**Supplementary data**

**Prenatal and Postnatal Exposure to NO2 and Child Attentional Function at 4-5 Years of Age**

Alexis Sentís, Jordi Sunyer, Albert Dalmau-Bueno, Ainara Andiarena, Ferran Ballester, Marta Cirach, Marisa Estarlich, Ana Fernández-Somoano, Jesús Ibarluzea, Carmen Íñiguez, Aitana Lertxundi, Adonina Tardón, Mark Nieuwenhuijsen, Martine Vrijheid, and Mònica Guxenson behalf of the INMA Project

**Table of contents**

Figure S1. Direct acyclic graph (DAG) ...……………................................….…… pag.2

Figure S2. Forest plots of fully adjusted association between postnatal NO2 exposure and attentional function outcomes………………………………………………...pag.3

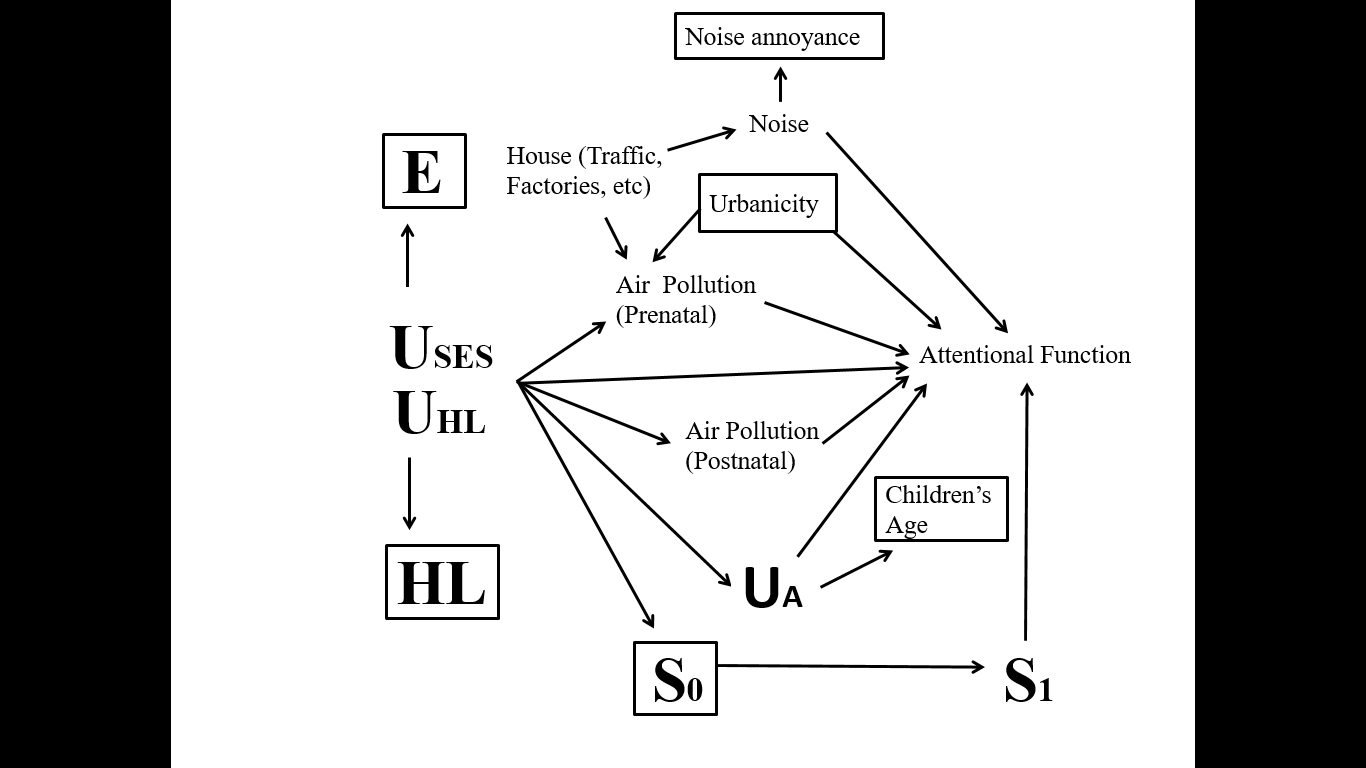
Table S1. Description of the region-specific LUR models for NO2…………………………………………………………..…………………….pag.4

