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Air Pollution Exposure Model for Individuals (EMI) in Health Studies: Evaluation for Ambient $PM_{2.5}$ in Central North Carolina

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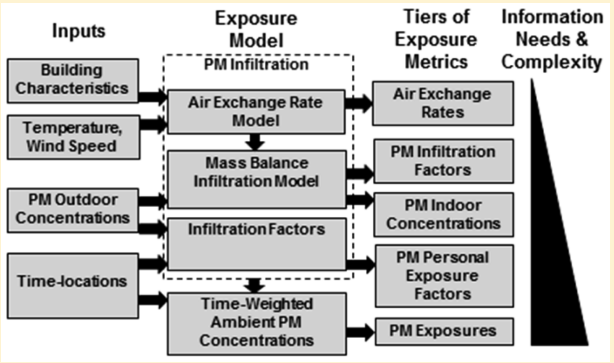
Supporting Information

ABSTRACT: Air pollution health studies of fine particulate matter (diameter ≤2.5 μm, $PM_{2.5}$) often use outdoor concentrations as exposure surrogates. Failure to account for variability of indoor infiltration of ambient $PM_{2.5}$ and time indoors can induce exposure errors. We developed and evaluated an exposure model for individuals (EMI), which predicts five tiers of individual-level exposure metrics for ambient $PM_{2.5}$ using outdoor concentrations, questionnaires, weather, and time-location information. We linked a mechanistic air exchange rate (AER) model to a mass-balance $PM_{2.5}$ infiltration model to predict residential AER (Tier 1), infiltration factors (Tier 2), indoor concentrations (Tier 3), personal exposure factors (Tier 4), and personal exposures (Tier 5) for ambient $PM_{2.5}$. Using cross-validation, individual predictions were compared to 591 daily measurements from 31 homes (Tiers 1−3) and participants (Tiers 4−5) in central North Carolina. Median absolute differences were 39% (0.17 h^{-1}) for Tier 1, 18% (0.10) for Tier 2, 20% (2.0 μg/m^3) for Tier 3, 18% (0.10) for Tier 4, and 20% (1.8 μg/m^3) for Tier 5. The capability of EMI could help reduce the uncertainty of ambient $PM_{2.5}$ exposure metrics used in health studies.



INTRODUCTION

Epidemiologic studies have shown associations between ambient (i.e., outdoor-generated) fine particulate matter ($PM_{2.5}$) and adverse respiratory and cardiovascular effects.[1] Due to cost and participant burden of personal measurements, most of these studies used central-site measurements of $PM_{2.5}$ as a surrogate for exposure to ambient $PM_{2.5}$. However, ambient $PM_{2.5}$ concentrations measured at central-site monitors may not reflect personal exposures to ambient $PM_{2.5}$ due to house-to-house and temporal variations in indoor infiltration (i.e., attenuation) of ambient $PM_{2.5}$, and variation in the time spent in different indoor and outdoor locations.[2,3] These exposure measurement errors can introduce bias and

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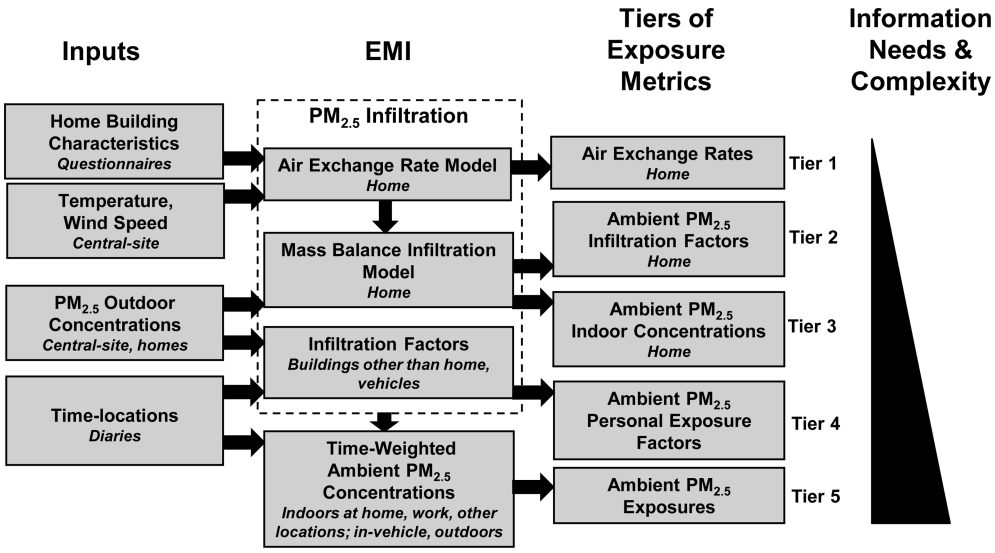

Figure 1. Conceptual model of EMI to predict five tiers of individual-level exposure metrics for ambient $PM_{2.5}$. Tiers 1−3 are related to homes, and Tiers 4−5 are related to personal exposures. Model input needs and complexity increases from Tier 1 to Tier 5.

incorrect confidence intervals in health effect estimates,[2−4] which diminish the power of such studies to establish correct conclusions about the exposure and health effects association. The significance of this issue was highlighted in The National Research Council's Report "Research Priorities for Airborne Particulate Matter: I: Immediate Priorities and a Long-Range Research Portfolio", which recommended the Environmental Protection Agency (EPA) to specifically address measurement error issues in PM health effect studies.[5] To address this recommendation, we developed the Exposure Model for Individuals (EMI) for application in epidemiologic studies.

