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Estimating risk of emergency room visits for asthma from personal versus fixed site measurements of NO_2

Scott Weichenthal [a,b,*], Patrick Bélisle [c], Eric Lavigne [a], Paul J. Villeneuve [d], Amanda Wheeler [a], Xiaohong Xu [e], Lawrence Joseph [c,f]

[a] Air Health Effects Science Division, Health Canada, Ottawa, Canada
[b] Department of Environmental and Occupational Health, University of Montreal, Montreal, Canada
[c] McGill University Health Center, Division of Clinical Epidemiology, Montreal, Canada
[d] Institute of Health: Science, Technology and Policy, Carleton University, Ottawa, Ontario, Canada
[e] Department of Civil and Environmental Engineering, University of Windsor, Windsor, Canada
[f] McGill University, Department of Epidemiology, Biostatistics and Occupational Health, Montreal, Canada

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ABSTRACT

Background: We examined the impact of data source and exposure measurement error for ambient NO_2 on risk estimates derived from a case-crossover study of emergency room visits for asthma in Windsor, Canada between 2002 and 2009.
Methods: Paired personal and fixed-site NO_2 data were available from an independent population (47 children and 48 adults) in Windsor between 2005 and 2006. We used linear regression to estimate the relationship and measurement error variance induced between fixed site and personal measurements of NO_2, and through a series of simulations, evaluated the potential for a Bayesian model to adjust for this change in scale and measurement error. Finally, we re-analyzed data from the previous case-crossover study adjusting for the estimated change in slope and measurement error.
Results: Correlations between paired NO_2 measurements were weak ($R^2 \leq 0.08$) and slopes were far from unity ($0.0029 \leq \beta \leq 0.30$). Adjusting the previous case-crossover analysis suggested a much stronger association between personal NO_2 (per 1 ppb) (Odds Ratio (OR) = 1.276, 95% Credible Interval (CrI): 1.034, 1.569) and emergency room visits for asthma among children relative to the fixed-site estimate (OR = 1.024, 95% CrI 1.004–1.045).
Conclusions: Our findings suggest that risk estimates based on fixed-site NO_2 concentrations may differ substantially from estimates based on personal exposures if the change in scale and/or measurement error is large. In practice, one must always keep the scale being used in mind when interpreting risk estimates and not assume that coefficients for ambient concentrations reflect risks at the personal level.

1. Introduction

Fixed-site monitors are often used to assign personal exposure levels in epidemiological studies of the health effects of ambient air pollution. While fixed-site monitors offer a cost-effective means of collecting exposure information for large numbers of study participants, exposure measurement error is a recognized limitation of this approach (Zeger et al., 2000). In general, the impact of exposure measurement error variance on risk estimates depends on several factors, including study design, the measurement error structure (classical or Berkson type error), and the extent of the measurement errors (Goldman et al., 2011; Thomas et al., 1993; Rhomberg et al., 2011; Zeger et al., 2000). In air pollution epidemiology, exposure measurement error often contains components of both classical and Berkson type error with the former resulting in bias toward the null and the latter resulting in little or no bias; however, both types of measurement error reduce precision (Armstrong, 1998; Sheppard et al., 2012; Zeger et al., 2000). Here we focus on the classical model, which typically leads to greater bias. Moreover, if fixed-site monitors systematically over or underestimate personal exposures, a scaling factor is required to further adjust model coefficients, since incremental changes in ambient concentrations translate into changes of a different magnitude at the personal level (Schwartz et al., 2007). Unfortunately, paired personal and fixed-site exposure data are rarely available in practice. As a result, it is usually not possible to evaluate the precise relationship between personal and fixed-site

* Corresponding author at: 269 Laurier Ave West, Ottawa, Ontario, Canada K1A 0K9. Fax: +1 613 954 7612.
E-mail address: scott.weichenthal@hc-sc.gc.ca (S. Weichenthal).

