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Supplemental Material

Long-Term Exposure to Low-Level NO_2 and Mortality among the Elderly Population in the Southeastern United States

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Table S1. Summary statistics[a] of Full cohort (N=13,590,387) and Below-WHO guidelines cohort (N=9,669,469) for area-level variables from 2000 to 2016, in seven southeastern U.S states [b]

	Full cohort	Below WHO guideline cohort [c]
NO_2, ppb	13.7 (5.9)	11.0 (3.7)
$PM_{2.5}$, µg/m^3	9.7 (2.6)	9.6 (2.5)
Ozone, ppb	40.3 (6.20	40.5 (5.6)
Percent Hispanic, %	9.4 (15.1)	8.0 (12.4)
Percent Black, %	18.4 (20.3)	17.7 (18.9)
Smoking rate, %	47.6 (7.1)	45.6 (7.1)
Below poverty Level, %	10.8 (6.8)	10.8 (6.4)
Not graduated from high school, %	26.8 (15.1)	27.1 (15.0)
Owner-occupied housing units, %	70.4 (13.4)	72.7 (11.4)
Population density, people per $mile^2$	1516.4 (2170.2)	857.9 (1396.9)
Body-mass index, kg/m^2	27.5 (1.0)	27.7 (1.0)
Median house value, US$1000	149.2 (85.9)	142.1 (83.5)
Median household income, US$1000	46.0 (15.8)	45.2 (15.0)
Winter mean temperature, Celsius	26.6 (1.7)	26.5 (1.6)
Summer mean temperature, Celsius	11.1 (5.9)	10.4 (5.5)

Note: WHO, World Health Organization

[a] Presented as mean (standard deviation)

[b] The seven states include Alabama, Florida, Georgia, Mississippi, North Carolina, South Carolina, and Tennessee

[c] The cohort was restricted to populations who were always exposed to annual mean NO_2 levels below the current WHO guidelines, i.e. 40 µg/m^3.

Table S2. Estimated Hazard Ratio of Mortality (95% CI) associated with an Increase of 10 μg/m^3 in $PM_{2.5}$ Concentration or 10 ppb in O_3 Concentration in the Full Cohort (N = 13,590,387).

	$PM_{2.5}$	O_3
Models	**HR (95% CI)**	**HR (95% CI)**
Single-pollutant [a]	1.078 (1.054, 1.103)	1.014 (1.002, 1.026)
Bi-pollutant (adjusted for NO_2) [b]	1.040 (1.016, 1.065)	0.995 (0.983, 1.007)
Tri-pollutant [c]	1.059 (1.032, 1.086)	0.985 (0.971, 0.998)

Note: CI, confidence interval; NO_2, nitrogen dioxide; $PM_{2.5}$, particulate matter < 2.5 μm in aerodynamic diameter; O_3, ozone

[a] Single-pollutant model: stratified by age at entry (5-year categories), gender (female, male), race (White, Black, and other), Medicaid eligibility, and adjusted for calendar-year, summer and winter mean temperature, median home value, median household income, population density, the proportion of owner-occupied housing units, the percentage of Black and Hispanic populations, education level, population below poverty level, body mass index, and the proportion of those who were ever smokers. The descriptive statistics for these variables were provided in Table 1 and Table S1

[b] Bi-pollutant (+NO_2): Single-pollutant model further adjusted for annual mean of NO_2

[c] Tri-pollutant: For estimates of $PM_{2.5}$, the Single-pollutant model further adjusted for annual mean of NO_2 and annual warm-season average of O_3**;** For estimates of O_3, the Single-pollutant model further adjusted for annual mean of NO_2 and annual warm-season average of $PM_{2.5}$

Table S3 Hazard Ratios of Mortality (95% CI) associated with an Increase of 10 ppb in NO_2 Concentration by Study Subgroups in Full Cohort (N = 13,590,387)

	Subgroups	HR (95% CI)	P-value [a]
Sex	Female	1.077 (1.062, 1.091)	Reference
	Male	1.009 (0.997, 1.021)	*<0.001*
Age	<80	1.055 (1.034, 1.076)	Reference
	≥80	1.029 (1.012, 1.046)	0.056
Race	White	1.060 (1.050, 1.071)	Reference
	Black	1.002 (0.984, 1.019)	*<0.001*
	Other	0.979 (0.937, 1.022)	*<0.001*
Medicaid Eligibility	Dual	1.029 (1.009, 1.049)	Reference
	Non-dual	1.054 (1.038, 1.070)	0.054
Poverty	High Poverty	1.049 (1.041, 1.056)	Reference
	Low Poverty	1.046 (1.035, 1.056)	0.629
Urbanicity [b]	Density Q1	1.010 (0.990, 1.030)	Reference
	Density Q2	1.036 (1.021, 1.051)	0.040
	Density Q3	1.032 (1.015, 1.048)	0.091
	Density Q4	1.057 (1.038, 1.076)	*<0.001*