The scientific basis of exposure assessment in health studies is the development and evaluation of appropriate exposure metrics.[6] The EMI predicts exposure metrics for actual individuals in the study using outdoor concentrations, meteorology, questionnaire information (e.g., building characteristics, occupant behavior related to building operation) and time-location information. This study describes the development and evaluation of five tiers of individual-level exposure metrics for ambient $PM_{2.5}$ (Figure 1), which includes three exposure metrics related to $PM_{2.5}$ infiltration into homes (Tier 1: air exchange rates (AER), Tier 2: infiltration factors, Tier 3: indoor concentrations) and two additional exposure metrics that account for time spent in different indoor and outdoor locations (Tier 4: personal exposure factors, Tier 5: exposures). The importance of these exposure metrics has been demonstrated in epidemiologic studies that applied population-level exposure metrics for Tiers 1 and 5, which accounted for indoor infiltration (Tiers 2−3) and time-locations (Tier 4).[7−10]

The EMI complements population-level exposure models (e.g., SHEDS,[11] APEX[12,13]). Population models predict distributions reflecting exposure variability for demographic groups (e.g., school-age children) rather than for specific individuals by using population-level inputs from other studies (e.g., U.S. Census, Consolidated Human Activity Database).[11] Population exposure models are appropriate for epidemiologic studies using the number of health outcomes experienced by people across a region (e.g., time-series studies). In contrast, EMI predicts exposures for specific individuals in a health study using individual-level input data (e.g., questionnaires,[14] time-locations from diaries or global positioning system devices[15]) from each study participant. Thus, EMI is appropriate for epidemiologic studies with individual-level health outcomes (e.g., panel studies), including studies using personalized exposure and genetic information to determine individual susceptibility (e.g., obesity, pre-existing health conditions) to adverse effects.[6] Also, modeled exposure metrics are needed for panel studies since the AER and infiltration can vary substantially from house-to-house and day-to-day, and since daily measurements of residential AER and indoor air pollutants are often not feasible for health studies due to substantial cost and participant burden.

We use data from the Research Triangle Park Particulate Matter Panel Study (PM Panel Study) to evaluate the five tiers of individual-level exposure metrics for ambient $PM_{2.5}$ predicted by EMI.[16−18] This study provides a unique data set for cross-validation of EMI. The PM Panel Study includes daily central-site, indoor and outdoor residential, and personal measurements of $PM_{2.5}$ and sulfate (tracer of ambient $PM_{2.5}$),[18] residential AER measurements, weather, questionnaires on housing characteristics, and time-location diaries of 31 occupied detached homes and participants for seven consecutive days in each of four consecutive seasons in central North Carolina (NC). These data represent various housing characteristics, occupant behavior, weather conditions, and ambient $PM_{2.5}$ outdoor and indoor concentrations, and personal exposures to ambient $PM_{2.5}$ for the same region of central NC as two cohort health studies: Diabetes and Environment Panel Study (DEPS),[19−21] and Coronary Artery Disease and Environmental Exposure (CADEE). Based on this cross-validation of EMI, we plan to develop multiple tiers of modeled exposures in DEPS and CADEE, and another study in Detroit, Michigan: Near-Road Exposures and Effects of Urban Air Pollutants Study (NEXUS).[22,23]

This manuscript addresses the cross-validation of EMI for use in future health studies. We will first describe the PM Panel Study, and then the EMI and the method used for parameter estimation and model cross-validation.

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MATERIALS AND METHODS

PM Panel Study. The PM Panel Study was a one year investigation measuring personal exposures, and residential and central-site concentrations of PM and gaseous copollutants for participants living in central NC. Previous publications describe the study design, methods, and measurement results.[16−18] Briefly, the study included one cohort of 29 participants with controlled hypertension living in Raleigh, NC and a second cohort of eight participants with implanted cardiac defibrillators living in Chapel Hill, NC. Participants and their homes were monitored for seven consecutive days in each of four consecutive seasons (Summer 2000 to Spring 2001) with all daily 24 h measurements performed from 8 a.m. to 8 a.m. (± 2 h). For $PM_{2.5}$ mass measurements, the Harvard Impactor (HI) operating at 20 L/min was used for residential indoor and outdoor monitoring, and at a central monitoring site in Raleigh. A personal exposure monitor (PEM) operating at 2 L/min was used for personal $PM_{2.5}$ samples. Sulfate measurements (tracer of ambient $PM_{2.5}$)[18] for the HI and PEM filters were determined using X-ray fluorescence. Residential AER were measured using a perfluorocarbon tracer method.[24,25] The reported accuracy (based on known AER), precision (based on replicate measurements), and limits of the PFT-derived AER measurements for occupied homes is estimated to be 20−25%, 5−15%, and 0.2−5.0 h^{-1}, respectively.[14] The precision and minimum quantification limit for the $PM_{2.5}$ mass measurements is reported to be 5% and 0.77 $\mu g\ m^{-3}$ for the HI, respectively, and 8% and 2.13 $\mu g\ m^{-3}$ for the PEM, respectively.[16,18] The precision of the sulfate measurements is estimated to be 8%.[18]

Data were collected on home building characteristics, participant time-activities, and weather. Daily questionnaires were used to collect occupant behavior related to building operation, including opening windows. Participants used time-activity diaries to record their locations and activities at 15 min intervals. The location categories included seven microenvironments (indoors: home, work, other locations; outdoors: home, work, other locations; inside vehicles). Indoor temperatures were measured at 1 min intervals in each home. Outdoor temperatures and wind speeds (2 m elevation) were measured hourly at the central monitoring site.

The PM Panel Study data consisted of 37 participants in 36 homes (two participants resided in the same home). The housing types included 31 detached homes, three trailers, one apartment, and one duplex. In this paper, we evaluated EMI for the 31 detached homes and 31 participants. Insufficient data were available for analysis of the other housing types.

Tiers of Exposure Metrics. We developed five tiers of daily exposure metrics for $PM_{2.5}$ for the 31 study participants and their homes (Figure 1). The five tiers, which have increasing levels of complexity and information needs, are (1) residential air exchange rates, (2) residential infiltration factors, (3) residential indoor concentrations, (4) personal exposure factors, (5) personal exposures. Measured tiers of exposure metrics were determined based on 24 h measurements and daily survey data. Equivalent tiers of exposure metrics were modeled using EMI (Figure 1), and were time-matched to the individual measured exposure metrics.

