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ORIGINAL ARTICLE

Application of alternative spatiotemporal metrics of ambient air pollution exposure in a time-series epidemiological study in Atlanta

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Exposure error in studies of ambient air pollution and health that use city-wide measures of exposure may be substantial for pollutants that exhibit spatiotemporal variability. Alternative spatiotemporal metrics of exposure for traffic-related and regional pollutants were applied in a time-series study of ambient air pollution and cardiorespiratory emergency department visits in Atlanta, GA, USA. Exposure metrics included daily central site monitoring for particles and gases; daily spatially refined ambient concentrations obtained from regional background monitors, local-scale dispersion, and hybrid air quality models; and spatially refined ambient exposures from population exposure models. Health risk estimates from Poisson models using the different exposure metrics were compared. We observed stronger associations, particularly for traffic-related pollutants, when using spatially refined ambient concentrations compared with a conventional central site exposure assignment approach. For some relationships, estimates of spatially refined ambient population exposures showed slightly stronger associations than corresponding spatially refined ambient concentrations. Using spatially refined pollutant metrics, we identified socioeconomic disparities in concentration–response functions that were not observed when using central site data. In some cases, spatially refined pollutant metrics identified associations with health that were not observed using measurements from the central site. Complexity and challenges in incorporating modeled pollutant estimates in time-series studies are discussed.

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INTRODUCTION

Numerous epidemiological time-series studies have shown positive associations between the major ambient air pollutants (including ozone (O_3), carbon monoxide (CO), nitrogen dioxide (NO_2), PM_{10} and $PM_{2.5}$ (particulate matter with aerodynamic diameter <10 and <2.5 microns, respectively)) and cardiorespiratory conditions using mortality, hospital admissions, and emergency department (ED) visit data.[1,2] These studies frequently use data from fixed-site ambient monitors as surrogates of population exposures to ambient pollutants. This practice may be considered reasonably valid for pollutants that have limited spatiotemporal heterogeneity (in particular, those of secondary origin, such as O_3 and $PM_{2.5}$ sulfate (SO_4)).[3] Exposure misclassification may be substantial, however, for traffic-related pollutants (e.g., CO, NOx, and $PM_{2.5}$ elemental carbon (EC)), whose concentrations vary considerably over short distances from roadways,[4] and that exhibit a high degree of spatiotemporal variability.[3,5,6] Exposure misclassification may also arise due to population characteristics, such as time-activity patterns, that reduce the representativeness of ambient concentrations for exposures to ambient pollution. In these cases, the use of an ambient population-wide concentration measure as an exposure surrogate may lead to increased analytical uncertainty and potentially biased estimates of health risk.[7]

The issue of exposure misclassification due to spatiotemporal heterogeneity is particularly pertinent given the growing body of research focusing specifically on the link between traffic-related emissions and adverse health.[8,9] It is conceivable that uncertainty and bias in health risk estimates may vary for subpopulations living at differing distances from an ambient monitor or in regions of the study area that are not well-represented by the monitor. In some locations, for example, populations of low socioeconomic status (SES) live closer to sources of air pollution and further from regulatory monitoring sites compared with the general population, which may result in the potential for differential exposure misclassification by subpopulation.[10,11] Air quality models that produce spatially refined air pollution concentrations at a large number of receptor locations may provide a means of addressing these sources of uncertainty and limitations. There have been several studies linking modeled mid- to long-term ambient concentration estimates with adverse health outcomes.[8,12–15] However, few previous epidemiological studies have applied spatially refined modeled estimates of daily ambient concentrations in studies of acute morbidity.[16,17]

Considering that on average people spend approximately 90% of their time indoors and that ambient pollutant infiltration indoors varies by pollutant and building type, human exposures to ambient pollutants may vary from measured ambient concentrations.[18,19] In addition to spatial refinement of ambient concentrations, incorporation of exposure prediction into epidemiological analyses may be relevant for better approximation of true etiological

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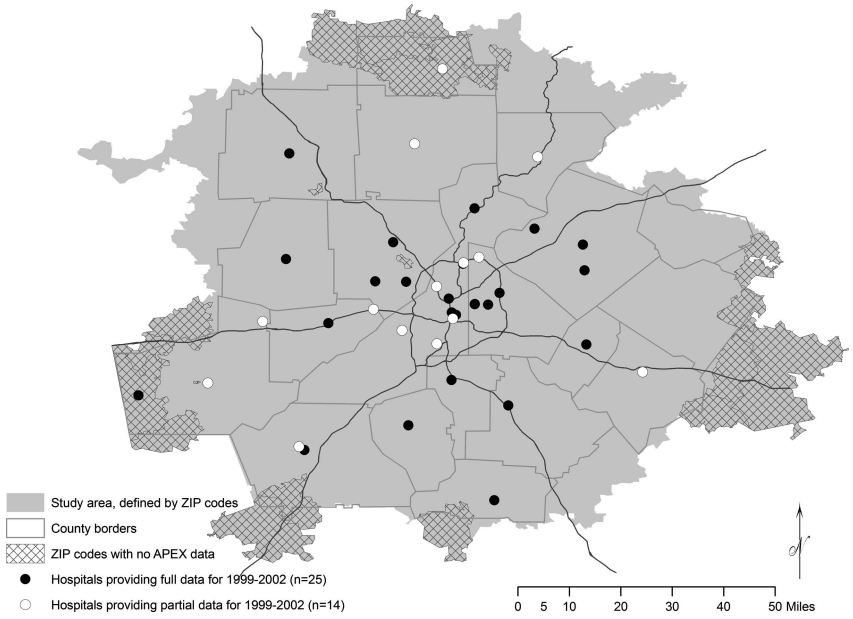

Figure 1. Map of 20-county Atlanta study area and locations of hospitals providing emergency department visit data during 1999–2002.

relationships. Exposure models, such as EPA's APEX (Air Pollution Exposure) and SHEDS (Stochastic Human Exposure and Dose Simulation) models account for these likely determinants of personal exposures to ambient air pollution.[20–22] Other than limited feasibility studies,[23,24] to our knowledge there have been no population-based studies of air pollution and acute morbidity that have considered spatially refined estimates of ambient exposures.

To address these research gaps, we developed and evaluated alternative metrics for ambient traffic-related and regional pollutants for use in the Study of Particles and Health in Atlanta (SOPHIA), an extensive time-series study examining ambient air pollution and acute morbidity via ED visits in Atlanta, GA, USA. Despite the large 20-county study area (approximately 6100 square miles), we have previously observed associations of both cardiovascular and respiratory outcomes with spatially variable pollutants (e.g., CO, NO_2, and $PM_{2.5}$ EC) when using central monitoring data.[25–29] In a simulation study examining the impacts of measurement error on our findings, however, we estimated that error due to spatial variability may result in reductions in observed relative risks (RRs) by 43–68% for primary pollutants (including CO, NOx, and $PM_{2.5}$ EC) compared with only 16% for secondary pollutants (including O_3 and $PM_{2.5}$ SO_4).[30]

For the current project, we developed a suite of daily spatially refined pollutant metrics in an effort to directly reduce exposure measurement error in our epidemiological study. In a companion paper in this journal issue, we detail the development of these metrics and conduct extensive characterization.[31] For the current paper, we applied the metrics in epidemiological analyses. Specifically, we examined the impact on observed associations when (1) using spatially refined estimates of ambient concentrations compared with our conventional approach of using central site measurements and (2) using spatially refined estimates of ambient population exposures compared with spatially refined ambient concentrations. We hypothesized that the use of spatially refined metrics would provide greater ability to detect epidemiological associations of interest than urban central site monitors, particularly for heterogeneous, traffic-related pollutants. We also explored whether our refined metrics aid in identifying disparities in associations across geographically defined socioeconomic subpopulations.

MATERIALS AND METHODS

ED Visit Data

For SOPHIA, computerized billing records for all ED visits between 1 January 1993 and 31 December 2004 were collected from 41 of 42 EDs in the 20-county Atlanta area. Relevant data elements for this analysis included admission date, primary International Classification of Diseases 9th Revision (ICD-9) diagnostic code, and residential ZIP code. We selected visits occurring during the period 1 January 1999 to 31 December 2002 to correspond with the availability of the exposure metrics of interest. For this time period, 39 hospitals provided usable data, with 24 hospitals providing data for the full study period (<1 month of data missing) and 14 hospitals providing data for part of the study (≥ 4 months of missing data) (Figure 1).