Note: CI, confidence interval; HR, hazard ratio; NO_2, nitrogen dioxide
[a] P-values were evaluated by Wald test (Kaufman and MacLehose 2013)
[b] Density Q1-Q4 stand for low population density, low-medium population density, medium-high population density, and high population density, respectively

Reference:
Kaufman JS, MacLehose RF. 2013. Which of these things is not like the others? Cancer 119:4216-4222.

Table S4. Estimated Hazard Ratio of Mortality (95% CI) associated with an Increase of 10 ppb in NO_2 Concentration at different levels of confounding adjustment

	Full cohort (N = 13,590,387)	Below WHO guideline cohort [a] (N = 9,669,469)
Main Analysis [b]	1.047 (1.044, 1.049)	1.047 (1.045, 1.049)
Excluding co-pollutants [c]	1.042 (1.039, 1.044)	1.042 (1.040, 1.045)
Excluding time trends [d]	1.250 (1.248, 1.253)	1.251 (1.248, 1.254)
Excluding meteorological variables [e]	1.043 (1.040, 1.045)	1.043 (1.041, 1.045)
Excluding BRFSS variables [f]	1.046 (1.044, 1.049)	1.047 (1.044, 1.049)
Excluding US Census variables [g]	1.065 (1.063, 1.067)	1.065 (1.063, 1.067)
Excluding baseline hazard stratification [h]	1.021 (1.019, 1.023)	1.021 (1.019, 1.024)
Adjusting for space at state level [i]	1.047 (1.044, 1.049)	1.047 (1.044, 1.049)
Adjusting for space using spatial smoother (with 5 d.f. for both latitude and longitude) [j]	1.045 (1.042, 1.047)	1.045 (1.043, 1.048)

Note: Estimates are based on 10 ppb increments for NO_2. WHO, World Health Organization; CI, confidence interval; NO_2, nitrogen dioxide; $PM_{2.5}$, particulate matter < 2.5 μm in aerodynamic diameter; O_3, ozone; BRFSS, Behavioral Risk Factor Surveillance System

[a] The cohort was restricted to populations who were always exposed to annual mean NO_2 levels below the current WHO guideline, i.e. 40 $\mu g/m^3$.

[b] Main Analysis: stratified by age at entry (5-year categories), gender (female, male), race (White, Black, and other), Medicaid eligibility, and adjusted for annual mean of $PM_{2.5}$ and annual warm-season average of O_3, calendar-year, summer and winter mean temperature, median home value, median household income, population density, the proportion of owner-occupied housing units, the percentage of Black and Hispanic populations, education level, population below poverty level, body mass index, and the proportion of those who were ever smokers. The descriptive statistics for these variables were provided in Table 1 and Table S1

[c] Adjusted covariates in Main Analysis except for $PM_{2.5}$ and O_3 [d] Adjusted covariates in Main Analysis except for calendar year

[e] Adjusted covariates in Main Analysis except for summer and winter mean temperature [f] Adjusted covariates in Main Analysis except for body mass index and proportion of those who were ever smokers

[g] Adjusted covariates in Main Analysis except for median home value, percentage of owner-occupied housing units, median household income, population density, percentage of Black population, percentage of Hispanic population, percentage of low education-level (i.e., with less than a high school degree), and the percentage of below the poverty level

[h] Adjusted covariates in Main Analysis except for age at entry (5-year categories), gender (female, male), race (White, Black, and other), and Medicaid eligibility [i] Main Analysis further adjusted for states

[j] Main Analysis further adjusted for a spatial smoother with 5 degrees of freedom for both latitude and longitude

Table S5. The Hazard Ratio of Mortality (95% CI) associated with an Increase of 10 ppb in NO_2 Concentration by state

	Full cohort (N = 13,590,387)	Below WHO guideline cohort [a] (N = 9,669,469)
Tennessee	1.006 (1.000, 1.013)	1.007 (1.001, 1.014)
Alabama	1.050 (1.038, 1.063)	1.050 (1.038, 1.063)
Florida	1.039 (1.034, 1.044)	1.039 (1.034, 1.044)
Georgia	1.018 (1.011, 1.025)	1.018 (1.011, 1.025)
Mississippi	1.049 (1.032, 1.067)	1.049 (1.032, 1.067)
North Carolina	1.067 (1.060, 1.074)	1.067 (1.060, 1.074)
South Carolina	1.031 (1.020, 1.043)	1.031 (1.020, 1.043)

Note: CI, confidence interval; NO_2, nitrogen dioxide; WHO, World Health Organization

[a] The cohort was restricted to populations who were always exposed to annual mean NO_2 levels below the current WHO guideline, i.e. 40 $\mu g/m^3$.