Measured Tiers of Exposure Metrics. For Tier 1, we used the measured residential AER. For Tier 2, we used sulfate as a tracer of ambient $PM_{2.5}$ to determine residential infiltration factors (indoor attenuation) of ambient $PM_{2.5}$ (F_{inf_home})[18] as defined by

$$F_{inf\_home} = S_{in\_home}/S_{out\_home} \quad (1)$$

where S_{in_home} and S_{out_home} are the measured residential indoor and outdoor sulfate concentrations derived from the HI filters.[18] Other studies have used residential indoor/outdoor sulfate ratios to estimate ambient $PM_{2.5}$ infiltration based on two assumptions: (1) no indoor sources of sulfate, and (2) physical behavior of sulfate is similar to other outdoor $PM_{2.5}$ components.[18,26−29] For the first assumption, studies show that few indoor sources exist,[28,29] and Wallace et al. verified this assumption for the homes in our study.[18] For the second assumption, Sarnat et al. showed that daily residential indoor/outdoor sulfate ratios compared closely to corresponding indoor/outdoor $PM_{2.5}$ ratios, with no significant bias and an absolute relative difference of 14% (mean).[27]

For Tier 3, we determined residential indoor concentrations of ambient $PM_{2.5}$ (C_{in}) using a steady-state solution

$$C_{in} = F_{inf\_home}C_{out\_home} \quad (2)$$

where C_{out_home} is the measured residential outdoor $PM_{2.5}$ concentration.[18] For Tier 4, we determined personal exposure factors of ambient $PM_{2.5}$ (F_{pex}) as defined by[18]

$$F_{pex} = S_{pers}/S_{out\_home} \quad (3)$$

where S_{Pers} is the measured personal sulfate concentration derived from the PEM filters. The F_{pex} is the fraction of ambient $PM_{2.5}$ that an individual is exposed to. The F_{pex} accounts for indoor attenuation of ambient $PM_{2.5}$ and the participant's daily time within different indoor and outdoor locations. For Tier 5, we calculated personal exposures of ambient $PM_{2.5}$ (E) as defined by[18]

$$E = F_{pex}C_{out\_home} \quad (4)$$

Modeled Tiers of Exposure Metrics. For Tier 1, residential AER were predicted from questionnaires and meteorology using two different models (Lawrence Berkeley Laboratory model, LBL, and the extended LBL model, LBLX).[14] These AER models were previously described and evaluated for the 31 study homes[14] (Supporting Information). Briefly, the two AER models include leakage, which is the airflow through unintentional openings in a building envelope (e.g., cracks around windows, doors), using the same algorithm. To calculate the leakage airflow, we used a literature-reported leakage area model that estimates a house-specific normalized leakage from the year built Y_{built} and floor area A_{floor} as described by

$$NL = \exp(\beta_0 + \beta_1 Y_{built} + \beta_2 A_{floor}) \quad (5)$$

where β_0, β_1, and β_2 are the regression parameters.[30] We used literature-reported parameters that were previously estimated from measurements of 70,000 homes (Supporting Information Table S4).[30] The LBLX model also includes natural ventilation, which is the airflow through controlled openings in a building envelope (e.g., open windows). Both models are mechanistic in nature accounting for the physical driving forces of the airflows (i.e., pressure differences across the building envelope from wind and indoor-outdoor temperature differences, the stack effect). Based on our previous evaluation using 642 days of individual model-predicted and measured AER, the median absolute difference was 43% (0.17 h^{-1}) and 40% (0.17 h^{-1}) for the LBL and LBLX models, respectively.[14] We developed separate exposure metrics using these two AER models to

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evaluate the potential benefit of including natural ventilation for future health studies.

For Tier 2, residential $PM_{2.5}$ infiltration factors ($\hat{F}_{inf\_home}$) were predicted with a steady-state mass balance infiltration model described by

$$\hat{F}_{inf\_home} = PAER/(AER + k_r) \quad (6)$$

where P is the penetration coefficient (dimensionless), and k_r is the indoor removal rate of $PM_{2.5}$ (h^{-1}).[18] The estimation of P and k_r is described below.

For Tier 3, residential indoor concentrations of ambient $PM_{2.5}$ ($\hat{C}_{in,home}$ and $\hat{C}_{in,central}$) were predicted from measured outdoor concentrations at home (C_{out_home}) and central-site ($C_{out\_central}$) based on the steady-state equations[18]

$$\hat{C}_{in,home} = \hat{F}_{inf\_home} C_{our\_home} \quad (7)$$

$$\hat{C}_{in,centeral} = \hat{F}_{inf\_home} C_{our\_central} \quad (8)$$

We developed separate residential indoor concentration predictions using C_{out_home} and $C_{out\_central}$ to evaluate the potential benefit of applying outdoor concentrations at individual homes as compared to central-site concentrations for future health studies.

For Tier 4, personal exposure factors of ambient $PM_{2.5}$ were predicted as defined by

$$\hat{F}_{pex} = f_{in\_home}\hat{F}_{inf\_home} + (f_{in\_work} + f_{in\_other})\hat{F}_{inf\_other\_bldg} + f_{in\_vehicle}\hat{F}_{inf\_vehicle} + (f_{out\_home} + f_{out\_work} + f_{out\_other}) \quad (9)$$

where f is the fraction of time spent in the seven microenvironments (indoors and outdoors at home, work, other; inside vehicles), which were determined from each participant's daily time-activity diary. The $\hat{F}_{inf\_other\_bldg}$ and $\hat{F}_{inf\_vehicle}$ are the $PM_{2.5}$ infiltration factors for buildings other than homes and for vehicles, respectively. We set $\hat{F}_{inf\_other\_bldg}$ to 0.64 based on the average of three literature-reported $PM_{2.5}$ infiltration factors for offices, stores, and restaurants.[11] We set $\hat{F}_{inf\_vehicle}$ to 0.44 based on the literature-reported $PM_{2.5}$ infiltration factor for cars.[31]

For Tier 5, we predicted personal exposures to ambient $PM_{2.5}$ from C_{out_home} and $C_{out\_central}$ as defined by[18]

$$\hat{E}_{home} = \hat{F}_{pex} C_{out\_home} \quad (10)$$

$$\hat{E}_{central} = \hat{F}_{pex} C_{out\_central} \quad (11)$$

We developed separate personal exposures predictions using C_{out_home} and $C_{out\_central}$ to evaluate the potential benefit of applying outdoor concentrations at individual homes as compared to central-site concentrations for future health studies.

Parameters Estimation and Cross-Validation of Tiers 2−5. We performed a leave-one-home-out jackknife method to estimate the parameters (P, k_r), for $\hat{F}_{inf\_home}$ and a leave-one-home-out cross-validation for model evaluation of Tiers 2−5.[32−34] We removed all samples from one home at a time (validation sample) and estimated parameters with the samples from the remaining 30 homes (training sample). We then used these estimated parameters to evaluate the models (Tiers 2−5) for the home left out (validation sample). The measured AER were used to estimate parameters. The modeled and measured AER were used to evaluate the models (Tiers 2−5). Each of the 31 homes was used as a validation sample to yield 31 parameter sets. The jackknife estimates were then determined for using in future applications of EMI in health studies (Supporting Information). The method for estimation of P and k_r is described in Supporting Information.