Table S2. Comparison of maternal, paternal, and child characteristics during pregnancy between subjects included and not included in the study, out of the 2,764 eligible subjects...........................................................................................................pag.5

Table S3. Association between prenatal NO2 levels and potential confounding variables …………………………………………………………………………………….pag.6

Table S4. Minimally-adjusted combined associations between prenatal and postnatal NO₂ (overall and by sex) and attentional function…………………………......pag.7

**Figure S1. Direct acyclic graph (DAG)**



E: proxy variables for the unmeasured socioeconomic status of the parents (i.e. parental educational level, parental social class, parental country of birth, parental age, maternal intelligence coefficient, maternal mental health, child’s number of siblings)

HL: proxy variables for unmeasured maternal and paternal health and life-style (i.e. maternal fish, fruits, and vegetables consumption during pregnancy, maternal pre-pregnancy body mass index, paternal body mass index, maternal folic acid and vitamin D levels during pregnancy, maternal smoking and alcohol consumption during pregnancy, maternal second hand smoking during pregnancy, and housesold gas appliances (cooking stove and heating) during pregnancy)

S0: selection into the cohort

S1: selection into the analysis

UA: unmeasured variables related to the time the child comes to the attentional function assessment (i.e. child’s sex and child’s age at attentional function assessment)

UUHL: unmeasured variables related to maternal and paternal health and life-style

USES: unmeasured variables related to socioeconomic status

Models were adjusted or conditioned by the boxed variables

|  |
| --- |
| **Figure S2. Forest plots of minimally-adjusted association between postnatal NO2 exposure and attentional function outcomes. Region-especific and summary risk estimates from random effects analysis (coefficient/IRR and 95% CI) for:** HRT (A), HRT(SE) (B), Detectability (C), Omission errors (D), and Commission errors (E) for each 10 μg/m³ increase in **postnatal NO₂ level**   1. **HRT B. HRT (SE)**   **C:\Users\61306\Desktop\Metanalysis_Adj_02_01_no2_4_hit_MI_1300.wmfC:\Users\61306\Desktop\Metanalysis_Adj_02_02_no2_4_hitsd_MI_1300.wmf**  **C. Detectability D. Omissions errors**  **C:\Users\61306\Desktop\Metanalysis_Adj_02_03_no2_4_detec_MI_1300.wmfC:\Users\61306\Desktop\Metanalysis_Adj_02_04_no2_4_omissions_MI_1300.wmf**  **E. Commission errors**  **C:\Users\61306\Desktop\Metanalysis_Adj_02_05_no2_4_comissions_MI_1300.wmf**  P-value from Heterogeneity test (p-heter)/I² index to quantify the degree of heterogeneity in a meta-analysis (I²(%)) for postnatal NO₂ exposure (overall) to HRT=0.54/0, HRT(SE)=0.15/43.8, Detectability=0.05/62.8, Omissions=0.78/0, Commissions= 0.01/71.1. Models were adjusted for child’s sex and child’s age at the time of the attentional function assessment. |

