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ORIGINAL ARTICLE

Spatiotemporally resolved air exchange rate as a modifier of acute air pollution-related morbidity in Atlanta

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Epidemiological studies frequently use central site concentrations as surrogates of exposure to air pollutants. Variability in air pollutant infiltration due to differential air exchange rates (AERs) is potentially a major factor affecting the relationship between central site concentrations and actual exposure, and may thus influence observed health risk estimates. In this analysis, we examined AER as an effect modifier of associations between several urban air pollutants and corresponding emergency department (ED) visits for asthma and wheeze during a 4-year study period (January 1999–December 2002) for a 186 ZIP code area in metro Atlanta. We found positive associations for the interaction between AER and pollution on asthma ED visits for both carbon monoxide (CO) and nitrogen oxides (NOx), indicating significant or near-significant effect modification by AER on the pollutant risk-ratio estimates. In contrast, the interaction term between particulate matter $(PM)_{2.5}$ and AER on asthma ED visits was negative and significant. However, alternative distributional tertile analyses showed $PM_{2.5}$ and AER epidemiological model results to be similar to those found for NOx and CO (namely, increasing risk ratios (RRs) with increasing AERs when ambient $PM_{2.5}$ concentrations were below the highest tertile of their distribution). Despite the fact that ozone (O_3) was a strong independent predictor of asthma ED visits in our main analysis, we found no O_3–AER effect modification. To our knowledge, our findings for CO, NOx, and $PM_{2.5}$ are the first to provide an indication of short-term (i.e., daily) effect modification of multiple air pollution-related risk associations with daily changes in AER. Although limited to one outcome category in a single large urban locale, the findings suggest that the use of relatively simple and easy-to-derive AER surrogates may reflect intraurban differences in short-term exposures to pollutants of ambient origin.

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INTRODUCTION

Previous air-pollution exposure panel studies have investigated the relationships between ambient concentrations and personal exposures with the goal of validating the use of ambient concentrations as surrogates of population exposures.[1–4] Findings from these studies suggest that the fraction of ambient pollution penetrating and remaining airborne indoors (i.e., infiltration factor) can vary considerably by home and pollutant. Estimates of infiltration for fine particulate matter ($PM_{2.5}$), for example, have been shown to range from ~0.3 to 1.0.[5] Results from the RIOPA study of over 250 measurements in New Jersey, Texas, and California showed that, on an average, ~60% of indoor $PM_{2.5}$ levels comprised $PM_{2.5}$ that infiltrated from outdoors.[3,6] These findings are noteworthy as most individuals spend the majority (~90%) of their time indoors and, consequently, exposures to ambient air pollutants occur for many people while indoors.[7] Understanding the infiltration characteristics of ambient pollutants, therefore, is a necessary step for accurately assessing personal exposures to ambient pollutants.

Studies conducted under controlled conditions highlight the importance of home ventilation as a central determinant of the fraction of pollution infiltrating indoors.[8–11] Ventilation is commonly expressed as the air exchange rate (AER), or the number of times an indoor air volume is replaced with outdoor air within an hour, and is related to several factors including building envelope construction, building age, and specific meteorological conditions.[12–14] Previous indoor and personal exposure assessment panel studies have observed considerable seasonal, between-home, and between-city variability in residential pollutant infiltration,[3,15–17] likely as a result of differences in home ventilation, or AER, across the homes within each panel.

Variability in home ventilation and pollutant infiltration patterns across a locale may contribute to intraurban exposure variability, and thus have considerable implications for epidemiological studies that use ambient monitors as surrogates of personal exposures. For studies of acute health effects, for example, day-to-day or seasonal differences in the fractional contribution of ambient concentrations to personal exposures may lead to increased exposure error in studies that use ambient monitoring sites as surrogate for exposure. Evidence of error can be seen in inflated SE estimates, reduced model power, or biased estimates of risk, depending on the distribution of this component of exposure variability.[18,19] Similarly, in chronic epidemiology, the use of ambient monitor surrogates may introduce bias into the observed risk estimates if the average exposure–surrogate relationship varies by city. Several epidemiological studies that

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have modeled pollutant spatial heterogeneity have demonstrated the importance of characterizing sources of long-term intraurban exposure variability.[20–22] In some of these analyses, the use of spatially resolved exposure estimates resulted in improved analytical power over the use of a single ambient monitor, attributed to a reduction in exposure misclassification.

To date, only a few studies have examined whether variability in residential ventilation conditions may modify observed acute air pollution-mediated health risk.[6,23–25] In a meta-analysis examining ozone (O_3) exposures and daily mortality over 27 cities, for example, we found a modest inverse relationship between health effect estimates and city-specific air-conditioning prevalence, a surrogate of ventilation.[15,25] Differences in residential AER within a city may be comparable to those between cities, and may thus be equally or more important to consider as a source of exposure variability in single-city epidemiological studies. For acute single-city studies (e.g., time series studies without intraurban characterization), temporal variations in AER, driven primarily by changes in several meteorological factors that affect indoor–outdoor air mass movement, adds further complexity to AER as a source of exposure variability. To examine these issues, we estimated spatiotemporal variability in residential AER within the metropolitan Atlanta area with the goal of testing the hypothesis that geographical and temporal sources of exposure variability explain heterogeneity in estimated epidemiological associations between air pollution and acute asthma emergency department (ED) visits.

METHODS

We examined associations between several urban air pollutants and corresponding ED visits for asthma and wheeze (''asthma''; International Classification of Diseases 9th revision codes: 493, 786.07) during a 4-year study period (January 1999–December 2002) for a 186 ZIP code area in metro Atlanta. For this analysis, we selected asthma visits exclusively, as associations between several pollutants and this outcome category have been previously shown to exhibit robustly positive and significant epidemiological associations in Atlanta.[26,27] As such, these models were optimal for an initial assessment of potential effect measure modification.

The pollutants of interest were carbon monoxide (CO) and nitrogen oxides (NOx), which we believe are primarily surrogates of local, traffic pollutant sources in Atlanta; O_3, a regional pollutant with typically elevated annual concentrations in the southeast; and fine $PM_{2.5}$, which in Atlanta comprises a mixture of both regional pollutants (i.e., sulfate) as well as local source contributions (i.e., elemental carbon). A spatial surface of daily ambient pollutant concentrations for the geographical study domain was generated using a hybrid modeling approach that fused spatially interpolated background pollutant concentrations and the local-scale air quality model AERMOD output for the 186 ZIP code centroids. AERMOD is a Gaussian plume dispersion model that utilizes information on local emission sources (from the 2002 National Emissions Inventory) and local meteorological conditions (from the Atlanta Hartsfield International Airport and ambient monitoring sites) to estimate spatially resolved daily pollutant concentrations. Thus, for every day during the time series, we generated a pollutant estimate for each ZIP code centroid, used in the health effect models as the exposure metric for subjects living within the ZIP code. For Atlanta, we found that output from this model was more representative of pollutant spatial distributions observed from the multisite network than stationary ambient monitoring alone while providing complete coverage for the modeling domain. Details of this modeling approach and comparisons with alternative methods for assigning population exposures for Atlanta are presented in a companion paper.[28]