Model Evaluation from Cross-Validation. Based on the cross-validation, we evaluated the model predictions for the five tiers of exposure metrics. We calculated the difference (Δ) and relative difference (ε) as

$$\varepsilon = 100\left(\frac{TIER_{i,pred} - TIER_{i,meas}}{TIER_{i,meas}}\right) \quad (12)$$

$$\Delta = TIER_{i,pred} - TIER_{i,meas} \quad (13)$$

where $TIER_{i,meas}$ and $TIER_{i,pred}$ are the individual measurements and model predictions, respectively, for Tier i where i = 1, 2, 3, 4, and 5. We also calculated the absolute values $|\varepsilon|$ and $|\Delta|$.

To determine the amount of variation explained by the model predictions, we calculated the coefficient of determination (R^2) which was weighted to account for the repeated measurements at the homes.[35] Each model prediction and measurement for a given home is replaced with the average for that home and the correlation coefficient is calculated with the revised values. It should be noted that the modeled values were not generated from a linear regression model. Also, since the focus of this study is model development and evaluation of model uncertainty, Δ and ε (eqs 12 and 13) are emphasized more than R^2, which is not a reliable indicator of model error.[36]

Sensitivity Analysis of Residential Mass Balance Infiltration Model. To determine the sensitivity of the modeled residential infiltration factor ($\hat{F}_{inf\_home}$; eq 6) to changes in the three parameters (AER, k_r,P), we performed a sensitivity analysis of the mass balance infiltration model. Sensitivities indicate the percentage of the parameter uncertainty that is propagated to the model output ($\hat{F}_{inf\_home}$). To compare the sensitivities of the estimated parameters, we calculated relative sensitivities ($RS\hat{F}_{inf\_home}\_AER$, $RS\hat{F}_{inf\_home}\_k_r$, $\hat{F}_{inf\_home}$ $RS\hat{F}_{inf\_home}\_P$) for $\hat{F}_{inf\_home}$ with respect to the parameters (AER, k_r, P), respectively.[37] Partial derivatives were analytically solved to yield the equations

$$RS\hat{F}_{inf\_home}\_AER = \frac{\partial \hat{F}_{inf\_home}}{\partial AER}\left(\frac{AER}{\hat{F}_{inf\_home}}\right) = \frac{k_r}{AER + k_r} \quad (14)$$

$$RS\hat{F}_{inf\_home}\_k_r = \frac{\partial \hat{F}_{inf\_home}}{\partial k_r}\left(\frac{k_r}{\hat{F}_{inf\_home}}\right) = -\frac{k_r}{AER + k_r} \quad (15)$$

$$RS\hat{F}_{inf\_home}\_P = \frac{\partial \hat{F}_{inf\_home}}{\partial P}\left(\frac{P}{\hat{F}_{inf\_home}}\right) = 1 \quad (16)$$

For $RS\hat{F}_{inf\_home}$–AER and $RS\hat{F}_{inf\_home}$–k_r, we calculated $k_r/(AER + k_r)$ with the measured AER and estimated k_r that were used for the leave-one-home-out cross validation of $\hat{F}_{inf\_home}$, as described above. Magnitudes range between 0 and 1, and represent fractional change in model output ($\hat{F}_{inf\_home}$) per unit change in parameter. Positive values indicate a direct relationship, whereas negative values indicate an inverse relationship.

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Table 1. Summary Statistics for Measured Tiers of Exposure Metrics

		measurements (24 h average)[c]									
tier of exposure metrics[a]	number of homes or participants[b]	Sample size	Mean	SD	Min	p5	p25	p50	p75	p95	Max
Tier 1: AER (h^{-1})	31	570	0.67	0.62	0.05	0.20	0.32	0.49	0.74	1.81	4.87
Tier 2: F_{inf_home}	31	570	0.58	0.16	0.17	0.32	0.47	0.58	0.68	0.84	1.04
Tier 3: C_{in} ($\mu g/m^3$)	31	570	11.2	6.0	1.6	3.7	7.1	10.2	13.9	21.9	42.5
Tier 4: F_{pex}	31	570	0.54	0.14	0.16	0.34	0.45	0.53	0.62	0.80	1.03
Tier 5: E ($\mu g/m^3$)	31	570	10.5	5.4	1.7	3.7	6.7	9.6	13.3	20.8	35.6

[a]AER: home air exchange rate, F_{inf_home}: home PM infiltration factor (dimensionless), F_{pex}: personal PM exposure factor (dimensionless), C_{in}: home indoor PM concentration, E: personal PM exposure. [b]AER, F_{inf_home}, C_{in} correspond to homes; F_{pex}, E correspond to participants. [c]SD corresponds to standard deviation, p5−p95 correspond to percentiles.

RESULTS

For the model inputs, summary statistics are provided for the building characteristics of the homes, weather, ambient $PM_{2.5}$ concentrations, and time-location data (Supporting Information Tables S5−S7). The day-to-day differences between the central-site and home-outdoor $PM_{2.5}$ concentrations were mostly small with a median difference of 7.6% (1.3 $\mu g/m^3$). The time-locations show the median daily time spent was highest indoors at home (75%), and lowest outdoors (4%) and inside vehicles (4%).

For the residential infiltration model (Tier 2), the jackknife estimates (95% confidence intervals) for P was 0.84 (0.74−0.93) and for k_r was 0.21 h^{-1} (0.13−0.29 h^{-1}). These estimates are consistent with those previously reported for other homes, which estimated P values from 0.73 to 1.00, and k_r values from 0.27 h^{-1} to 0.99 h^{-1}.[11,29,38]

Summary statistics are provided for the distributions of measured and cross-validated modeled exposure metrics (Table 1; Supporting Information Table S8, Figure S1). We first examined the exposure metrics related to the homes (Tiers 1−3). For Tier 1, the measured and modeled AER had similar medians and range of values, except the upper range was substantially lower for the LBL model, which does not account for natural ventilation. For Tier 2, the measured and modeled (i.e., using all three AER methods: LBL, LBLX, measured) distributions for the residential infiltration factors (F_{inf_home}) were similar, with the upper range slightly lower for the model predictions. For Tier 3, the distributions of the measured and modeled (i.e., using all three AER methods: LBL, LBLX, measured) residential indoor concentrations were similar using either central-site or home-outdoor $PM_{2.5}$ as model inputs.

