Supplementary Materials

Table of Contents

eAppendix I: Exposure to Air Pollution, Noise, and Heat and Road-adjacent tree coverage

Exposure to air pollution

We assessed maternal exposure to ambient levels of nitrogen dioxides (NO_2), nitrogen oxides (NO_x), particulate matter with aerodynamic diameter less than 2.5μm ($PM_{2.5}$), between 2.5μm and 10μm ($PM_{2.5\text{-}10}$, i.e. coarse particulate matter), and less than 10μm (PM_{10}), and $PM_{2.5}$ light absorption (hereafter referred to as $PM_{2.5}$ absorbance) during different exposure windows. We utilized a spatiotemporal exposure assessment framework based on temporally-adjusted spatial estimates of air pollutant levels by land use regression models developed as part of the European Study of Cohorts for Air Pollution Effects (ESCAPE).[1-3] These land use regression models predicted 73% - 87% of the variation in pollutant levels in our study area during 2008-2009 (eFigure 1). Predictor variables included in the final land use regression models for each pollutant together with the coefficients of determination (R^2) and root mean square error (RMSE) and their corresponding leave-one-out cross-validations are presented in eTable 2 (See below). As shown in eTable 2, while an indicator of distance to major roads (i.e. square of inverse distance to the nearest major road) was used in LUR models for NO_2 and NO_x, in LUR models for $PM_{2.5}$, PM_{10}, and $PM_{2.5}$ absorbance, distance to any road (e.g. major roads, local streets, etc) was used that was weakly correlated (Spearman's correlation coefficient (rho) of -0.17) with the indicator of distance to major roads. Adding this indicator of distance to major roads to LUR models for $PM_{2.5}$, $PM_{2.5\text{-}10}$, PM_{10}, and $PM_{2.5}$ absorbance did not improve model and cross-validation R^2 and RMSE. We estimated levels of pollutants at geocoded address of residence of each participant for each week of her pregnancy by temporal adjustment of spatial estimates by land use regression models using *ratio method* according to ESCAPE guidelines. Further details on this exposure assessment have been published elsewhere.[1-4]

We assessed exposure during four windows: the entire pregnancy and each trimester of pregnancy. We developed exposure estimates for each pollutant by averaging land use regression models predicted weekly levels of that pollutant over these four exposure window periods.

Exposure to noise

To assess noise exposure, we used Barcelona's strategic noise map developed in 2007 under the guidelines of the European Environmental Noise Directive (Directive 2002/49/EC). Detailed information on the map can be found elsewhere.[5] Briefly, the map accounted for total environmental noise in front of façades, which was obtained by standard measurements or noise modeling depending on the available information in each area (eFigure 3). The minimal resolution of the noise map was the street section between two crossroads (median length of 78.9 meters). We used the long-term average noise level indicator for the 24h period (L_{den}, in dB(A)), as defined in the Directive. We defined exposure to noise in buffers of 50m[6] and 250m[7] around each maternal geocoded address of residence in order to better represent the surrounding noise environment.

Exposure to heat

Land surface temperature has been used to evaluate the fine-scale intra-urban spatial variation in heat stress and heat-related mortality.[8-11] Our assessment of exposure to heat was based on land surface temperature derived from the Landsat 5 Thematic Mapper (TM) data at 30m x 30m resolution. We first extracted radiant temperature from TM thermal infrared band (band 6 with wavelength of 10.4-12.5μm) using the formula by

Marlet et al.[12] and then converted radiant temperature to surface temperature using the method described by Artis and Carnahan.[13] Based on the available body of evidence on the health impacts of heat in mid-latitude regions,[8-11] we hypothesized that any impact of heat on fetal growth could occur during the warm seasons. We therefore looked for available cloud-free Landsat TM images during warm seasons of our study period from the NASA's Earth Observing System Data and Information System. Based on this search, we generated three heat maps using images obtained on June 21st, 2002 (eFigure 3), August 11th, 2003, and May 18th, 2007. We then averaged land surface temperature (separately for each map) in a buffer of 50m around each maternal address of residence, generating three residential surrounding land surface temperature for each subject. Finally, we defined heat exposure as the average of these three residential surrounding land surface temperatures.

Road-adjacent tree coverage

Our assessment of the road-adjacent tree coverage was based on Vegetation Continuous Fields maps derived from data collected by Moderate Resolution Imaging Spectroradiometer aboard the Terra satellite.[14] The Vegetation Continuous Fields maps provide annual percent tree cover at rasters of 250m x 250m based on monthly composites of Terra Moderate Resolution Imaging Spectroradiometer land surface reflectance data.[14] We acquired the Vegetation Continuous Fields map for the period 6 March 2002 to 6 March 2003 from the NASA's Earth Observing System Data and Information System (eFigure 4). For each major road, we abstracted the road-adjacent tree coverage as the average of percent tree coverage across a buffer of 200m on each side of that road.