Table S6 Descriptive characteristics of NO_2 and mortality cohort studies published from 2006-2021

Study	Study period	Total population	Mean age (SD[a]) or range in years	Exposure assessment	Exposure window	Mean annual exposure (SD[a]) or range	Study population	Hazard Ratio (95% CI) per 10 ppb increase	Co-pollutant adjusted in the model
USA									
Ritz et al. (2006)	1989-2000	55,818	0-1	Air monitoring stations	2-month average	3.84 (1.51) pphm	South Coast Air Basin (SoCAB)	1.08 (1.04, 1.11)	-
Lipfert et al. (2006)	1997-2001	26,843	51 (12)	Air monitoring sites	Annual average	21.5 (6.1) ppb	Infants	1.02 (0.98, 1.06)	-
Hart et al. (2011)	1985-2000	53,814	42.1 (9.9)	Spatial smoothing exposure model	Annual average	14.2 (7.1) ppb	US Trucking Industry cohort	1.10 (1.06, 1.15)	Either PM_{10} or $PM_{2.5}$ with SO_2
Lipsett et al. (2011)	1997-2005	12,366	≥ 20	Air monitoring stations	Monthly average	33.59 (9.63) ppb	California Teachers Study (CTS)	0.97 (0.91, 1.03)	-
Hart et al. (2013)	1990-2008	84,562	30-55	Generalized additive models	2-year average	13.9 ppb[b]	Nurses' Health Study (NHS)	1.34 (0.43, 4.16)	-
Jerrett et al. (2013)	1982-2000	73,711	≥30	Land use regression	Annual average	12.27 (2.92) ppb	American Cancer Society's Cancer Prevention Study II (ACS CPS-II)	1.15 (1.04, 1.28)	-
Eckel et al. (2016)	1988-2009	352,053	69.3 (11.0)	Air monitoring stations	Monthly average	21.9 (10.2) ppb	Lung cancer patients	1.13 (1.12, 1.14)	-
Turner et al. (2016)	1982-2004	669,046	≥ 30	Land use regression	Annual average	11.6 (5.1) ppb	American Cancer Society's Cancer Prevention Study II (ACS CPS-II)	1.04 (1.03, 1.05)	$PM_{2.5}$, O_3
Eum et al. (2019)	2000-2008	14.1million	65-120	Air monitoring stations	Annual average	14.2 ppb[b]	U.S. Medicare cohort	1.04 (1.04, 1.05)	$PM_{2.5}$
Canada									
Jerrett et al. (2009)	1992-2002	2,360	60[b]	Land use regression	2-year average	22.9 ppb	Toronto respiratory cohort	1.48 (1.02 2.14)	-

Crouse et al. (2015)	1991-2006	2,521,525	25-89	Land use regression	Annual average	11.6 (6.7) ppb	Canadian Census Health and Environment Cohort (Can CHEC)	1.06 (1.06, 1.07)	$PM_{2.5}$, O_3
Crouse et al. (2015)	1991-2006	735,590	25-89	Land use regression	Annual average	25.2 (2.5) ppb	Canadian Census Health and Environment Cohort (Can CHEC)	1.10 (1.06, 1.15)	-
Paul et al. (2020)	2001-2015	4,774,984	53.0 (13.0)	Land use regression	Annual average	16.0 ppb	The Ontario Population Health and Environment Cohort (ONPHEC)	1.03 (1.03, 1.05)	-
Zhang et al. (2021)	2009-2017	88,615	52.1 (12.1)	Land use regression	Annual average	10.9 ppb	The Ontario Health Study	1.40 (1.31, 1.49)	$PM_{2.5}$
Germany									
Gehring et al. (2006)	1985-2003	4,752	50-59	Air monitoring stations	5-year average	39 μg/m^3	German cohort	1.23 (1.02, 1.47)	-
Heinrich et al. (2013)	1985-2008	4,752	50-59	Air monitoring sites	Annual average	39 μg/m^3	German Women's Health cohort	1.22 (1.08, 1.36)	-
Netherlands									
Beelen et al. (2008)	1987-1996	120,852	58-67	Interpolation, regressions, and GIS	10-year average	36.9 (8.2) μg/m^3	The Netherlands Cohort Study on Diet and Cancer (NLCS)	1.05 (1.00, 1.10)	-
Fischer et al. (2015)	2004-2011	7,218,363	≥ 30	Land use regression	Annual average	31 μg/m^3 *b*	The Dutch Environmental Longitudinal Study (DUELS)	1.06 (1.04, 1.08)	PM_{10}
Klompmaker et al. (2020)	2013-2017	244,814	≥ 30	Land use regression	Annual average	23.08 (7.54) μg/m^{3b}	A national health survey (Public Health Monitor, PHM)	0.98 (0.93, 1.02)	-
Klompmaker et al. (2021)	2008-2012	10,532,360	>29	Dispersion model	Annual average	23.9 (6.8) μg/m^3	Dutch national cohort	1.03 (1.01, 1.05)	-
UK									
Maheswaran et al. (2010)	1995-2006	3,320	70.3 (14.6)	Air monitoring sites	Annual average	41 (3.3) μg/m^3	South London Stroke cohort	1.91 (1.28, 2.85)	-