There were 187 residential ZIP codes located partially or wholly within the 20-county Atlanta area, in effect during the study period and with complete US Census 2000 information. Air quality (i.e., APEX) modeling was conducted for 169 of these ZIP codes (Figure 1). Therefore, only patients residing in one of the 169 ZIP codes were included in the analytic database; this excluded data from 18 ZIP codes located in the outskirts of the study area and reduced the analytical ED visit database by $<1\%$ compared with the full database of 187 ZIP codes.

The individual-level data were aggregated to daily counts for each ZIP code for the following outcome groups, identified using primary ICD-9 codes: (1) respiratory disease (RD; which included visits for upper respiratory infection (ICD-9 codes: 460–465, 466.0, 477), bronchiolitis (ICD-9 codes: 466.1, 466.11, 466.19), pneumonia (ICD-9 codes: 480–486), chronic obstructive pulmonary disease (ICD-9 codes: 491, 492, 496), and asthma/wheeze (ASW; ICD-9 codes: 493, 786.07)); (2) ASW, a subset of the RD group; and (3) cardiovascular disease (CVD; which included visits for ischemic heart disease (ICD-9 codes: 410–414), cardiac dysrhythmia (ICD-9 code: 427), congestive heart failure (ICD-9 code: 428), peripheral and cerebrovascular disease (ICD-9 codes: 433–437, 440, 443–445, 451–453)).

Exposure Metrics Data

This project focused on the development of five alternative indicators of exposure to ambient traffic and regional pollutants

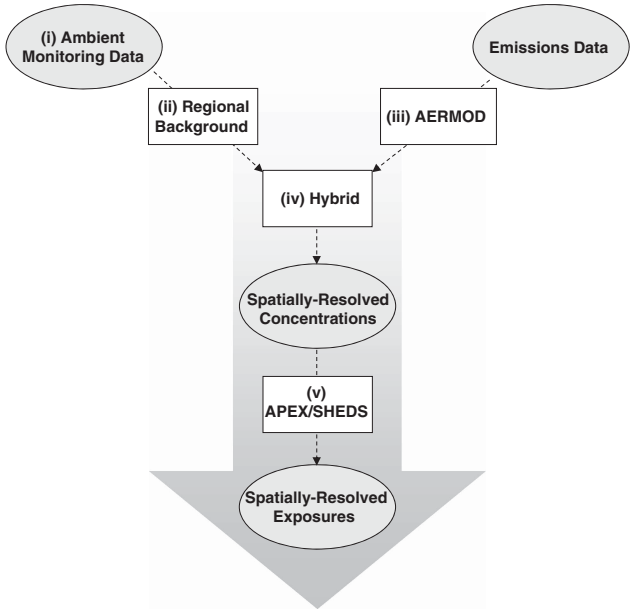

Figure 2. Schematic of the five exposure metrics.

(Figure 2). The metrics estimated daily 24-h average CO, NOx, $PM_{2.5}$, $PM_{2.5}$ SO_4, $PM_{2.5}$ EC, and 8-h maximum O_3 ambient concentrations and ambient population exposure distributions at each of the 169 ZIP code centroids. By modeling pollutant levels at ZIP code centroids, we assumed that the at-risk population density was flat within each spatial unit. A full description and characterization of the monitoring and modeling inputs and outputs are provided in a companion paper in this journal issue[31] and are described only briefly here.

Metric i: Central Site (CS). Ambient monitoring data for the 1999–2002 period were analyzed from various sources, including the Southeastern Aerosol Research and Characterization (SEARCH) network, the Environmental Protection Agency's Air Quality System (AQS), and the Assessment of Spatial Aerosol Composition in Atlanta (ASACA) network. For metric i, we selected a single central monitoring site for each pollutant, as was done in our previous analyses[25,26,32] (Supplementary Figure S1). For each pollutant, we then assigned the daily central site value to each ZIP code centroid (i.e., same daily values for each ZIP code) for the study period.

Metric ii: Regional Background (BG). We estimated spatially resolved regional background ambient concentrations, associated with synoptic patterns and photochemical transformations, for each of the pollutants using a modified version of our previously developed distance-squared weighting approach for ambient monitoring data.[33] In the current application, hourly data from six NO_x monitors, four CO monitors, 14 O_3 monitors, five $PM_{2.5}$ monitors, and two $PM_{2.5}$ composition monitors (which included the central sites used for metric i, Supplementary Figure S1) over the 1999–2002 study period were standardized, interpolated, and de-standardized using modeled annual means and SDs to provide estimates of regulatory ambient concentrations resolved to ZIP code centroids. For O_3 and $PM_{2.5}$ SO_4, these concentrations were taken directly as estimates of regional background concentrations. To obtain regional background levels of four primary pollutants (CO, NO_x, $PM_{2.5}$, and $PM_{2.5}$ EC), we removed the average fraction at each ZIP code attributed to local sources as predicted by local-scale modeling (see Metric iii).

Metric iii: AERMOD. Local-scale pollutant concentrations, associated with local-scale variations of emissions and meteorology, were estimated using the AERMOD (American Meteorological Society/Environmental Protection Agency Regulatory Model) dispersion model (version 09292). This model utilized information on local emission sources from the 2002 National Emissions Inventory, roadway emissions using detailed road network locations and traffic activity from the Atlanta Regional Commission Travel Demand Model (version 2008) using an improved methodology,[34] and local meteorological conditions from the Atlanta Hartsfield International Airport and the Jefferson St. site to estimate daily pollutant concentrations for CO, NOx, $PM_{2.5}$, $PM_{2.5}$ SO_4, and $PM_{2.5}$ EC at each ZIP code centroid. Because O_3 is formed by photochemical processes and has no direct emissions, O_3 concentrations were not modeled with AERMOD.

Metric iv: Hybrid. Daily estimates of total concentrations at each ZIP code centroid were obtained using a hybrid model that summed the local pollutant impacts obtained from AERMOD (Metric iii) and regional background levels obtained from BG (Metric ii) for CO, NOx, $PM_{2.5}$, $PM_{2.5}$ SO_4, and $PM_{2.5}$ EC. For O_3, regional background (Metric ii) levels were considered representative of total concentrations.

Metric v- APEX and SHEDS. Two different, but highly compatible, US EPA exposure models (APEX—the Air Pollutants Exposure model and SHEDS—the Stochastic Human Exposure and Dose Simulation model) were used to predict ambient exposure distributions for the population at each ZIP code, depending on availability of pollutant and Atlanta-specific inputs for each model. Exposure distributions for CO and NOx were estimated using the APEX[35,36] and those for O_3, $PM_{2.5}$, $PM_{2.5}$ SO_4, and $PM_{2.5}$ EC were estimated using the SHEDS.[20–22] The models were initially run at the census tract level, and outputs were aggregated to the ZIP code level for use in epidemiological analyses. The models used microenvironmental stochastic simulation algorithms to estimate the daily distribution of exposures for 100 simulated people per census tract considering all microenvironments (e.g., outdoor, indoor, commuting) in which individuals spend time. In this application, the APEX and SHEDS models utilized data on spatially resolved ambient concentrations from the hybrid model (Metric iv), time–location–activity data from the US EPA's Consolidated Human Activity Database,[37] spatiotemporally varying local air exchange rates,[38] and census tract-level home-to-work commuting data.[36,39] The models included infiltration of ambient pollution to indoor microenvironments, but did not include the contribution from indoor source emissions. As such, the exposure estimates represent exposure of individuals to ambient pollution resulting from the time spent in various microenvironments. In the current analysis, we considered the daily mean (APEXMEAN, SHEDSMEAN), 50th percentile (APEXP50, SHEDSP50), and 95th percentile (APEXP95, SHEDSP95) values from the predicted exposure distribution profiles for each pollutant.

Census Data

We obtained Census 2000 five-digit ZIP code tabulation area (ZCTA) data to describe area-level SES of the study population. We considered percentage of the population below the federal poverty line (% below poverty) as our primary SES indicator of interest; race (% black), educational attainment (% high school graduation), and income (median household income) were used in descriptive analyses. These data were linked to the ED visit records by the residential ZIP code of each patient.

