Pm: monitoring sites, P_p: prediction sites.

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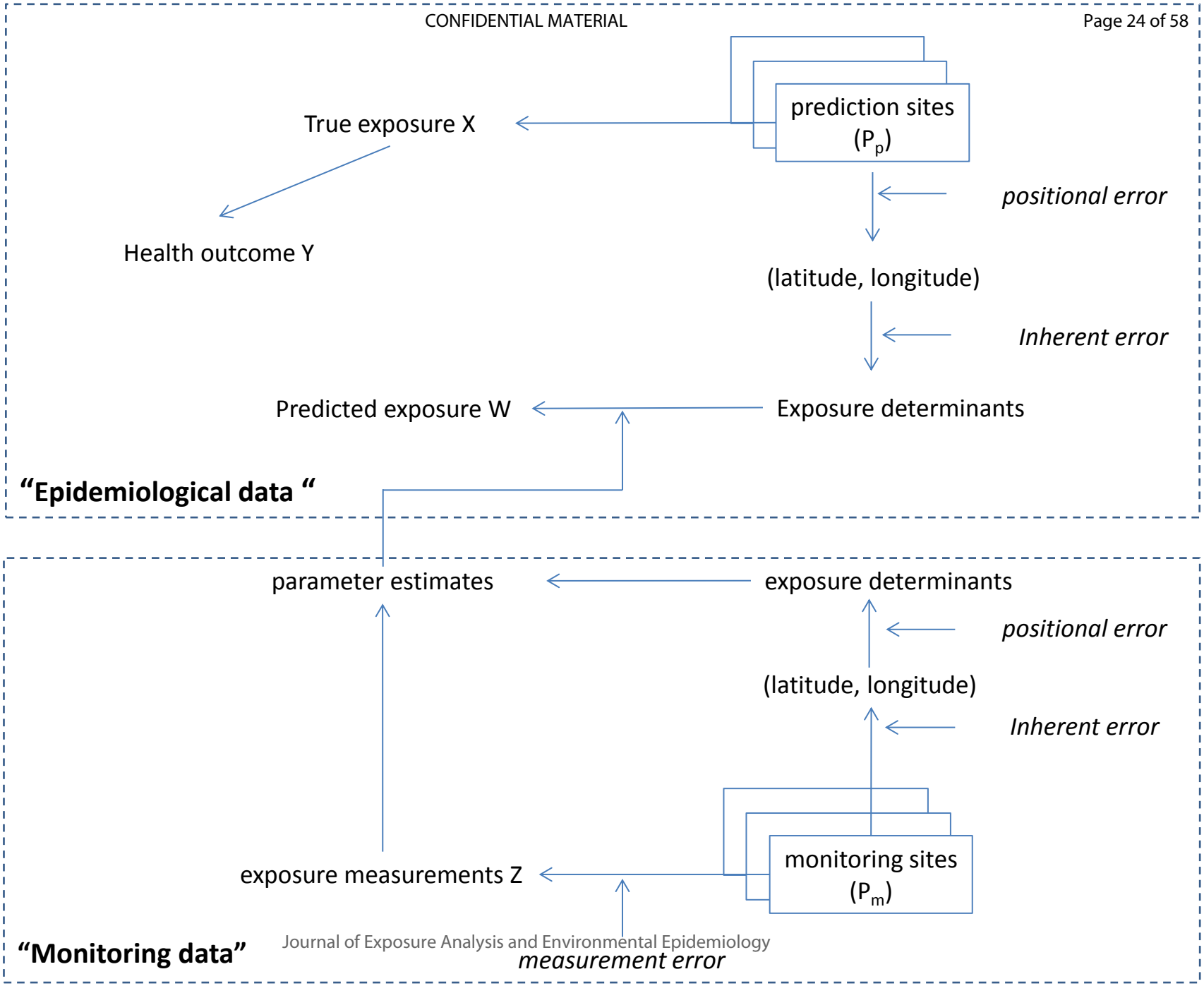
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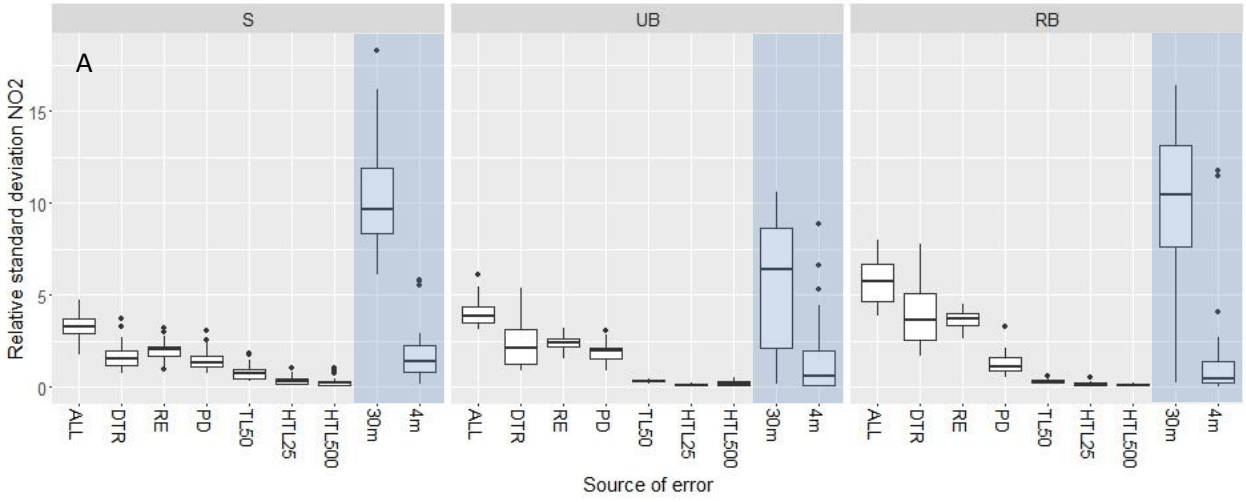