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measurements in a given study, and therefore to adjust risk estimates for any change in scale or measurement error. In this study, our aim was to apply a Bayesian measurement error adjustment method that accommodates both a change in scale and measurement error variance to adjust risk estimates from fixed site values to those from personal exposures. This method was applied using paired personal and fixed-site data for ambient nitrogen dioxide (NO_2) in Windsor, Canada (Wheeler et al., 2011) along with data from a previous case-crossover study of ambient NO_2 and asthma emergency room visits in the same location (Lavigne et al., 2012). We first evaluated the method through simulations, and then applied our method to re-estimate the effect of NO_2 on asthma emergency room visits in Windsor, Canada. While the original study estimated the risk of asthma emergency room visits from fixed site NO_2 data, we estimate the effect had personal exposures been used.

2. Methods

2.1. Paired personal and fixed-site NO_2 data

Paired personal and fixed-site NO_2 data were available from participants in a previous panel study conducted in Windsor, Canada (Wheeler et al., 2011). Fixed-site data were collected at participants' homes (i.e. backyard measures) and from 2 separate fixed-site monitors operated by the Canadian National Air Pollution Surveillance (NAPS) program. This analysis focuses primarily on fixed-site NO_2 data collected from NAPS monitors; the average value of the two monitors in Windsor was used in the analyzes. All participants lived within approximately 12 km of the NAPS monitors.

All participants were non-smokers and lived in non-smoking homes, and were recruited through a school-based questionnaire distributed to elementary school children (Dales et al., 2009). Briefly, five consecutive 24-h personal NO_2 samples were collected from 47 asthmatic children (ages 9–12 years) and 48 healthy adults (children's parents) between 2005 and 2006, along with paired fixed-site measurements. All personal and backyard NO_2 measurements were collected using Ogawa passive sampling badges (Ogawa and Company). Personal NO_2 samplers were located in participants' breathing zones using a backpack that was carried (or kept nearby) for the duration of monitoring. NO_2 data from NAPS sites were collected using real-time chemiluminescence. Co-located Ogawa samplers were previously shown to correspond well with NAPs monitors in Windsor (Wheeler et al., 2011).

All adults lived in separate homes and all children lived in separate homes with the exception of two siblings. Age and sex data were not collected for adults in Windsor; children were predominantly female (77%). For simplicity, we treated all observations independently to estimate a single value for the average exposure measurement error; however, we recognize that there may be differences in measurement error between individuals. To verify this approach, we compared between- and within-cluster standard deviations in personal NO_2 exposures, which were approximately equivalent ($\sim$6 ppb), thus supporting our simplified approach. Relationships between personal and fixed-site NO_2 data were estimated separately for children and adults.

For this study, fixed-site NO_2 measurements were treated as imperfect measures of personal exposure. Sampling error in monitoring devices was ignored for both personal and fixed-site monitors as the primary objective was to evaluate the impact of using "measured" fixed-site data in place of "measured" personal data recognizing that both of these values may differ from unknown true values.

2.2. Previous case-crossover study of asthma emergency room visits and NO_2

Lavigne et al. (2012) conducted a case-crossover study of outdoor NO_2 and emergency department visits for asthma in Windsor, Ontario, Canada between April 1, 2002 and March 31, 2009. Briefly, this study included 3738 emergency room visits captured through the National Ambulatory Care Reporting System in Canada (http://www.cihi.ca/CIHI-ext-portal/internet/EN/Home/home/cihi000001). In total, approximately 33% of participants were 2–14 years of age, 40% were 15–39 years of age, and 27% were 40 years of age or older. Referent periods (3–4 per case period) were selected using a time-stratified approach (Janes et al., 2005) with reference days selected on the same day of the week, month, and year as the case. Daily mean concentrations of ambient NO_2 were calculated using fixed-site NAPS monitors in Windsor (the same monitors as above). Odds ratios and 95% confidence intervals describing the relationship between ambient NO_2 and asthma emergency room visits were estimated using conditional logistic regression adjusted for temperature, relative humidity, and daily number of influenza visits. Analyzes were conducted for all seasons combined and separately by age group for the warm (April–September) and cold (October–March) months. The strongest association between ambient NO_2 and emergency department visits was observed in the warm season for children 2–14 years of age (OR = 1.25 per 9 ppb change in NO_2, 95% CI: 1.04, 1.50). The original study was approved by the Health Canada research ethics board.

