Annotated Bibliography: Effects of Air Pollution on Neurodevelopment: ADHD, ASD and LD 2009-2015 Susan Katz, MD

1.Raz R, Roberts AL, Lyall K, Hart JE, Just AC, Laden F, Weisskopf MG. [Autism Spectrum Disorder and Particulate Matter Air Pollution before, during, and after Pregnancy: A Nested Case-Control Analysis within the Nurses' Health Study II Cohort.](http://www.ncbi.nlm.nih.gov/pubmed/25522338) Environ Health Perspect. 2014 Dec 18. [Epub ahead of print] PubMed P

MID: 25522338.

Over 100,000 nurses were followed yearly to determine if their children developed an autism spectrum disorder, by maternal report , validated by a telephone Autism Diagnostic Interview questionnaire. N =245 cases , with 1522 controls.Mother’s address before and after pregnancy, as well as during each trimester of pregnancy was used to estimate exposure, from historical EPA data on PM 2.5 and PM 10 ( a spatiotemporal model). Exposure to PM 2.5 during the entire pregnancy increased risk of ASD with adjusted Odds Ration 1.57, P .05 and PM 10 did not correlate with increased risk. Exposure during the third trimester was the more highly correlated with increased risk than the first and second trimesters.

2. Jedrychowski WA, Perera FP, Camann D, Spengler J, Butscher M, Mroz E, Majewska R, Flak E, Jacek R, Sowa A. [Prenatal exposure to polycyclic aromatic hydrocarbons and cognitive dysfunction in children.](http://www.ncbi.nlm.nih.gov/pubmed/25253062) Environ Sci Pollut Res Int. 2014 Sep 26. [Epub ahea

This paper is from Krakow Poland mirroring Perera’s work at Columbia, , with a prospective birth cohort, N =170. It measures individual exposure to PAHs from prenatal cord blood PAH-DNA adducts, following Full Scale and Verbal IQ at age 7. It finds a decrease in verbal IQ with increased prenatal PAH exposure. OR 3.0 , P< .05 , also decrease with postnatal exposure OR 1.6 , with some protection from exclusive breast feeding for 6 months.

3.Lin CC, Yang SK, Lin KC, Ho WC, Hsieh WS, Shu BC, Chen PC. [Multilevel analysis of air pollution and early childhood neurobehavioral development.](http://www.ncbi.nlm.nih.gov/pubmed/24992486) Int J Environ Res Public Health. 2014 Jul 2;11(7):6827-41. doi: 10.3390/ijerph110706827. PubMed

This paper from Taiwan measures all criteria pollutants except PM2.5, and looks for neurobehavioral effects related to exposure from Air quality monitoring stations in a prospective birth cohort of infants, N = 533, for all three trimesters and postnatally, The measurement of neurodevelopment was by their own parent reported questionnaire at 6 months 12 months and 18 months. (They claim that instrument correlates with the Bayley scale). They find significant effects on fine motor development only from SO2 exposure, and gross motor development effected by Non Methane Hydrocarbons ( equivalent to PAH) Their statistical analyses are unconventional.

4.Kim E, Park H, Hong YC, Ha M, Kim Y, Kim BN, Kim Y, Roh YM, Lee BE, Ryu JM, Kim BM, Ha EH. [Prenatal exposure to PM₁₀ and NO₂ and children's neurodevelopment from birth to 24 months of age: mothers and Children's Environmental Health (MOCEH) study.](http://www.ncbi.nlm.nih.gov/pubmed/24631606) Sci Total Environ. 2014 May 15;481:439-45. doi: 10.1016/j.scitotenv.2014.01.107. Epub 2014 March

This is a prospective birth cohort in Korea, part of the “MOCEH” study, N= 520

that measures prenatal exposure to PM10 and NO2 and effects on the Korean Bayley scale of infant development during the first 24 months of life. Motor Development Index and Psychomotor Development Index were measured. They report decreased psychomotor development at 6 months with NO2 exposure, P,.05 but not at 12 or 24 months. With PM10 exposure they find significant decreases in pyschomotor as well as cognitive development, P<.001

5.Tang D, Li TY, Chow JC, Kulkarni SU, Watson JG, Ho SS, Quan ZY, Qu LR, Perera F. [Air pollution effects on fetal and child development: a cohort comparison in China.](http://www.ncbi.nlm.nih.gov/pubmed/24239591) Environ Pollut. 2014 Feb;185:90-6. doi: 10.1016/j.envpol.2013.10.019. Epub 2013 Nov 13. PubMed PMID: 24239591.