“Green area within a 1000m buffer” was used in LUR predicting the $PM_{2.5}$ levels. Spearman’s correlation coefficient between road-adjacent tree coverage of the nearest major road to the participants’ home addresses and green area within 1000m buffer around participants’ home addresses was 0.24. This relatively low correlation could suggest that inclusion of green area within 1000m in the LUR model predicting $PM_{2.5}$ should not have resulted in a notable bias in our analyses.

References

1. Beelen R, Hoek G. European Study of Cohorts for Air Pollution Effects (ESCAPE) manuals. Utrecht 2010, Available at: http://www.escapeproject.eu/manuals/index.php, Accessed on June 14

2. Eeftens M, Tsai M-Y, Ampe C, et al. Spatial variation of PM2.5, PM10, PM2.5 absorbance and PMcoarse concentrations between and within 20 European study areas and the relationship with NO2 - Results of the ESCAPE project. *Atmos Environ.* 2012; 62(0):303-317.

3. Beelen R, Hoek G, Vienneau D, et al. Development of NO2 and NOx land use regression models for estimating air pollution exposure in 36 study areas in Europe – the ESCAPE project. *Atmos Environ.* 2013; 72:10-23.

4. Dadvand P, Figueras F, Basagaña X, et al. Ambient Air Pollution and Preeclampsia: a Spatiotemporal Analysis. *Environ Health Perspect.* 2013; DOI:10.1289/ehp.1206430.

5. Departamento Control i Reducció de la Contaminació Acústica. Mapa Estratègic de Soroll de Barcelona. Barcelona: Ajuntament de Barcelona, 2007.

6. Birk M, Ivina O, von Klot S, Babisch W, Heinrich J. Road traffic noise: self-reported noise annoyance versus GIS modelled road traffic noise exposure. *J Environ Monit.* 2011; 13(11):3237-3245.

7. Havard S, Reich BJ, Bean K, Chaix B. Social inequalities in residential exposure to road traffic noise: An environmental justice analysis based on the RECORD Cohort Study. *Occup Environ Med.* 2011; 68(5):366-374.

8. Harlan SL, Declet-Barreto JH, Stefanov WL, Petitti DB. Neighborhood effects on heat deaths: social and environmental predictors of vulnerability in Maricopa County, Arizona. *Environ Health Perspect.* 2013; 121(2):197-204.

9. Smargiassi A, Goldberg MS, Plante C, et al. Variation of daily warm season mortality as a function of micro-urban heat islands. *J Epidemiol Community Health.* 2009; 63(8):659-664.

10. Johnson D, Wilson J, Luber G. Socioeconomic indicators of heat-related health risk supplemented with remotely sensed data. *Int J Health Geogr.* 2009; 8(1):57.

11. Johnson DP, Wilson JS. The socio-spatial dynamics of extreme urban heat events: The case of heat-related deaths in Philadelphia. *Applied Geography.* 2009; 29(3):419-434.

12. Malaret E, Bartolucci LA, Lozano DF, Anuta PE, McGillem CD. Landsat-4 and Landsat-5 Thematic Mapper data quality analysis. *Photogrammetric Engineering and Remote Sensing.* 1985; 51:1407-1416.

13. Artis DA, Carnahan WH. Survey of emissivity variability in thermography of urban areas. *Remote Sensing of Environment.* 1982; 12(4):313-329.

14. Townshend JRG, Carroll M, Dimiceli C, et al. Vegetation Continuous Fields MOD44B, 2002 Percent Tree Cover, Collection 5. University of Maryland, College Park, Maryland, 2001, Available at: https://lpdaac.usgs.gov/sites/default/files/public/modis/docs/VCF_C5_UserGuide_Dec2011.pdf, Accessed on 15 January

eTable 1. Median of participants' exposure levels to air pollution (during the entire pregnancy), heat, and noise (250m buffer) in across buffers of ≤50m, 50m-200m, 200m-500m, and >500m around the major roads.

