# Air Pollution, Autism spectrum disorders, and brain imaging in CHildren among Europe – the APACHE Project


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## BACKGROUND

Air pollution effects on brain development are one of the most important emerging and newly recognized scientific challenges in air pollution research.

Three of the main remaining open research questions are:

i) whether air pollution exposure during pregnancy is truly associated with autism spectrum disorders (ASD) after the contradictory published results between studies from the US and Europe
ii) which brain structures and functions are impaired due to air pollution exposure leading to the cognitive delays and behavioral problems observed in previous epidemiological studies
iii) which are the relevant time windows of air pollution exposure for these effects

## AIMS

The overall objectives of the APACHE Project are:

i) to assess the relationship between prenatal air pollution exposure at different time windows and the development of ASD
ii) to assess the relationship between prenatal and postnatal air pollution exposure at different time windows and brain structural and functional changes in children

## METHODS

### WP1. Epidemiological studies

The APACHE project includes two epidemiological studies:

**ASD Study.** Population-based case-cohort of ASD in Catalunya (Spain), where children diagnosed with ASD identified through the Catalan mental health network are linked to the Catalan birth registry

**Imaging Study.** Population-based birth cohort, the Generation R (the Netherlands) with existing longitudinal data on brain structural and functional imaging in children at 6-10 years (n=1,070) and at 8-12 years (n=3,992)

### WP2. Exposure assessment

**a)** For both epidemiological studies we compiled existing land use regression models for:

- $NO_2$, $NO_x$, $PM_{10}$, $PM_{coarse}$, $PM_{2.5}$, $PM_{2.5}$ absorbance
- $PM_{2.5}$ composition (8 particle related polycyclic aromatic hydrocarbons, 8 selected trace elements: Cu, Fe, Zn for representing non-tailpipe traffic emission; S for long-range transport; Si for crustal material; K for biomass burning; Ni and V for mixed oil burning/industry, organic carbon, oxidative potential)
- Black carbon
- Ultrafine particles

**b)** For the study of Catalunya, we combine land use variables and satellite data remote sensing of aerosol optical depth to develop new $PM_{2.5}$ and $PM_{10}$ models

**c)** We estimate air pollution levels at participants' home addresses at different time-windows: i) during pregnancy (entire pregnancy, monthly, and weekly) for the ASD and the brain imaging study and ii) during childhood (entire childhood, yearly, and monthly) for the brain imaging study

### WP3. Statistical methods

**a)** Methods for measurement error: We quantify the measurement error in air pollution model predictions and transfer resulting uncertainty to the assessment of dose-response relationships

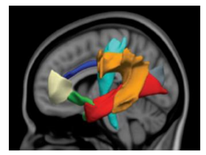
**b)** Multi-pollutant models: We apply the Deletion/Substitution/Addition algorithm to identify the specific pollutants associated with ASD and brain imaging

## RESULTS

**ASD Study.** No results yet.

**Imaging Study – Manuscript 1.** Prenatal $PM_{2.5}$ exposure was associated with a thinner cortex in several brain regions in 6-10 years old children and these alterations partially mediated the association between prenatal $PM_{2.5}$ exposure and impaired child inhibitory control (n=783) *(Guxens et al. Biol Psychiatry. 2018; pii: S0006-3223(18)30064-7)*

**Imaging Study – Manuscript 2.** Association between fetal and childhood exposure to several traffic-related air pollutants and white matter microstructure in 8-12 years old children (n=2,954) *(Lubczynska et al. in preparation)*



**Prenatal air pollution exposure**

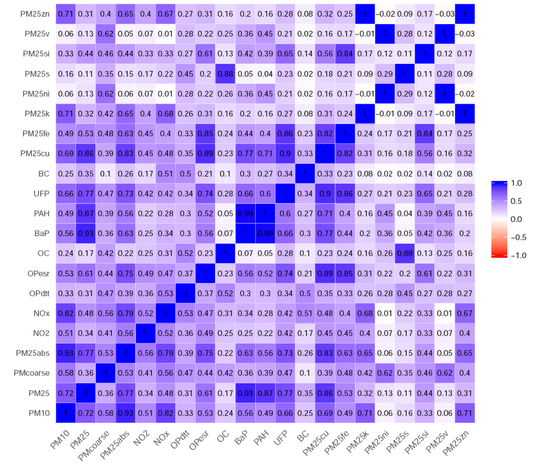
| | Fractional anisotropy | | | | | Mean diffusivity | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | 95% CI | | | Multi-pollutant analysis | | 95% CI | | | Multi-pollutant analysis |
| Pollutant | Coef. | | | p-value | | Coef. | | | p-value | |
| $NO_X$ | **-0.09** | **-0.17** | **-0.01** | **0.028** | --- | 0.01 | 0.00 | 0.02 | 0.118 | |
| $NO_2$ | -0.08 | -0.17 | 0.01 | 0.083 | | 0.01 | 0.00 | 0.02 | 0.250 | |
| $PM_{10}$ | **-0.46** | **-0.86** | **-0.05** | **0.027** | --- | 0.05 | 0.00 | 0.10 | 0.053 | |
| $PM_{25}$ | -0.65 | -1.34 | 0.03 | 0.062 | | **0.09** | **0.01** | **0.18** | **0.036** | --- |
| $PM_{coarse}$ | -0.05 | -0.37 | 0.26 | 0.735 | | 0.03 | -0.01 | 0.07 | 0.150 | |
| $PM_{25}$abs | **-0.27** | **-0.49** | **-0.04** | **0.020** | **selected** | **0.03** | **0.01** | **0.06** | **0.015** | **selected** |
| PAHs | 0.01 | -0.18 | 0.21 | 0.889 | | 0.01 | -0.01 | 0.04 | 0.236 | |
| B[a]P | -0.44 | -2.32 | 1.43 | 0.640 | | 0.17 | -0.06 | 0.40 | 0.140 | |
| OC | -0.10 | -0.27 | 0.07 | 0.255 | | 0.01 | -0.01 | 0.04 | 0.175 | |
| $OP_{DTT}$ | 0.16 | -0.31 | 0.62 | 0.501 | | 0.05 | -0.01 | 0.10 | 0.111 | |
| $OP_{ESR}$ | 0.00 | 0.00 | 0.00 | 0.383 | | **0.00** | **0.00** | **0.00** | **0.047** | --- |
| $PM_{25}$Cu | -0.29 | -0.67 | 0.09 | 0.140 | | **0.05** | **0.01** | **0.10** | **0.031** | --- |
| $PM_{25}$Fe | -0.18 | -0.52 | 0.16 | 0.297 | | **0.05** | **0.01** | **0.09** | **0.015** | --- |
| $PM_{25}$K | -0.34 | -0.79 | 0.12 | 0.143 | | 0.03 | -0.02 | 0.09 | 0.230 | |
| $PM_{25}$Si | -0.25 | -0.67 | 0.17 | 0.233 | | **0.07** | **0.02** | **0.12** | **0.008** | --- |
| $PM_{25}$Zn | -0.11 | -0.27 | 0.05 | 0.177 | | 0.01 | -0.01 | 0.03 | 0.241 | |
| UFP | 0.00 | 0.00 | 0.00 | 0.204 | | **0.00** | **0.00** | **0.00** | **0.020** | --- |
| BC | -0.04 | -0.13 | 0.05 | 0.363 | | 0.00 | -0.01 | 0.01 | 0.608 | |