2.3. Predicting personal NO_2 exposures from fixed-site measures and covariates

Linear regression was used to predict personal NO_2 exposures from fixed-site measures. Separate models were evaluated for the warm (April–September) and cold (October–March) months and for children and adults to evaluate potential differences in the relationships between personal and fixed-site NO_2. Data for ambient temperature, relative humidity, and home indoor sources of NO_2 (i.e. presence/absence of natural gas appliances) were available for all participants from Environment Canada and participant questionnaires, respectively. These factors were evaluated in multivariable models describing the relationship between personal NO_2 exposures and fixed-site measures; however, adjusting for these factors had little impact on the relationship between personal and fixed-site NO_2 measurements. Therefore, these factors were not included in models used to estimate residual standard deviations for measurement error correction. Furthermore, as most studies do not have detailed information on factors such as gas appliance use, adjustments based on these factors may not be generally applicable. Linear regression parameters for personal and fixed-site NO_2 were estimated using STATA version 11 (StataCorp. 2009. College Station, TX: StataCorp LP).

2.4. Change of scale and measurement error correction

We used a modification of the Bayesian conditional independence model of Richardson and Gilks (1993) to adjust for measurement error. The model can be described in three stages: the first stage predicts asthma emergency visits from personal NO_2 exposure data via a conditional logistic regression model, assuming no error in NO_2. As discussed above, we assumed that the NO_2 values were independent both between and within subjects. While at first it may seem intuitive that NO_2 values within subjects may be dependent, these values are centered at individual-specific values, and separated by time. Hence it is likely that the values were uncorrelated within subjects or with correlations low

enough to be ignored in the model. At the second stage, we predict personal NO_2 from fixed site NO_2 data using the paired data from Windsor via linear regression; thus, we estimate both the slope and error variance. Using this method, multiply-imputed personal NO_2 values are available to plug into the first stage of the model, where personal data are in fact not available. By using multiple rather than single imputation, we account for the fact that the data are not available, and thus each "true personal value" is imputed with uncertainty. Since our model is Bayesian, the third stage of the model inserts prior densities for all unknown parameters including parameters from the conditional logistic regression from the first stage, the linear regression parameters at the second stage, and the unknown true mean and variance of personal exposure to NO_2. Non-informative prior densities were used across all parameters so that the data inform the final inferences.

In summary, our main model assumes that fixed site NO_2 data vary randomly about unknown personal measurements according to a normal density with mean and variance derived from the regression equation estimated from paired data for personal and fixed-site measures in Windsor. We thus assumed a classical measurement error model, but with an adjustment for a possible change in slope in addition to random measurement error about the true values. This modifies the classical measurement error model to account for a change in scale, which can be viewed as an extra source of bias. In effect, if the linear regression slope predicting personal exposures from fixed-site values is b, then the ambient coefficient (β_A) relating changes in ambient concentrations to a given health outcome is the product of b and β_P, where β_P is the coefficient for that health outcome estimated from personal data. If the coefficient is from a conditional logistic regression model, then the odds ratio for personal exposure (OR_P) is given by $\exp(\beta_P) = OR_A^{1/b}$, where OR_A is the odds ratio estimated from fixed-site measurements. This procedure was applied to adjust coefficients for the observed slope between personal and fixed-site NO_2 concentrations following an initial adjustment for measurement error variance as described by our three stage model above.