Buffer	**NO_2**	**NO_x**	**$PM_{2.5}$**	**$PM_{2.5\text{-}10}$**	**PM_{10}**	**Noise**	**Heat**
≤50m	64.5	150.0	18.9	23.4	41.8	68.7	35.6
50m-200m	54.7	102.2	16.7	22.0	38.8	68.2	35.3
200m-500m	52.8	95.0	16.1	22.0	38.7	66.1	34.9
>500m	52.6	93.7	16.0	22.0	38.4	66.5	33.1

eTable 2. Number of sampling sites (N), predictor variables for the final land use regression (LUR) models for each pollutant and the coefficients of determination (R^2) and root mean square error (RMSE) for the final LUR models and their corresponding leave-one-out cross-validations, Barcelona, 2009.

	N	**LUR models**			**Cross-validation**	
		Predictor variables	**Adjusted R^2**	**RMSE**	**R^2**	**RMSE**
NO_x	40	High density residential area within a 300m buffer, square of inverse distance to the nearest major road, and traffic intensity within a 25m buffer.	0.71	24.94	0.65	27.68
NO_2	40	High density residential area within a 300m buffer, square of inverse distance to the nearest major road, inverse distance to the nearest road*traffic intensity in the nearest road, and length of roads within a 1000m buffer.	0.72	10.74	0.68	11.59
$PM_{2.5}$	20	Green area within a 1000m buffer, traffic intensity within a 100m buffer, and square of inverse distance to the nearest road*traffic intensity in the nearest road.	0.80	1.71	0.71	2.10
$PM_{2.5-10}$	20	Square root of altitude, and traffic intensity of major roads within a 50m buffer.	0.72	2.13	0.70	2.27
PM_{10}	20	Square root of altitude, inverse distance to the nearest road*traffic intensity in the nearest road, and length of roads within a 25m buffer.	0.85	2.78	0.82	3.11
$PM_{2.5}$ absorbance	20	High density residential area within a 300m buffer, inverse distance to the nearest road*traffic intensity in the nearest road, and traffic intensity within a 50m buffer.	0.83	0.38	0.80	0.43

eTable 3. Description of Multiple Imputation.

Software used and key setting: STATA 12 software (Stata Corporation, College Station, Texas) – Ice command (100 imputations with 10 cycles)
Number of imputed datasets created: 100
Variables included in the imputation procedure: *Variables used in the main analyses (outcome, exposures, and covariates) together with other relevant variables as follows:* Gestational age at delivery, history of preterm birth, history of gynecologic problems, premature rupture of membrane, gestational age at booking, fetus position, maternal blood hemoglobin level at delivery, maternal blood platelet count at delivery, preeclampsia, maternal working status, use of assisted reproductive technology, multiple pregnancy, and delivery mode.
Treatment of non-normally distributed variables: log-transformation.
Treatment of binary/categorical variables: logistic, ordinal, and multinomial models.
Statistical interactions included in imputation models: none.

eTable 4. Median (Interquartile range) of estimated exposure levels of study participants (N=6,438) averaged over each exposure window period, Barcelona, 2001-2005.

Pollutant	Entire Pregnancy	Trimester 1	Trimester 2	Trimester 3
NO_2 (µg m^{-3})	55.5 (16.8)	56.1 (20.5)	55.3 (19.9)	54.2 (18.7)
NO_x (µg m^{-3})	102.8 (41.3)	103.4 (59.0)	103.9 (57.6)	102.3 (56.8)
$PM_{2.5}$ (µg m^{-3})	16.9 (3.1)	16.8 (3.7)	16.8 (3.7)	17.0 (3.6)
$PM_{2.5-10}$ (µg m^{-3})	22.3 (2.3)	22.1 (3.4)	22.2 (3.4)	22.4 (3.1)
PM_{10} (µg m^{-3})	39.2 (3.9)	39.4 (5.7)	39.5 (5.6)	39.8 (5.2)
$PM_{2.5}$ absorbance (10^{-5} m^{-1})	3.1 (1.1)	3.0 (1.6)	3.1 (1.6)	3.0 (1.5)

eTable 5. Spearman's Correlation Coefficients (rho) Between Estimated Exposure Levels to Air Pollutants During Each Trimester (N=6,438).

Pollutant	**Trimester 1**	**Trimester 2**	**Trimester 3**
NO_x			
Trimester 1	1		
Trimester 2	0.55	1	
Trimester 3	-0.20	0.54	1
NO_2			
Trimester 1	1		
Trimester 2	0.68	1	
Trimester 3	0.47	0.70	1
$PM_{2.5}$			
Trimester 1	1		
Trimester 2	0.76	1	
Trimester 3	0.65	0.77	1
$PM_{2.5-10}$			
Trimester 1	1		
Trimester 2	0.48	1	
Trimester 3	0.19	0.47	1
PM_{10}			
Trimester 1	1		
Trimester 2	0.45	1	
Trimester 3	0.16	0.44	1
$PM_{2.5}$ absorbance			
Trimester 1	1		
Trimester 2	0.44	1	
Trimester 3	0.01	0.44	1

eTable 6. Spearman's Correlation Coefficients (rho) Between Estimated Exposure Levels to Air Pollutants (the Entire Pregnancy), Noise (50m buffer), and Heat (N=6,438).