**Table S1. Description of the region-specific LUR models for NO2**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Region** | **Period** | **no. passive samplers** | **Date campaigns** | **Predictor variables** | **R2 model** | **Number of monitoring stations** | **Pollutant used to correct for seasonality** |
| Asturias | During pregnancy | 67 | June 05  November 05 | Altitude  Distance to nearest major road  Agricultural or forest land cover (300 m-buffer) | 0.521 | 4 | NO2 |
| Gipuzkoa | During pregnancy | 79 | February 07  June 07 | Altitude (3 categories)  Valley factor  Distance to nearest major road (MDI>20000)  Urban land cover (100 m-buffer)  Industrial land cover (300 m-buffer) | 0.509 | 3 | NO2 |
| At 4-5 years | 70 | November 2012 | Valley factor  Distance to nearest major road (MDI>20000)  Urban land cover (100 m-buffer)  Industrial land cover (300 m-buffer) | 0.570 | 3 | NO2 |
| Sabadell | During pregnancy | 57 | April 05  June 05  October 05  March 06 | Altitude  Urban or industrial land cover (500 m-buffer)  Road tipe | 0.750 | 1 | NO2 |
| Valencia | During pregnancy | 93 | April 04  June 04  November 04  February 05 | Kriginga  Industrial or urban land cover (500 m-buffer)  Distance to nearest major road (MDI=10000) | 0.730 | 4 | NO2 |
| At 4-5 years | 98 | February 09  April 09  July 09 | Universal kriging with covariates:  Major road length of all roads in a buffer of 300m  Industrial land use in a buffer of 100m  High density residential land use in a buffer of 1000m | 0.790 | 4 | NO2 |
| MDI: Mean daily traffic count  aMean of estimated NO2 from kriging among campaigns | | | | | | | |

**Table S2. Comparison of maternal, paternal, and child characteristics of included subjects during pregnancy to those of non-included subjects, out of 2,764 eligible individuals**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Subjects** |  | **Subjects** |  | **P-value** |
|  | **included** |  | **not included** |  | **of the** |
|  | **(n=1,298)** |  | **(n=1,466)** |  | **difference** |
| **Maternal characteristics** |  |  |  |  |  |
| **Educational level during pregnancy** |  |  |  |  | <0.001 |
| University | 36.3 |  | 30.8 |  |  |
| Secondary | 42.1 |  | 41.2 |  |  |
| Primary | 21.6 |  | 28.0 |  |  |
| **Social class during pregnancy** |  |  |  |  | <0.001 |
| I/II managers/technicians | 23.5 |  | 19.2 |  |  |
| III skilled manual/non-manual | 27.5 |  | 23.9 |  |  |
| IV/V semiskilled/unskilled | 49.0 |  | 56.9 |  |  |
| **Country of birth (Spain vs. elsewhere)** | 94.0 |  | 87.8 |  | <0.001 |
| **Residence urbanicity during pregnancy (rural vs. urban)** | 17.0 |  | 19.1 |  | 0.167 |
| **Age at child's birth (years)** | 30.9 (4.0) |  | 30.2 (4.8) |  | <0.001 |
| **Pre-pregnancy body mass index** |  |  |  |  | 0.275 |
| Normal weight/underweight | 74.2 |  | 72.2 |  |  |
| Overweight | 18.6 |  | 18.9 |  |  |
| Obese | 7.2 |  | 8.9 |  |  |
| **Smoking during pregnancy (yes vs. no)** | 30.3 |  | 32.8 |  | 0.169 |
| **Alcohol consumption during the pregnancy** |  |  |  |  | 0.315 |
| No consumption | 78.6 |  | 80.8 |  |  |
| Below the mediana | 11.9 |  | 11.2 |  |  |
| Above the medianb | 9.5 |  | 8.0 |  |  |
| **Paternal characteristics** |  |  |  |  |  |
| **Educational level during pregnancy** |  |  |  |  | 0.726 |
| University | 21.2 |  | 20.7 |  |  |
| Secondary | 43.6 |  | 42.6 |  |  |
| Primary | 35.2 |  | 36.7 |  |  |
| **Social class during pregnancy** |  |  |  |  | 0.068 |
| I/II managers/technicians | 20.3 |  | 18.7 |  |  |
| III skilled manual/non-manual | 18.5 |  | 15.8 |  |  |
| IV/V semiskilled/unskilled | 61.2 |  | 65.5 |  |  |
| **Country of birth (Spain vs. elsewhere)** | 94.9 |  | 86.1 |  | <0.001 |
| **Age at child's birth (years)** | 32.9 (4.8) |  | 32.6 (5.3) |  | 0.203 |
| **Child characteristics** |  |  |  |  |  |
| **Sex (female vs. male)** | 49.9 |  | 46.9 |  | 0.121 |
| **Number of siblings at attentional function assessment** |  |  |  |  | 0.604 |
| 0 | 34.1 |  | 31.9 |  |  |
| 1 | 57.3 |  | 59.2 |  |  |
| ≥ 2 | 8.6 |  | 8.9 |  |  |