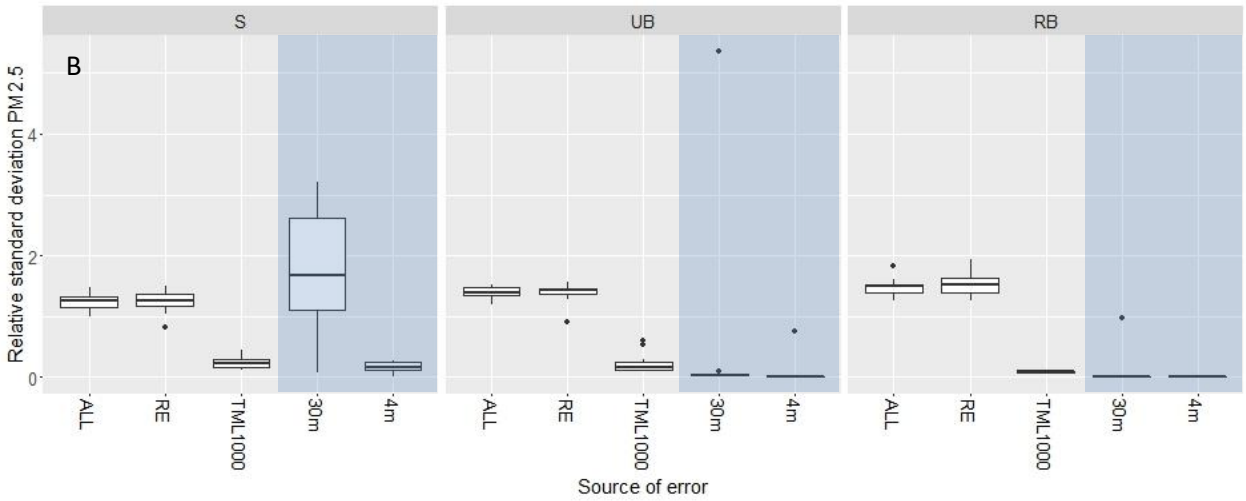

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Error in air pollution exposure model determinants and bias in health estimates

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Abstract

Background

Land use regression (LUR) models are commonly used in environmental epidemiology to assign spatially resolved estimates of air pollution to study participants. In this setting estimated LUR model parameters are assumed to be transportable to a main study (the 'transportability assumption'). We provide an empirical illustration of how violation of this assumption can affect exposure predictions and bias health effect estimates.

Methods

We based our simulation on two existing LUR models, one for nitrogen dioxide, the other for particulate matter with aerodynamic diameter < 2.5 µm. We assessed the impact of error in exposure determinants used in the LUR models on resultant air pollution predictions and on bias in an exposure health-effect estimate assessed in a hypothetical cohort. We assigned error to predictors at monitoring sites (sites used to develop the LUR model) and at prediction sites (sites for which exposure predictions were needed), allowing for different error levels between site types.

Results

Realistic error in the exposure determinants of the selected LUR models did not induce large additional error in exposure predictions and resulted in only minor (<1%) bias in health effect estimates. Bias in the health-effect estimates strongly increased (up to 13.6%) when exposure determinant errors were different for monitoring sites than for prediction sites.

Conclusions

These results suggest that only modest reductions in bias in estimated exposure health-effects are to be expected from reducing error in exposure determinants. It is important to avoid heterogeneous errors in exposure determinants between monitoring sites and prediction sites to satisfy the transportability assumption and avoid bias in estimated exposure health-effects.

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Introduction

Land use regression (LUR) models are commonly used in environmental epidemiology to assign spatially resolved estimates of air pollution markers to study participants[1]. For example, in the pan-European ESCAPE project of ± 30 cohort studies including approximately ~~±~~ 900,000 subjects, LUR derived exposure estimates[2,3] were shown to be associated with a variety of health outcomes such as birth weight, cardiovascular and respiratory disease, cancer incidence, and mortality[4–11].

Exposure prediction using LUR models proceeds in two steps. First, LUR models are estimated by regressing exposure measurement data collected at a limited number of sites (monitoring sites) on a set of geographical exposure determinants[3,12]. Second, these LUR models are used to predict exposure levels for study subjects using the same set of exposure determinants collected using the geographical location of their whereabouts (prediction sites, e.g. residence(s), work location). These predicted exposures are then used in an epidemiological analysis to assess the association between this exposure and a health outcome of interest (See Figure 1 for a graphical representation).

Usually, the locations of monitoring sites do not match the locations of the prediction sites, a situation known as spatial misalignment[13]. Spatial misalignment can induce error in the exposure estimates which in turn has an impact on the estimation of the exposure-health association.

How much error is introduced depends on the degree to which the exposure measurement error model is transportable, i.e. to which extent the measurement error model at the monitoring sites also holds true at the prediction sites[14].

Error in LUR model exposure determinants can be the result of inherent error in the source information that is used to generate a certain exposure determinant (e.g. in the database that is used to estimate the number of vehicles on the road), but can also be due to error in the measured geographical location of monitoring and prediction sites (See figure 1 for an illustration of where these errors occur).

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Following standard "errors-in-variables" theory[15], classical error in the exposure determinants at monitoring sites will bias the LUR model parameter estimates. However, there is generally little intrinsic interest in the LUR model parameters, but only in the impact of these errors on the health effect estimates that result from using a biased LUR model (i.e. a model with biased parameter estimates).

Here, using a Monte Carlo approach, we illustrate the impact of realistic error in the exposure determinants of the Netherlands/Belgium LUR models for nitrogen dioxide (NO_2) and for particulate matter with aerodynamic diameter < 2.5 μm ($PM_{2.5}$) that were developed within the ESCAPE project. We illustrate the extent to which these errors are translated into error in predicted exposures at an external set of prediction sites and into subsequent bias of exposure-health effect parameter estimates. We show the importance of balancing the error in exposure determinants at prediction sites with the error in exposure determinants at monitoring sites, the only situation that yields essentially unbiased health effect estimates. We compare the impact of error in LUR model exposure determinants in our simulation to other sources that have been reported to contribute to measurement error in LUR model estimates.

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Methods

We conducted a Monte Carlo simulation to illustrate how realistic error in exposure determinants of a LUR model could induce error in predicted exposures and bias exposure-health effect estimates. We based our simulation on two LUR models, for NO_2 and $PM_{2.5}$, that were developed for the Netherlands and Belgium within the ESCAPE project[3,12]. The models were developed using measurement data from 80 (NO_2), and 40 ($PM_{2.5}$) monitoring sites classified as 'regional background' (RB), 'urban background' (UB), or 'street' (S)[16,17]. For each monitoring site three two-week-long measurements were available distributed over the seasons and corrected for temporal variation with the use of a reference site[16,17]. A number of geographical exposure determinants were used to predict the spatial variation in NO_2 and $PM_{2.5}$ concentrations at the monitoring sites (Table 1). For each exposure determinant included in the LUR models we estimated the error in the exposure determinant that was introduced by error in the source data (inherent error). Furthermore we estimated the error in each of the exposure determinants resulting from error in the geographical location of monitoring and prediction sites (positional error).