Epidemiological Models

We used Poisson generalized linear models to examine associations between daily measures of air pollution and daily counts of

ED visits. The basic form of the model was:

$$\log(\mathrm{E}(Y_{kt})) = \alpha + \beta pollution_{kt} + \sum_k \lambda_k ZIP_k + \sum_m \lambda_m DOW_{mt} + \sum_n \nu_n hospital_{nt} + g(\gamma_1,\ldots,\gamma_N; time_t) + \sum_o \xi_o IOtemp_{ot} + \eta_1 dewpt_t + \eta_2 dewpt_t^2 + \eta_3 dewpt_t^3 + \delta_1 temp_t + \delta_2 temp_t^2 + \delta_3 temp_t^3$$

where Y_{kt} is the count of ED visits in ZIP code k on day t for the outcome of interest. For each pollutant (*pollution*), 3-day moving averages (of 0-, 1-, and 2-day lags) were used as the *a priori* lag structure for assessing RD and ASW ED visits, and same-day (lag 0) pollution levels were used when assessing the CVD ED visits. The geographical area (*ZIP*) from which ED counts were spatially aggregated was represented by indicator variables, to control for spatially varying factors and enable the analysis to rely solely on temporal contrasts; this also stringently controlled for spatial autocorrelation in the baseline ED visits across the ZIP codes. The models included dummy variables for day of week and holidays (*DOW)*. Hospital dummy variables (*hospital)* accounted for the entry and exit of hospitals during the study period, which impact ED visit counts over time. 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. Meteorology was controlled 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). For respiratory outcomes, we also included cubic terms for the moving average of minimum temperature (lags 1 and 2) and a dummy variable for season. For cardiovascular outcomes, we included cubic terms for the moving average of maximum temperature (lags 1 and 2). Variance estimates were scaled to account for Poisson overdispersion. These modeling decisions (e.g., choice of *a priori* lags and meteorological control) were derived largely from our previous analyses of these data.[28,29]

We compared associations for each pollutant-outcome combination among the five exposure metrics. In order to make valid comparisons, exposure metrics were also matched for missing values. For example, if data for a certain pollutant (e.g., CO) were missing for one exposure metric (e.g., CS) for a specific date, the data for that pollutant for all other exposure metrics were also set to missing for that date; the resulting sample size was the same for all epidemiological models for the same pollutant. We conducted analyses to examine the sensitivity of our results to this matching. We also conducted SES-stratified analyses, with stratum cut-points determined by the median value of % below poverty, to explore whether the spatially refined exposure metrics aid in identifying disparities in air pollution–health associations across socioeconomic subpopulations.

To compare the magnitude of effects across the different exposure metrics of the same pollutant, we scaled relative risks (RR) and 95% confidence intervals (CI) to interquartile range (IQR) increases in pollutant concentrations, determined from the distribution of all measurements across all ZIP codes and days separately for each metric. Standardizing the RRs by metric-specific IQRs (rather than a standard unit) allowed for more comparable comparisons of effects among exposure metrics that had very different distributions for the same pollutant. All epidemiological analyses were conducted in SAS V9.3 (SAS Institute, Cary, NC, USA), and mapping was conducted using ArcMap V10.0 (ESRI, Redlands, CA, USA).

RESULTS

Study Area Population and ED Visit Outcomes

Based on Census 2000, the population of the 169 ZIP codes was 4,207,873. Across ZIP codes, the population was on average 26% (range: 0–98%) black, 10% (range: 1–77%) below poverty, 81% (44–98%) with high school graduation, and had an average median household income of $51,530 (range: $14,094–$113,773). Our ED visit database included 453,069 visits (mean of 310.1 visits/day) for RD and 101,177 visits (mean of 69.3 visits/day) for CVD (Table 1). Daily outcome counts by ZIP code were low on average; 34.3%, 95.3%, and 93.5% of ZIP codes had a mean of <1 count/day for RD, ASW, and CVD, respectively. For RD, another 34.3% of ZIP codes had a mean of >2 counts/day. ZIP codes with highest mean daily counts were spread out over the study area, in part following trends in total population per ZIP code (Figure 3). Daily ED visits for the respiratory outcomes, RD and ASW, were moderately correlated with each other, with Spearman's correlation coefficients ranging from 0.26 to 0.65 across the ZIP codes; the respiratory outcomes were weakly correlated with CVD (Table 2).

Exposure Metrics Summary

Table 3 presents a summary of the exposure metrics data before and after the matching procedure. Matching increased the missingness substantially for some pollutants (e.g., for $PM_{2.5}$ SO_4) but enabled the sample size and days included to be the same across pollutant-specific exposure metrics.

For the traffic-related pollutants (i.e., CO, NOx, $PM_{2.5}$ EC), central site concentrations were generally higher than those estimated using the BG, AERMOD, and hybrid metrics. This was expected given that the central sites were located in the heavily trafficked urban area of Atlanta, whereas the other metrics incorporated concentration estimates from the entire study area. CO and NOx exposures estimated using APEX were on average higher than the hybrid concentrations, likely due to the fact that the APEX model accounted for proximity to low, moderate, and high traffic activity roads in modifying the hybrid ambient CO and NOx concentrations that were used as APEX inputs.[31]

For the regionally distributed pollutants (i.e., O_3, $PM_{2.5}$, $PM_{2.5}$ SO_4), central site concentrations were similar on average to those estimated using the BG and hybrid metrics (note, as discussed in the Materials and Methods section, hybrid levels were not

Table 1. Summary of the ED visit data for the three outcome groups of interest, overall and by ZIP code[a] for 20-county Atlanta, 1999–2002.

	Total ED visits				*Mean daily ED visits*			
	Overall	*By ZIP code*			*Overall*	*By ZIP code*		
		Median	*Min*	*Max*		*Median*	*Min*	*Max*
Respiratory disease	453,069	2,143	55	11,656	310.1	1.5	0	8.0
Asthma/wheeze[b]	84,526	373	6	2,724	57.9	0.3	0	1.9
Cardiovascular disease	101,177	551	8	2,101	69.3	0.4	0	1.4

[a]169 ZIP codes included.
[b]Asthma/wheeze group was a subset of the respiratory disease group.