Estimating AER

For this analysis, we used a relatively simple AER estimation technique based on publicly accessible data (e.g., Census records, meteorological station measurements), which could increase its use broadly in epidemiological settings as compared with more time- and field-intensive approaches. Specifically, we modified a method derived from surveys assessing US building ventilation and leakage characteristics.[12,29,30] This method is based on empirical relationships between direct and indirect predictors of AER collected from field surveys, and includes parameters that can vary spatially and temporally across a geographical area.[12,14,15,31–34] Spatially varying AER predictors that do not exhibit daily changes for a given home include the year a structure was built, as well as its size.[12,33] Newer homes are generally more tightly sealed with lower AERs because of modern methods for constructing and sealing building envelopes.[13,30] Similarly, larger houses typically have higher AERs compared with smaller houses, as they contain a greater surface area for leaks to develop.[12] A second component of AER consists of factors that exhibit variation over time. These include opening and closing windows and ambient indoor temperature gradients,[34,35] which induce movement across building envelopes via the ''stack effect'' and wind speed.[36]

Spatially, we estimated AERs at the ZIP code level to correspond to the spatial resolution of the ED visit data. For the 186 ZIP codes in the Atlanta study area, we first estimated mean ''normalized leakage (NL) area'' for homes. NL is a unitless value that describes leakage area per exposed envelope area for different building types. Most single-family homes have NL values between 0.2 and 2.0.[12] We used empirically derived regression equations to estimate the NL values in the study domain.[12] These equations are based on relationships between home size (in m^2) and age (in year it was built), and differ according to whether a residence is classified as either a conventional or low income home and expressed as:

$$\text{Normalized leakage for low income homes} = e^{11.1+(-0.0537\times\text{median year built})+(-0.0418\times m^2)} \quad (1)$$

$$\text{Normalized leakage for conventional homes} = e^{20.7+(-0.0107\times\text{median year built})+(-0.0022\times m^2)} \quad (2)$$

The weighted contribution of Eqs. (1) and (2) to total ZIP code NL was based on the fraction of low income residences within a given ZIP code, using 1999 census data on median household incomes. Households with a 1999 median household income less than one-half the median (median: $41,994) were classified as low income.[37] Information for ''median year built'' by ZIP code was also obtained from 1999 census data.

Median home size by ZIP code is not published in the US census. To address the limitation, we used data from the 2004 American Housing Survey for metropolitan Atlanta pertaining to the distribution of ZIP code-resolved median rooms per residence, along with empirical values for mean area per room to estimate median household area by ZIP code.[38] For residences with fewer than three rooms, interpolated values were estimated using linear regression.

Predictors of AER that may vary temporally include indoor–outdoor temperature differences, which can induce infiltration via stack effect air movement and wind speed.[39] After estimating NL, we estimated daily AERs by ZIP code as:[12]

$$\text{AER} = \frac{\text{NL}}{1000\times H}\left[\frac{2.5}{H}\right]^{0.3} S \quad (3)$$

where NL is the normalized leakage values estimated using Eqs. (1) and (2), H is building height (in m). For floor areas $> 92\ m^2$,

H was estimated at 3 m, as has been the convention used in other published analyses using this algorithm.[30] For these models, "S" is an infiltration rate defined as function of various physical factors:

$$S = \sqrt{f_s^2 \times (T_{in} - T_{out}) + f_w^2 \times u^2} \quad (4)$$

where "T_{in}" is an assumed constant indoor temp of 290 K; "T_{out}" is a mean daily ambient temperature reading obtained from Hartsfield-Jackson Airport (in K); "u" is the mean 24-h wind speed (in m/s), also obtained from Hartsfield-Jackson Airport; "f_s" is a stack coefficient estimated as:

$$\sqrt{\frac{1 + \frac{R_{fac}}{2}}{3} \times \left(\frac{1 - X_{fac}^2}{(2 - R_{fac}^2)}\right)^{\frac{3}{2}} \times \text{grav} \times \frac{H}{T_{ref}}} \quad (5)$$

where "R_{fac}" is the fraction of total leakage from floors and ceilings and assumed to be 0.5 for these analyses; "X_{fac}" is the difference between the leakage from a ceiling compared with that from a floor and assumed to be 0.25; "grav" is the earth's gravitational force = 9.8 m/s^2; and "T_{ref}"is a reference temperature of 298 K; and "f_w" is a wind coefficient estimated as:

$$C_{fac} \times (1 - R_{fac})^{1/3} \times A_{fac} \times \left(\frac{H}{10}\right)^{B_{fac}} \quad (6)$$

where "C_{fac}" is a parameter developed by the Lawrence Berkeley National Laboratory related to wind shielding from obstructions around a home. Values for C_{fac} range from 0.11 for homes with large obstructions around its perimeter to 0.34 for residences with no surrounding obstructions. Here, we assumed a C_{fac} value of 0.19. A_{fac} and B_{fac} represent the geophysical terrain around a residence. For the current analyses, we assumed a terrain consistent with urban, industrial, or forest areas, and A_{fac} and B_{fac} values of 0.67 and 0.25, respectively.

Twenty-four hour average daily wind speed measurements and ambient temperatures were obtained from a meteorological station located at Hartsfield-Jackson airport and applied across all study homes. Therefore, the temporal variability across ZIP codes in their respective daily AER estimates (i.e., expressed as ZIP code-specific coefficients of variation (CVs)) are identical. Moreover, our use of this simplifying assumption likely resulted in lower spatiotemporal variability in the data than that truly exists, where spatial changes in temperature and true wind speed on individual homes is undoubtedly more variable.

Health Effect Analyses

Epidemiological analyses of the ED data were conducted using a spatially resolved time series approach. The association between daily measures of air pollution and daily counts of asthma ED visits in each ZIP code was modeled using Poisson generalized linear models.

$$\begin{aligned}\log(E(Y_{kt})) = {} & \alpha + \beta pollution_{kt} + \sum_k \lambda_k ZIP_{kt} + \sum_m \lambda_m DOW_{kt} \\ & + \sum_n \nu_n hospital_{nt} + g(\gamma_1, \ldots, \gamma_N\ time_t) \\ & + \sum_o \xi_o l0temp_{ot} + \eta_1 dewpt_t + \eta_2 dewpt_t^2 + \eta_3 dewpt_t^3 \\ & + \delta_1 temp_t + \delta_2 temp_t^2 + \delta_3 temp_t^3 + \gamma_1 \text{spring} \\ & + \gamma_2 \text{summer} + \gamma_3 \text{autumn}\end{aligned} \quad (7)$$

where Y_{kt} is the count of asthma-related ED visits in ZIP code k on day t. For each pollutant (*pollution*), a 3-day moving average (of 0-, 1-, and 2-day lags) was used as the *a priori* lag structure. Each model included the daily, modeled ZIP code-specific pollutant concentrations derived using the hybrid modeling approach described above. The geographical area (*ZIP*), from which ED counts were spatially aggregated, was represented by indicator variables and modeled as fixed effects. The models included dummy variables for season (*spring, summer, autumn*), day of week, and holidays (*DOW)*. Hospital dummy variables (*hospital)* accounted for the entry and exit of hospitals during the study period. Long-term trends and seasonality in case presentation rates (*time*) were controlled with parametric cubic splines, $g(\gamma_1, \ldots, \gamma_N; x)$, with monthly knots. Meteorological effects were modeled using indicator variables for lag 0 maximum temperature (for each degree Celsius) and a cubic term for the moving average of dew point (lags 0, 1, and 2). Cubic terms for the moving average of minimum temperature (lags 1 and 2) were also included for meteorological control.