Inherent error in model exposure determinants

Full details of our approach to derive realistic error estimates for all exposure determinants are provided in the Supplemental Material. Briefly, error in the regional contribution of NO_2 or $PM_{2.5}$ at each site (REG) was estimated using the variation in measurement data at regional background sites across three sampling campaigns.~~as the median standard error of the mean inverse distance weighted and season-corrected regional estimate across three sampling campaigns, across all regional background sites~~. Error in the population density (PD) and distance to the nearest road (DTR) was estimated by calculating the standard deviation of the difference in estimates for each site from two independent data sources. Estimates for error in traffic load exposure determinants–traffic load in a 50m buffer (TL50), heavy traffic load in a 25m buffer (HTL 25), heavy traffic load in a 25m to 500m buffer (HTL500), and traffic load on major roads in a 1000m buffer (TML1000)–were taken

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from a study that reported relative standard deviations (RSDs) per road type for estimates of vehicle miles traveled (a quantity very similar to buffer variables used in the ESCAPE LUR models) from the U.S.A: 7.8 % for street sites and urban background sites and 3.0 % for regional background sites[18]. We assumed that very precise source data was available for exposure determinant road length (RL) and had no data available to reject this assumption. This exposure determinant was therefore not included in the Monte Carlo simulation.

Error in the geographical location of monitoring and prediction sites

Geographical location for prediction sites in the Netherlands and Belgium were geocoded In the ESCAPE study using individual building matching techniques based upon cadastral data. The accuracy of cadastral data is high. For example, in the Address Coordinates Netherlands database 93.5% of all coordinates are located at the centroid of the correct building, 6.0% located at the centroid of the correct parcel, and only 0.5% not located in the correct building or parcel[19]. For the simulations we assume that the average geographical location error in residential addresses in the Netherlands and Belgium was 4 meters, based on the average width and depth of a home in NL/BE[20]. We contrast this situation with that where the average error is 30 meters, which has been reported for settings where sub-optimal spatial interpolation techniques have been used[21].

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Monte Carlo simulation

The design of the simulation is described in detail in the Supplemental Material. Linking GIS data to the geographical coordinates is a time-consuming operation, and we therefore restricted the simulated study size to include 200 prediction sites (randomly sampled from residential locations of participants in the PIAMA birth cohort[22]), and 68 (NO_2 model) respectively 34 ($PM_{2.5}$ model) monitoring sites. To avoid introducing unnecessary additional Monte Carlo error, we used a fully deterministic model for the outcome Y (i.e. the sampling variance σ_y^2 was set to 0).

For the true parameters of the exposure-health model we used an arbitrary intercept (β_0) of 1.8, and a slope (β_1) of -5. This slope resembles the percentage decrease in FEV1 in children with a roughly 20 µg/m3 increase in NO_2 or a 5 µg/m3 increase in $PM_{2.5}$ in the PIAMA study[23].

For each simulation, we sampled exposure determinant data contaminated with non-differential measurement error from a multivariate normal distribution based on mean zero (all variables were standardized) and the covariance matrix of the original exposure determinants at monitoring and prediction sites. This matrix was then used in all subsequent simulations to draw multivariate normal errors. We calculated the average β_1 across the simulations. To improve coverage we estimated 95% confidence intervals using a parametric bootstrap.

As a sensitivity analysis, we sampled exposure determinant data setting all off-diagonal values of the covariance matrix to zero (removing covariance between the exposure determinants).Similarly, we conducted analyses using the original covariance matrix of the error in the exposure determinants, and by setting all off-diagonal values to zero (removing covariance between the errors in the exposure determinants).

REG was included in the ESCAPE LUR models to capture regional variability in $PM_{2.5}$ and NO_2. REG is unlikely to change as a result of relatively small positional errors in the estimated geographical

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location of the monitoring and prediction sites, and we therefore only assessed the impact of error in the source information for this determinant.

Within the ESCAPE project all exposure determinants at the prediction sites were constrained to be within the range of values that were observed at the monitoring sites. We applied the same approach in our simulation, but assessed the sensitivity of our results to removing this constraint.

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Results

~~In~~ Table 1 presents an overview of the exposure determinants that were included in the Netherlands/Belgium $PM_{2.5}$ and NO_2 LUR models developed within the ESCAPE project. We report the parameter estimates and the change in R^2 due to removal of the exposure determinant from the regression model (ΔR^2). The overall R^2 was 86.5% for the NO_2 model, and 66.6% for the $PM_{2.5}$ model which is higher than the summed ΔR^2 for each individual exposure determinant because of correlations between exposure determinants. In Tables S1 and S2 we report the error variance that we assigned to exposure determinants in the LUR models and in Figures S1–S8 we show the simulated error distribution of the exposure determinants at the monitoring sites.

Exposure simulation

Boxplots in Figure 2 show the impact on exposure predictions of either inherent error in the source data of the geographical exposure determinants (either adding error to all model exposure determinants simultaneously or adding error to one of the exposure determinants while retaining the original values for the remaining exposure determinants) and of positional error introduced in all exposure determinants simultaneously as a result of error in the recorded geographical location of prediction sites (using either a 4 or 30 meter error radius).

When applied simultaneously, realistic error in the exposure determinants of the NO_2 model resulted in median RSDs of the predicted NO_2 concentrations of 6.6%, 4.1%, and 3.2% at regional background (RB), urban background (UB), and street (S) locations, respectively. Error in NO_2 predictions due to inherent error in exposure determinant sources was primarily due to error in DTR, PD, REG, while error in TL50, HTL25, and HTL500 had only minor impact. An error radius of 4 meter in the geographical location of the monitoring sites resulted in median RSDs of 2.0%, 1.8%, and 1.8%, at RB, UB, and S sites, respectively, while a 30m error radius resulted in much larger mean RSDs of 9.5%, 5.8%, and 10.2%.

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Combined error in exposure determinant sources resulted in median RSDs of predicted $PM_{2.5}$ concentrations of 1.5%, 1.4%, and 1.2% at RB, UB, and S locations, respectively. The error in these predictions was primarily the result of error in REG. Error in traffic on a major road in a 1000m buffer (TML1000) contributed to some (<0.5%) error at S and UB sites, but not at RB sites. Positional error within a 4 meter radius in the geographical location had very little impact on predicted $PM_{2.5}$ concentrations (RSD <0.2%), regardless of site type. Impact of positional error in a 30 meter radius was restricted almost completely to street sites (median RSD 1.7%). In Figures S9 and S10 we show the impact of positional error within a 4m and 30m radius on the variance of the standardized exposure determinants at both monitoring and exposure determinant sites.

Health simulation

For each simulation we calculated as a reference the results from a two-stage analysis where the true (i.e. error-free) exposure determinants were available at both monitoring and prediction sites (first column with estimates in Tables 2 and 3). The results indicate that the slope estimates (β_1) from this analysis are slightly biased downwards (ranging from -4.85 to -4.95), probably due to error in the LUR model parameter estimates. Average β_1 for the $PM_{2.5}$ -health model were generally slightly lower than the average β_1 for the NO_2-health model, reflecting the lower coefficient of determination (R^2 66.6%) of the $PM_{2.5}$ exposure model. Coverage of the parametric bootstrap derived confidence intervals varied around 95% (deviations due to the limited number of simulations).