	NO_2	NO_x	$PM_{2.5}$	$PM_{2.5\text{-}10}$	PM_{10}	$PM_{2.5}$ absorbance	Noise	Heat	Road-adjacent tree
NO_2	1.00								
NO_x	0.90	1.00							
$PM_{2.5}$	0.48	0.52	1.00						
$PM_{2.5\text{-}10}$	-0.04	0.03	0.28	1.00					
PM_{10}	0.33	0.45	0.69	0.47	1.00				
$PM_{2.5}$ absorbance	0.91	0.88	0.57	-0.02	0.39	1.00			
Noise	0.45	0.56	0.57	0.17	0.51	0.48	1.00		
Heat	-0.02	0.08	-0.02	-0.11	0.08	0.01	0.19	1.00	
Road-adjacent tree	-0.21	-0.14	-0.11	-0.11	-0.02	-0.18	0.09	0.26	1.00

eTable 7. Medians of exposure to air pollution (during the entire pregnancy), noise, and heat for study participants living within and further than 200m from a major road.

	Within 200m (N=3,980)	**Further than 200m (N=2,458)**
NO_2[a]	57.2	53.0
NO_x[a]	109.7	94.5
$PM_{2.5}$[a]	17.4	16.1
$PM_{2.5-10}$[a]	22.4	22.2
PM_{10}[a]	39.6	38.7
$PM_{2.5}$ absorbance[b]	3.3	2.9
Noise (50m buffer)[c]	67.3	65.0
Noise (250m buffer)[c]	68.3	66.2
Heat[d]	37.3	36.6

[a] $\mu g\ m^{-3}$

[b] $10^{-5}\ m^{-1}$

[c] dB(A)

[d] Degree Celsius

eTable 8. Number of sampling sites (N) and coefficients of determination (R^2) and root mean square error (RMSE) for the LUR models with proximity to major roads (i.e. within 200m of a major road: yes/no) as the predictor.

Pollutant	**N**	**R^2**	**RMSE**
NO_2	40	0.19	18.4
NO_x	40	0.18	42.4
$PM_{2.5}$	20	0.34	3.2
$PM_{10-2.5}$	20	0.02	4.1
PM_{10}	20	0.16	6.7
$PM_{2.5}$ absorbance	20	0.39	0.8

eTable 9. Adjusted[a] odds ratios (95% confidence intervals (CI)) of small for gestational age associated with residential proximity to a major road and one inter-quartile range increase in exposure to heat and noise, Barcelona, 2001-2005 (N=6,438).

	OR (95% CI)
Residential Proximity	
Continuous distance	0.92 (0.84, 1.01)
Binary distance	1.14 (0.97, 1.34)
Heat	1.08 (0.96, 1.20)
Noise	
50m buffer	1.07 (0.96, 1.19)
250m buffer	1.07 (0.96, 1.20)

[a] Adjusted for neighborhood socioeconomic status, ethnicity, education level, marital status, age, smoking during pregnancy, alcohol consumption during pregnancy, booking body mass index less than 20, diabetes, infection during pregnancy, parity, and season and year of conception.

eTable 10. Adjusted[a] odds ratios (95% confidence intervals (CI)) of small for gestational age associated with one inter-quartile range increase in exposure to each pollutant separately for each exposure window period, Barcelona, 2001-2005 (N=6,438).

Pollutant	**Entire Pregnancy**	**Trimester 1**	**Trimester 2**	**Trimester 3**
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
NO_2	1.03 (0.98, 1.10)	1.04 (0.97, 1.11)	1.04 (0.97, 1.11)	1.03 (0.97, 1.10)
NO_x	1.02 (0.97, 1.07)	1.04 (0.98, 1.11)	1.03 (0.97, 1.09)	1.01 (0.94, 1.08)
$PM_{2.5}$	1.07 (0.97, 1.17)	1.06 (0.96, 1.17)	1.08 (0.97, 1.20)	1.07 (0.97, 1.18)
$PM_{2.5-10}$	1.06 (0.96, 1.17)	1.04 (0.93, 1.16)	1.08 (0.95, 1.22)	1.06 (0.95, 1.18)
PM_{10}	1.02 (0.93, 1.11)	1.00 (0.90, 1.11)	1.03 (0.92, 1.16)	1.02 (0.93, 1.13)
$PM_{2.5}$ absorbance	1.06 (0.97, 1.17)	1.07 (0.95, 1.21)	1.07 (0.97, 1.18)	1.05 (0.93, 1.18)

[a] Adjusted for neighborhood socioeconomic status, ethnicity, education level, marital status, age, smoking during pregnancy, alcohol consumption during pregnancy, booking body mass index less than 20, diabetes, infection during pregnancy, parity, and season and year of conception.

eTable 11. Percentage (95% confidence interval) of the association between residential proximity to a major road (binary distance) and small for gestational age (fully-adjusted model) that was explained by each of the mediators.