This prospective cohort study of an area in China before and after closure of a coal fired power plant, enrolled two cohorts, one in 2002 before closure and one in 2005 , after closure, N= 110 and 107. Exposure to PAHs was measured by cord blood PAH-DNA adducts and several previous studies have looked at various measure of outcome, including Developmental Delay. This study found a increase in Head Circumference ( P< .001) in children born after closure of the coal plant, as well as a decrease in PAH-DNA adducts (P<.001) and decrease in levels of ambient PAHs (P< .01)

6.Perera FP, Chang HW, Tang D, Roen EL, Herbstman J, Margolis A, Huang TJ, Miller RL, Wang S, Rauh V. [Early-life exposure to polycyclic aromatic hydrocarbons and ADHD behavior problems.](http://www.ncbi.nlm.nih.gov/pubmed/25372862) PLoS One. 2014 Nov 5;9(11):e111670. doi: 10.1371/journal.pone.0111670. eCollection 2014. PubMed PMID: 25372862; PubMed Central PMCID: PMC4221082.

This is the latest in a 12 year long progression of prospective studies based on the CCEHC ( Columbia Children’s Environmental Health Cohort) consisting of a maternal-child cohort, originally N = 740 in this paper, 250, of Black and Dominican mothers and children being studied episodically for neurodevelopmental ( and other) effects related to prenatal personal air samples measuring exposure of the mother and DNA-PAH adducts in cord blood which show what level of PAH actually was absorbed into the cord blood. Children have been studied over the last 9 years for various neurodevelopmental effects. Many important confounding factors have been considered and corrected for, including Maternal ADHD and postnatal PAH exposure via air and diet. This paper reports a correlation between PAH exposure and inattentive type ADHD symptoms measured with both the Connors and the Child Behavior Checklist ( DSM IV related) OR 5.06 P<.05

(Previous studies by the same author and her coworkers demonstrated developmental delay at age 3, reduced IQ at age 5 and and anxiety and depression at age 7 all correlated significantly with prenatal PAH exposure. Correction was made for postnatal exposure by measuring PAH adducts in the children’s urine. )

7.Costa LG, Cole TB, Coburn J, Chang YC, Dao K, Roque P. [Neurotoxicants are in the air: convergence of human, animal, and in vitro studies on the effects of air pollution on the brain.](http://www.ncbi.nlm.nih.gov/pubmed/24524086) Biomed Res Int. 2014;2014:736385. doi: 10.1155/2014/736385. Epub 2014 Jan 12. Review. PubMed PMID: 24524086; PubMed Central PMCID: PMC3912642.

This comprehensive review of animal, human and in vitro studies of the evidence of how air pollutants probably affect the etiology of both neurodevelopmental and neurodegenerative diseases. It proposes that these mechanisms include oxidative stress ( by overproduction of Reactive Oxidative Species or interference with antioxidative mechanisms of protecting the cell) These include the Paraoxanase 2 enzyme (PON 2) which is expressed differently in male and female humans and may account for the gender differences in neurotoxicity, and the preponderance of male children in both ADHD and ASD.

8.Roberts AL, Lyall K, Hart JE, Laden F, Just AC, Bobb JF, Koenen KC, Ascherio A, Weisskopf MG. [Perinatal air pollutant exposures and autism spectrum disorder in the children of Nurses' Health Study II participants.](http://www.ncbi.nlm.nih.gov/pubmed/23816781) Environ Health Perspect. 2013 Aug;121(8):978-84. doi: 10.1289/ehp.1206187. Epub 2013 May

This study N =325 considers diesel and PM 2.5 modeled from EPA data and geographically linked to mother’s address , with ASD as a health outcome, a diagnosis reported by mother by telephone and verified by questions asked the mother. Exposure to the highest vs the lowest quintiles of diesel exposure revealed an increased risk of ASD significant at p<0.05 with an odds ratio of 2.0

30. Erratum in: Environ Health Perspect. 2014 Jun;122(6):A152. PubMed PMID: 23816781; PubMed Central PMCID: PMC3734496.

9.Chiu YH, Bellinger DC, Coull BA, Anderson S, Barber R, Wright RO, Wright RJ. [Associations between traffic-related black carbon exposure and attention in a prospective birth cohort of urban children.](http://www.ncbi.nlm.nih.gov/pubmed/23665743) Environ Health Perspect. 2013 Jul;121(7):859-64. doi: 10.1289/ehp.1205940. Epub 2013 May 1. PubMed PMID: 23665743; PubMed Central PMCID: PMC3701996.

