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Supplemental Material

Prenatal Ambient Air Pollution, Placental Mitochondrial DNA Content, and Birth Weight in the INMA (Spain) and ENVIR*ON*AGE (Belgium) Birth Cohorts

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Table S1. Data from each campaign and predictor variables of air pollution in each cohort

Cohort	No. Passive samplers	Campaign dates	Predictor variables	R^2 model	Number of monitoring stations
INMA-Asturias	67	June 2005 November 2005	Altitude Distance to nearest road[a] Agricultural or forest land cover (300m-buffer)	0.521	4
INMA-Gipuzkoa	85	February 2007 June 2005	Altitude (3 cat) Valley factor Distance to nearest road[a] (MDI[b] > 20000) Urban land cover (100m-buffer) Industrial land cover (300m-buffer)	0.509	3
INMA-Sabadell	57	April 2005 June 2005 October 2005 March 2006	Altitude Urban or industrial land cover (500m-buffer) Road type (minor, major, secondary road)	0.750	1
INMA-Valencia	93	April 2004 June 2004 November 2004 February 2005	Kriging[c] Industrial or urban land cover (500m-buffer) Distance to nearest major road[a] (MDI[b] > 10000)	0.730	7
ENVIR*ON*AGE	N/A	N/A	Kriging[d] Land use[d] Road emission and locations[e] Point sources, characteristics and locations[e]	0.820	64

[a]Distance to the nearest major road (in logarithms)
[b]MDI: Mean daily traffic count
[c]Mean of estimated NO_2 from kriging among campains
[d]Predictor variables of the land-use regression model for the background (RIO)
[e]Predictor variables of the emission for the bi-gaussian plume model.

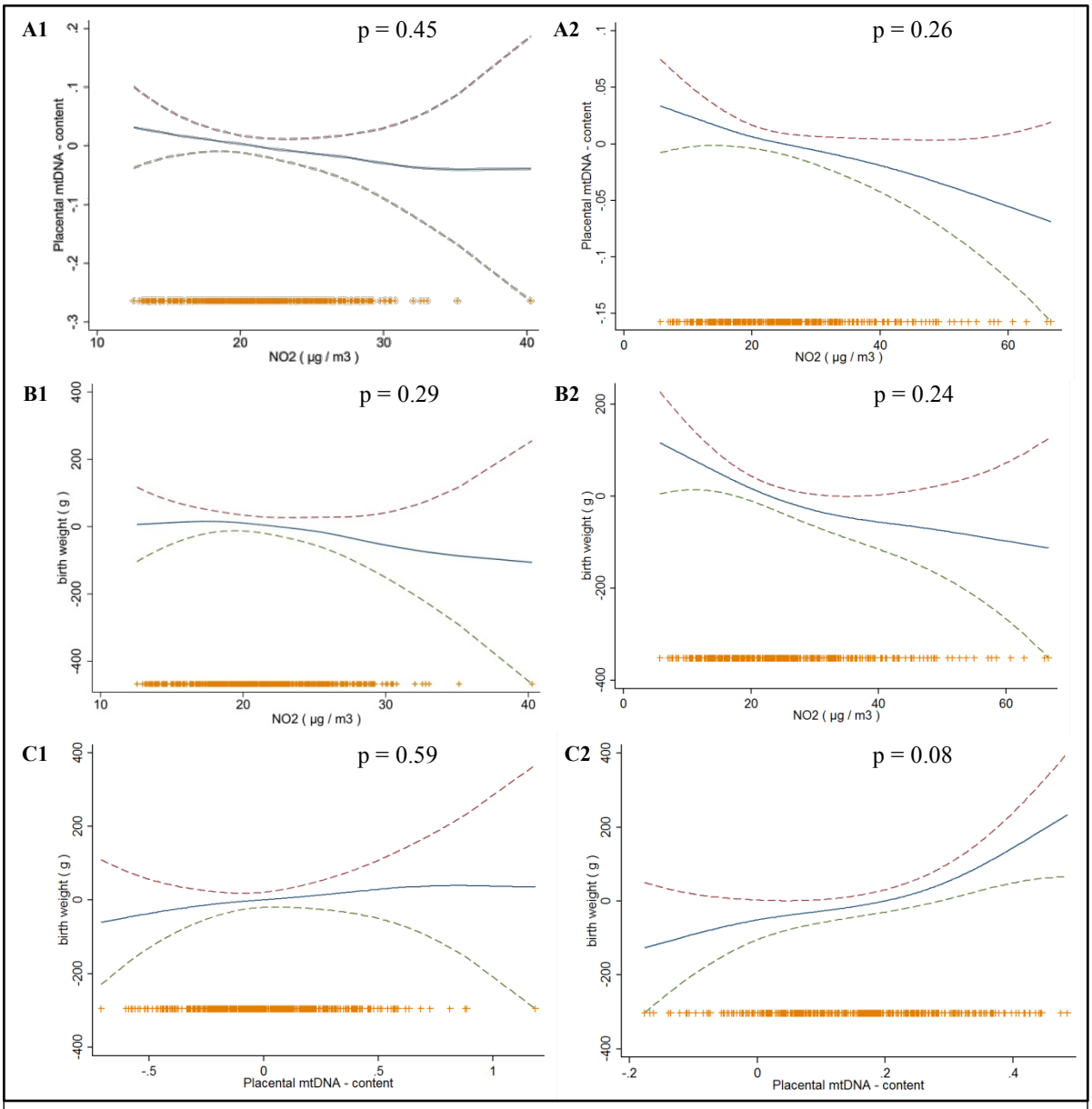

Figure S1. GAM models that show the relation between (A) NO_2 exposure (µg/m3) during the entire pregnancy and mtDNA content, (B) NO_2 exposure (µg/m3) during the entire pregnancy and birth weight (g), and (C) mtDNA content and birth weight (g). This model provides p-values for the null hypothesis of no linearity. 1: ENVIRONAGE, 2: INMA