Values are percentages for categorical variables and mean (SD) for continuous variables

a0.01/0.938 servings/week

b>0.939/maximum servings/week

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Table S3. Association between prenatal NO2 levels and potential confounding variables** | | | | | |
|  | **Prenatal NO2 levelsa** | | |  |  |
|  | **Low** | **Medium** | **High** | **P-difference** | **P-trend** |
| **Maternal characteristics** |  |  |  |  |  |
| **Educational level during pregnancy** |  |  |  | <0.001 | <0.001 |
| University | 42.6 | 35.1 | 31.4 |  |  |
| Secondary | 41.7 | 42.5 | 41.8 |  |  |
| Primary | 15.7 | 22.4 | 26.8 |  |  |
| **Social class during pregnancy** |  |  |  | 0.080 | 0.030 |
| I/II managers/technicians | 26.7 | 24.2 | 19.4 |  |  |
| III skilled manual/non-manual | 27.7 | 25.2 | 29.8 |  |  |
| IV/V semiskilled/unskilled | 45.6 | 50.6 | 50.8 |  |  |
| **Country of birth (Spain vs. elsewhere)** | 97.0 | 94.5 | 90.5 | <0.001 | <0.001 |
| **Residence urbanicity during pregnancy (rural vs. urban)** | 39.4 | 9.0 | 2.5 | <0.001 | <0.001 |
| **Age at child's birth (years)** | 31.2 (3.7) | 30.9 (4.1) | 30.6 (4.3) | 0.012 | 0.030 |
| **Pre-pregnancy body mass index** |  |  |  | 0.140 | 0.160 |
| Normal weight/underweight | 76.0 | 72.5 | 73.9 |  |  |
| Overweight | 19.4 | 18.7 | 17.8 |  |  |
| Obese | 4.6 | 8.8 | 8.3 |  |  |
| **Smoking during pregnancy (yes vs. no)** | 27.2 | 31.2 | 33.3 | 0.143 | 0.072 |
| **Alcohol consumption during the pregnancy** |  |  |  | 0.009 | <0.001 |
| No consumption | 82.0 | 80.8 | 72.8 |  |  |
| Below the medianb | 10.4 | 10.2 | 15.2 |  |  |
| Above the medianc | 7.6 | 9.0 | 12.0 |  |  |
| **Paternal characteristics** |  |  |  |  |  |
| **Educational level during pregnancy** |  |  |  | <0.001 | <0.001 |
| University | 24.0 | 21.2 | 18.0 |  |  |
| Secondary | 48.6 | 42.5 | 39.7 |  |  |
| Primary | 27.4 | 36.3 | 42.3 |  |  |
| **Social class during pregnancy** |  |  |  | 0.642 | 0.060 |
| I/II managers/technicians | 22.4 | 20.1 | 18.5 |  |  |
| III skilled manual/non-manual | 18.0 | 19.7 | 18.2 |  |  |
| IV/V semiskilled/unskilled | 59.7 | 60.2 | 63.3 |  |  |
| **Country of birth (Spain vs. elsewhere)** | 97.0 | 94.7 | 87.0 | <0.001 | <0.001 |
| **Age at child's birth (years)** | 33.6 (4.8) | 32.8 (4.7) | 32.2 (4.7) | 0.780 | <0.001 |
| Values are percentages for categorical variables and mean (SD) for continuous variables  aLow levels = 3.8-24.5 μg/m³; medium levels = 24.5-36.8 μg/m³; and high levels = 36.8-74.2 μg/m³  b0.01/0.938 servings/week  c>0.939/maximum servings/week | | | | | |