Both daily- and long-term trends in AER may influence exposures to ambient pollution and subsequent health risk. Correspondingly, we examined the potential effect of AER on the pollutant-specific epidemiological associations using models: (a) stratifying by median AERs, (b) including AER-pollutant product terms, and (c) through tertile analyses based on both the pollutant and AER distributions.

Stratified Analyses

As an assessment of the potential influence of spatial differences in AERs on the overall model results, we conducted stratified analyses by categorizing ZIP codes as being "low" or "high" AER areas (defined by the ZIP code-specific median AER being above or below the 50th percentile) ("*stratified models*"). For these models, ZIPs with median AERs $< 0.247\ h^{-1}$ were categorized as being "low AER" ZIPs, as those with median AERs $> 0.247\ h^{-1}$ were "high AER" ZIPs. We then ran separate time series models (Eq. (1)) for each of the AER strata. As these strata reflect central tendencies and include no daily indicators of change in AERs, heterogeneity among the strata in RRs can be interpreted as representing long-term differences in pollutant risks by AERs.

The AER estimates contain several parameters that may serve as surrogates of other potential confounders (i.e., home size as a surrogate of socioeconomic status (SES)). To address this potential bias, we conducted analyses further stratifying low and high AER ZIP codes into low and high poverty substrata. From data of census 2000, we used percentage below poverty as our primary indicator of aggregate-level SES in the AER analyses, based on previous research in this field.[37] Using this approach, we might expect that potential confounding of AER by SES would be minimized within a given poverty-AER strata.

Interaction Term Analyses

Similar to our primary analytical approach examining potential AER effect modification, we supplemented Eq. (1) with an AER main effect as well as a pollutant–AER interaction term along with all other covariates. For these analyses, as the models included ZIP code as a fixed effect, model coefficients functionally describe effect modification due to within-ZIP code temporal trends in air pollution solely. As such, the results controlled for potential confounding in baseline risks from spatially varying factors (e.g., between-ZIP differences in SES).

Tertile Analyses

Finally, to further examine the direction and strength of association in the exposure–response relationships across the range of observed values, we estimated the joint effects of AER

and pollution by their tertiles. For these models, we classified each day during the 4-year time series as being either a low, moderate, or high pollutant day based on the distribution of the respective pollutants, as well as a low, moderate, or high AER day. Thus, each day and the corresponding asthma ED visits fell into a 3×3 pollutant-AER matrix. We then included nine indicator terms for each of the pollutant and AER tertile combinations along with the other covariates as independent variables in Eq. (1).

RESULTS

Between 1999 and 2002, the grand median AER across 186 ZIP codes in the metropolitan Atlanta area was $0.25\,h^{-1}$ and ranged from 0.168 to $0.371\,h^{-1}$ for individual ZIP codes (Figure 1). Daily pollutant concentrations and variability were typical during this 4-year period for Atlanta (Table 1). The within-ZIP code CV in AERs owing to temporal changes was 36.7%, compared with a between-ZIP code CV in median daily AERs of 17%. Each of the pollutant distributions were weakly, yet negatively temporally correlated with corresponding AER (Table 2), which was expected because of the joint countervailing effects of wind speed on increasing AERs (Eq. (5)), while also increasing horizontal dispersion and atmospheric dilution leading to reduced ambient pollutant concentrations. As expected, given their shared primary emission sources, NOx and CO were strongly correlated with each other (mean $r_S = 0.93$; Table 2). O_3 was also moderately and positively correlated with $PM_{2.5}$ (mean $r_S = 0.51$).

We examined correlations between several ambient temperature metrics and corresponding daily AER to assess the potential that observed variability in AERs may be truly reflecting variability in this potential confounder of air-pollution health effects. Despite the inclusion of ambient temperature as an input parameter within the AER estimation algorithm (Eq. (5)), observed AERs were generally weakly and negatively correlated with 3-day moving averages, maximum, and minimum temperatures (Spearman's r (r_S) $= -0.16$, -0.29, and -0.19, respectively). The inverse correlations suggest that as ambient temperature extremes deviated from our assumed indoor temperature constant (20 °C), AERs decreased. This finding is not consistent with our *a priori* expectations of enhanced stack effect-induced infiltration occurring when T_{in}–T_{out} is presumably maximized during the summer months. As these correlations were generally weak, however, it is unlikely that the AER estimates were serving as direct surrogates of ambient temperature.

Epidemiological Results

Models including only univariate pollutant terms and the other covariates ("overall models") without any AER estimates (Eq. (1)) showed positive associations between each of the four pollutants and asthma ED visits with RRs ranging from 1.008 (for CO) to 1.046 (for O_3; Table 3). These results are consistent with our previous findings of significant associations between numerous pollutant metrics and asthma ED visits in Atlanta.[26,27]

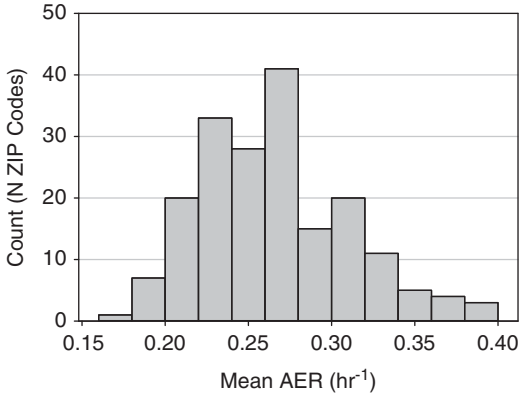

Figure 1. Histogram of the estimated median air exchange rates (AERs) across the 186 ZIP codes.

Typically, stratified analysis results showed that magnitudes of association were higher for ZIP codes with higher AERs than those with low AERs for all the pollutants, with the exception of O_3 (Table 3). For CO and NOx, there were significant associations for ZIP codes with high AER, and null findings for low AER ZIPs. For O_3, in contrast, the observed RR for the low AER strata was also significant and nearly three times that of the RR for ZIP codes in the high AER strata (RRs = 1.066 and 1.028, respectively).