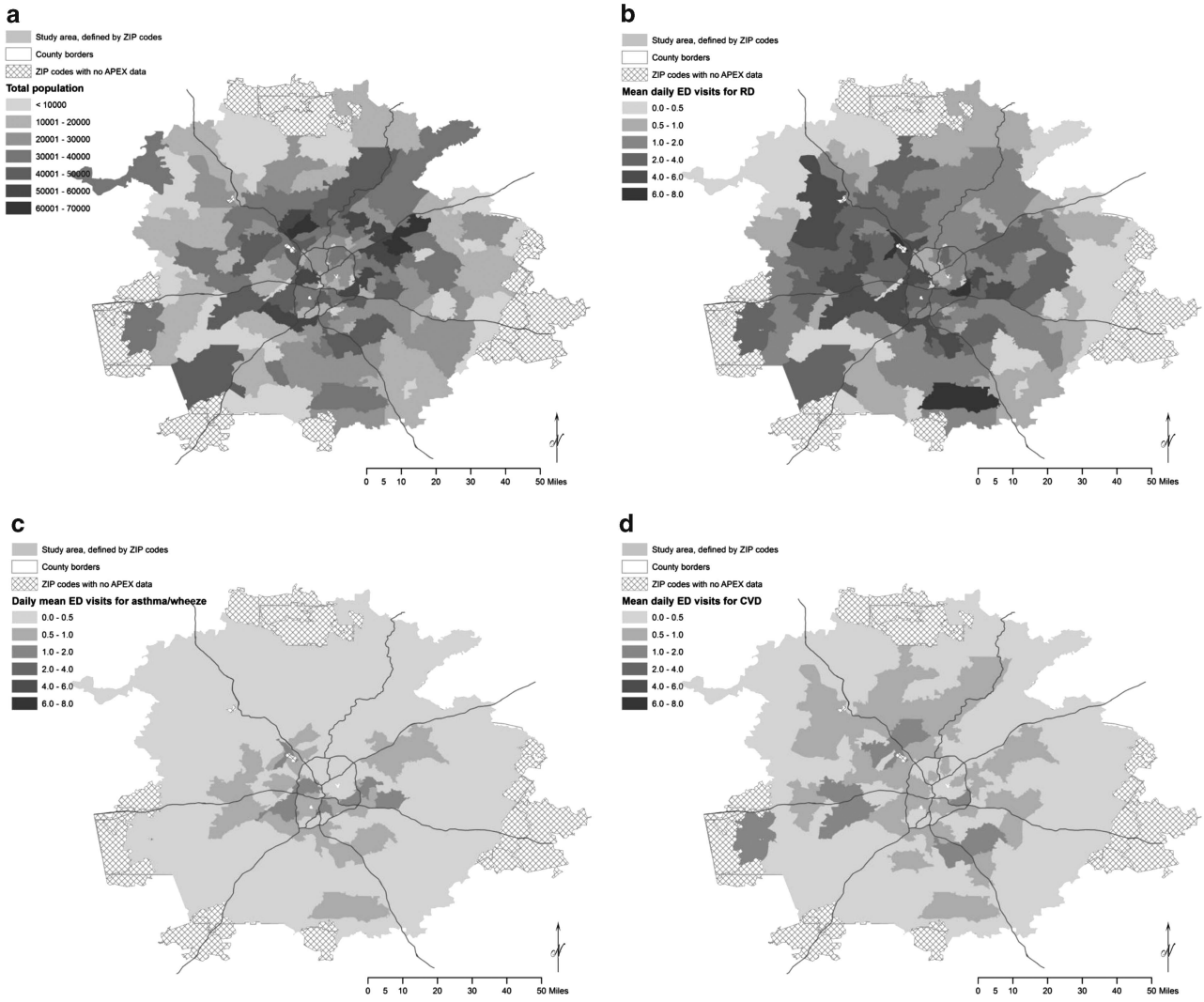

Figure 3. Total population (**a**) and mean daily ED visit counts across 169 ZIP codes in Atlanta during 1999–2002 for respiratory disease (**b**), asthma/wheeze (**c**), and cardiovascular disease (**d**).

Table 2. Spearman's correlation coefficients among daily ED visit counts for the outcome groups of interest for Atlanta, 1999–2002[a].

	Respiratory disease	*Asthma/ wheeze*	*Cardiovascular disease*
Respiratory disease		0.43 (0.26–0.65)	0.02 (− 0.07–0.35)
Asthma/wheeze	0.55		0.00 (− 0.07–0.18)
Cardiovascular disease	0.27	0.14	

[a]Bottom half of the table presents overall correlations across all ZIP code-days ($N = 246{,}909$); top half of the table presents median (range) of correlations within the 169 ZIP codes.

calculated for O_3). AERMOD estimates for $PM_{2.5}$ and $PM_{2.5}$ SO_4 were substantially lower compared with the corresponding BG estimates, as these pollutants arise mostly from regional (secondary) sources and not local (primary) sources. Ambient exposures estimated via SHEDS were lower for these pollutants on average than concentrations estimated using the BG and hybrid models, largely because the SHEDS model accounts for infiltration and removal losses of pollutants in indoor environments.[21,31]

Figure 4 presents the frequency distribution of ZIP code-specific Spearman's correlation coefficients relating each exposure metric to CS concentrations. For O_3, $PM_{2.5}$, and $PM_{2.5}$ SO_4, temporal correlations were high ($r > 0.8$) among all exposure metrics (except for AERMOD) and CS concentrations for each ZIP code. The results suggest that CS concentrations for these pollutants may adequately reflect temporal fluctuations in pollutant concentrations in all the ZIP codes in the study area,[31] which is characteristic of pollutants that exhibit high levels of spatiotemporal homogeneity. The distributions of correlation coefficients for the traffic-related pollutants (CO, NOx, and $PM_{2.5}$ EC) were wider, suggesting that the observed pattern of temporal variability at central sites for CO, NOx, and $PM_{2.5}$ EC may not reflect temporal patterns occurring in all the ZIP codes.

Epidemiological Results

Use of Central Site vs Spatially Refined Ambient Concentrations. When using our conventional approach of central site exposure assignment, we observed four significant (at a 0.05 significance level) positive associations: CVD with CO, RD with O_3, and ASW with O_3 and $PM_{2.5}$ EC (Figure 5, Supplementary Table S1). Broadly, we observed a pattern of stronger associations (larger RRs and/or

Table 3. Summary of daily ZIP code-level pollutant data for each exposure metric for the 169 ZIP codes in 20-county Atlanta, 1999–2002.

Pollutant	*Metric*[a]	*Prior to matching*							*After matching*						
		N	*No. of miss*	*Min*	*P25*	*P50*	*P75*	*Max*	*N*	*No. of miss*	*Min*	*P25*	*P50*	*P75*	*Max*
24-h avg CO	CS[b]	223,587	23,322	0.0042	0.40	0.55	0.77	2.52	223,080	23,829	0.0042	0.40	0.55	0.77	2.52
(ppm)	BG	246,740	169	0.027	0.16	0.19	0.25	1.54	223,080	23,829	0.042	0.16	0.20	0.25	1.54
	AERMOD	246,909	—	0.0000	0.037	0.12	0.32	9.15	223,080	23,829	0.0000	0.037	0.12	0.33	9.15
	HYBRID	246,740	169	0.054	0.21	0.33	0.57	9.68	223,080	23,829	0.073	0.21	0.33	0.58	9.68
	APEXMEAN	246,233	676	0.066	0.47	0.66	1.01	13.10	223,080	23,829	0.090	0.47	0.67	1.02	13.10
	APEXP50	246,233	676	0.066	0.33	0.47	0.72	9.75	223,080	23,829	0.084	0.34	0.48	0.73	9.75
	APEXP95	246,233	676	0.10	1.14	1.64	2.54	33.81	223,080	3829	0.144	1.15	1.65	2.57	33.81
24-h avg NOx	CS	240,149	6,760	0.0013	0.018	0.030	0.055	0.41	239,473	7436	0.0013	0.018	0.030	0.054	0.41
(ppm)	BG	246,909	—	0.0003	0.0033	0.0063	0.012	0.12	239,473	7436	0.0003	0.0033	0.0063	0.012	0.12
	AERMOD	246,909	—	0.0000	0.0035	0.011	0.029	0.83	239,473	7436	0.0000	0.0035	0.011	0.029	0.83
	HYBRID	246,909	—	0.0004	0.0079	0.018	0.041	0.87	239,473	7436	0.0004	0.0079	0.018	0.041	0.87
	APEXMEAN	246,233	676	0.0013	0.022	0.040	0.071	0.94	239,473	7436	0.0013	0.022	0.039	0.071	0.94
	APEXP50	246,233	676	0.0008	0.015	0.028	0.051	0.73	239,473	7436	0.0008	0.015	0.028	0.051	0.73
	APEXP95	246,233	676	0.0030	0.056	0.10	0.18	2.29	239,473	7436	0.0030	0.056	0.101	0.181	2.29
8-h max O_3	CS	237,276	9,633	0.0013	0.027	0.041	0.060	0.14	237,276	9633	0.0013	0.027	0.041	0.060	0.14
(ppm)	BG	246,740	169	0.0016	0.027	0.039	0.056	0.15	237,276	9633	0.0016	0.027	0.040	0.056	0.15
	SHEDSMEAN	246,909	—	0.0003	0.0080	0.012	0.017	0.046	237,276	9633	0.0003	0.0082	0.012	0.017	0.046
	SHEDSP50	246,909	—	0.0002	0.0069	0.010	0.015	0.041	237,276	9633	0.0002	0.0070	0.011	0.015	0.041
	SHEDSP95	246,909	—	0.0006	0.018	0.026	0.039	0.12	237,276	9633	0.0006	0.018	0.027	0.040	0.12
24-h avg $PM_{2.5}$	CS	239,473	7,436	1.74	11.06	15.81	22.14	65.81	220,038	26,871	1.74	10.89	15.37	21.72	65.81
($\mu g/m^3$)	BG	239,980	6,929	1.19	8.28	12.15	17.73	67.84	220,038	26,871	1.19	8.18	11.94	17.48	67.84
	AERMOD	246,909	—	0.0024	0.36	0.92	2.15	139.05	220,038	26,871	0.0024	0.36	0.92	2.16	139.05
	HYBRID	230,854	16,055	2.01	9.20	13.62	19.74	176.48	220,038	26,871	2.01	9.20	13.59	19.65	176.48
	SHEDSMEAN	246,909	—	0.87	4.42	6.45	9.23	62.73	220,038	26,871	0.87	4.38	6.34	9.11	62.73
	SHEDSP50	246,909	—	0.78	4.39	6.46	9.34	66.75	220,038	26,871	0.78	4.35	6.37	9.20	66.75
	SHEDSP95	246,909	—	1.34	6.31	9.35	13.43	86.46	220,038	26,871	1.36	6.21	9.13	13.15	86.46
24-h avg $PM_{2.5}$ SO_4	CS	218,686	28,223	0.53	2.51	3.96	6.25	19.04	204,490	42,419	0.53	2.51	3.97	6.29	19.04
($\mu g/m^3$)	BG	243,529	3,380	0.012	2.33	3.66	5.97	21.92	204,490	42,419	0.23	2.35	3.77	6.03	21.92
	AERMOD	246,909	—	0.0003	0.027	0.066	0.14	37.39	204,490	42,419	0.0003	0.027	0.067	0.14	9.69
	HYBRID	229,333	17,576	0.26	2.42	3.79	6.12	41.19	204,490	42,419	0.26	2.45	3.90	6.18	21.34
	SHEDSMEAN	246,233	676	0.016	1.30	1.97	3.18	23.33	204,490	42,419	0.15	1.32	2.03	3.24	13.96
	SHEDSP50	246,233	676	0.015	1.28	1.93	3.11	23.09	204,490	42,419	0.14	1.29	1.99	3.17	13.91
	SHEDSP95	246,233	676	0.022	1.70	2.60	4.25	29.29	204,490	42,419	0.19	1.72	2.68	4.30	17.91
24-h avg $PM_{2.5}$ EC	CS	235,417	11,492	0.054	0.86	1.34	2.01	11.89	214,461	32,448	0.054	0.83	1.27	1.89	7.79
($\mu g/m^3$)	BG	234,572	12,337	0.024	0.38	0.58	0.88	5.42	214,461	32,448	0.024	0.36	0.56	0.84	3.07
	AERMOD	246,909	—	0.0001	0.082	0.28	0.80	21.64	214,461	32,448	0.0001	0.082	0.28	0.81	15.09
	HYBRID	232,037	14,872	0.048	0.56	0.93	1.61	16.84	214,461	32,448	0.048	0.55	0.92	1.60	16.84
	SHEDSMEAN	246,909	—	0.036	0.37	0.60	1.01	15.29	214,461	32,448	0.036	0.36	0.58	0.98	8.50
	SHEDSP50	246,909	—	0.036	0.37	0.59	1.00	15.61	214,461	32,448	0.036	0.36	0.57	0.97	8.79
	SHEDSP95	246,909	—	0.042	0.45	0.74	1.26	19.64	214,461	32,448	0.042	0.44	0.71	1.22	11.75