Table S2. Percent change in placental mtDNA content in association with prenatal NO_2 exposure in the four different INMA subcohorts

Pregnancy period	Differences in placental mtDNA content (%)	95% CI	P-value
Asturias (n=37)			
Trimester 1	-13.6	-31.4, 8.8	0.20
Trimester 2	-12.8	-26.0, 2.9	0.10
Trimester 3	-16.8	-30.8,-0.07	0.05
Entire pregnancy	-15.1	-29.9, 2.9	0.09
Gipuzkoa (n=156)			
Trimester 1	-6.3	-12.6, 0.5	0.07
Trimester 2	-6.5	-13.0, 0.4	0.06
Trimester 3	-5.4	-12.3, 2.1	0.15
Entire pregnancy	-4.6	-11.8, 3.2	0.23
Sabadell (n=120)			
Trimester 1	-2.6	-7.3, 2.3	0.29
Trimester 2	-3.4	-8.3, 1.8	0.16
Trimester 3	-3.4	-8.3, 1.8	0.19
Entire pregnancy	-4.1	-9.4, 1.6	0.15
Valencia (n=63)			
Trimester 1	-3.1	-8.5, 2.6	0.27
Trimester 2	-1.6	-8.1, 2.6	0.27
Trimester 3	-2.6	-8.3, 3.4	0.38
Entire pregnancy	-2.8	-8.9, 3.7	0.38

Effect size was estimated for each 10 $\mu g/m^3$ increment in exposure to NO_2 at each mother's residence during the corresponding period;

Models were adjusted for newborn's sex, maternal age, maternal smoking status, gestational age (linear and quadratic), pre-pregnancy BMI, parity, ethnicity, season of birth, and education;

Table S3. Association between pregnancy average NO_2 exposure and birth weight in the four different INMA subcohorts.

INMA subcohort	N	Differences in birth weight (g)	95% CI	*p*-value
Asturias	37	-155.6	-378.3, 67.1	0.16
Gipuzkoa	156	-75.6	-168.1, 13.1	0.08
Sabadell	120	-110.3	-178.3, -42.4	0.002
Valencia	63	-11.8	-20.1, 12.4	0.83

Effect size was estimated for each $10\mu g/m^3$ increment in pregnancy average exposure to NO_2 at each mother's residence during the corresponding period.

Models were adjusted for newborn's sex, maternal age, maternal smoking status, gestational age (linear and quadratic), pre-pregnancy BMI, parity, ethnicity, season of birth, and education

Table S4. Mediation analysis of the estimated effects of prenatal NO_2 exposure (µg/m3) on birth weight through placental mtDNA content in the pooled sample and the boys of the pooled sample.

Exposure period	Proportion of mediation (%)	95% CI	*p*-value
Pooled data (n = 926)			
Trimester 1	1.4	-2.6, 5.5	0.54
Trimester 2	2.9	-2.6, 7.9	0.29
Trimester 3	3.2	-2.2, 8.1	0.24
Entire pregnancy	2.2	-2, 6.1	0.29
Boys of pooled data (n = 471)			
Trimester 1	1.5	-4.7, 7.0	0.62
Trimester 2	4.3	-0.2, 8.5	0.06
Trimester 3	6.4	2.4, 10.1	0.002
Entire pregnancy	2.8	-0.8, 6.2	0.12

Effect size was estimated for each $10\mu g/m^3$ increment in exposure to NO_2 at each mother's residence during the corresponding period.

Models were adjusted for newborn's sex, maternal age, maternal smoking status, gestational age (linear and quadratic), pre-pregnancy BMI, parity, ethnicity, season of birth, and education.

Table S5. Percent change in placental mtDNA content in association with prenatal NO_2 exposure in INMA mothers that spent ≥ 15 hours a day at home.

Exposure period	N	Differences in placental mtDNA content (%)	95% CI	P-value
Trimester 1	214	-6.1	-9.5, -2.5	<0.01
Trimester 2	214	-7.5	-11.1, 3.8	<0.01
Trimester 3	214	-7.8	-11.4, -4.0	<0.01
Entire pregnancy	214	-8.9	-12.8, -4.8	<0.01

Effect size was estimated for each 10 $\mu g/m^3$ increment in exposure to NO_2 at each mother's residence during the corresponding period;
Models were adjusted for newborn's sex, maternal age, maternal smoking status, gestational age (linear and quadratic), pre-pregnancy BMI, parity, ethnicity, season of birth, and education;
Results followed the same direction in all 4 INMA subcohorts (data not shown);
INMA subcohort was included as random effect.

Table S6. Association between prenatal NO_2 and birth weight in INMA mothers that spent ≥ 15 hours a day at home.

Exposure period	N	Differences in birth weight (g)	95% CI	P-value
Trimester 1	214	-64.9	-114.1, -15.6	0.01
Trimester 2	214	-65.9	-118.5, -13.3	0.01
Trimester 3	214	-75.1	-127.9, -22.2	< 0.01
Entire pregnancy	214	-83.7	-141.8, -25.6	< 0.01

Effect size was estimated for each $10\mu g/m^3$ increment in exposure to NO_2 at each mother's residence during the corresponding period.

Models were adjusted for newborn's sex, maternal age, maternal smoking status, gestational age (linear and quadratic), pre-pregnancy BMI, parity, ethnicity, season of birth, and education;

Results followed the same direction in all 4 INMA subcohorts (data not shown);

INMA subcohort was included as random effect.