Correlation analyses examining the linear association between median AERs by ZIP code and ZIP code-level percent-below-poverty showed strong, positive correlations ($r_S = 0.76$; $N = 186$ ZIP codes, Figure 2), suggesting that one of these terms may potentially serve as a confounder of the other in the stratified analyses, given their strength of covariance. This was expected as the empirical estimates of ZIP code-resolved NL were derived using median income data (Eqs. (2) and (3)). RRs between each of the pollutants and asthma ED visits were consistently higher for the low AER ZIPs compared with the high AER ZIPs for strata characterized as having high poverty levels. In contrast, there was not a uniform trend in the magnitudes of association for the low poverty ZIPs. For CO and NOx, RRs in these low poverty ZIPs were higher for the high AER strata compared with the low strata. For O_3 and $PM_{2.5}$, there was an inverse trend, with slightly higher RRs observed for the low AER ZIP codes.

In contrast to the stratified models, the interaction term models included ZIP code as a fixed effect, with model coefficients functionally describing temporally trends solely. Potential confounding from spatially varying SES, which appears to be a realistic concern for the spatially stratified models, is thus minimized using this modeling approach. There were positive associations for the interaction between AER and pollution on asthma ED visits for both CO and NOx (interaction term P-value = 0.07 and 0.04, respectively), indicating significant or near-significant effect modification by AER on the pollutant risk-ratio estimates (Table 4). In contrast, the interaction term between $PM_{2.5}$ and AER on asthma ED visits was negative and significant (P-value = 0.012), with significant, positive main effects for both $PM_{2.5}$ and AER. Finally, O_3 was strongly associated with asthma ED visits in models including AERs ($P = 0.002$), although we observed no associations between asthma, and either an AER main effect or the interaction term between O_3 and AER.

Results from the tertile analyses showed that RRs for NOx and CO were consistently highest when daily AERs were within the highest tertile of their distribution and lowest when AERs fell within the lowest tertile, across each of the pollutant concentration tertiles (Figure 3). As expected from the overall model results, RRs for these pollutants, while holding AERs constant, were also highest on days when pollutant concentrations were highest. In contrast, and consistent with the previous interaction-term model results, the tertile analyses did not indicate effect modification by AER for O_3. For a given tertile in O_3 concentrations, RRs did not vary by AER but did increase substantially, within AER tertile, with increasing O_3 concentration. We note, however, that these results may have been influenced by much reduced sample size when the full data set was partitioned into nine different sub categories for this analysis.

The $PM_{2.5}$ and AER model results were mixed and exhibited similar trends as NOx and CO (i.e., increasing RRs with increasing AERs while holding $PM_{2.5}$ concentrations constant) within the low and moderate $PM_{2.5}$ tertiles only. Conversely, observed RRs increased with decreasing AERs for days binned within the highest tertile of $PM_{2.5}$ concentrations. The RR on days when $PM_{2.5}$ concentrations were typically highest ($>19.2\,\mu g/m^3$) and AERs

Table 1. Summary of daily AER values and pollutant concentrations in Atlanta between January 1999 and December 2002 across 186 ZIP codes.

	Observations (N)	*Units*	*Mean*	*SD*	*5th Percentile*	*25th Percentile*	*50th Percentile*	*75th Percentile*	*95th Percentile*	*Minimum*	*Maximum*	*Inter-quartile range*
AER	271,746	hr^{-1}	0.265	0.108	0.128	0.188	0.245	0.321	0.474	0.027	1.040	0.132
CO	270,816	p.p.m.	0.46	0.39	0.16	0.22	0.33	0.55	1.20	0.07	7.48	0.33
NOx	271,374	p.p.b.	30.1	33.5	3.1	8.0	18.5	40.1	94.4	0.7	517.8	32.1
$PM_{2.5}$	229,896	$\mu g/m^3$	15.2	7.1	6.6	10.0	13.6	18.7	28.7	2.5	78.2	8.7
O_3	270,816	p.p.b.	41.9	18.6	16.4	27.7	39.3	53.8	76.2	3.5	132.7	26.1

Abbreviations: AER, air exchange rate; CO, carbon monoxide; NOx, nitrogen oxides; O_3, ozone; PM, particulate matter.

Table 2. Mean Spearman's correlation coefficients among pollutant concentrations and AERs.

	CO	*NO_X*	*$PM_{2.5}$*	*O_3*	*AER*
CO		0.93	0.44	−0.03	−0.26
NO_X			0.40	−0.03	−0.25
$PM_{2.5}$				0.51	−0.26
O_3					−0.19

Abbreviations: AER, air exchange rate; CO, carbon monoxide; NOx, nitrogen oxides; O_3, ozone; PM, particulate matter.
Mean values averaged across 186 ZIP codes.

lowest ($< 0.23\ h^{-1}$), for example, was twice as high that compared with days with high $PM_{2.5}$ and high AERs ($> 0.31\ h^{-1}$; RR = 1.056, CI: 1.019–1.095; and 1.021, CI: 0.98–1.063, respectively.

We examined frequency distribution patterns within the pollutant-AER tertiles to provide an initial graphical assessment of the potential of seasonal confounding within the tertile analysis epidemiological results (Figures 4–6, CO not shown). As expected, distinct seasonal differences in pollutant levels existed for O_3 and NOx, with the highest O_3 and lowest NOx days typically occurring during the warmer summer months. For most of the pollutants, however, monthly frequencies for specific pollutant-AER pairings did not vary substantially by AER tertile. For example, high NOx and high AER observations occurred during roughly the same months throughout the year (i.e., at greater frequencies during cooler months) as did high NOx and low AER days (Figure 4).

DISCUSSION

Our results provide an initial indication that accounting for daily variability in AER within a single-city time series model may explain heterogeneity in longitudinal asthma ED risk associated with several common urban pollutants. Although limited to one outcome category in a single urban locale, the findings suggest that the use of relatively simple and easy-to-derive AER surrogates reflect intraurban differences in short-term exposures to some pollutants with ambient origins. For the spatially heterogeneous, predominantly traffic-related pollutants CO and especially NOx, ZIP codes with typically higher AERs were generally found to have higher RRs for asthma ED visits. Moreover, assessed temporally across ZIP codes, NOx- and CO-related asthma ED visits tended to be significantly higher on days when AERs were also higher. Tertile analyses for NOx and CO showed that this apparent effect modification occurred across all concentrations of the observed NOx and CO distributions.