[a]Exposure metric definitions: CS, central site; BG, background; AERMOD, American Meteorological Society/Environmental Protection Agency Regulatory Model; HYBRID, hybrid of BG and AERMOD model outputs; APEX, Air Pollution Exposure model (mean, 50th percentile (P50), and 95th percentile (P95) values from the predicted exposure distributions assessed); SHEDS, Stochastic Human Exposure and Dose Simulation model (mean, 50th percentile (P50), and 95th percentile (P95) values from the predicted exposure distributions assessed). Note: because O_3 is formed by photochemical processes and has no direct emissions, O_3 concentrations were not modeled with AERMOD, and therefore HYBRID levels were also not calculated for O_3.
[b]The CS metric includes daily central site values assigned to each ZIP code centroid (i.e., same daily values for each ZIP code).

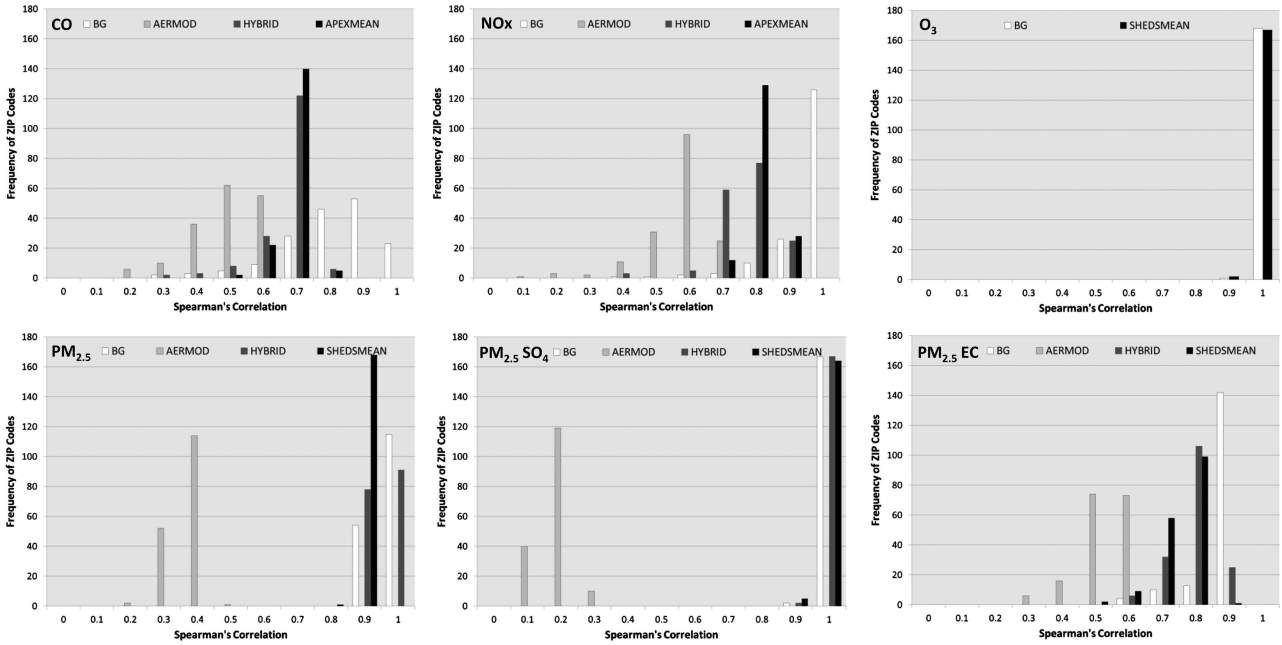

Figure 4. Frequency of Spearman's correlations between daily pollutant levels from the central site and each of the alternative exposure metrics across the 169 ZIP codes. Exposure metric definitions: BG = regional background; AERMOD = American Meteorological Society/ Environmental Protection Agency Regulatory Model; HYBRID = hybrid of BG and AERMOD model outputs. Note: because O_3 is formed by photochemical processes and has no direct emissions, O_3 concentrations were not modeled with AERMOD, and therefore HYBRID levels were also not calculated for O_3.

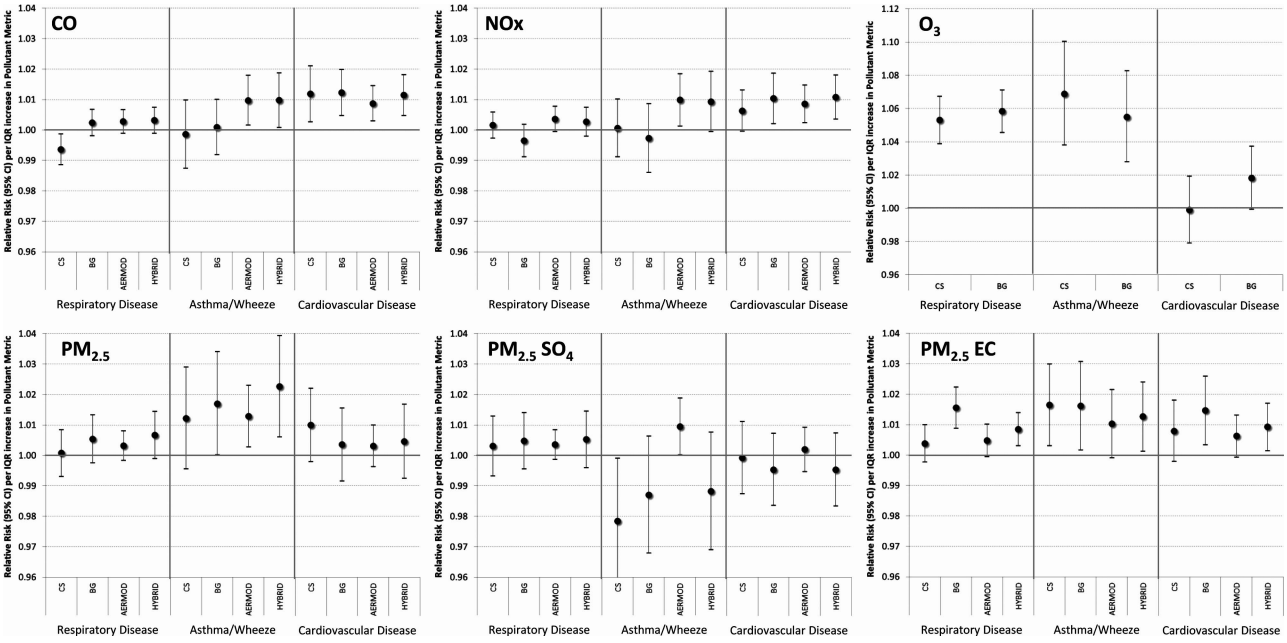

Figure 5. Associations between cardiorespiratory ED visits and central site and spatially refined ambient concentrations. Pollutant lag structures: 3-day moving average (of lags 0, 1, and 2) pollutant concentrations for respiratory disease and asthma/wheeze outcomes; lag 0 for cardiovascular outcomes. Exposure metric definitions: CS = central site; BG = regional background; AERMOD = American Meteorological Society/Environmental Protection Agency Regulatory Model; HYBRID = hybrid of BG and AERMOD model outputs. Note: because O_3 is formed by photochemical processes and has no direct emissions, O_3 concentrations were not modeled with AERMOD, and therefore HYBRID levels were also not calculated for O_3.