Mediators	% explained (95% CI)
NO_2[a]	7% (-36, 75)
NO_x[a]	10% (-50, 98)
$PM_{2.5}$[b]	14% (-70, 115)
$PM_{2.5-10}$[b]	9% (-59, 82)
PM_{10}[b]	2% (-32, 44)
$PM_{2.5}$ absorbance[a]	7% (-35, 73)
Heat	6% (-32, 66)
Noise	11% (-70, 119)
Heat and $PM_{2.5}$[b]	22% (-118, 174)
Heat, noise, and $PM_{2.5}$[b]	24% (-124, 198)

[a] Exposure during the first trimester

[b] Exposure during the third trimester

eTable 12. Adjusted[a] odds ratios (95% confidence intervals (CI)) of small for gestational age associated with residential proximity to a major for the strata of percentages of road-adjacent tree coverage (terciles of vegetation continuous fields (VCF)), Barcelona, 2001-2005 (N=6,438).

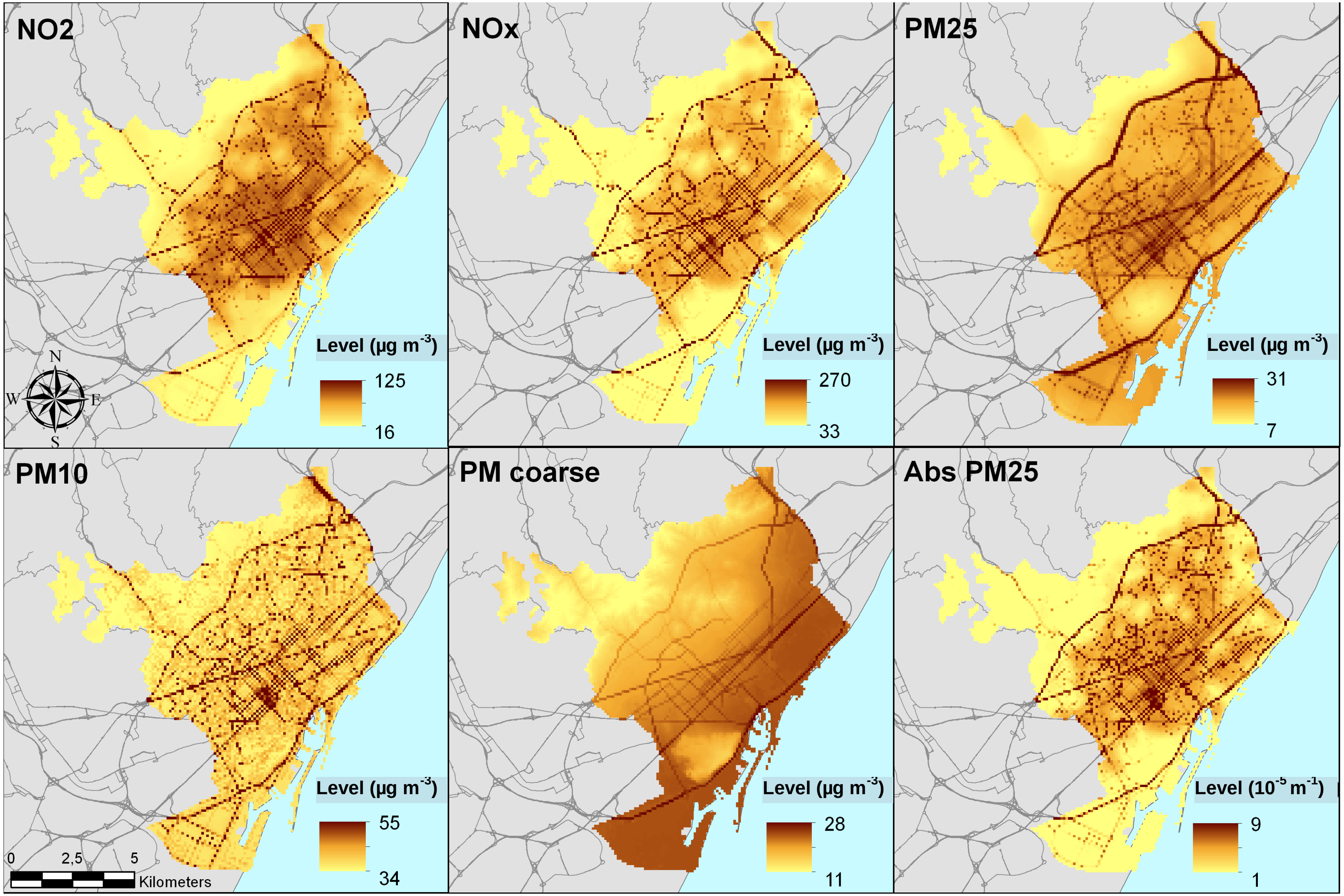
	VCF		
	First tercile[b]	**Second tercile**	**Third tercile[c]**
Residential Proximity to a major road	1.34 (0.99, 1.83)	0.98 (0.74, 1.30)	1.17 (0.89, 1.54)