There was also general concordance in the interpretation of the NOx and CO results between the stratified and interaction-term epidemiological models, despite the fact that these modeling approaches describe different aspects of AER and its potential influence on exposure and health risk with varying sample size. For both models, higher AER was associated with greater pollutant effects and is a finding that is consistent with our *a priori* hypotheses that higher AER values result in greater infiltration of outdoor air indoors, thus leading to higher personal exposures to pollutants of ambient origin. ZIP code stratification by median AER over several years may reflect long-term AER spatial pattern, whereas the interaction term models reflect temporal changes in within-ZIP code AERs primarily. Despite the general consistency, however, the stratified epidemiological results should be interpreted cautiously as median AERs were shown to be highly correlated with poverty indices. Differences ostensibly associated with AER strata, therefore, may in fact be due to SES differences. Even after we conducted substratification to address this by accounting for within-ZIP code percent-below-poverty values, it is likely that residual confounding in these models may still exist. A visual examination of Figure 2, for example, reveals apparent patterns of correlation between percent-below-poverty and median AER even within some of the stratified quadrants, indicating that further control for SES may be necessary.

To our knowledge, the interaction term findings for CO and NOx, and to a lesser degree $PM_{2.5}$, are the first to provide an indication of short-term (i.e., daily) effect modification of gaseous and PM pollution-related risks associated with daily changes in AER. As such, the results are broadly similar to previous studies that have hypothesized and reported higher mean air-pollution risks for locations with higher overall AERs or pollutant infiltration efficiencies.[2,6,23–25,40,41] In contrast to our findings, for these previous studies differences in infiltration and AERs were inferred from broad surrogate indicators of these processes. Janssen et al.,[2] for example, found that city-specific air-conditioning prevalence estimates in 14 US locations were inversely associated with city-specific effect estimates of PM_{10} on hospital admissions for chronic obstructive pulmonary disease and cardiovascular disease. Cities with a greater percentage of homes with central air-conditioning had significantly lower relative risks than cities with less central air-conditioning. For this study, the authors assumed that homes with central air-conditioning had lower AERs as compared with homes that used open windows for ventilation. A more recent analysis included actual estimates of city-specific AERs to examine modification of short-term O_3 mortality risk.[23] AER-adjusted O_3 exposure coefficients were strongly correlated with observed mortality rates, which suggest that between-city differences in AER, which was greater than seen within our multi-ZIP code Atlanta study domain, partially explained corresponding differences in actual exposures to O_3. The AERs used were derived using results from a probabilistic survey of 209 US homes, where hourly pollutant infiltration rates were measured and frequency distributions calculated for 80% of the US housing stock.[13] Daily and within-city variability in AER, however, was not directly examined as a predictor of heterogeneity in risk.

In contrast to these previous studies as well as our *a priori* expectations, we observed no evidence suggestive of O_3–AER effect modification, despite the fact that O_3 was a strong,

independent predictor of asthma ED visits in our analysis. Weschler[42] recently hypothesized that ambient O_3 is closely associated with by-products (e.g., carbonyls and dicarbonyls) of O_3-initiated chemistry occurring indoors. These by-products vary directly with outdoor O_3, yet are weakly associated with AER. Thus, assuming a causal role in the link between the by-products and asthma ED visits, it is possible that our null results for O_3–AER modification reflect this or some other indirect exposure–response pathway.

Although unexpected, a more plausible explanation for the O_3 findings may be that the relatively small within-ZIP code range of the estimated AERs in Atlanta during this study period was not sufficiently variable to elicit measurable differences in O_3 fate and transport, infiltration, and subsequent exposure. Correspondingly, epidemiological models including interactions involving AERs would be no more parsimonious than models without this interaction term. The differential impact of AER on pollutant-specific penetration efficiency is well supported in theory and practice,[5,10,11,16,43] and based on the steady-state solution to the pollutant mass-balance equation positing ambient pollutant infiltration, and subsequent exposures, to be a function of AER and a series of pollutant-specific removal and decay constants. Thus, the impact of the observed intertertile increase in AERs ($\sim 0.1\ h^{-1}$) on highly reactive indoor O_3 may have been limited, as even at the high range of observed AERs during this study O_3 infiltration within an indoor microenvironment may be low relative to other pollutants. Conversely, the variability of AERs within this range could have led to biologically meaningful differences in exposures to less reactive pollutants, such as NOx, CO, and $PM_{2.5}$. It is also plausible that, for most people, exposures to O_3 specifically occur while outdoors,[44] and range from 24% to 57% of total daily exposures.[42] Therefore, variability in AERs affecting exposures to O_3 while indoors may have minimal influence on total daily exposures to this pollutant. Replicating this analysis in cities known to have greater ranges in AERs throughout the year may provide greater power to detect

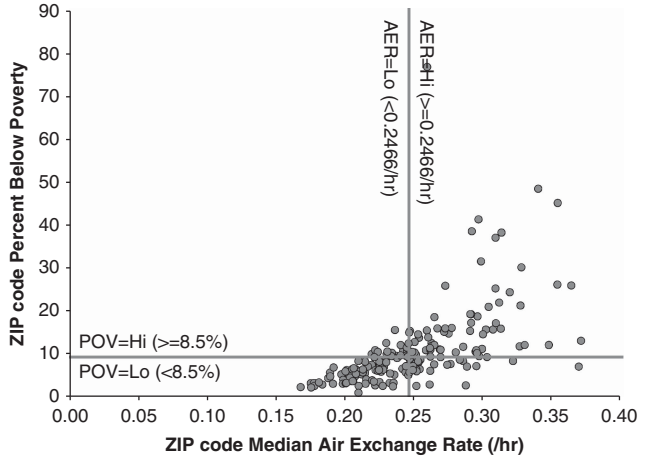

Figure 2. Scatterplot of ZIP code-level median air exchange rates (AERs) and percent below poverty, with lines denoting 50th percentile strata cut-points.

Table 4. Associations between pollutant concentrations and asthma ED visits including interaction terms with air exchange rates in Atlanta: 1999–2002.

	Estimate	*95% LCL*	*95% UCL*	χ^2	P-*value*
CO	−0.0071	−0.0501	0.0358	0.11	0.75
AER	−0.0406	−0.163	0.0817	0.42	0.52
CO–AER	0.1419	−0.0099	0.2936	3.36	0.07
NOx	−0.1084	−0.6203	0.4034	0.17	0.68
AER	−0.0348	−0.1486	0.079	0.36	0.55
NOx–AER	1.9055	0.0797	3.7312	4.18	0.04
$PM_{2.5}$	0.0058	0.0025	0.0091	11.87	0.0006
AER	0.281	0.093	0.469	8.59	0.003
$PM_{2.5}$–AER	−0.0145	−0.0259	−0.0032	6.27	0.012
O_3	2.2561	0.8176	3.6946	9.45	0.002
AER	0.0597	−0.1111	0.2304	0.47	0.49
O_3–AER	−1.511	−5.5843	2.5624	0.53	0.47

Abbreviations: AER, air exchange rate; CO, carbon monoxide; ED, emergency department; NOx, nitrogen oxides; O_3, ozone; PM, particulate matter.

Table 3. Associations between pollutant concentrations and asthma ED visits, overall and stratified by ZIP code-level air exchange rate and poverty status in Atlanta: 1999–2002.