Compared to the reference scenario, we observed only limited additional bias in slopes for the scenario where we added the same degree of error to exposure determinants at both monitoring and prediction sites. For inherent error (Table 2) mean additional bias was < 0.8% for the NO_2 model and < 1.0% for the $PM_{2.5}$ model. For positional error (Table 3) the mean additional bias was between -0.2% and -0.6% for the NO_2 model and between 0.2% and -1.0% for the $PM_{2.5}$ model. For both pollutants constraining of the exposure determinants had a small but unpredictable (both up- and downwards) impact on the mean additional bias. Mean additional bias increased with increasing

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error in estimated geographical location of the prediction sites (4m vs. 30m). Coverage of 95% confidence intervals was generally unaffected for all settings.

Considerable additional negative bias (compared to the reference scenario) was observed in the scenario where we added error to the exposure determinants at prediction sites, but not at monitoring sites. For inherent error (Table 2) the additional biases were -10.5% and -13.6% for the NO_2 model and -7.3% (twice) for the $PM_{2.5}$ model. For positional error (Table 3) large additional mean bias was observed for the NO_2 model when exposure determinants were not constrained (-80.8% for 4m error and -96.0% for 30m). Average bias was restricted when exposure determinants were constrained (-0.8% (4m) and -9.3% (30m)). For the $PM_{2.5}$ model, mean bias ranged between 0.0% and -6.0%, increased with increasing positional error of the prediction sites (4m vs. 30m) and was restricted when exposure determinants were constrained. Coverage of the 95% confidence intervals changed in parallel to the bias induced in β_1.

Considerable additional positive bias (compared to the reference scenario) was observed in the scenario where we added error to the exposure determinants on the monitoring sites, but not on the exposure determinant sites (mean additional bias ranging from +0.4% to +2.6% for the NO_2 model and from +0% to +5.6% for the $PM_{2.5}$ model). Mean bias increased with increasing positional error of the prediction sites, while constraining of the exposure determinants had minimal impact. Coverage of the 95% confidence intervals changed in parallel to the bias induced in β_1.

Results in Tables S3-S6 indicate that removing the covariance between exposure determinants resulted in stronger bias in all scenarios were exposure determinants were affected by error. Removing the covariance between the errors of the exposure determinants had only negligible impact under all scenarios.

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Discussion

Impact of error in determinants on exposure predictions

Our analysis demonstrates that, perhaps with the exception of the regional contribution of NO2 or PM2.5 at each site ~~regional background~~ (REG), added error in the exposure determinants that were used in our LUR models did not induce large error in exposure predictions. Realistic error in exposure determinant REG had the largest influence on error in predictions of both NO_2 and the $PM_{2.5}$. Based on its large contribution to the coefficient of determination of the LUR models used in this exercise this was expected, and it shows that accurate measurement of this exposure determinant is important. Within the ESCAPE study this was done by conducting three two-week sampling campaigns at 20 sites (10 for $PM_{2.5}$) to estimate the long-term average regional contribution to ambient air pollution levels[3,12]. An approach to reduce the influence of the error in the REG would be to further increase the number of measurements per measurement site to reduce the error in the average. Alternatively, the REG could be better characterized by utilizing additional data to represent regional variation in ambient air pollution such as satellite data or modelled regional background levels from chemical transport models.

In our simulation the impact on exposure predictions of realistic error in model exposure determinants on monitoring and exposure determinant sites was higher for the NO_2 model than for the $PM_{2.5}$ model. As the LUR models primarily captured small scale spatial variability in ambient air pollution, these observations correspond to the notion that spatial variability in NO_2 concentrations, for which local traffic is a primary source, occurs on a smaller scale than spatial variability in $PM_{2.5}$ concentrations, to which many sources contribute in addition to local traffic[24]. This is also reflected in the higher number of exposure determinants of small scale variation that is included in the NO_2 model compared to the $PM_{2.5}$ model.

Impact of error in exposure determinants on bias in health effect estimates

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Using a simulation framework we showed that realistic (non-differential) error in the exposure determinants of the ESCAPE LUR models introduced bias in health effect estimates when there was an imbalance in the degree of error between exposure determinants at the monitoring sites and exposure determinants at the prediction sites.

We explain this observation as follows: error in the exposure determinants of the exposure model results in a wider distribution of the measured exposure determinant values compared to the true exposure determinant values at the monitoring sites. Consequently, parameter estimates for the measured exposure determinants derived from a linear regression model will be biased. When these biased parameter estimates are used on a new set of exposure determinants at the exposure determinant sites that are equally affected by error (have a similar error structure) the resulting predicted exposure distribution will approach the true exposure distribution and health effect estimates will be largely unbiased. However, when exposure determinants at the monitoring sites are not affected by error and exposure determinants at the prediction sites are, parameter estimates for the measured exposure determinants will not be biased, but the exposure distribution predicted for the prediction sites will be wider than the true exposure distribution and health effect estimates will be biased downwards. Furthermore, in the (admittedly unrealistic) situation of exposure determinants at the monitoring sites are affected by error, but exposure determinants at the prediction sites being unaffected, the exposure distribution predicted for the prediction sites will be narrower than the true exposure distribution and health effect estimates will be biased upwards.

Our observation contributes to the realization that one sided investments in improving the quality of exposure determinants at monitoring sites while similar improvements cannot be made at the prediction sites will introduce bias in health effect estimates. An example of such a situation would be the location of the monitoring sites being determined using higher quality information (e.g. using Global Positioning System equipment) and therefore measured with less error than the locations of the prediction sites (e.g. only determined with 'building matching techniques'). In this example bias

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in health effect estimates will be reduced when similar techniques are used on both monitoring and prediction sites.

Results from our simulation are also consistent with patterns that have been observed in studies that assessed the impact of the quality of geocoding techniques on the magnitude of the association between exposure to air pollution and (simulated) health outcomes. In these studies the strength of the relationship between air pollution and disease decreased with decreasing geocoding accuracy[21,25].

Figures S9 and S10 illustrate that in this simulation a similar degree of error in the location of a site had a differential effect on the error in the model exposure determinants between monitoring and prediction sites. This phenomenon occurred because there was a difference in the distribution of site characteristics between monitoring and prediction (e.g. on average more monitoring than prediction sites in an urban area or vice versa) and highlights the importance of the exposure determinants at monitoring sites having the same distribution as the exposure determinants at prediction sites (no misspecification)[26], a situation that is not necessarily reached when monitoring sites are selected to achieve highest contrast in exposure determinants (as was done in ESCAPE and other studies)[1]. A weighting approach (using weights representing exposure determinant distributions from the study population in the LUR development phase) might be a viable approach to correct for this source of bias.