[a] Adjusted for neighborhood socioeconomic status, ethnicity, education level, marital status, age, smoking during pregnancy, alcohol consumption during pregnancy, booking body mass index less than 20, diabetes, infection during pregnancy, parity, and season and year of conception.

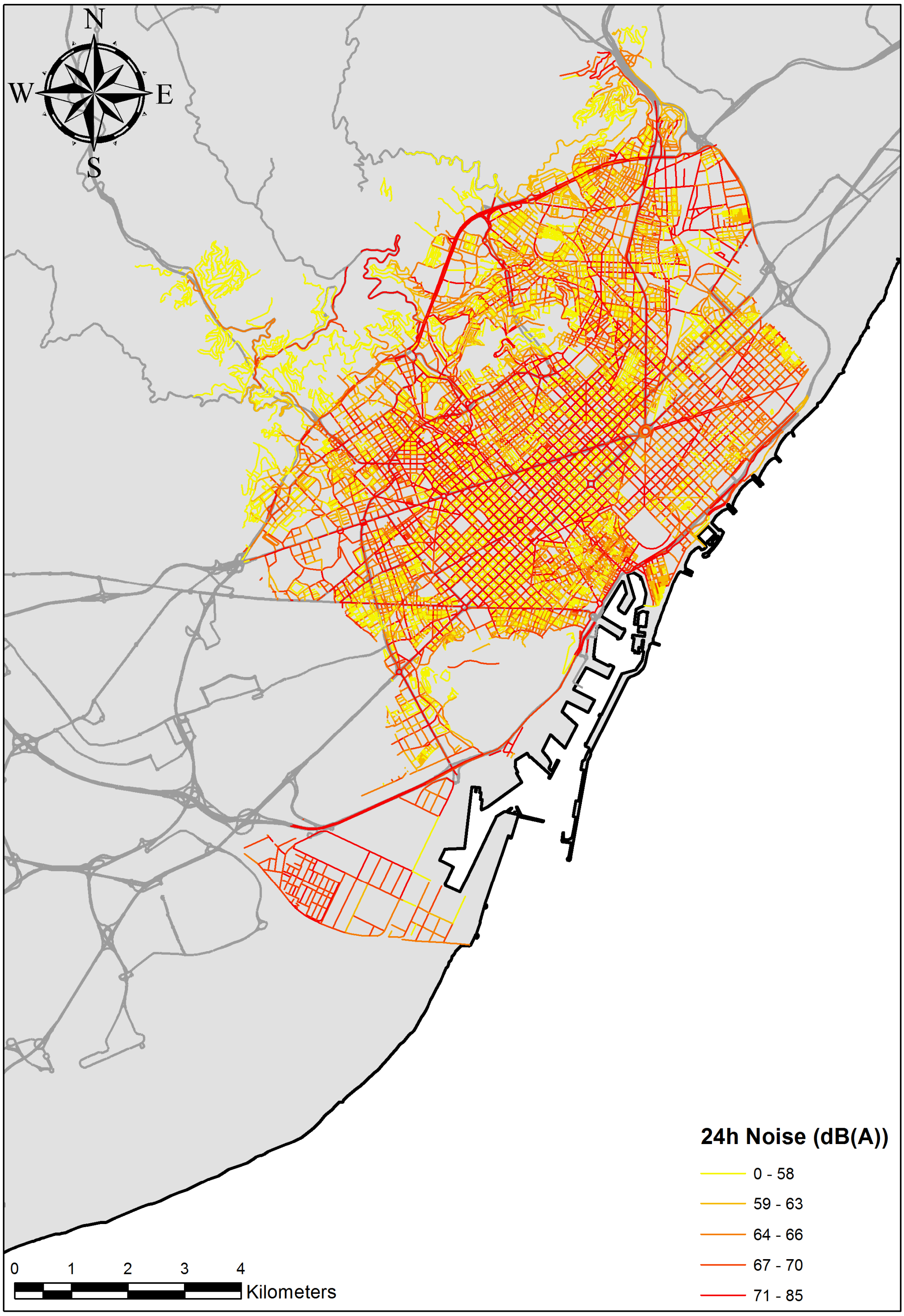
[b] The lowest tree coverage.