**Table S4. Minimally-adjusted combined associations between prenatal and postnatal NO₂ (overall and by sex) and attentional functiona**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **HRT** | | **HRT(SE)** | | **Detectability** | | **Omissions** | | **Commissions** | |
| **Prenatal NO₂ (per ∆ 10 μg/m³)** | **N** | **β** | **(95% CI)** | **β** | **(95% CI)** | **β** | **(95% CI)** | **IRR** | **(95% CI)** | **IRR** | **(95% CI)** |
| **Overall** | 1298 | 2.67 | (-3.47; 8.82) | 1.02 | (0.31; 1.74) | -0.03 | (-0.08; 0.02) | 1.06 | (1.02; 1.11) | 1.03 | (0.97; 1.08) |
| **By sex** |  |  |  |  |  |  |  |  |  |  |  |
| **Girls** | 648 | 5.91 | (-3.36; 15.19) | 0.50 | (-0.63; 1.63) | -0.05 | (-0.12; 0.03) | 1.05 | (0.99; 1.11) | 1.04 | (0.96; 1.13) |
| **Boys** | 650 | 0.28 | (-7.91; 8.46) | 1.43 | (0.36; 2.51) | -0.01 | (-0.06; 0.04) | 1.07 | (1.00; 1.14) | 1.00 | (0.95; 1.07) |
| **Postnatal NO₂ (per ∆ 10 μg/m³)** |  |  |  |  |  |  |  |  |  |  |  |
| **Overall** | 1298 | 0.87 | (-6.27; 8.02) | 0.73 | (-0.12; 1.58) | -0.03 | (-0.08; 0.02) | 1.05 | (1.00; 1.11) | 1.04 | (0.97; 1.12) |
| **By sex** |  |  |  |  |  |  |  |  |  |  |  |
| **Girls** | 648 | 5.80 | (-4.94; 16.54) | 0.18 | (-0.78; 1.14) | -0.01 | (-0.07; 0.05) | 1.05 | (0.98; 1.13) | 1.04 | (0.94; 1.15) |
| **Boys** | 650 | -2.82 | (-12.47; 6.84) | 0.93 | (-0.94; 2.80) | -0.03 | (-0.09; 0.03) | 1.05 | (0.97; 1.14) | 1.02 | (0.95; 1.10) |

β = beta coefficient. 95%CI = 95% confidence interval. IRR= Incidence-rate ratio. HRT = Hit reaction time (ms). HRT (SE) = Hit reaction time standard error (ms). Omissions = Omission errors (n). Commissions = Commission errors (n). NO₂ = Nitrogen dioxide.

p-value from Heterogeneity test (p-heter)/ I² index to quantify the degree of heterogeneity in a meta-analysis(%)(I²(%)) for prenatal NO₂ exposure (overall) to HRT = 1.00/0, HRT (SE) = 0.85/0, Detectability = 0.03/67.54, Omissions = 0.68/0, Commissions 0.07/56.74.

p-heter/I²(%) for prenatal NO₂ exposure in girls to HRT =0.87/0, HRT(SE) =0.32/14.07, Detectability= 0.03/65.87, Omissions =0.95/0, Commissions = 0.06/58.82.

p-heter/I²(%) for prenatal NO₂ exposure in boys to HRT =0.81/0, HRT(SE) =0.82/0, Detectability= 0.12/48.83, Omissions =0.33/13.16, Commissions = 0.12/49.16.

p-heter/I²(%) for postnatal NO₂ exposure (overall) to HRT = 0.72/0, HRT (SE) = 0.47/0, Detectability = 0.04/65.22, Omissions = 0.37/4.55, Commissions = 0.01/72.26.

p-heter/I²(%) for postnatal NO₂ exposure in girls to HRT =0.59/0, HRT(SE) =0.49/0, Detectability= 0.19/37.25, Omissions =0.56/0, Commissions = 0.03/65.72.

p-heter/I²(%) for postnatal NO₂ exposure in boys to HRT =0.99/0, HRT(SE) =0.15/43.65, Detectability= 0.13/46.92, Omissions =0.32/13.65, Commissions = 0.10/52.28.

aEstimated associations by random-effects meta-analysis by region. Models were adjusted for child’s sex and child’s age at the time of the attentional function assessment.