2.5. Model evaluation via simulated data

Before applying Bayesian bias adjustment models to real data from the case-crossover study of ambient NO_2 and emergency room visits for asthma, we first conducted a simulation study to evaluate the properties of our approach using simulated data with known "true" NO_2 exposures and effect estimates. All simulations assumed a sample size of 4000 subjects, to closely match the real Windsor data; NO_2 and asthma data were simulated based on the distribution of NO_2 values measured in Windsor and true odds ratio (OR) values of 1.01, 1.02 and 1.03 per unit change in NO_2 (ppb). All simulations assumed the same data structure as the Windsor asthma study, with four observations per subject: one time point with an emergency room visit for asthma and three times without. Asthma positive time points were selected according to the odds ratio for asthma and the four simulated "true" values for NO_2 for each subject. The true values were selected from a normal density, with mean and variance generated from the personal data gathered in Windsor. Measurement error, including slope and error variance was then added to the NO_2 data using the linear regression parameters described above. In particular, we used a root mean square error (RMSE) equal to 6, approximately centered on the range of values observed, and a slope of 0.1 relating personal to fixed-site NO_2 concentrations, close to the value for children and adults in Windsor during the summer months. Conditional logistic regression models were run to compare OR estimates with and without measurement error, and in the presence of measurement error, with and without Bayesian adjustment for the measurement error. The OR for the effect of NO_2 on emergency room visits for asthma was thus estimated three times for each simulation: once using the "true" NO_2 data without measurement error, which should return an OR close to the true value simulated; a second OR using NO_2 data with measurement error but without adjusting for measurement error variance or slope; and a third applying measurement error correction, including slope (or scale) adjustment. Our main interest was to compare ORs estimated from simulated mis-measured NO_2 data to the known estimate based on simulated "true NO_2 data." Two-hundred data sets were run for each choice of OR, and the 95% credible interval coverage and RMSE were calculated across each set of 200 runs. The 95% credible interval coverage provides the proportion of time simulated 95% credible intervals included the true OR.

2.6. Measurement error correction for previous case-crossover study

Following the simulation study above, a similar procedure was applied using NO_2 and asthma data from the previous case-crossover study in Windsor. This procedure was completed in two steps: the first analysis simply replicated findings from the original study using a Bayesian conditional logistic regression model while the second step adjusted for exposure measurement error via the Bayesian methods described above. Specifically, our adjustments focused on the relationship between ambient NO_2 and emergency department visits for asthma among children (2–14 years) during the summer months as this was the strongest association reported. All simulations and measurement error correction models were conducted using WinBUGS (version 1.4.3, MRC Biostatistics Unit, Cambridge UK).

Table 1
Personal, fixed-site, and backyard NO_2 (ppb) data from Windsor, Canada (2005–2006).

	Personal NO_2			Fixed-site NO_2			Backyard NO_2		
	Mean (SD)	*N*	IQR	Mean (SD)	*N*	IQR	Mean (SD)	*N*	IQR
Adults									
Summer	10.5 (8.2)	208	7.7	15.3 (5.6)	223	6.2	13.9 (14)	219	11
Winter	10.6 (10.7)	225	7.6	24.2 (10.2)	239	12	19.4 (10.6)	228	13
Children									
Summer	7.3 (4.1)	215	4.9	15.3 (4.6)	228	5.6	11.8 (7.5)	222	8.6
Winter	13.0 (7.7)	227	6.4	20.9 (6.2)	232	8.8	20.9 (7.8)	228	12

IQR, interquartile range; SD, standard deviation.