We then examined the distributions of exposure metrics related to personal exposure (Tiers 4−5). For Tier 4, the measured and modeled distributions for personal exposure factors (F_{pex}) were similar to those for F_{inf_home} but often slightly lower, which could be due to the time spent in other locations (e.g., outdoors) that have lower attenuation of ambient $PM_{2.5}$, as compared to indoors at home. For Tier 5, the measured exposures and the LBLX modeled distributions for $E_{central}$ were similar. Using the LBL model and measured AER, the median and percentiles were slightly lower and higher, respectively, than using the LBLX model.

Based on the cross validation, we compared daily individual model predictions with measurements. Scatter plots (Figure 2: results using LBLX model, Supporting Information Figure S2−S3: all results) and weighted R^2 (Supporting Information Table S9) are shown. The individual differences between model predictions and measurements are shown (Figures 3 and 4, Supporting Information Figures S4−S5). For Tier 1, the LBL and LBLX modeled AER show similar quartiles with the same median $|\Delta|$ of 0.17 h^{-1} and similar median $|\varepsilon|$ of 41% and 39%, respectively. The LBL and LBLX models generally underestimated the AER with median ε of −28% and −18%, respectively. For Tier 2, F_{inf_home} had similar quartiles using the LBL and LBLX models with median $|\varepsilon|$ of 20% and 18%; and median $|\Delta|$ of 0.11 and 0.10, respectively. Using measured AER, F_{inf_home} had a slightly smaller median $|\varepsilon|$ of 14%. Using the LBL and LBLX models generally underestimated F_{inf_home} with median ε of −10% and −7%, respectively. For Tier 3, $C_{in,home}$ and $C_{in,central}$ had similar $|\Delta|$ and $|\varepsilon|$. For Tier 4, F_{pex} had similar quartiles using modeled (LBL, LBLX) and measured AER with median $|\varepsilon|$ of 20%, 18%, 18%; and median $|\Delta|$ of 0.11, 0.10, and 0.10 respectively. Using modeled (LBL, LBLX) and measured AER generally overestimated F_{pex} with median ε of 6%, 9%, and 14%, respectively. For Tier 5, E_{home} and $E_{central}$ had similar $|\Delta|$ and $|\varepsilon|$.

For the relative sensitivities of $\hat{F}_{inf\_home}$, the magnitude of $RS\hat{F}_{inf\_home}$–AER varied between 0.04 and 0.80 with a median of 0.30. Since $RS\hat{F}_{inf\_home}$–k_r is the negative of $RS\hat{F}_{inf\_home}$–AER (eqs 14−16), the $\hat{F}_{inf\_home}$ model is equally sensitive to the parameters AER and k_r. For the parameter P, the $\hat{F}_{inf\_home}$ model is highly sensitive since $RS\hat{F}_{inf\_home}$–P is always 1.

DISCUSSION

Our model evaluation for multiple tiers of exposure metrics has several implications for applying EMI in cohort health studies. First, since $|\varepsilon|$ for $E_{central}$ and $C_{in,central}$ were not substantially different than for E_{home} and $C_{in,home}$, health studies for this central NC geographical location can use central-site $PM_{2.5}$ concentrations as EMI inputs to reduce cost and effort of measuring outdoor $PM_{2.5}$ at homes. This is consistent with data from other cities in various U.S. regions that show $PM_{2.5}$ mass concentrations are spatially homogeneous between monitors within each city, and that point and mobile sources have only limited influence.[1] This spatial homogeneity can be attributed to several factors, including the slow settling velocity that results in long atmospheric lifetimes for $PM_{2.5}$, and the significant fraction of $PM_{2.5}$ that is of secondary origin.[1] Unlike $PM_{2.5}$ components that can have substantial neighborhood-scale spatial variations from nearby sources (e.g., black carbon near major roads with high diesel traffic),[39] our study investigated total $PM_{2.5}$ mass and the homes were not near major sources. This indicates that homes in central NC are not likely to be substantially impacted by the various factors that can affect neighborhood-scale spatial variability of $PM_{2.5}$ mass (e.g., land and building topography, meteorology, population density, proximity to major sources).[1] Second, since $|\varepsilon|$ using measured and modeled AER did not differ substantially, health studies investigating $PM_{2.5}$ in detached homes in central NC

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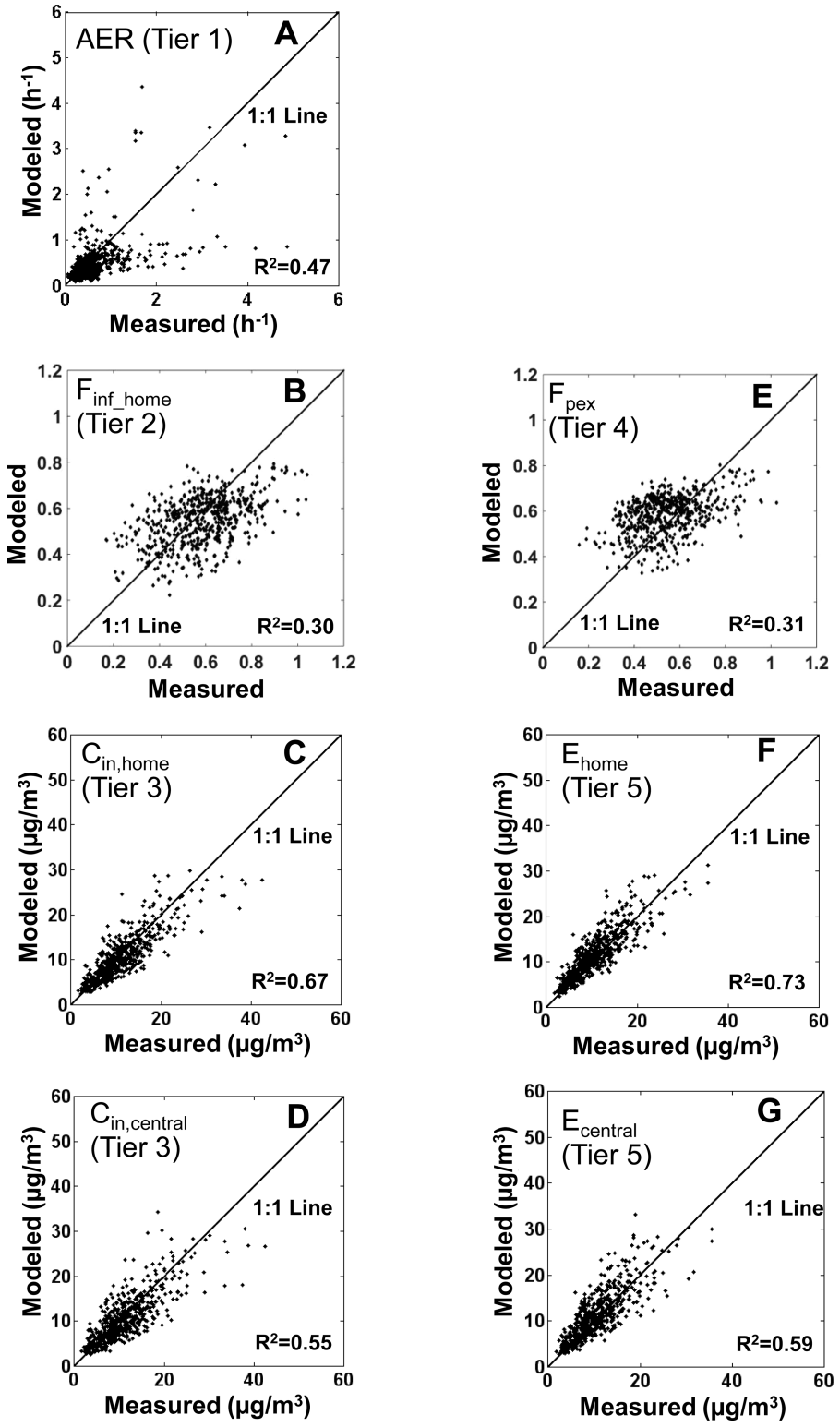