[c] The highest tree coverage.

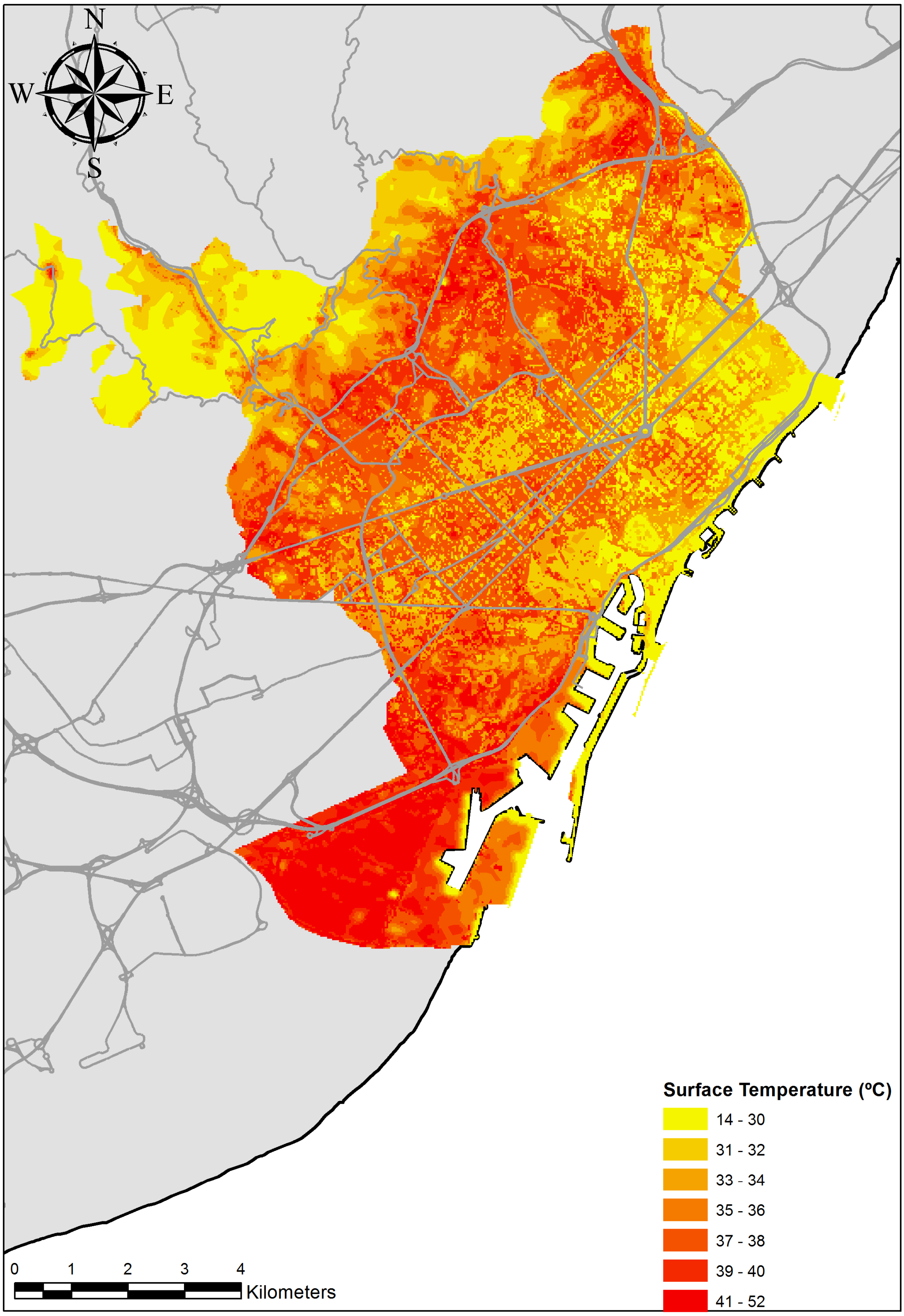
eFigure 1. Spatial surface of predicted air pollutant levels by land use regression models, Barcelona, 2008-2009.