**Postnatal air pollution exposure**

| | Fractional anisotropy | | | | | Mean diffusivity | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | 95% CI | | | Multi-pollutant analysis | | 95% CI | | | Multi-pollutant analysis |
| Pollutant | Coef. | | | p-value | | Coef. | | | p-value | |
| $NO_X$ | **-0.12** | **-0.22** | **-0.03** | **0.012** | **selected** | **0.02** | **0.00** | **0.03** | **0.009** | --- |
| $NO_2$ | **-0.12** | **-0.23** | **-0.01** | **0.038** | --- | **0.02** | **0.01** | **0.03** | **0.005** | --- |
| $PM_{10}$ | -0.42 | -0.87 | 0.04 | 0.075 | | **0.06** | **0.00** | **0.12** | **0.037** | --- |
| $PM_{25}$ | 0.29 | -0.60 | 1.18 | 0.520 | | 0.08 | -0.03 | 0.19 | 0.156 | |
| $PM_{coarse}$ | -0.29 | -0.62 | 0.04 | 0.086 | | **0.04** | **0.00** | **0.08** | **0.041** | --- |
| $PM_{25}$abs | **-0.24** | **-0.48** | **0.00** | **0.050** | --- | **0.04** | **0.01** | **0.07** | **0.013** | --- |
| PAHs | 0.14 | -0.09 | 0.38 | 0.232 | | 0.01 | -0.02 | 0.04 | 0.409 | |
| B[a]P | 1.09 | -1.33 | 3.52 | 0.373 | | 0.16 | -0.14 | 0.45 | 0.298 | |
| OC | **-0.20** | **-0.38** | **-0.03** | **0.025** | --- | 0.02 | 0.00 | 0.04 | 0.077 | |
| $OP_{DTT}$ | -0.14 | -0.68 | 0.39 | 0.603 | | **0.08** | **0.02** | **0.15** | **0.015** | **selected** |
| $OP_{ESR}$ | 0.00 | 0.00 | 0.00 | 0.292 | | 0.00 | 0.00 | 0.00 | 0.082 | |
| $PM_{25}$Cu | -0.19 | -0.62 | 0.24 | 0.377 | | 0.03 | -0.02 | 0.08 | 0.231 | |
| $PM_{25}$Fe | -0.23 | -0.53 | 0.08 | 0.148 | | 0.03 | -0.01 | 0.07 | 0.101 | |
| $PM_{25}$K | **-0.54** | **-1.04** | **-0.04** | **0.035** | --- | **0.09** | **0.03** | **0.15** | **0.006** | --- |
| $PM_{25}$Si | -0.25 | -0.67 | 0.18 | 0.254 | | **0.06** | **0.00** | **0.11** | **0.040** | --- |
| $PM_{25}$Zn | -0.13 | -0.28 | 0.02 | 0.080 | | **0.03** | **0.01** | **0.05** | **0.003** | **selected** |
| UFP | 0.00 | 0.00 | 0.00 | 0.259 | | 0.00 | 0.00 | 0.00 | 0.128 | |
| BC | 0.08 | -0.11 | 0.27 | 0.391 | | -0.01 | -0.03 | 0.01 | 0.428 | |

Models adjusted for parental age, parental educational level, parental country of birth, marital status, household income, maternal prenatal smoking, maternal prenatal alcohol consumption, maternal parity, parental psychiatric symptoms, parental height, parental body mass index, maternal intelligence quotient, and child's age at scanning

**Correlation matrix - Prenatal air pollutants**




- Similar correlations between postnatal air pollutants
- Correlations between prenatal and postnatal air pollution exposure of between 0.4 and 0.6.

**Conclusions**

- Exposure to fetal and childhood exposure to traffic-related air pollutants representative of brake linings, tire wear, and tailpipe emissions originating mainly from combustion of diesel were associated with lower fractional anisotropy and higher mean diffusivity of the white matter in school-age children.
- Such alterations in white matter microstructure have previously been associated with psychiatric and neurological disorders.