narrower CIs) for most relationships when using spatially refined ambient concentrations obtained through BG, AERMOD, and/or hybrid approaches. For example, the four significant associations observed when using CS data were similar or slightly stronger when incorporating the spatially refined metrics (e.g., CVD-CO from CS: 1.012 (95% CI: 1.003–1.021) compared with CVD-CO from hybrid: 1.011 (95% CI: 1.005–1.018)). Several additional significant associations were observed when using the spatially refined metrics that were not observed when using CS data, including: ASW with CO, NOx, and $PM_{2.5}$; CVD with NOx and $PM_{2.5}$ EC; and RD

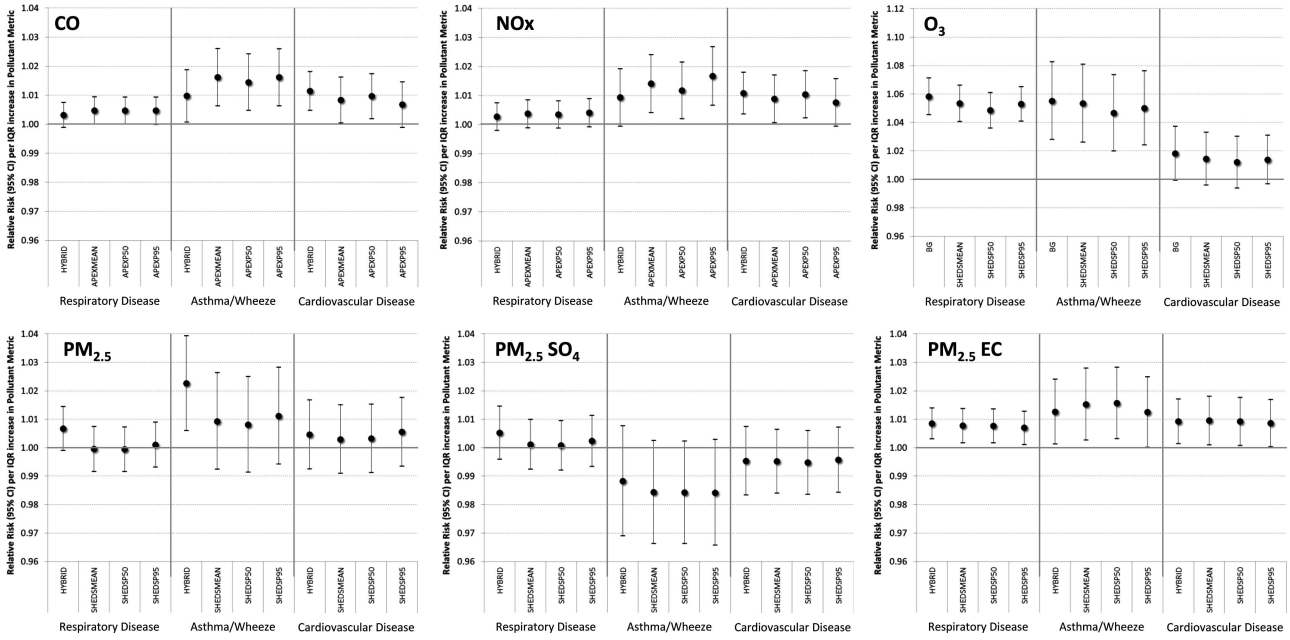

Figure 6. Associations between cardiorespiratory ED visits and spatially refined ambient concentrations and population exposures. Pollutant lag structures: 3-day moving average (of lags 0, 1, and 2) pollutant concentrations for respiratory disease and asthma/wheeze outcomes; lag 0 for cardiovascular outcomes. Exposure metric abbreviations: BG = regional background (used for O_3, where background levels were taken to represent total ambient concentrations and for which HYBRID levels were not calculated); HYBRID = hybrid of BG and AERMOD model outputs; APEX = Air Pollution Exposure model (using mean, 50th percentile (P50), and 95th percentile (P95) values from the predicted exposure distributions); SHEDS = Stochastic Human Exposure and Dose Simulation model (using mean, 50th percentile (P50), and 95th percentile (P95) values from the predicted exposure distributions).

Figure 7. Spatial distribution of 20-county Atlanta percentage of below poverty from the Census 2000 five-digit ZIP code tabulation area data, presented for strata used in epidemiological analyses.

with $PM_{2.5}$ EC (e.g., ASW-CO from CS: 0.999 (95% CI: 0.987–1.010) compared with ASW-CO from hybrid: 1.010 (95% CI: 1.001–1.019)).

Results of analyses on unmatched pollutant values (results not shown) were largely similar to those using data for matched pollutant values, particularly for CO, NOx, and O_3. Some differences in magnitude and significance of associations were noted for $PM_{2.5}$, $PM_{2.5}$ SO_4, and $PM_{2.5}$ EC, for which sample sizes between matched and unmatched data sets were most different.

Use of Spatially Refined Ambient Concentrations vs Ambient Population Exposures. For most relationships, associations were similar or slightly weaker when using ambient population exposure estimates from the SHEDS models compared with ambient concentrations from the hybrid model (Figure 6, Supplementary Table S2). However, associations of ASW with CO and NOx were modestly stronger using APEX predictions than using hybrid data (e.g., ASW-CO from hybrid: 1.010 (95% CI: 1.001–1.019) compared