3. Results

3.1. Personal and fixed-site NO_2 measurements

In total, 875 personal, 921 fixed-site, and 897 backyard NO_2 measures were available for Windsor (Table 1). On average, fixed-site NO_2 concentrations were higher than personal NO_2 exposures with the highest values observed during the winter months. Specifically, on average backyard concentrations were 6.24 ppb (95% CI: 5.44, 7.04) higher than personal exposures whereas fixed-site monitors were 8.70 ppb (95% CI: 8.01, 9.40) higher than personal exposures. Backyard measures offered little advantage over typical fixed-site monitors as correlations between personal and both backyard and fixed-site measures were weak for both children and adults during the summer and winter months ($R^2 \leq 0.10$) (Table 2); backyard and fixed-site measures were moderately correlated ($R^2 = 0.35$). Moreover, the magnitude of linear regression slopes describing relationships between personal and backyard/fixed-site NO_2 data among children and adults were weak with values ranging from a maximum of 0.33 (95% CI: 0.20, 0.46) to a minimum of 0.0029 (−0.17, 0.17). A scatter plot of personal and fixed-site NO_2 data for children during the summer months is shown in Fig. 1.

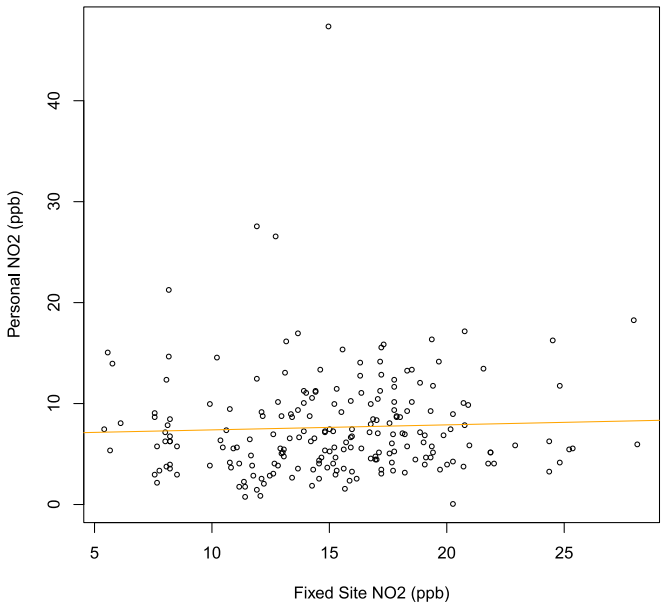

Fig. 1. Scatter plot of personal versus fixed-site NO_2 data for children in Windsor Canada (2005–2006) during the summer.

3.2. Measurement error correction using simulated case-crossover study data

Table 3 presents the coverage and average interval length of 95% credible intervals across the 200 simulations run within each scenario. In the case of no measurement error, coverage of the true value by the 95% credible interval was, as expected, close to the nominal 95% value, with average lengths in the range of 0.007–0.008 (that is, intervals that were accurate to within ±0.0035 to ±0.004, approximately, around the true OR values of 1.01, 1.02, and 1.03). As expected, when measurement error was added, assuming a standard deviation of 6 and a regression slope of 0.1, but the model was not adjusted for measurement error, the coverage dropped to zero. When adjusting for measurement error variance and slope using our Bayesian model, coverage improved to a range of 83–90%, lower than the nominal value, but quite good considering the large degree of measurement error, and the zero coverage prior to adjustment. Further, the credible interval lengths were near identical (about ±0.0035) to those when there was no measurement error. In other words, our model was able to capture most of the information lost through measurement error in terms of reasonable 95% credible interval coverage without increasing interval lengths.

Table 3
Results from the simulated case-crossover study data.

True OR (per 1 ppb NO_2)	Model[a]	95% credible interval coverage	Average length of 95% credible interval
1.01	No ME	0.98	0.0074
1.01	ME unadjusted	0	0.00044
1.01	ME adjusted	0.90	0.0070
1.02	No ME	0.97	0.0074
1.02	ME unadjusted	0	0.00048
1.02	ME adjusted	0.83	0.0069
1.03	No ME	0.97	0.0077
1.03	ME unadjusted	0	0.00052
1.03	ME adjusted	0.84	0.0071

ME, measurement error; All results are averaged across 200 simulated data sets; OR, odds ratio.