Figure 2. Scatterplots of cross-validated model predictions versus measured exposure metrics. Results are shown for exposure metrics modeled using the LBLX AER model. Tiers 3 and 5 are modeled using measured outdoor $PM_{2.5}$ concentrations at homes (C,F) and at central-site (D,G).

can use modeled AER to reduce cost and participant burden of measuring residential AER. Finally, since the LBL and LBLX modeled AER had similar $|\varepsilon|$, the LBL model can be used in health studies for similar homes in this geographical region to reduce participant burden of collecting window opening information.

Since the AER is an input parameter for $\hat{F}_{inf\_home}$, a propagation of uncertainty analysis can help explain the substantial decrease in the uncertainties between the AER models (LBL, LBLX) and $\hat{F}_{inf\_home}$. For the LBLX model, the median $|\varepsilon|$ decreased by a factor of 0.46 (from 39% for AER to 18% for $\hat{F}_{inf\_home}$). Similarly for the LBL model, the median $|\varepsilon|$ decreased by a factor of 0.49 (from 41% for AER to 20% for

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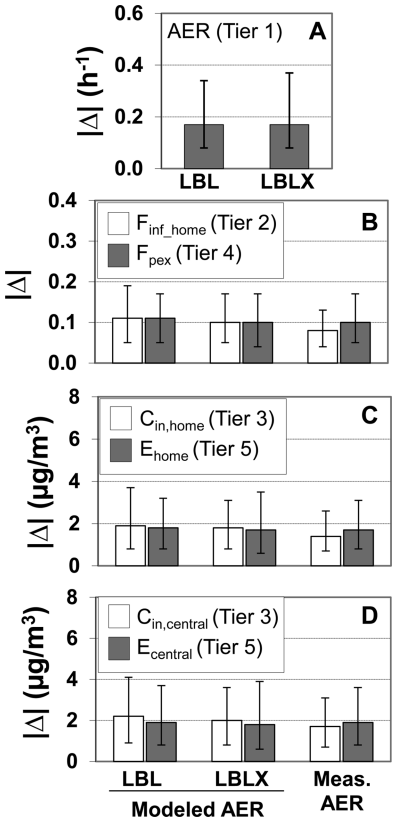

Figure 3. Comparison of differences |Δ| between individual cross-validated model predictions and measurements. Tiers 3 and 5 are modeled using measured outdoor $PM_{2.5}$ concentrations at homes (C) and at central-site (D). For Tier 1, results are separated by AER model (LBL, LBLX). For Tiers 2−5, results are separated by three methods used to set AER in mass balance infiltration model (LBL, LBLX modeled AER; measured AER). Shown are medians with 25th and 75th percentiles.

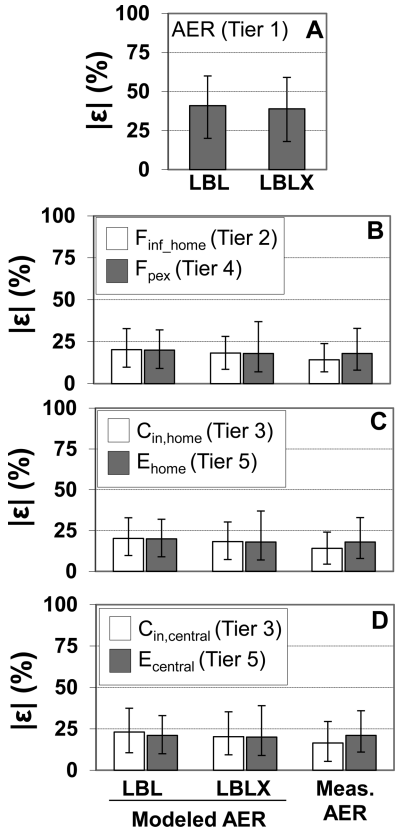

Figure 4. Comparison of relative differences |ε| between individual cross-validated model predictions and measurements. Tiers 3 and 5 are modeled using measured outdoor $PM_{2.5}$ concentrations at homes (C) and at central-site (D). For Tier 1, results are separated by AER model (LBL, LBLX). For Tiers 2−5, results are separated by three methods used to set AER in mass balance infiltration model (LBL, LBLX modeled AER; measured AER). Shown are medians with 25th and 75th percentiles.

$\hat{F}_{inf\_home}$). Based on the sensitivity analysis, the median $RS\hat{F}_{inf\_home}$–AER was 0.30, which indicates that 30% of the AER uncertainty was generally propagated to $\hat{F}_{inf\_home}$ Therefore, a substantial amount of the decrease in the uncertainty between the AER models and $\hat{F}_{inf\_home}$ may be explained by the sensitivity of the AER input parameter for $\hat{F}_{inf\_home}$, which limits the extent to which uncertainty in the AER is propagated through to $\hat{F}_{inf\_home}$.