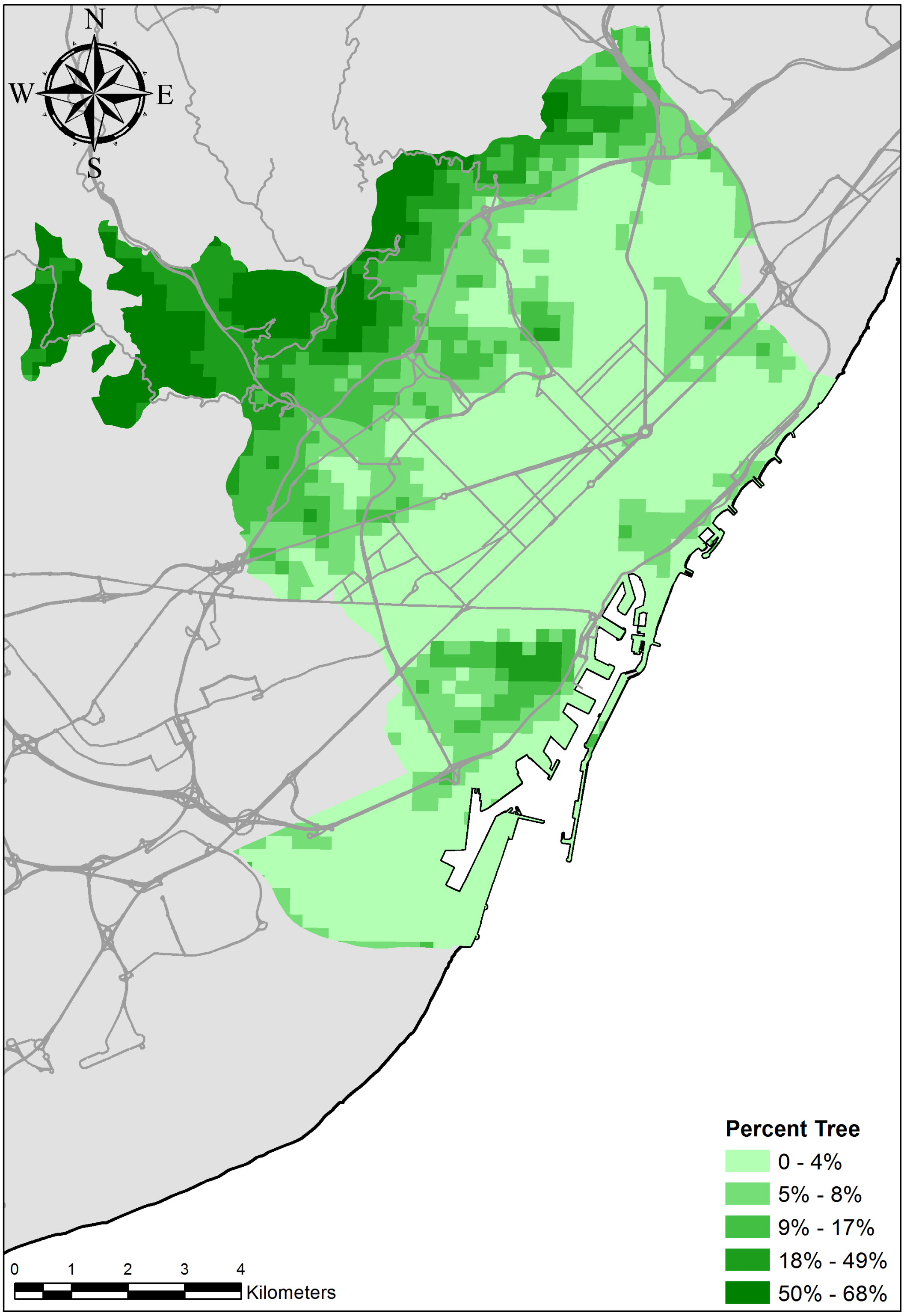
eFigure 2. Long-term average noise levels for the 24h period (L_{den}, in dB(A)) over Barcelona, 2007. (Source: Barcelona's strategic noise map)



eFigure 3. Land surface temperature (ºC) across Barcelona on June 21st, 2002, based on Landsat 5 TM data.



eFigure 4. Percentage of tree coverage across Barcelona, 2002-203, based on Vegetation Continuous Fields by Terra-MODIS.



eFigure 5. Plots for the fitted generalized geoadditive models with term low birth weight as outcome and exposure to air pollution (during the entire pregnancy), heat, and noise as predictor.