[a] ME adjusted models account for measurement error variance and the slope relating personal and fixed-site NO_2 data.

3.3. Bias adjustment for the case-crossover study data

Table 4 presents our re-analysis of data originally presented by Lavigne et al. (2012), focusing on results for children during the summer months. When no error was assumed, we were able to replicate the results presented by Lavigne et al. (2012) using our Bayesian conditional logistic regression model (OR = 1.024, 95% CrI

Table 2
Linear regression slopes relating personal and fixed-site NO_2 for children and adults in Windsor, Canada (2005–2006).

Dependent Variable	Independent variable	Season	Slope	95% CI	RMSE	R^2
Adults						
Personal NO_2	Fixed-site NO_2	Summer (n=236)	0.12	−0.065, 0.31	8.2	0.007
		Winter (n=249)	0.30	0.17, 0.43	10.3	0.08
	Backyard NO_2	Summer (n=233)	0.15	0.085, 0.22	7.8	0.08
		Winter (n=242)	0.33	0.20, 0.46	10.3	0.10
Children						
Personal NO_2	Fixed-site NO_2	Summer (n=187)	0.072	−0.057, 0.20	4.1	0.007
		Winter (n=203)	0.0029	−0.17, 0.17	7.7	0.00
	Backyard NO_2	Summer (n=182)	0.12	0.045, 0.20	4.1	0.05
		Winter (n=199)	0.14	0.0089, 0.28	7.7	0.02

CI, confidence interval; RMSE, root mean square error (equivalent to the SD around the regression line, or regression error).

Table 4
Measurement error and slope correction for previous case-crossover study of emergency room visits for asthma among children in Windsor, Canada (2002–2009).

Measurement error SD	Slope	ME adjusted OR[a]	95% CrI
SD=0	1	1.024	1.004, 1.045
SD=0	0.5	1.049	1.008, 1.093
SD=0	0.1	1.271	1.041, 1.568
SD=5	1	1.030	1.004, 1.057
SD=5	0.5	1.052	1.008, 1.102
SD=5	0.1	1.276	1.034, 1.569

CrI, Credible Interval; ME, measurement error; OR, Odds Ratio; SD, Standard deviation.

[a] per 1 ppb change in NO_2 for emergency room visits for asthma among children (2–14 years) in Windsor between 2002 and 2009. All analyzes are adjusted for temperature, relative humidity, and influenza.

1.004, 1.045 per 1 ppb change in NO_2). Adjusting for various degrees of measurement error appreciably modified our estimates. We provide results for a measurement error standard deviation of 5, but results for other values of the standard deviation were nearly identical. Assuming a measurement error slope of 0.1 (close to the value of 0.072 reported in Table 2 for children during the summer months), the OR describing the relationship between personal NO_2 and emergency department visits for asthma among children is OR=1.276 (95% CrI: 1.034, 1.569) per 1 ppb change in 24 h average personal NO_2. This striking change in the magnitude of association arises from the very small linear regression slope between personal and fixed site NO_2. Given that the observed asthma rate remains the same regardless of how NO_2 is measured, the smaller scale for personal NO_2 requires a larger regression coefficient to predict the same asthma rate. This result is accompanied by a correspondingly larger credible interval, reflecting the change in scale.