A number of other sources of measurement error in modeled exposure estimates have been described in air pollution epidemiology studies using LUR models[14,27–30]. For example, Basagaña et al. showed that the number of monitoring sites, the number of available exposure determinants for model selection, and the amount of explainable variability in the true exposure had a large impact on the estimated LUR model parameters and assigned air pollution exposure, and consequently substantially attenuated health effect estimates (up to 78% in the worst case scenario)[31]. Alexeeff et

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al demonstrated the impact of model mis-specification, showing that a LUR models with low R-squared sometimes yielded biases ranging from 60% upward bias to 70% downward in the health effect estimates[32]. The degree of bias we report here is much smaller than what has been reported in these two studies, thereby suggesting that error in model exposure determinants is not a major contributor to bias in air pollution epidemiology studies based on LUR models.

Several methods have been developed to correct health effect estimates for the bias and error introduced by the use of a model that does not account for all sources of the 'true' exposure (model mis-specification) or from error in estimating exposure model parameters (see refs[26,29,30] for some examples). However, the bias due to imbalance in error in the model exposure determinants described here cannot be corrected for by these methods.

One limitation of our simulation was a necessarily limited number of iterations (n=200) that was possible in each scenario. Using a *t*-test we compared the distributions of the generated health effect estimates in each scenario (Tables S3 and S4). We observed that, with the exception of the scenario in which 4m positional error was introduced, sufficient statistical power was obtained in all other scenarios.

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In conclusion, our results suggest that modest reductions in bias in estimated effects of LUR modeled air pollutants on health outcomes are to be expected from reducing error in model exposure determinants. To minimize bias in health effect estimates it is important that (errors in) exposure determinants at monitoring sites and at prediction sites have a similar distribution thereby adhering to the assumption of transportability.

Acknowledgments

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Conflict of interest

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The authors declare no potential conflicts of interest.

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Table 1. Exposure determinants included in ESCAPE LUR models for the Netherlands and Belgium.

	NO_2 model		$PM_{2.5}$ model	
Exposure determinant	**β[a] (s.e)**	**ΔR^2 [b]**	**β[a] (s.e)**	**ΔR^2 [b]**
Intercept	-7.80 (4.18)		9.46 (2.65)	
Inverse distance to the nearest road (DTR)	$1.22*10^{1}$ (4.59)	1.3%		
Regional estimate (REG)[c]	1.18 ($2.02*10^{-1}$)	6.4%	$4.25*10^{-1}$ ($1.66*10^{-1}$)	6.1%
Population density[d] in a 5000m buffer (PD)	$2.30*10^{-5}$ ($6.32*10^{-6}$)	2.5%		
Traffic load[e] in a 50m buffer (TL50)	$2.47*10^{-6}$ ($6.65*10^{-7}$)	2.6%		
Road length of all roads in a 1000m buffer (RL1000)	$1.06*10^{-4}$ ($3.30*10^{-5}$)	2.0%		
Heavy traffic load[e] in a 25m buffer (HTL 25)	$9.84*10^{-5}$ ($3.78*10^{-5}$)	1.3%		
Heavy traffic load[e] in a 25m to 500m buffer (HTL500)	$4.47*10^{-7}$ ($1.92*10^{-7}$)	1.0%		
Road length of all major roads in a 50m buffer (MRL50)			$1.37*10^{-2}$ ($2.35*10^{-3}$)	3.1%
Traffic load[e] on major roads in a 1000m buffer (TML1000)			$2.28*10^{-9}$ ($1.04*10^{-9}$)	4.5%
R^2	**86.5%**		**66.6%**	

[a] Coefficient (and standard error) of the exposure determinant included in the original model.
[b] Change in R^2 due to removal of the exposure determinant from the regression model (does not add up to total R^2 due to correlation between the exposure determinants).
[c] Inverse distance weighted regional background concentration based on 10 regional background sites.
[d] Number of inhabitants in a buffer.
[e] Sum of the length of a road segment * the traffic intensity on that road segment for all road segments. in a buffer. Calculated for total traffic and heavy traffic, and for all roads and major.

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Table 2. Impact on ~~bias[a] in~~ β_1[a] and coverage of its bootstrapped confidence intervals[b] of inherent error in exposure determinants at monitoring (Pm) and prediction (Pp) sites of two land use regression models (NO_2 and $PM_{2.5}$). True beta is -5.00[a]

Model	Exposure determinants constrained[c]	No error on P_m, no error on P_p[a,b,d]	Error on P_m, error on P_p[a,b,d]	Error on P_p, no error on P_m[a,b,d]	error on P_m, no error on P_p[a,b,d]
NO_2	yes				
		-4.94 (-5.33, -4.61)	-4.90 (-5.39, -4.45)	-4.42 (-4.84, -3.94)	-5.03 (-5.50, -4.59)
		92.5%	*92.5%*	*44.5%*	*94.5%*
NO_2	no				
		-4.94 (-5.34, -4.56)	-4.93 (-5.37, -4.47)	-4.27 (-4.79, -3.75)	-5.06 (-5.57, -4.61)
		99.5%	*93.0%*	*35.5%*	*97.0%*
$PM_{2.5}$	Yes	-4.94 (-6.13 , -4.03)	-4.89 (-6.06 , -4.05)	-4.58 (-5.83 , -3.71)	-5.11 (-6.28 , -4.19)
		91.5%	*93.0%*	*80.0%*	*94.5%*
$PM_{2.5}$	No				
		-4.92 (-6.07, -4.10)	-4.93 (-6.07, -4.09)	-4.56 (-5.54, -3.75)	-5.14 (-6.42, -4.17)
		89.5%	92.5%	79.5%	95.5%

[a] mean, 5th and 95th percentile of β_1 estimated in 200 simulations. True beta is -5.00. Parameter reflects a realistic estimate in percentage decrease in FEV1 in children for a roughly 5 µg/m3 increase in PM2.5 and a 20 µg/m3 increase in NO2 reported in the PIAMA cohort.
[b] In italic: percentage of 95% confidence intervals of β_1, calculated during each simulation, that contains the true beta.
[c] 'yes': exposure determinants of the land use regression (LUR) model were constrained within the minimum and maximum values that were observed during the monitoring campaign, 'no': exposure determinants were not constrained.
[d] Pm: monitoring sites, P_p: prediction sites.

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Table 3. Impact on ~~bias[a] in~~ β_1[a] and coverage of its bootstrapped confidence intervals[b] of positional error on monitor(P_m) and prediction(P_p) sites of two land use regression models (NO_2 and $PM_{2.5}$).