		Overall			*Low poverty*			*High poverty*		
		N	*RR*	(95% *CI*)	N	*RR*	(95% *CI*)	N	*RR*	(95% *CI*)
CO	Overall	270,816	1.008	(1.000–1.016)	136,864	1.002	(0.990–1.014)	133,952	1.012	(1.001–1.022)
(IQR = 0.33 p.p.m.)	*Low AER*	135,408	1.004	(0.991–1.016)	106,288	0.999	(0.985–1.013)	29,120	1.026	(0.997–1.055)
	High AER	135,408	1.010	(0.999–1.020)	30,576	1.014	(0.986–1.043)	104,832	1.009	(0.998–1.021)
NOx	Overall	271,374	1.010	(1.000–1.019)	137,146	1.002	(0.988–1.016)	134,228	1.015	(1.002–1.027)
(IQR = 32 p.p.b.)	*Low AER*	135,687	1.003	(0.989–1.017)	106,507	0.997	(0.981–1.013)	29,180	1.032	(0.999–1.066)
	High AER	135,687	1.013	(1.001–1.026)	30,639	1.024	(0.991–1.058)	105,048	1.012	(0.998–1.025)
O_3	Overall	270,816	1.050	(1.024–1.075)	136,864	1.068	(1.030–1.107)	133,952	1.032	(0.998–1.067)
(IQR = 26 p.p.b.)	*Low AER*	135,408	1.069	(1.031–1.108)	106,288	1.068	(1.026–1.112)	29,120	1.054	(0.971–1.145)
	High AER	135,408	1.033	(0.999–1.068)	30,576	1.063	(0.977–1.157)	104,832	1.029	(0.993–1.068)
$PM_{2.5}$	Overall	229,896	1.018	(1.003–1.033)	116,184	1.010	(0.989–1.031)	113,712	1.019	(0.999–1.039)
(IQR = 8.7 μg/m^3)	*Low AER*	114,948	1.013	(0.992–1.035)	90,228	1.011	(0.987–1.035)	24,720	1.026	(0.978–1.078)
	High AER	114,948	1.018	(0.998–1.039)	25,956	1.007	(0.958–1.059)	88,992	1.016	(0.995–1.038)

Abbreviations: CO, carbon monoxide; NOx, nitrogen oxides; O_3, ozone; PM, particulate matter; RR, risk ratio.

	Low AER (< 0.227 hr^{-1})	Moderate AER (0.228 – 0.308 hr^{-1})	High AER (> 0.309 hr^{-1})
High CO (> 0.69 ppm)	1.006 (0.979 - 1.034)	0.999 (0.961 - 1.039)	1.015 (0.973 - 1.058)
Moderate CO (0.51 – 0.68 ppm)	1.001 (0.977 - 1.027)	0.994 (0.960 - 1.030)	1.010 (0.972 - 1.049)
Low CO (< 0.50 ppm)	1.000 (NA)	0.993 (0.970 - 1.016)	1.009 (0.983 - 1.035)

	Low AER (< 0.227 hr^{-1})	Moderate AER (0.228 – 0.308 hr^{-1})	High AER (> 0.309 hr^{-1})
High NOx (> 49 ppb)	1.040 (1.011 - 1.070)	1.040 (1.000 - 1.081)	1.052 (1.009 - 1.098)
Moderate NOx (28 – 48 ppb)	1.041 (1.017 - 1.066)	1.041 (1.006 - 1.076)	1.053 (1.015 - 1.093)
Low NOx (< 27 ppb)	1.000 (NA)	1.000 (0.978 - 1.022)	1.012 (0.987 - 1.037)

High $PM_{2.5}$ (> 19.2 μg/m^3)	1.056 (1.019 – 1.095)	1.018 (0.977 – 1.060)	1.021 (0.981 – 1.063)
Moderate $PM_{2.5}$ (13.4 – 19.1 μg/m^3)	1.031 (0.995 – 1.068)	1.040 (1.003 – 1.079)	1.043 (1.005 – 1.083)
Low $PM_{2.5}$ (< 13.3 μg/m^3)	1.000 (NA)	1.022 (0.986 – 1.059)	1.044 (1.009 – 1.081)

High O_3 (> 54 ppb)	1.078 (1.034 - 1.125)	1.075 (1.024 - 1.128)	1.079 (1.028 - 1.132)
Moderate O_3 (33 – 53 ppb)	1.023 (0.994 - 1.053)	1.020 (0.983 - 1.057)	1.024 (0.987 - 1.062)
Low O_3 (< 32 ppb)	1.000 (NA)	0.997 (0.974 - 1.020)	1.001 (0.976 - 1.026)

< 1.005	1.006 – 1.010	1.011 – 1.015	1.016 – 1.020	1.021 – 1.025	1.026 – 1.030	1.031 – 1.035	1.036 – 1.040	1.041 – 1.045	> 1.045

Figure 3. Associations between pollutant concentrations and asthma emergency department (ED) visits by tertile of pollutant concentration and air exchange rate (AER) values in Atlanta: 1999–2002. Shading indicates magnitude of association corresponding to the values listed in the legend.