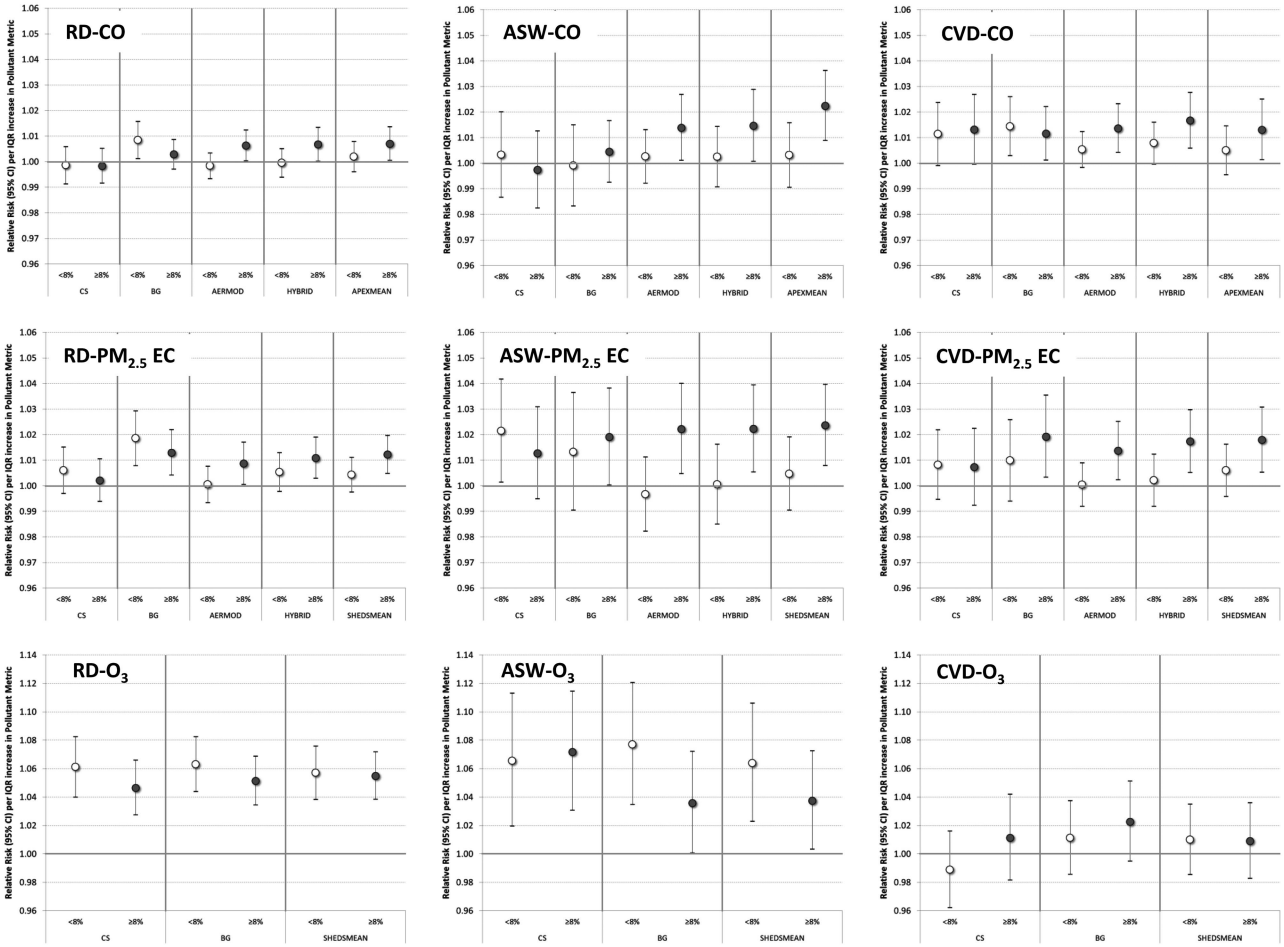

Figure 8. Associations between cardiorespiratory ED visits and CO, EC, and O_3 for each exposure metric, stratified by percentage of below poverty. Pollutant lag structures: 3-day moving average (of lags 0, 1, and 2) pollutant concentrations for respiratory disease and asthma/wheeze outcomes; lag 0 for cardiovascular outcomes. Exposure metric abbreviations: CS = central site; BG = regional background; AERMOD = American Meteorological Society/Environmental Protection Agency Regulatory Model; HYBRID = hybrid of BG and AERMOD model outputs; APEXMEAN = air pollution exposure model (using mean values from the predicted exposure distributions); SHEDS = Stochastic Human Exposure and Dose Simulation model (using mean values from the predicted exposure distributions). Note: because O_3 is formed by photochemical processes and has no direct emissions, O_3 concentrations were not modeled with AERMOD, and therefore HYBRID levels were also not calculated for O_3.

with ASW-CO from APEXMEAN: 1.016 (95% CI: 1.006–1.026)). Results of models examining the 50th and 95th percentile values from the APEX and SHEDS daily exposure distributions were very similar to those obtained using the daily mean values.

Assessment of Socioeconomic Subpopulations. We examined Census 2000 data on % below poverty to describe SES patterns in the study area and their relationship with our outcomes and pollutants of interest. Poverty levels varied widely over the 169 ZIP codes with a median value of 8% (range: 0.8–76.7%) and were correlated with other SES indicators (Spearman's r of -0.70 with % high school graduation and -0.89 with median household income). Percentage below poverty showed weak correlations with mean daily ED visit counts by ZIP code (Spearman's r of 0.09, 0.13, and -0.14 for RD, ASW, and CVD, respectively) and weak-to-moderate correlations with mean hybrid pollutant levels by ZIP code (Spearman's r of 0.18, 0.21, 0.31, 0.13, 0.31, and 0.14 for CO, NOx, O_3 (using BG metric), $PM_{2.5}$, SO_4, and EC, respectively), suggesting moderately higher pollution levels in ZIP codes with higher poverty. The spatial distribution of % below poverty, when stratified by its median value of 8%, showed a general pattern of high poverty in the inner and outer study areas and a ring of lower poverty in the middle suburban area (Figure 7).

We assessed and compared patterns of effect modification by % below poverty when using the different exposure metrics and present results for a subset of pollutants (CO, $PM_{2.5}$ EC, and O_3) (Figure 8). In general, observed associations when using central site data showed little difference by SES strata. However, for traffic-related pollutants (CO, $PM_{2.5}$ EC) when using spatially refined data, associations for the low SES group were consistently stronger than the high SES group—trends expected based on air pollution–health disparities literature.[40–42] For O_3, the results showed different patterns across poverty strata, but interpretation of results remained similar (i.e., observed associations were significant in both the strata). Patterns of results across SES strata for NOx and $PM_{2.5}$ were largely similar to those for CO and $PM_{2.5}$ EC; results for $PM_{2.5}$ SO_4 were mostly consistent with the null, with no clear pattern across SES strata (results not shown).

DISCUSSION

In this study, we developed and evaluated five alternative exposure metrics for a study of ambient air pollution and acute morbidity in Atlanta, GA, USA. These results add to the limited number of studies that have compared alternative estimates of measured and modeled exposures within a single study.[14,15]

Traffic emissions comprise a major source of ambient air pollution in Atlanta.[43] Consistent with results reported for other locations,[5,6] our previous work has shown that traffic-related pollutants exhibit a high degree of spatiotemporal variability in Atlanta,[3] and in simulation studies we have found that exposure misclassification may be substantial for these pollutants when using fixed site ambient monitoring data as the measure of exposure in epidemiological analyses.[30,44] Here, we applied an approach to directly reduce exposure measurement error in our epidemiological study with application of exposure metrics that were designed to enhance the spatial resolution of our ambient air concentration data, particularly for traffic-related pollutants (CO, NOx, $PM_{2.5}$ EC).

We observed patterns of association across the incrementally refined exposure metrics that were largely consistent with our *a priori* expectations. We observed greater estimated effects when using the spatiotemporally refined ambient concentrations and exposures compared with the use of central site monitoring data; this pattern was observed for most pollutants but was particularly evident for CO and NOx with respiratory outcomes. In keeping with the traditional time-series framework, our analyses were based on temporal comparisons, so any differences in observed associations between exposure metrics for a given relationship were due to the additional spatial resolution of temporal variability in pollutant levels. Although previous studies have used modeled mid- to long-term exposure estimates in epidemiological analyses,[8,12–15] few studies have explored the use of spatially refined exposure metrics in studies of acute morbidity that rely on temporal (and not spatial) variability as the driving exposure contrast.[16,17] Inadequate spatial resolution in a temporal analysis may cause bias and reduced significance due to both bias in the concentration estimates and lack of perfect correlation over time of concentrations in different areas of the study region.[30,44,45]

Our exposure metric time-series for each ZIP code centroid showed a range of correlation patterns with the central site measurements, particularly for the traffic-related pollutants (Figure 4). We anticipated that the temporal variability of the refined exposure metrics would better reflect the true temporal variability of ambient concentrations or ambient population exposures for a given ZIP code than would data from the central site. Thus, we expected a reduction in exposure misclassification when using the spatiotemporally refined exposure metrics as compared with central site monitoring data, particularly for traffic-related pollutants (e.g., CO, NOx, $PM_{2.5}$ EC). As a means of comparison, we also considered pollutants of secondary origin, particularly O_3 and $PM_{2.5}$ SO_4, which each exhibit little spatiotemporal variation in Atlanta,[3] and for which refined estimates of exposure may not be as critical. For these pollutants, associations were generally similar among the exposure metrics.

It is important to note that the different exposure metrics applied here describe different aspects of air quality. Although the CS and hybrid metrics estimated total pollutant concentrations, the BG metric estimated regional background concentrations, and the AERMOD metric estimated concentrations from local sources. Thus, when comparing observed associations among use of BG, AERMOD, and hybrid metrics, we ultimately compare the effects of different aspects of air quality. This was particularly evident when assessing the ASW-$PM_{2.5}$ SO_4 association, for which the only positive association was for $PM_{2.5}$ SO_4 from AERMOD. Although in total ambient air, $PM_{2.5}$ SO_4 is largely from regional sources, AERMOD $PM_{2.5}$ SO_4 provides estimates of primary sulfate from diesel vehicles and thus may be a surrogate for diesel emission impacts. This was evident by strong correlations (Spearman's $r \geq 0.89$) between AERMOD $PM_{2.5}$ SO_4 and other AERMOD measures (CO, NOx, $PM_{2.5}$, and $PM_{2.5}$ EC). In comparison, the correlation between hybrid $PM_{2.5}$ SO_4 and other hybrid traffic-related pollutant measures was substantially lower (Spearman's $r < 0.30$ with CO, NOx, and $PM_{2.5}$ EC; $r = 0.77$ with $PM_{2.5}$).