Carey et al. (2013)	2003-2007	830,429	40-89	Air dispersion model	Annual average	22.5 (7.4) μg/m^3	Clinical Practice Research Datalink	1.13 (1.07, 1.18)	-
Tonne et al. (2013)	2004-2010	154,204	68 (13)	Gaussian dispersion model	Annual average	18.8 μg/m^3	Myocardial Ischaemia National Audit Project (MINAP)	1.02 (0.96, 1.08)	NO_x, $PM_{2.5}$, PM_{10}
Halonen et al. (2015)	2003-2010	>8,000,000	≥ 25	KCL urban dispersion model	Annual average	38.9 (6.21) μg/m^3	London cohort	0.95 (0.87, 1.05)	-
Italy									
Cesaroni et al. (2012)	2001-2006	684,204	45-80	Land use regression	Annual average	45.7 (5.9) μg/m^3	Rome Longitudinal Study (RoLS)	1.12 (1.08, 1.16)	-
Cesaroni et al. (2013)	2001-2010	1,265,058	≥ 30	Land use regression	Annual average	43.6 (8.4) μg/m^3	Rome Longitudinal Study (RoLS)	1.06 (1.04, 1.08)	-
Denmark									
Hvidtfeldt et al. (2019)	1993-2015	49,564	50-64	THOR/AirGIS dispersion model	Annual average	25.0 μg/m^3 [b]	The Diet, Cancer and Health cohort	1.10 (1.02, 1.18)	-
So et al. (2020)	1993-2013	24,541	53.2 (8.0)	Danish air pollution dispersion modeling system (DEHM/UBM /AirGIS)	Annual average	13.4 (8.0) μg/m^3	Danish Nurse Cohort	0.83 (0.76, 0.92)	$PM_{2.5}$
France									
Bentayeb et al. (2015)	1989-2013	20,327	43.7 (3.5)	CHIMERE chemistry- transport model	Annual average	23 (12.1) μg/m^3	Gazel cohort	1.09 (0.89, 1.34)	-
Sanyal et al. (2018)	1999-2012	13,239	≥ 15	CHIMERE chemistry- transport model	Annual average	4.55-46.96 μg/m^3	French cohort	1.01 (1.00, 1.01)	$PM_{2.5}$, O_3
Spain									
de Keijzer et al. (2017)	2009-2013	44,561,414	NA[c]	CALIOPE air quality forecasting system	Annual average	9.48 μg/m^3	Spain cohort	1.00 (1.00, 1.01)	-
Nieuwenhuijsen et al. (2018)	2010-2014	792,649	50.9 (18.3)	Land use regression	Annual average	53.42 μg/m^3	SIDIAP cohort [d]	1.04 (1.00, 1.08)	-
Greece									
Kasdagli et al. (2021)	2011	NA[c]	NA[c]	Hybrid land use regression	Annual average	13.26 (7.84) μg/m^3	Census data	1.14 (1.14, 1.18)	-
Europe									