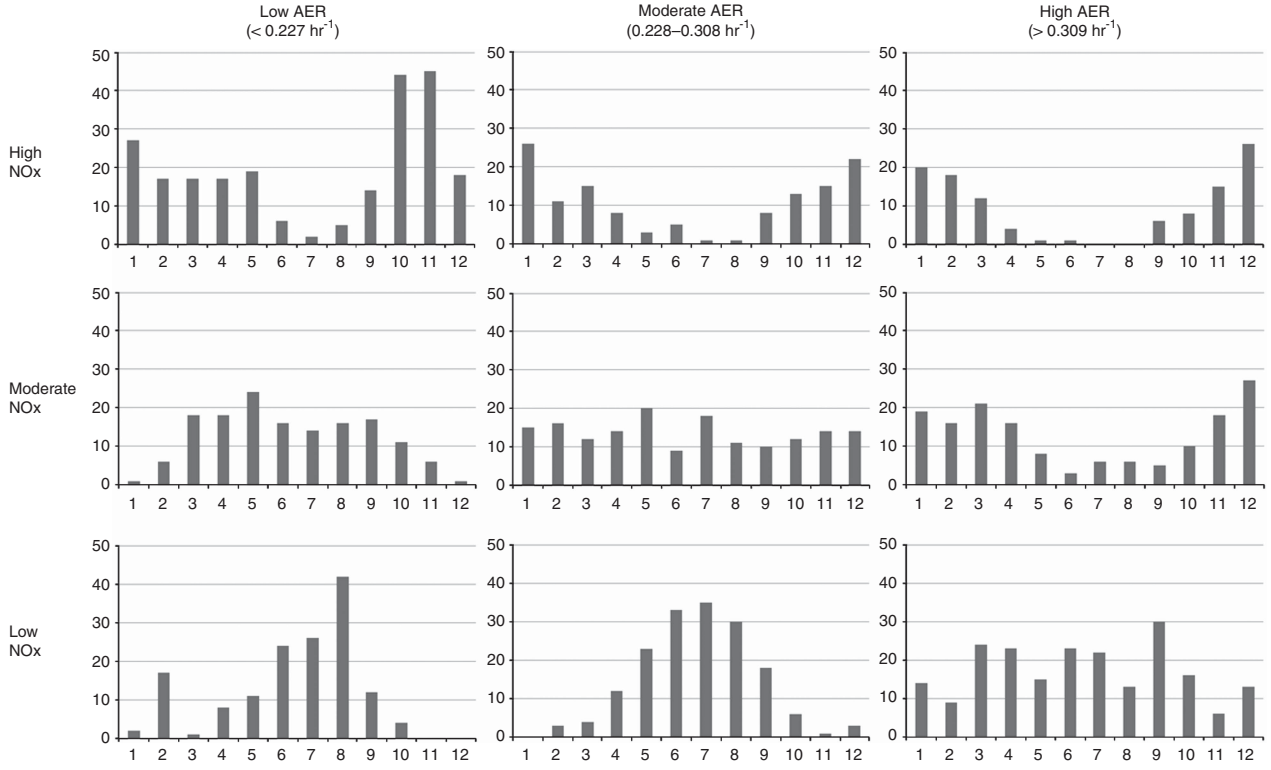

Figure 4. Monthly distribution of observations (i.e., days) for each nitrogen oxides (NOx)–air exchange rate (AER) tertile pairing in Atlanta: 1999–2002.

potential AER effect modification for pollutants like O_3 than our Atlanta results.

Our overall pollutant–AER interaction term models also indicated opposite effect modification trends for $PM_{2.5}$ as compared with NOx and CO, with generally higher risks seen for days with lower AERs. Although somewhat anomalous, however, this finding was consistent with the tertile analysis results, which showed that this divergent finding was largely driven by strong inverse-effect modification trends on days when ambient $PM_{2.5}$ concentrations were highest. In particular, on days when $PM_{2.5}$

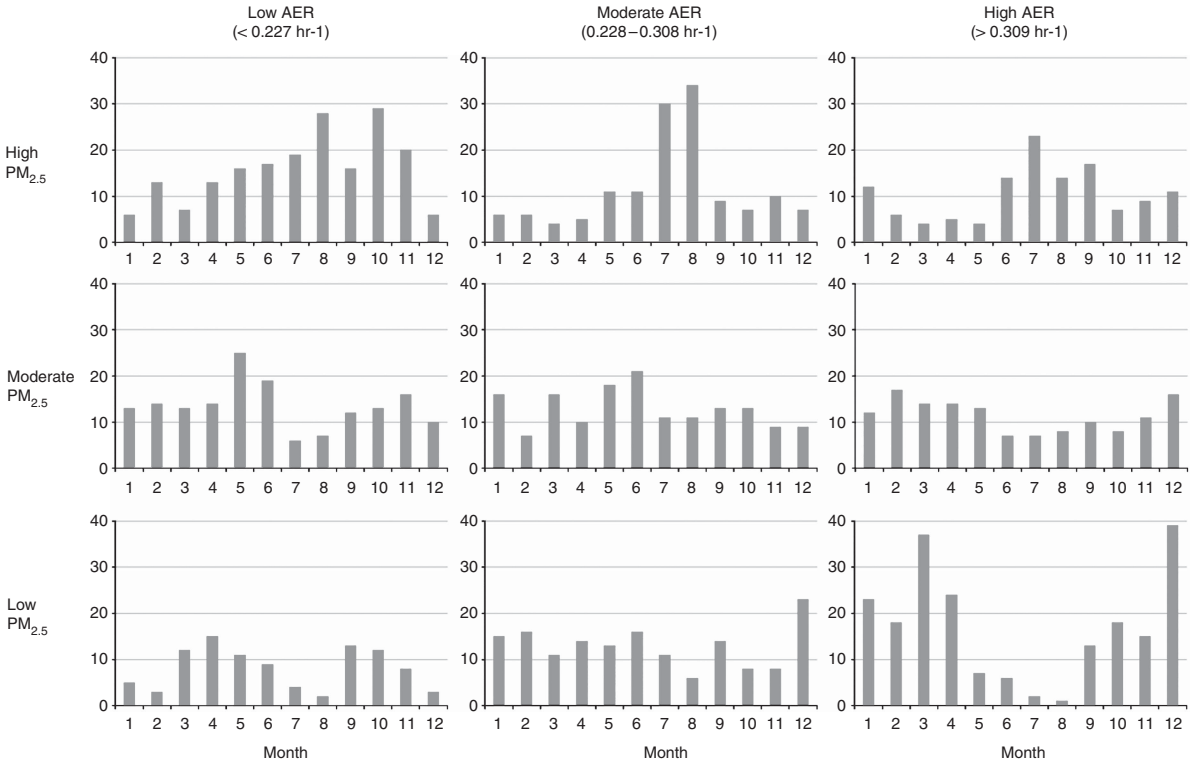

Figure 5. Monthly distribution of observations (i.e., days) for each particulate matter $(PM)_{2.5}$–air exchange rate (AER) tertile pairing in Atlanta: 1999–2002.