Model	Positional error[c]	Exposure determinants constrained[d]	No error on P_m, no error on P_p[a,b,e]	Error on P_m, error on P_p[a,b,e]	Error on P_p, no error on P_m[a,b,e]	error on P_m, no error on P_p[a,b,e]
NO_2	4m	Yes	-4.92 (-5.31, -4.54)	-4.92 (-5.30, -4.54)	-4.88 (-5.28, -4.50)	-4.94 (-5.32, -4.57)
			91.0%	*92.5%*	*91.5%*	*93.0%*
NO_2	4m	No	-4.95 (-5.36, -4.60)	-4.94 (-5.36, -4.55)	-0.95 (-3.12, -0.21)	-4.98 (-5.41, -4.57)
			95.5%	*92.0%*	*8.0%*	*95.5%*
NO_2	30m	Yes	-4.92 (-5.31, -4.54)	-4.91 (-5.38, -4.45)	-4.46 (-4.91, -4.00)	-5.02 (-5.49, -4.54)
			91.0%	*92.5%*	*55.0%*	*93.5%*
NO_2	30m	No	-4.95 (-5.36, -4.60)	-4.92 (-5.36, -4.54)	-0.20 (-0.46, 0.01)	-5.02 (-5.46, -4.61)
			95.5%	*93.5%*	*1.5%*	*96.5%*
$PM_{2.5}$	4m	Yes	-4.90 (-6.42 , -3.77)	-4.90 (-6.38 , -3.78)	-4.90 (-6.41 , -3.76)	-4.90 (-6.39 , -3.79)
			91.0%	*90.5%*	*91.5%*	*91.5%*
$PM_{2.5}$	4m	No	-4.85 (-6.38 , -3.80)	-4.85 (-6.41 , -3.83)	-4.84 (-6.37 , -3.80)	-4.85 (-6.42 , -3.83)
			91.5%	*90.5%*	*91.5%*	*92.0%*
$PM_{2.5}$	30m	Yes	-4.85 (-6.42 , -3.70)	-4.83 (-6.56 , -3.62)	-4.57 (-5.96 , -3.43)	-5.10 (-7.06 , -3.84)
			86.0%	*85.5%*	*82.0%*	*93.5%*
$PM_{2.5}$	30m	No	-4.85 (-6.38 , -3.80)	-4.83 (-6.57 , -3.66)	-4.56 (-6.15 , -3.58)	-5.10 (-6.87 , -3.85)
			91.5%	*91.5%*	*80.5%*	*95.5%*

[a] Mean, 5th and 95th percentile of β_1 estimated in 200 simulations. True beta is -5.00. Parameter reflects a realistic estimate in percentage decrease in FEV1 in children for a roughly 5 µg/m3 increase in PM2.5 and a 20 µg/m3 increase in NO2 reported in the PIAMA cohort.

[b] In italic: percentage of 95% confidence intervals of β_1, calculated during each simulation, that contains the true beta.

[c] Error (in meters) in the geographical location of monitoring sites (P_m) and prediction sites (P_p).

[d] 'yes': exposure determinants of the land use regression (LUR) model were constrained within the minimum and maximum values that were observed during the monitoring campaign, 'no': exposure determinants were not constrained.

[e] Pm: monitoring sites, P_p: prediction sites.

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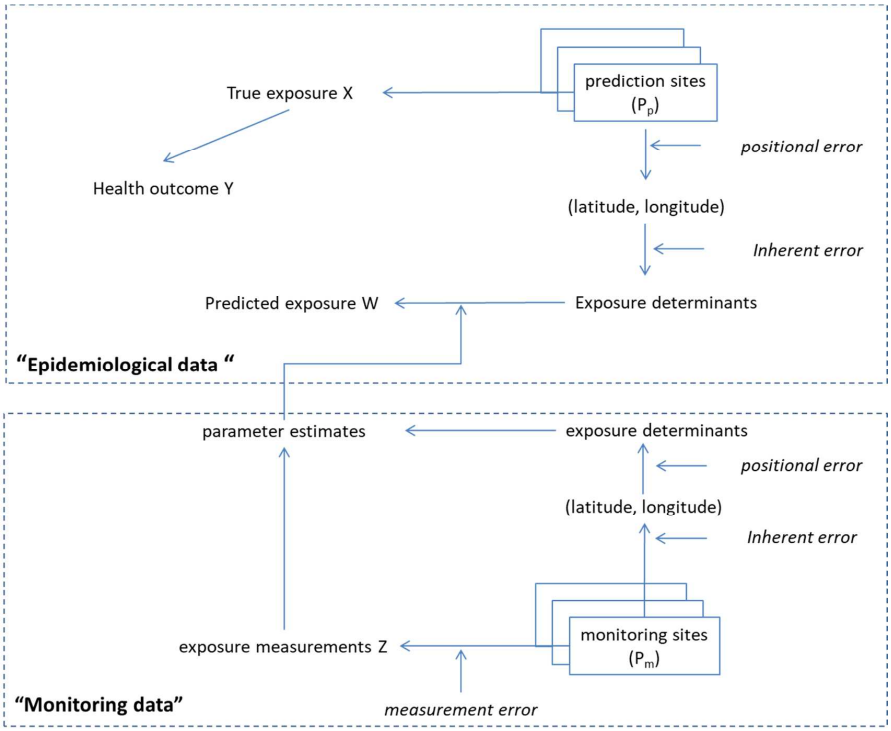

Figure 1.

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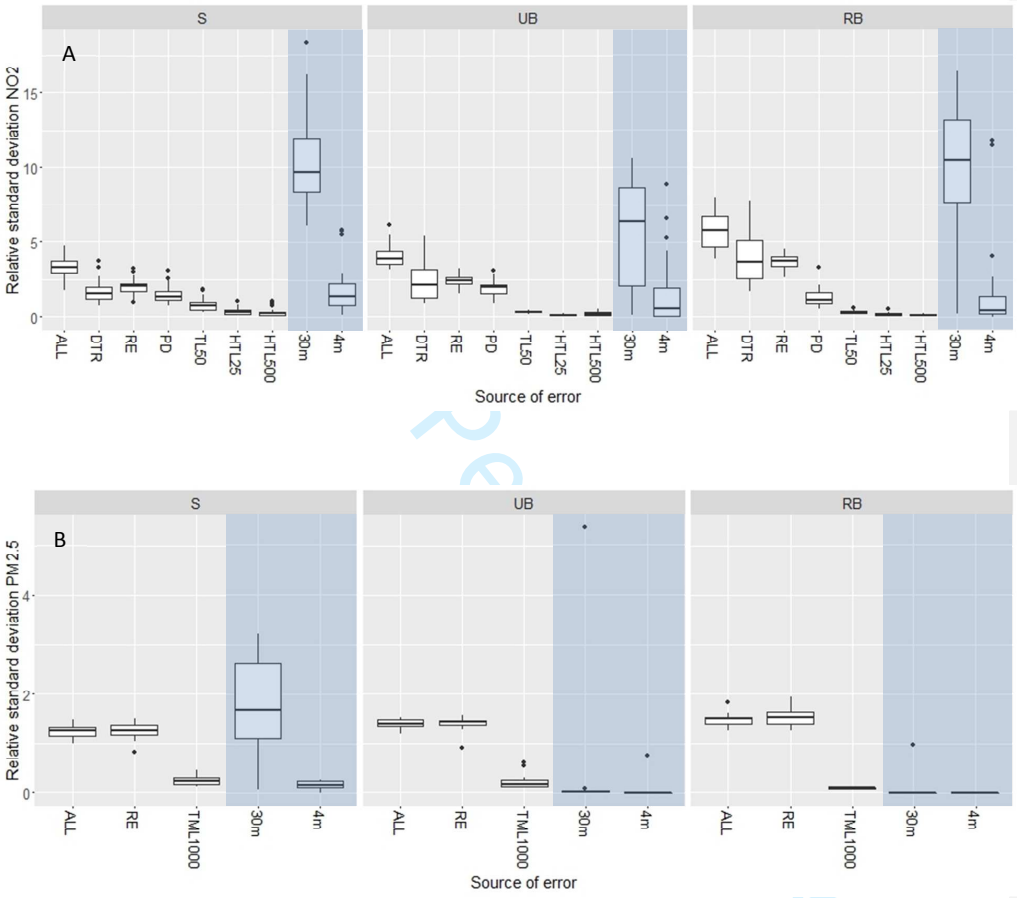
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Figure 2.