For the relative sensitivities of $\hat{F}_{inf\_home}$, the large variability of $RS\hat{F}_{inf\_home}$–AER (0.04 and 0.80) is due to substantial variability of the ratio AER/k_r (0.2−25.5) (Supporting Information Figure S6). This variability is driven by the large variations of AER (0.05−4.87 h^{-1}), as compared to the small variations of k_r (0.19−0.23 h^{-1}). Larger $RS\hat{F}_{inf\_home}$–AER occur when AER < k_r (AER/k_r < 1), whereas smaller $RS\hat{F}_{inf\_home}$–AER occur when AER > k_r (AER/k_r > 1).

The EMI has several benefits for exposure assessments in health studies. First, EMI addresses a critical need, identified by Sarnat et al.,[40] for new approaches to define indoor attenuation of ambient pollutants that will likely include cohort- and house-specific estimates. Second, EMI can predict multiple tiers of exposure metrics. Using these various exposure metrics with different levels of complexity in the epidemiologic analysis can help determine the benefit of more sophisticated exposure metrics to optimize the design of health studies. Also, the various tiers can help support health studies with different levels of available information for model inputs. Third, EMI can supplement studies with home-indoor and personal pollutant measurements when exposures have occurred in the past (e.g., to account for time lags in health effects) or when future predictions are needed (e.g., future scenario analysis). Thus, EMI can broaden the range of human health studies feasible, which may have been limited by availability of exposure estimates. Fourth, EMI can be calibrated for health studies with measurements from a subset of participants. For example, the residential AER models were previously calibrated for the NEXUS health study based on measurements from a subset of 24 study homes in two seasons, and then applied for all 213 homes across the three-year study.[23] Finally, the uncertainty of the residential infiltration parameters assessed in this study could be used for uncertainty analysis (e.g., Monte Carlo simulations) of residential indoor concentrations. Also, the uncertainty determined for the individual exposure metrics could be used in epidemiological analysis to assess, and possibly correct, bias in health effect estimates.[41]

Our models can be applied for panel health studies with different cohort sizes and durations of exposures. We plan to apply EMI for two smaller health studies (DEPS, CADEE) with <30 participants and health outcomes across two years,[19−21] a larger health study (NEXUS) with >140 asthmatic children across three years,[22,23] and a long-term exposure study: Multi-Ethnic Study of Atherosclerosis and Air Pollution (MESA Air)

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with >6000 participant homes.[42] We also proposed using EMI for another large cohort study with 32 000 mother-child pairs: Human Early-Life Exposome (HELIX).[43] For large cohort studies, the LBL model can be applied to predict daily house-specific AER from questionnaires or property assessments, and weather. For a large exposure study in central North Carolina, we are applying the LBL model and mass balance infiltration model to predict daily AER for homes in >16 000 census blocks for three counties across one year. The LBLX model can also be applied for large cohorts by collecting typical window opening behavior for different months or seasons from questionnaires. For studies without window opening data, the LBL model may be sufficient since we previously showed that the LBL and LBLX model uncertainties were similar (median errors of 48% and 41% respectively) for days with open windows.[14] Finally, the time spent in different microenvironments, which is used to predict personal exposures, can be estimated from time-location patterns for different day types (e.g., weekday, weekend) collected in questionnaires or determined with a previously developed MicroTrac model[15] based on GPS data from smartphones.

EMI addresses several challenges of personal monitoring. First, EMI can avoid the issue of representativeness (i.e., number of participants and number of days) often associated with personal monitoring studies that rely on small, short-term samples due to cost and participant burden. Second, personal monitoring combines both ambient and nonambient pollutants, whereas EMI predicts exposure metrics for ambient pollutants. The ability of EMI to predict exposures for ambient pollutants is important since the US EPA regulates only ambient pollutants, and health effects from ambient and nonambient $PM_{2.5}$ can be different due to variations in their sources and composition.[44]

We can compare our AER model performance using an alternative approach to determine the parameters (β_0, β_1, and β_2) for the leakage area (Supporting Information Equation S6). Instead of using literature-reported parameters as described in the Materials and Methods, we estimated the three parameters using the AER measurements and the LBLX model based on a previously described method[23] (Supporting Information Equation S12). Using this alternative approach, the median $|\varepsilon|$ for the LBLX model decreased from 40% to 36%, but the median $|\Delta|$ increased from 0.17 h^{-1} to 0.20 h^{-1}, 75th percentile for $|\varepsilon|$ increased from 59% to 64%. Since the overall model performance did not improve with the estimated parameters, we used literature-reported parameters that were previously estimated with a national database of leakage areas for 70,000 homes across 30 states based on blower-door tests.[30] This demonstrates the robustness of the literature-reported leakage area parameters for homes in central NC, which is critical since we are applying EMI for the DEPS and CADEE health studies with participants living in the same geographical location.

We can compare our models with previously reported ones. For Tier 1, we used mechanistic AER models (LBL, LBLX) that do not require building leakage measurements and account for the stack and wind effects. The stack and wind effects can account for a substantial amount of house-to-house and temporal AER variations.[23] Other reported AER models are either mechanistic-based that require on-site leakage measurements,[45] or empirical regression-based models that do not include the stack and wind effects.[30,46] Meng et al. developed a regression model that explained 7% of the AER variation (R^2 = 0.07) based on fitted parameters, which is substantially lower than the R^2 of 0.47 for our LBLX model that used literature-reported parameters (i.e., no model fitting).[46]

For Tier 2, various linear regression models for F_{inf_home} were reported.[46−48] Unlike the mechanistic AER models used by our mass balance infiltration model, these regression models are empirical and do not directly consider stack and wind effects. Allen et al. developed a regression model with some predictors that seem arbitrary (e.g., windows open > half time in past summer to predict $PM_{2.5}$ infiltration in cold seasons).[47] For homes in Winston-Salem, North Carolina, which is the same geographical region as our study in central North Carolina, the reported predictions were cross-validated with indoor/outdoor sulfate measurements (two-week averages), and the root-mean-square error (RMSE) was 0.13.[47] Our LBLX-based $\hat{F}_{inf\_home}$ were cross-validated with indoor/outdoor sulfate measurements of substantially (14 times) higher temporal resolution (24 h averages), and the RMSE of 0.14 was nearly the same. Since the reported R^2 of 0.31 did not account for repeated measurements,[47] the results can be misleading and cannot be reliably compared to our weighted R^2 (0.30 for LBLX-modeled $\hat{F}_{inf\_home}$) which accounts for repeated measurements. The other regression-based models[46,48,49] reported R^2 of 0.49, 0.54, and 0.66, respectively, without accounting for repeated measurements, but no model error. Although R^2 can be interpreted as the fraction of the measured variation explained by the model, R^2 is not a reliable indicator of model error.[36]