Beelen et al. (2014)	1985-2007[e]	367,251	All ages	Land use regression	Annual average	5.2-59.8 μg/m^3	European Study of Cohorts for Air Pollution Effects (ESCAPE)	1.02 (0.98, 1.06)	-
Samoli et al. (2021)	1992-2005	325,367	49 (13)	Land use regression	Annual average	25 (8) μg/m^3	European Study of Cohorts for Air Pollution Effects (ESCAPE)	1.08 (1.02, 1.14)	-
Japan									
Yorifuji et al. (2010)	1999-2006	13,444	74 (5.5)	Land use regression	Annual average	35.75 (11.28) μg/m^3	The Shizuoka elderly cohort	1.04 (1.93, 1.16)	-
Yorifuji et al. (2013)	1999-2009	13,412	74 (5.4)	Land use regression	Annual average	22 (15) μg/m^3	The Shizuoka elderly cohort	1.24 (0.45, 3.43)	-
Yorifuji et al. (2020)	2006-2016	73,970	>40	Land use regression	Annual average	31.4 (4.7) μg/m^3	Health checkups in Okayama City, Japan	1.12 (1.04, 1.22)	-
China									
Chen et al. (2016)	1998-2009	39,054	44.29 (13.95)	Air monitoring stations	Annual average	40.66 μg/m^3	Four Northern Chinese city	0.96 (0.95, 0.97)	PM_{10} or SO_2
Yang et al. (2018)	1998-2011	66,820	70.2 (5.5)	Land use regression	Annual average	104 (25.6) μg/m^3	Hong Kong Elderly Health Service Cohort	1.00 (0.90, 1.11)	BC, $PM_{2.5}$
South Korea									
Kim et al. (2017)	2007-2013	136,094	42.05 (14.83)	Air monitoring stations	Annual average	34.45 (12.92) ppb	National Health Insurance Service-National Sample (NHIS-NSC) Cohort	1.48 (1.41, 1.55)	$PM_{2.5}$, $PM_{2.5-10}$, CO, SO_2, O_3
Jung et al. (2020)	2008-2015	5,041	60.48 (13.52)	Air monitoring stations	Annual average	28.13 (6.89) ppb	Clinical Research Center for End-Stage Renal Disease (CRC-ESRD) cohort	1.34 (1.07, 1.68)	-
Australia									
Dirgawati et al. (2019)	1996-2012	11,627	72.1 (4.4)	Land use regression	Annual average	13.4 (4.1) μg/m^3	Health in Men Study (HIMS)	1.12 (1.00, 1.25)	-
Hanigan et al. (2019)	2007-2015	75,145	45-79	Satellite-based spatial Regression model	Annual average	17.75 (4.80) μg/m^3	"45 and up study" Cohort	1.12 (0.93, 1.35)	-

Note: CI, confidence interval; WHO, World Health Organization; HR, hazard ratio; NO_2, nitrogen dioxide; $PM_{2.5}$, particulate matter < 2.5 μm in aerodynamic diameter; PM_{10}, particulate matter < 10 μm in aerodynamic diameter; NO_x, nitrogen oxide; O_3, ozone; CO, carbon oxide; SO_2, sulfur dioxide; BC, black carbon

[a] SD = standard deviation

[b] median

[c] NA indicates Not Applicable

[d] SIDIAP = Sistema d'Informació pel Desenvolupament de la Investigació en Atenció Primària

[e] baseline study period

Table S7. Standard Errors Estimated before and after accounting for Spatial Dependence in both cohorts.

	Model	Before bootstrapping	After bootstrapping
Full cohort	**Single pollutant**	0.0001138	0.0001142
	Bi-pollutant (NO_2+$PM_{2.5}$)	0.0001145	0.0001150
	Bi-pollutant (NO_2+O_3)	0.0001163	0.0001165
	Tri-pollutant	0.0001164	0.0001168
Below WHO guideline *cohort* [a]	**Single pollutant**	0.0001139	0.0001142
	Bi-pollutant (NO_2+$PM_{2.5}$)	0.0001146	0.0001151
	Bi-pollutant (NO_2+O_3)	0.0001164	0.0001166
	Tri-pollutant	0.0001165	0.0001168

Note: WHO, World Health Organization; NO_2, nitrogen dioxide; $PM_{2.5}$, particulate matter < 2.5 μm in aerodynamic diameter; O_3, ozone
[a] The cohort was restricted to populations who were always exposed to annual mean NO_2 levels below the current WHO guideline, i.e. 40 μg/m^3.