Our observed RRs for most of the relationships were small (RRs per IQR ≈ 1.01) but consistent with levels of association observed among other time-series studies of acute morbidity, including those from our other published studies.[25,26,28] For several relationships, associations were modestly stronger when using hybrid than when using central site data; out of the 18 pollutant–outcome associations considered, four significant positive associations were observed when using central site-exposure assignment; these associations plus six additional significant positive associations were observed when using the spatially refined BG or hybrid data. Enhanced detection of effects with such refined exposure metrics, when verified further, will be important for better ascertaining air pollution-related health risks in future epidemiological investigations. As the Atlanta population density is highest towards the study area center and location of central monitoring sites, the observation of only modest increases in observed risk ratios in overall analyses is a reasonable finding. Indeed, the main benefit of spatially resolved time-series data may be for application in spatially stratified analyses.

It is possible that spatial refinement in ambient concentrations and exposures may enable more accurate estimates of associations among population subgroups, which could ultimately inform targeted intervention efforts. For example, an increasing number of studies suggest that higher pollution–health associations exist among those with high poverty/deprivation,[46] low educational attainment,[47] and low income.[48–51] Inconsistencies in the epidemiological literature examining air pollution and SES are apparent, however, with some studies finding only weak or no impact of these factors on pollution–health associations.[16,52–55] Lack of agreement among study findings may be due to a variety of factors, including factors related to exposure measurement error. Most studies examining air pollution–SES interactions have utilized city- or county-wide air pollution metrics as the measure of exposure.[41] Disparities in monitoring representation among socioeconomic subsets in some locales may lead to differential exposure misclassification by subpopulation when relying on monitoring data for exposure assignment.[10,11] The presence of differing levels of exposure error across subgroups could lead to differential bias in observed air pollution health associations across subgroups that could ultimately result in an appearance of heterogeneity in the effect measure or to a masking of true heterogeneity (if groups with truly higher risk ratios have a stronger degree of bias to the null).

In our current analysis, we anticipated that use of spatially refined metrics would reduce the potential for differential exposure measurement error between geographically defined subpopulations and that this would enable identification of disparities in associations between groups. We observed that groups defined by SES had similar concentration-response functions when using central site data as the measure of exposure. These results could suggest either no difference in air pollution health risk between groups or perhaps the presence of exposure measurement error in one or both the groups that impact the pattern of observed associations. When using the spatially refined exposure metrics, our results indicated that low SES groups had considerably stronger concentration-response functions than the high SES groups, as is consistent with current air pollution–health disparities literature.[40–42] The difference in the SES-stratified results between the use of central site and spatially refined metrics supports the notion that the refined exposure metrics improved exposure estimation for the low socioeconomic subpopulation, at least to the degree that allowed for anticipated gradients in air pollution health risk to be observed.

There are several limitations of our analysis and corresponding interpretation of results. We conducted a semi-quantitative comparison of health risk estimates obtained from using different measures of exposure. In making certain assumptions (e.g., that refining the spatiotemporal resolution of our exposure estimates

will result in a lower amount of exposure measurement error), differences in estimated RRs when different exposure metrics are used may serve to illustrate differences in exposure measurement error between exposure metrics. If exposure measurement error is classical and non-differential with respect to a health outcome, we expect the bias to be towards the null when using an exposure measure containing error. According to this model, if the health outcome is caused by the exposure, using a more refined measure of exposure should result in less bias towards the null. Comparing estimated RRs is an indirect means of evaluating measurement error. As such, our comparisons may be considered exploratory and hypothesis generating. Conducting a more direct assessment of exposure misclassification for each of the exposure metrics, quantifying the nature and magnitude of uncertainties, and propagating them through to the epidemiological results was not possible given the scope of the current project but is of interest for future applications.

There were also limitations to the exposure modeling approaches that likely introduced error. We increased the spatial refinement in pollutant concentration estimates by utilizing AERMOD—the inputs to AERMOD included limited temporally varying input related to local emission sources and limitations of fine-scale meteorological inputs. Temporal variability in the predicted pollutant concentrations were, in turn, mainly driven by meteorological inputs and thus may have been attenuated compared with true temporal patterns of ambient pollution. This may have reduced the precision of the estimated coefficients in the epidemiological analyses. Even given these limitations, however, the results of epidemiological models using AERMOD and hybrid outputs corresponded with our expectations.

With regards to spatial refinement, the AQ modeling was conducted at the ZIP code centroid receptor locations. It is possible that these point receptors may experience pollutant concentrations that are not representative of an entire ZIP code. For example, if pollutant levels within a ZIP code are spatiotemporally heterogeneous, exposure assignment based on ZIP code centroids will likely contain errors that are analogous to the use of central site data to represent an entire study area. Spatial averages of multiple receptor locations (e.g., by census tract or block group resolution) in each spatial unit may have provided more representative estimates and will be considered in future work.

In the epidemiological models, estimates of population exposures (i.e., from APEX and SHEDS) produced modestly stronger estimates of effect than ambient concentrations for select relationships (e.g., CO and NOx with ASW). However, for most other relationships observed associations were similar or slightly weaker when using APEX or SHEDS data compared with ambient concentration data. As APEX and SHEDS model exposure factors, such as pollutant infiltration and population mobility patterns, and are derived to estimate population exposure more accurately, we anticipated that use of these modeled data would aid in identifying air pollution–health associations by reducing exposure measurement error. The propagation of modeling errors through these complex exposure models, which incorporate multiple model inputs and algorithms with varying degrees of uncertainty (e.g., uncertainties in predicting roadway emissions, atmospheric dispersion near roadways, microenvironmental infiltration factors, etc.), may have hampered the ability to discern the benefits gained by using refined exposure metrics, in comparison to much simpler monitoring-based measurement data. Although time-activity diaries, exposure factors, and non-residential microenvironmental infiltration factors were selected to be representative for the study area, these may not have been fully accurate locally, spatially, or temporally. Development of approaches that incorporate exposure uncertainties in health models[56–58] will be key to furthering the application of these approaches to air pollution epidemiology.

In addition, we considered the daily mean and 50th and 95th percentile values from the predicted exposure distributions in each ZIP code in our epidemiological models. As such, we did not utilize the distributional aspect of the exposure data, and as a result our modeling is still subject to ecological bias (assigning a common exposure value to the entire population of each ZIP code).[59] Moreover, as these models predict exposures for a simulated population, it is not directly possible to understand how the exposure distribution for the simulated population relates to that experienced by the ED visit patient population and which patients received which exposures. Future analyses are planned that will consider subsets of the simulated and ED visit populations (e.g., by age and gender) that may make the exposure profiles from APEX and SHEDS more tailored to our outcomes.

Finally, a few unexpected associations were observed. For O_3, associations with CVD ED visits were different between use of CS (RR = 0.999, *P*-value = 0.919) and BG (RR = 1.018, *P*-value = 0.058) data, despite the strong correlation (>0.90) between these metrics. For EC, associations tended to be strongest when using the BG metric. It is possible that the results were sensitive to slight differences between the daily ZIP code-level exposure metrics due to the low ED visit counts per day per ZIP code (e.g., 93.5% of ZIP codes had a mean of <1 count/day for CVD); this is a limitation for all the reported results.

In summary, we developed and evaluated five alternative exposure metrics for a study of air pollution and acute morbidity in Atlanta, GA, USA. In doing so, we importantly addressed two key areas of benefit to environmental health related to exposure assessment in epidemiological models—incorporation of spatial refinement and prediction of population exposures. We observed that incorporation of spatially refined ambient concentration data enabled greater detection of air pollution–health associations than did central site exposure assignment, particularly for traffic-related pollutants and in geographically defined socioeconomic subpopulations. We anticipate that the results of this research will be useful in improving exposure assessment in future air pollution epidemiology studies, by providing alternative methods as well as by providing a further understanding as to the situations that might require refined exposure metrics. Overall, these outputs will help to reduce uncertainty in health risk assessments of ambient air pollution, which in turn will increase the efficiency and effectiveness of federal and state/local air quality management strategies.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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