Legend Figure 1. Illustration of a two-stage analysis and aspects contributing to error in land use regression model predictions. Inherent error in exposure determinants occurs at both monitoring (P_m) and prediction (P_p) sites due to error in the data sources that were used to derive these exposure determinants. Positional error is the error resulting from error in the exact latitude and longitude of monitoring and prediction sites. Exposure measurements Z (affected by measurement error) are conducted at the monitoring sites and are used to derive parameter coefficients for the exposure determinants to allow prediction of exposure estimates W at the prediction sites. If true exposure X explains x percent of the variability in health outcome Y, the goal of the two stage analysis is for health effect β to approach x.

Legend Figure 2. Impact of realistic error in exposure determinants on NO_2 (plot A) and $PM_{2.5}$ (plot B) exposure levels predicted by the ESCAPE NL/BE LUR model. Relative standard deviation (expressed in percentage and obtained by multiplying the standard deviation by 100 and dividing this product by the average ~~%~~) of the exposure predictions is calculated across 200 simulations for 68 sites for NO_2 and 34 sites for $PM_{2.5}$. Boxplots are ordered by site type (street site (S), urban background site (UB), and regional background site (RB)) and source of error. The blue shaded area contains results for the impact of positional error(30 and 4 meters). The boxplot for 'ALL' represents the error as the result of the combined error in the all exposure determinants (not incorporating positional error) of the LUR model that were included in the simulation. DTR (inverse distance to the nearest road), REG (regional estimate), PD (population density in a 5000m buffer), TL50 (traffic load in a 50m buffer), RL1000 (road length of all roads in a 1000m buffer), HTL25 (heavy traffic load in a 25m buffer), HTL500 (heavy traffic load in a 25m to 500m buffer), MRL50 (road length of all major roads in a 50m buffer), TML1000 (traffic load on major roads in a 1000m buffer).

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Reviewer(s)' Comments to Author:

Reviewer: 1

Comments to the Author
Epidemiologic studies often build regression models to predict exposure to air pollution based on a few determinants (e.g. traffic counts or street configuration). This paper examines the effect of measuring those determinants with error on the results of an analysis linking a health outcome and the air pollution predictions. They do that by performing a simulation study in which they add realistic error to the predictors and observe the effects of such error addition. They conclude that the realistic error on the determinants does not have important consequences on bias, except when the error is different in monitoring and prediction sites.

1) It would be useful to clarify throughout the paper, but especially in the first sentences of pages 12 and 13 and the last sentence of page 14, that the conclusions are valid for the case of adding random error (i.e. non-differential or not related to other variables).

The error that we added in this simulation was non-differential (assignment of error was not dependent on the outcome) and additive (not depended on the value of the predictor). Furthermore, in the simulations where we added error to the source data of the geographical exposure determinants, the error was assigned separately for each individual determinant and therefore not related to error assigned to other variables. In the simulations where we added error to the geographical location of either monitoring sites or prediction sites the resulting error in exposure determinants was potentially correlated.

We assessed the sensitivity of the results of our simulation for the potential correlation in errors by also conducting an analysis in which we forced the covariance in determinant error to be zero. Removing the covariance between the errors of the exposure determinants had only negligible impact under all scenarios.

In the methods section on page 7 we describe the structure of our error models in detail. To highlight that the error was non-differential we added this information at the following places.

Page 7 (methods)

"For each simulation, we sampled exposure determinant data contaminated with non-differential measurement error from a multivariate normal distribution based on mean zero (all variables were standardized) and the covariance matrix of the original exposure determinants at monitoring and prediction sites."

Page 13 (discussion)

"Using a simulation framework we showed that realistic (non-differential) error in the exposure determinants of the ESCAPE LUR models introduced bias in health effect estimates when there was an imbalance in the degree of error between exposure determinants at the monitoring sites and exposure determinants at the prediction sites."

2) Other papers have examined the effects of using different geocoding methods, it would be good to discuss them. For example, in https://www.ncbi.nlm.nih.gov/pubmed/23823697

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they found substantial bias in health effects estimates. Maybe this can be due to the fact that errors in geocoding may be related to other variables (e.g. urban vs rural)?.

Effectively, our study demonstrates the mechanism behind the effect that was observed in the study by Jacquemin et al. In that study the authors observed that increasing uncertainty in geocoding of prediction sites (while using the same exposure model, ie the same error structure at the monitoring sites, in all analyses) leads to attenuation of the health effect estimate. The conclusions of these studies and ours are therefore coherent.

To highlight this, we added the following paragraph (and two references) to the manuscript:

"Results from our simulation are also consistent with patterns that have been observed in studies that assessed the impact of the quality of geocoding techniques on the magnitude of the association between exposure to air pollution and (simulated) health outcomes. In these studies the strength of the relationship between air pollution and disease decreased with decreasing geocoding accuracy."

3) This is just a detail, but are the geocodes assigned at the centroid of the the building, as mentioned in page 6? I guess this can affect the distance to the nearest road.

Geocodes were indeed assigned at the centroid of the buildings and this has an impact on the predicted 'absolute' exposure levels. In this study we show that for an optimal performance of a land use regression model in an epidemiological study it is advisable use the same geocoding structure for the monitoring locations as for the study population locations. Therefore, even though the exact location of the sampling locations might be known, we advise to assign these to the building centroids as well.