Figure S1

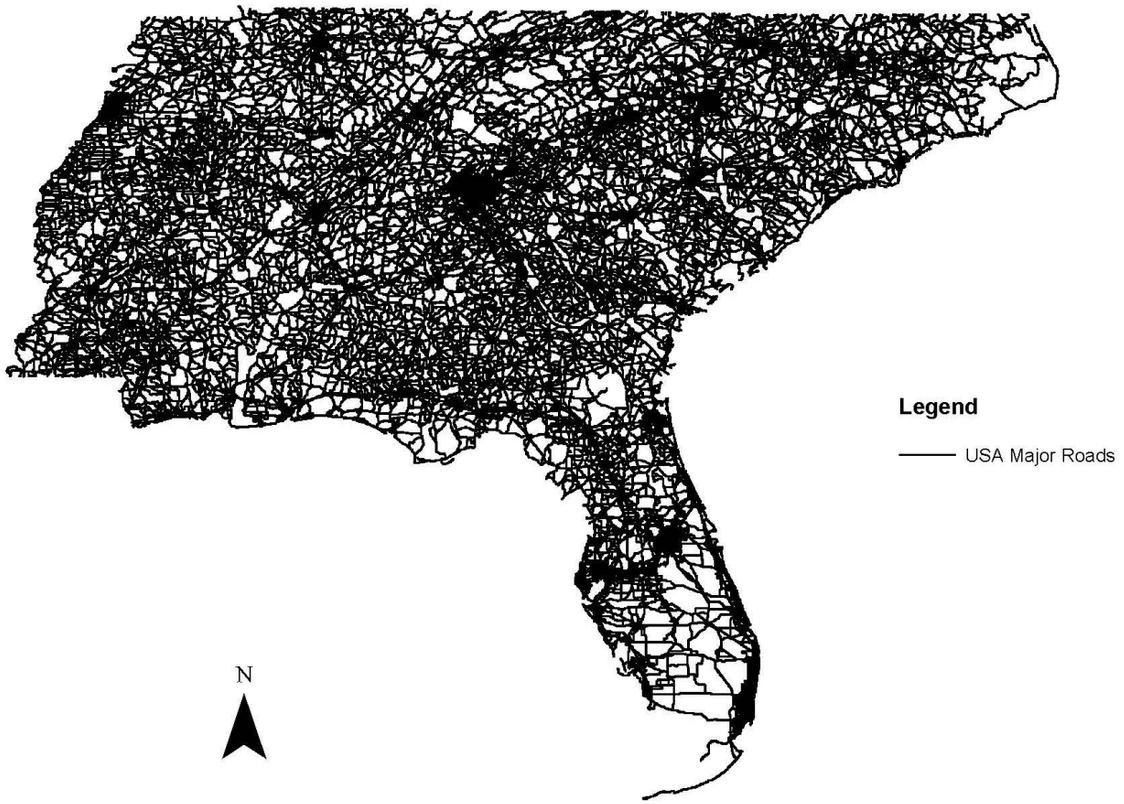

Figure S1. The map of major roadways in the southeastern US

Figure S2

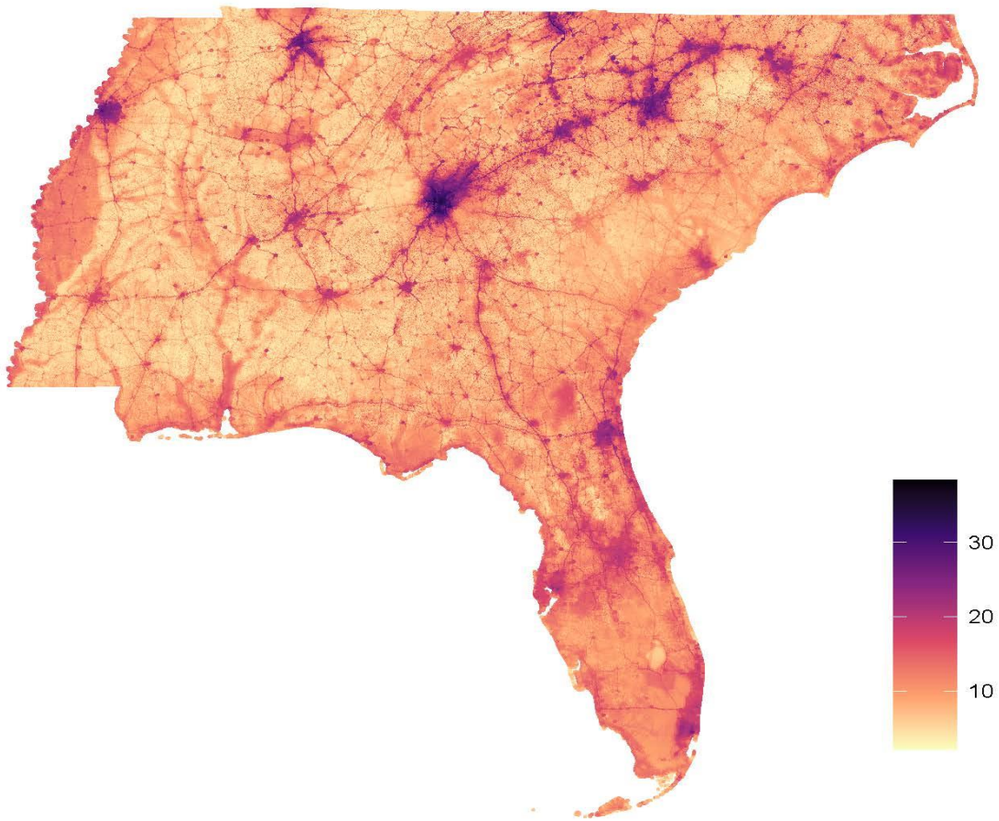

Figure S2. The spatial distribution of 17-year mean concentrations of annual