In Meng et al., linear regression models were developed for F_{inf_home} and F_{pex}.[46] The AER explained the largest percentage of the F_{inf_home} variation (36%) and the F_{pex} variation (24%), and each of the other predictors (e.g., outdoor temperature, operation of air conditioner) accounted for less than 4%.[46] This highlights the importance of AER to predict F_{inf_home}, F_{pex}, and the subsequent indoor concentrations and personal exposures. Also, the AER has been shown to modify health effect estimates in previous air pollution epidemiology studies.[50] Thus, our mechanistic AER model, which can predict both the temporal and house-to-house variations, is a critical feature of EMI.

For Tier 5, Wu et al. predicted annual average personal exposures to ambient $PM_{2.5}$ based on outdoor concentrations and time-spent in multiple microenvironments (e.g., indoors at home, in-vehicle, outdoors), and they used a mass balance infiltration model for homes.[51] An annual average AER was estimated based on two predictors (house type, cooking stove type), and in-vehicle concentrations were set to constant literature-reported values based on the local traffic density. The exposure model did not consider temporal variations, and no model evaluation was reported. Koenig et al. predicted daily average exposures based on outdoor concentrations and time-spent in two microenvironments (indoors and outdoors) and used a regression-based infiltration model for homes, but no exposure model evaluation was reported.[49] We predicted and evaluated daily average exposures based on concentrations and time-spent in four microenvironments (indoors at home, other buildings, in-vehicle; outdoors) and used a mass balance infiltration model for homes based on a mechanistic AER model, and used infiltration factors for nonresidential buildings and vehicles.

Our study has important and novel features. First, we developed five tiers of modeled exposure metrics and evaluated the model uncertainty of each tier. Previous studies developed models for only one tier (e.g., F_{inf_home})[47] and calculated R^2 values without assessing the model uncertainty, as described above.[46,48] The model uncertainty can be used to help improve

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the accuracy of the health effect estimates.[41] Also, our models are mechanistic, whereas other reported models were empirical (i.e., regression-based).[46−49] Therefore, our models may be more accurate for extrapolation to other homes and weather conditions.

The inputs needed for EMI are relatively accessible, which should support the application of EMI for a broad range of health studies. Electronic files are available for house-specific building characteristics from public property assessment or real-estate databases, and for local airport temperatures and wind speed histories from weather databases. Time spent in different indoor and outdoor locations can be determined from diaries. Alternatively, global positioning system (GPS) devices (e.g., data loggers, smartphones) can be used. We previously developed and evaluated a GPS-based classification model, called MicroTrac, to estimate time-of-day and duration spent in eight locations (indoors and outdoors at home, work, school; inside vehicles; other locations) from GPS data. MicroTrac correctly classified the location for 99.5% of the daily time spent by the participants.[15]

Most air pollution health studies use outdoor concentrations as an exposure surrogate, which can impact health effect estimates. The exposure to ambient $PM_{2.5}$ is the product of outdoor concentration multiplied by an indoor attenuation factor, which depends on the time spent and infiltration factor for different indoor locations. Since people spend more time indoors than outdoors,[52] the infiltration factor is a substantial component of indoor attenuation. In our study, the measured indoor attenuation factor (F_{pex}) was substantial (5th and 95th percentiles of 0.34 and 0.80). When outdoor concentrations are used as exposure surrogates, the health effect estimate is reduced (i.e., biased toward the null) since the effect estimate is the product of the toxicity (i.e., true health effect) and indoor attenuation factor.[2,3] Using exposure instead of outdoor concentration in health studies can improve health effect estimates, but the potential impact depends on various factors (e.g., study design).[40,49,50,53] Ebelt et al. found that for several health outcomes, using ambient $PM_{2.5}$ exposures resulted in significant associations with larger effect estimates and smaller confidence intervals than using outdoor $PM_{2.5}$ concentrations, which were not significant.[26]

One limitation of this study is that modeled exposure metrics for Tiers 1−3 were evaluated for homes in central North Carolina. The uncertainty of the exposure metrics for homes in other geographical regions with different weather and housing stock will need to be evaluated. Since the AER and F_{inf_home} models are mechanistic, we expect similar results in other regions. We plan to further evaluate the exposure metrics in other locations with different housing stock.[38,54] In this study, we evaluated the models with data from the RTP Panel Study data since we are planning our initial model application for DEPS and CADEE health studies with participants also living in central North Carolina in detached homes.[19−21]

Another limitation is that the mass balance F_{inf_home} model, which consists of three parameters (AER, P, k_r), accounts for house-to-house and temporal variability of AER, but not for P and k_r. P depends on the particle size distribution and characteristics of building envelope openings, while k_r depends on surface-to-volume ratio, operation of heating, ventilation, and cooling (HVAC) systems, and particle size distributions. Thus, these parameters could vary across homes, season, and geographical locations. The 95% confidence intervals for P (0.74−0.93) and k_r (0.13−0.29 h^{-1}) were reasonably small. This suggests that the house-to-house variations of P and k_r were small. Furthermore, our estimates for P and k_r are consistent with previously reported estimates for homes in other geographical regions with different housing stock.[29,38,55]

This study demonstrates the ability to predict multiple tiers of individual-level $PM_{2.5}$ exposure metrics with different levels of complexity and information needs, and for detached homes and participants living in central North Carolina. To improve exposure assessments, EMI accounts for (1) daily house-specific infiltration of ambient $PM_{2.5}$ based on a mechanistic AER model linked to a mass balance infiltration model, and (2) time spent in different indoor and outdoor locations. The application of EMI can help improve the accuracy of risk estimates in health studies that currently rely on central-site monitoring for exposure surrogates.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.est.5b02765.

Six figures and nine tables (PDF)

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Notes

The authors declare no competing financial interest.

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