4) The sentence in lines marked as 39-45 in page 5 is quite difficult to understand. In particular, it is not clear to me why inverse distance weights are needed.

We have made the following modification to improve the readability of this sentence:

"Briefly, error in the regional contribution of NO_2 or $PM_{2.5}$ at each site (REG) was estimated using the variation in measurement data at regional background sites across three sampling campaigns."

For a more detailed description of the followed approach, we refer to the supplemental material (page 1).

5) Figure 2. What is the relative standard deviation? Relative to the the data without adding errors? This should be defined.

We added the following text to the footnote of Figure 2.

"Relative standard deviation (expressed in percentage and obtained by multiplying the standard deviation by 100 and dividing this product by the average) of the exposure predictions is calculated across 200 simulations for 68 sites for NO_2 and 34 sites for $PM_{2.5}$."

6) Tables 2 and 3. Maybe the "impact on bias" in the table caption could be changed, as the table shows estimates of beta_1, not of bias.

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The table caption was changed following the suggestion of the reviewer.

7) First sentence of page 12. Add “pollution” after “background”?

We changed the wording of this part of the sentence to “the regional contribution of NO2 or PM2.5 at each site”

Reviewer: 2

Comments to the Author
This paper evaluates the impact of selected sources of error in NO2 and PM2.5 exposure models on estimated exposures as well as on regression coefficients linking exposures to health outcomes. The paper is well written and clearly describes the impacts of these errors alone and in combination using Monte Carlo simulations. Conclusions are well supported by study findings.

My only substantive comment is that impacts of errors are estimated using a limited number of iterations (n=200) in Monte Carlo simulations. Typically, simulations of this kind might employ 1000 or even 10000 iterations. This could underestimate the impact of model errors by constraining the range of outputs. At a minimum, this should be noted as a limitation, but it would be preferable to increase the number of iterations.

The reason we limited ourselves to 200 iterations is that the generation of exposure determinants (using ArcGIS software) for each geographical location is very time consuming. Our current simulation framework required 20 days of runtime, extending this to 1000 simulations would require 90 days.

In our analysis the number of iterations has an impact on the precision with which we can estimate the mean health effect (β_1) in each scenario. Had this precision become too low, we would not have had sufficient statistical power to observe meaningful differences between mean health effects across scenarios.

In light of the limited number of iterations that was possible, we avoided introducing unnecessary additional Monte Carlo error by using a fully deterministic model for the outcome Y.

To address the reviewers concern, we conducted a *t*-test (assuming unequal variance) comparing the distribution of estimated β_1 in each scenario with the distribution of β_1 generated in the scenario in which exposure determinants were not affected by error.

The results indicate that our simulation set-up and the number of iterations used provided sufficient statistical power in almost all scenarios. The exception was the scenario in which 4m positional error was introduced and exposure determinants were constrained (both in the NO_2 and in the $PM_{2.5}$ model) and the scenario in which 4m positional error was introduced and exposure determinants were not constrained (in the $PM_{2.5}$ model). Two tables containing these results were added to the supplemental material and the following sentences were added to the manuscript:

“One limitation of our simulation was a necessarily limited number of iterations (n=200) that was possible in each scenario. Using a t-test we compared the distributions of the generated health effect

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estimates in each scenario (Tables S3 and S4). We observed that, with the exception of the scenario in which 4m positional error was introduced, sufficient statistical power was obtained in all other scenarios."

To further demonstrate the impact of additional iterations in our simulation, we compare in the tables below (for a model in which inherent error was introduced in exposure determinants – the only model for which we are able to increase the number of iterations), p-values based on a t-test (rev.Table 1) and estimates (rev.Table 2) for a simulation in which we ran 200 iterations (as reported in the manuscript) and a simulation in which we ran 1000 iterations. As expected, differences between the different scenarios became more significant with an increasing number of iterations.

Rev.Table 1

Model	Number of iterations	Exposure determinants constrained[a]	Error on P_m, error on P_p[b]	Error on P_p, no error on P_m[b]	error on P_m, no error on P_p[b]
NO_2	200	yes	$7.51*10^{-01}$	$8.84*10^{-60}$	$8.38*10^{-05}$
NO_2	1000	yes	$7.63*10^{-02}$	$2.76*10^{-308}$	$9.00*10^{-18}$
NO_2	200	no	$3.60*10^{-01}$	$2.86*10^{-85}$	$1.30*10^{-05}$
NO_2	1000	no	$2.34*10^{-03}$	$<5.0*10^{-324}$	$3.23*10^{-16}$

Rev.Table 2

Model	Number of iterations	Exposure determinants constrained[c]	No error on P_m, no error on P_p[a,b,d]	Error on P_m, error on P_p[a,b,d]	Error on P_p, no error on P_m[a,b,d]	error on P_m, no error on P_p[a,b,d]
NO_2	200	yes	-4.94 (-5.33, -4.61)	-4.90 (-5.39, -4.45)	-4.42 (-4.84, -3.94)	-5.03 (-5.50, -4.59)
NO_2	1000	yes	-4.92 (-5.31, -4.57)	-4.90 (-5.38, -4.47)	-4.39 (-4.85, -3.99)	-5.03 (-5.38, -4.47)
NO_2	200	no	-4.94 (-5.34, -4.56)	-4.93 (-5.37, -4.47)	-4.27 (-4.79, -3.75)	-5.06 (-5.57, -4.61)
NO_2	1000	no	-4.96 (-5.35, -4.60)	-4.93 (-5.43, -4.47)	-4.30 (-4.79, -3.80)	-5.06 (-5.56, -4.59)

Minor comments:
p. 3, line 10, suggest replacing +/- with "approximately"

We made the revision as suggested.

p. 9, first sentence of results is missing a verb i.e. should be "Table 1 presents…"

We made the revision as suggested.

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- the **exact sample size (*n*)** for each experimental group/condition, given as a number, not a range;
- a **description of the sample collection** allowing the reader to understand whether the samples represent **technical or biological replicates** (including how many animals, litters, culture, etc.);
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1. How was the sample size chosen to ensure adequate power to detect a pre-specified effect size? (Give section/paragraph or page #)	Page 15
For animal studies, include a statement about sample size estimate even if no statistical methods were used.	NA
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3. If a method of randomization was used to determine how samples/animals were allocated to experimental groups and processed, describe it. (Give section/paragraph or page #)	NA
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5. For every figure, are statistical tests justified as appropriate?	yes, page 7 of manuscript (methods) and supplemental material pages 4-6.
Do the data meet the assumptions of the tests (e.g., normal distribution)?	yes
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8. Report species, strain, sex and age of animals	NA
9. For experiments involving live vertebrates, include a statement of compliance with ethical regulations and identify the committee(s) approving the experiments.	NA

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