NO_2 (ppb) at 1-km^2 grids in the southeastern US (2000-2016)

Figure S3

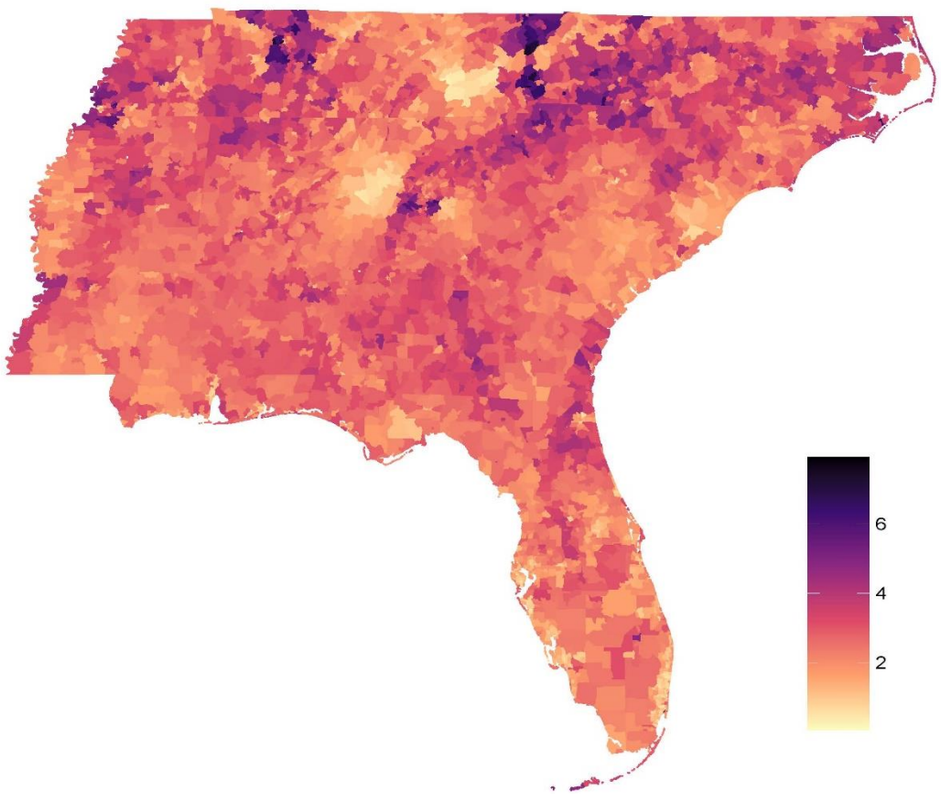

Figure S3. The standard deviations of 1-km^2 NO_2 concentrations (ppb) within ZIP code areas in the southeastern US in 2010