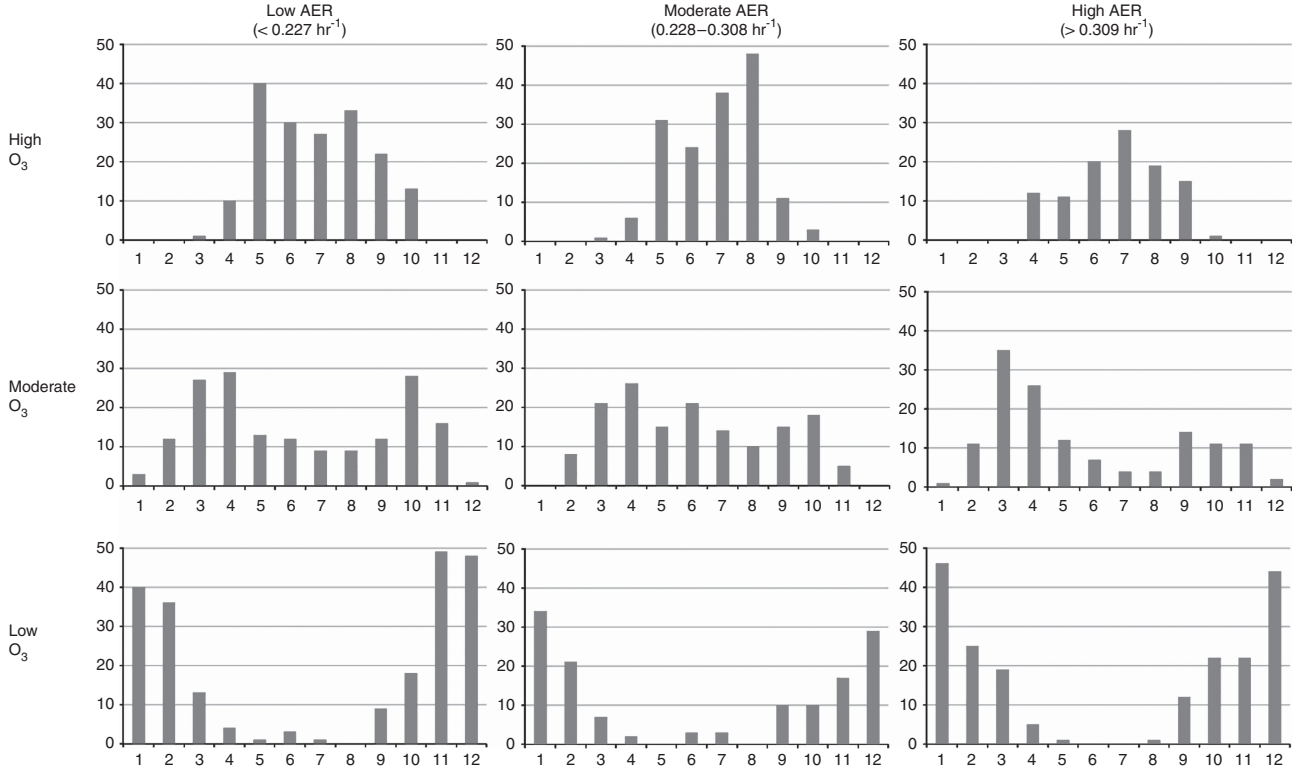

Figure 6. Monthly distribution of observations (i.e., days) for each O_3–air exchange rate (AER) tertile pairing in Atlanta: 1999–2002.

concentrations were below the upper tertile of its distribution (i.e., $< 19.2\ \mu g/m^3$), similar positive trends associated with AER existed as those observed for NOx and CO.

No compelling explanation for these countervailing trends exists at the highest $PM_{2.5}$ concentrations; however, it is worth noting that there was a difference in the monthly frequency

pattern between the high and both moderate and low AERs tertiles across this highest $PM_{2.5}$ tertile (Figure 5). Generally, there was a greater prevalence of high $PM_{2.5}$–low AER days occurring during the non-summer months compared with the other tertile pairings, which could indicate unspecified seasonal confounding in the tertile analyses for high $PM_{2.5}$ days. It has been suggested, for example, that differences in ambient $PM_{2.5}$ across the different New Jersey cities may lead to differential infiltration efficiencies that, in turn, may account for differences in observed epidemiological RRs.[6] Alternatively, it is possible that the mean time spent outdoors is greater in Atlanta during these non-summer months, leading to reductions in measurement error associated with the use of outdoor monitors as surrogates of population exposures in time series epidemiological analyses. It follows that during these months we might expect to see RRs that were less attenuated to the null than results affected by a greater degree of measurement error.[19] Importantly, the monthly frequency distribution patterns for the other $PM_{2.5}$ tertiles, as well as for NOx and O_3 were similar across the AER strata (Figures 4 and 6, respectively), suggesting that effect modification attributed to AER is unlikely confounded by other seasonal factors within these models.

In the interaction term models, we also examined the potential for confounding from meteorology. In acute air-pollution time series studies, meteorological confounding is a common concern, given the temporal covariance patterns between many pollutants and weather-related factors, such as ambient temperature. Although the method we used to estimate AER does include ambient temperature, we showed that the correlation between temperature and AER was weak. This is not surprising as temperature was one of the several terms used to characterize AER, and it was expressed as a non-linear term within the algorithm. Similarly, these findings do not appear to be biased by other unspecified seasonal confounding. Temperature and relative humidity terms were also included as covariates within our standard epidemiological models as a general means of controlling for potential confounding of air pollution-related effect estimates.

A key limitation to the current analysis lies in the use of estimated, rather than actual AERs, and we did not validate this estimation approach within the scope of current study. The central tendency of the estimated AERs we used in the current analysis although possible (median AER $= 0.25\,h^{-1}$), is substantially lower than AER estimates from other US locations and for analyses that predict Atlanta AERs specifically.[13,23,30,31] Persily et al.,[13] for example, estimated annual mean AERs for Atlanta to be $0.43\,h^{-1}$, which did not factor in fraction of time when windows were open. Chen et al.[23] assumed a default estimate of the difference in AERs when windows were open compared with when closed to be $1.5\,h^{-1}$ in modifying the Persily et al.[13] estimate to derive an average annual air-exchange rate for residences in Atlanta of $0.48\,h^{-1}$. Notably, we acknowledge that this estimate is difficult to ascertain. For the purposes of our epidemiological analyses, however, discrepancies in the absolute AERs are less important than whether the modeled spatiotemporal variability within- and between-ZIP codes is accurate from a relative sense. If the current method accurately expresses day-to-day variability of AERs within a given ZIP code, then epidemiological models examining the strengths of associations for the main effects, covariates, and effect modification terms within the model are also likely to be unbiased.

Other factors that may have led to low overall AER estimates were several simplifying assumptions. These assumptions include fraction of low income *vs* conventional housing stock within a ZIP code. The empirical function for calculating NL (Eqs. (2) and (3)) is heavily dependent on this assumption, with overestimates of low-income housing stock resulting in substantially attenuated AERs. We do not have any prior reason to believe that the fractional contribution used in the current analysis is inaccurate; however, alternative methods for quantifying the presence of low income stock within a given ZIP code may provide a more precise indicator of housing stock composition and, perhaps, lead to revised total estimates of AER throughout the modeling domain. Similarly, for this empirical-statistical method of AER estimation, NL was based on associations that were collected on homes throughout the United States, which may not necessarily be representative of the Atlanta housing stock. Analyses simulating the robustness of our results to functions derived using alternate values can clarify the suitability of this approach for use in cities like Atlanta and the need to derive alternative functions.

Finally, we used uniform values for the model meteorological and terrain-type terms, which is unquestionably a broad simplification. Temperature gradients throughout the city, including those induced via urban heat islands, were not included in this model and may lead to greater between-ZIP code variability in AERs as well as increased AERs for ZIP codes affected by microscale elevations in ambient temperature. As with the lack of information regarding open windows status, it is difficult to both model and predict the distribution of this source of variability, as well as estimate how this may have affected the epidemiological model results. For our main, within-ZIP temporal modeling approach (Eq. (1)), however, we believe that the impact of errors associated with this assumption is likely minimal.

In conclusion, we believe that these results provide an initial indication that the use of short-term indicators of changes in daily AER may explain heterogeneity in observed short-term risk from air pollution. Admittedly, our approach and resulting findings may not be generalizable to other locations or other pollutant–outcome associations. We specifically used AER indicators based on data that were relatively easy to obtain and include within an established analytical framework, thereby facilitating replication of this approach in other settings. Collectively, our results contribute to a growing understanding of the role of AER as a factor affecting ambient pollutant infiltration, intraurban exposure variability, and possible exposure misclassification in health risk estimates in acute single-city time series studies of air pollution.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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