4. Discussion

Exposure measurement error is a recognized limitation in air pollution epidemiology and has been discussed in detail (Goldman et al., 2011; Sheppard et al., 2012; Zeger et al., 2000). Recent studies have documented the potential for measurement error to bias risk estimates toward the null for pollutants with high spatial variability (Suh and Zanobetti, 2010; Van Roosbroeck et al., 2008) and previous analyzes of exposure measurement error in time-series studies of mortality suggest that risk estimates based on fixed-site ambient air pollution data are smaller than those estimated from personal measures (Schwartz et al., 2007; Zeger et al., 2000). In this study we examined the potential impact of exposure measurement error for short-term (24-h) exposure to NO_2 on risk estimates derived from a case-crossover analysis using existing data from Windsor, Ontario (Lavigne et al., 2012; Wheeler et al., 2011). In general, extremely weak correlations and slopes were observed between personal and fixed-site NO_2 concentrations among children and adults in Windsor and previous studies also report weak correlations (Linaker et al., 2000; Sarnat et al., 2000; 2006; Van Roosbroeck et al., 2008). For asthmatic children specifically, Linaker et al. (2000) reported no correlation (median Pearson correlation $=-0.02$) between personal and fixed-site NO_2 measures in Southampton, UK. Relative to our findings in Windsor, Van Roosbroeck et al. (2008) reported a stronger correlation ($r=0.35$) and a higher slope (0.42) between personal NO_2 and fixed-site concentrations outside children's schools in the Netherlands; this relationship was still weak, however, and Van Roosbroeck et al. (2008) reported that adjusting for measurement error arising from the use of fixed-site measures appreciably increased risk estimates for the relationship between NO_2 and respiratory symptoms in children. In general, the weak correlation between short-term measures of personal and fixed-site NO_2 observed in Windsor is consistent with existing evidence and suggests that caution is required when using fixed-site monitors to estimate short-term variations in personal NO_2 exposures.

We are unaware of other studies that have used paired personal and fixed-site NO_2 data to examine the impact of exposure measurement error on risk estimates derived from a case-crossover analysis. Therefore, we present the first study to estimate the small slope relating personal and fixed-site measures on NO_2 risk estimates in case-crossover studies, and to adjust for this large error. While in practice this type of adjustment is rarely possible owing to the absence of paired exposure data, this is an important finding as it suggests that risk estimates based on fixed-site NO_2 concentrations may differ substantially from estimates based on personal exposures when the slope relating these two measures is far from one. It is important to note, however, that both coefficients are "correct" in that one estimates asthma risk for ambient NO_2 *concentrations* and one estimates asthma risk for personal NO_2 *exposure*. The difference between the two largely arises from a scaling factor determined by the slope relating personal exposures and fixed-site concentrations. For regulators, the coefficient of interest is likely the coefficient relating ambient concentrations to health risk as governments cannot regulate personal exposures. However, our findings highlight the fact that incremental changes in ambient NO_2 concentrations may not translate into similar changes in personal exposure owing to the weak relationship between personal exposures and fixed-site NO_2 concentrations.

In general, our findings illustrate two important points. First, for slopes far from unity, adjusting for the slope can be as or more important than adjusting for measurement error variance. Second, in the absence of exposure studies relating personal and fixed-site measurements, the slope remains unknown and adjusting for the slope becomes an exercise in sensitivity analysis. Ideally, these analyzes would be based on expert knowledge of the most likely slope values. In the absence of this knowledge, the OR corresponding to personal exposures cannot be estimated.

While this study has several strengths including the availability of a large number of paired NO_2 measurements, it is important to recognize several limitations. First, the data used to estimate exposure measurement errors (and slopes) were not collected from the same population examined in the case-crossover study. As a result, measurement error estimates and slopes between personal and fixed-site NO_2 concentrations may not be representative of actual values during the time period examined in the case-crossover study. Nevertheless, paired exposure data were collected from both children and adults in Windsor during years included in the case-crossover analysis. In particular, paired exposure data were available from asthmatic children in Windsor, a population particularly relevant to the previous case-crossover study of emergency room visits for asthma.

In conclusion, our findings suggest that case-crossover studies relying on fixed-site NO_2 data may underestimate the health risks of short term NO_2 exposures if misinterpreted as the true risk associated with personal NO_2 exposures. This impact is largely determined by slope values relating personal and fixed-site measurements. Further application of these methods to studies in other cities may help clarify the relationship between short-term personal and fixed-site NO_2 concentrations and the associated impact on risk estimates in epidemiological studies.

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