Figure S4

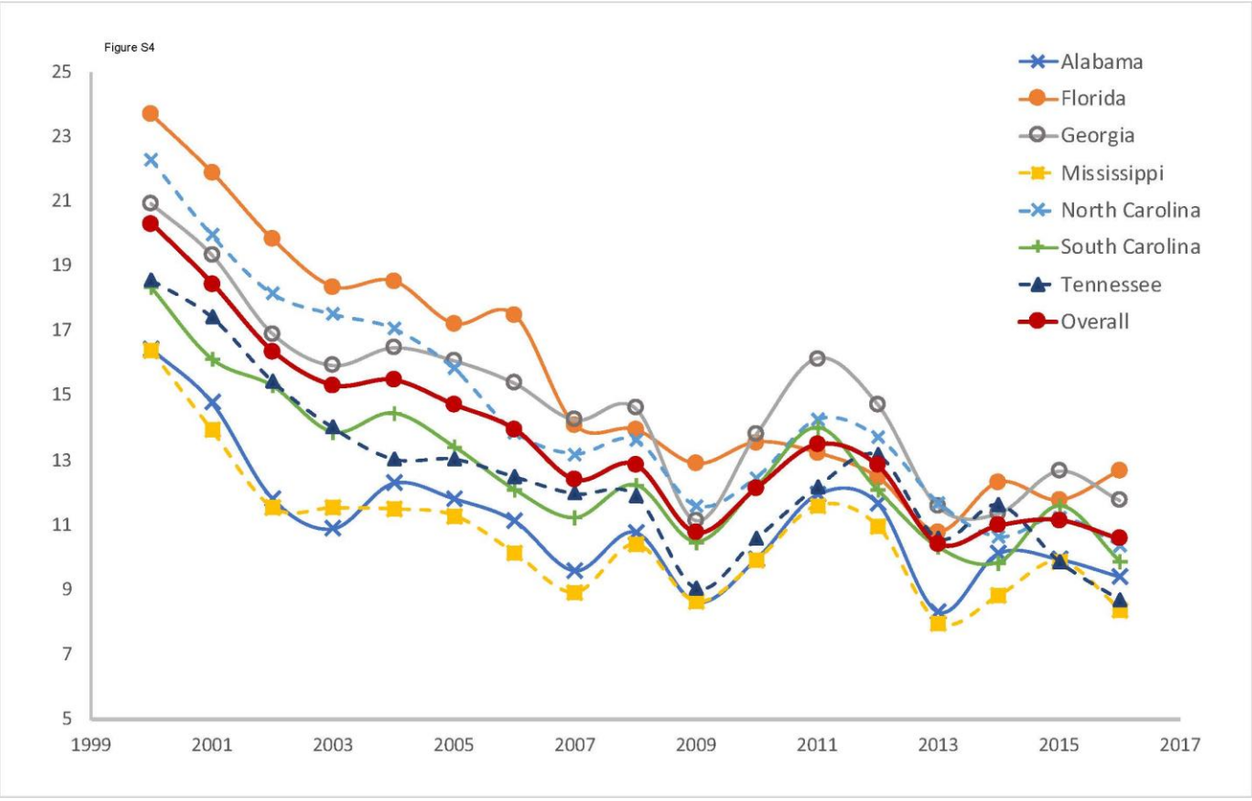

Figure S4. The temporal trend of NO_2 concentrations in the southeastern US from 2000-2016

Figure S5

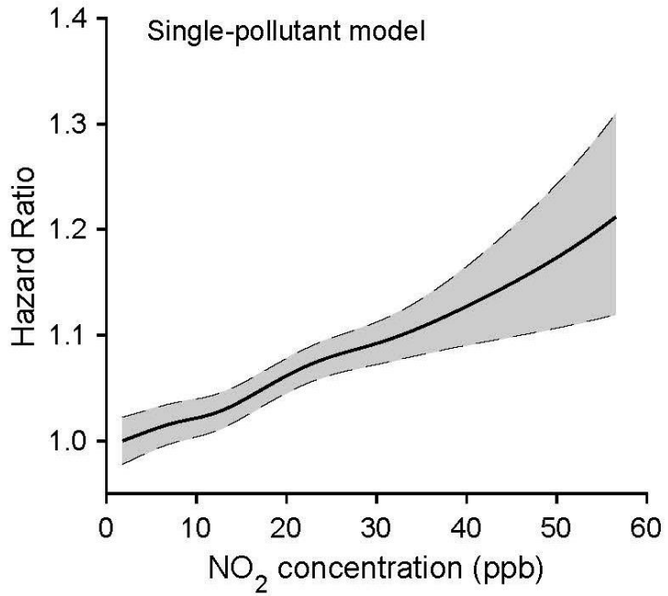

Figure S5. The relationship between long-term exposure to NO2 and all-cause mortality, derived from single pollutant models with adjustment of age at entry (5-year categories), gender (female, male), race (White, Black, and other), Medicaid eligibility, calendar-year, summer and winter mean temperature, median home value, median household income, population density, the proportion of owner-occupied housing units, the percentage of Black and Hispanic populations, education level, population below poverty level, body mass index, and the proportion of those who were ever smokers. The descriptive statistics for these variables were provided in Table 1 and Table S1. Shaded areas indicate the 95% confidence bands.