This Massachusetts cross sectional cohort study examines lifetime exposure to black carbon ( soot, surrogate for PM 2.5 and smaller particles and PAHs which adhere to soot particles) in 174 7-14 year old children, and specific measures of inattention and impulsivity on the Connors Scale, the CPT or continuous performance scale. A complex spatio –temporal model from 82 monitoring sites and children’s residences was used to estimate lifetime exposure. Black soot quartiles were compared to CPT scores. They report non linear associations of Black Carbon exposure and higher commission errors and slower reaction time, (markers for ADHD), with OR 2.66-6 for the second and third quartiles. Oddly the 4th quartile with most exposure was not correlated significantly.

10.Newman NC, Ryan P, Lemasters G, Levin L, Bernstein D, Hershey GK, Lockey JE, Villareal M, Reponen T, Grinshpun S, Sucharew H, Dietrich KN. [Traffic-related air pollution exposure in the first year of life and behavioral scores at 7 years of age.](http://www.ncbi.nlm.nih.gov/pubmed/23694812) Environ Health Perspect. 2013 Jun;121(6):731-6. doi: 10.1289/ehp.1205555. Epub 2013 Apr 5. PubMed PMID: 23694812; PubMed Central PMCID: PMC3672910.

This study from Cincinnati is a birth cohort study and purports to examine relationship between Traffic related air pollution , namely elemental Carbon and hyperactivity , measured by Behavioral Assessment System a parent questionnaire at age 7. Pollution is modeled from 27 air sampling sites and birth residence less than 400m or more than 1500 m from a major traffic bearing highway. N= 576 .The highest tertile in exposure has increased hyperactivity behaviors only, OR1.7 P< .003 and controlled for higher education in mothers OR 2.3. ( Did not include parental history of ADHD in study)

11.Volk HE, Lurmann F, Penfold B, Hertz-Picciotto I, McConnell R. [Traffic-related air pollution, particulate matter, and autism.](http://www.ncbi.nlm.nih.gov/pubmed/23404082) JAMA Psychiatry. 2013 Jan;70(1):71-7. doi: 10.1001/jamapsychiatry.2013.266. PubMed PMID: 23404082; PubMed Central PMCID: PMC4019010.

This case control study of N=279 children with ASD from a California CHARGE study, examined traffic related air pollution modeled from EPA measured air toxics and address during each trimester of pregnancy and first year of life. ( Measuring stations were within 5 km of the home) Autism was determined by personal interview and multiple instruments designed to assess presence of ASD and features of ASD. Exposure to the highest quartile of Traffic Related Pollution ( NO2, PM10, PM2.5 all associated with an increased risk of autism.) OR 1.98 for exposure during pregnancy and 3.0 for 95% confidence interval for exposure during the first year compared to children in the lowest quartile. Exposure during all three trimesters was associated with increased risk. Effects in the first trimester were the smallest. This work corroborates a previous study  which reported that children born to mothers living within 309 m of a freeway during pregnancy were more likely to be diagnosed with autism than children whose mothers lived > 1,419 m from a freeway (Volk et al. 2010).

12. Jung CR et al J Alzheimers Dis. 2015 Jan 1;44(2):573-84. doi: 10.3233/JAD-140855. PubMed PMID: 25310992.

This retroprospective study of 95,690 subjects in Taiwan measured exposure to Ozone and to PM 2.5 ( measured by EPA data and modeled for home address) and increased risk of Alzheimer’s disease. Significant positive evidence of increased risk with each toxicant is reported, with OR 2-3 P<.05

13.Siddique S, Banerjee M, Ray MR, Lahiri T (2011) Attention-deficit hyperactivity disorder in children chronically exposed to high level of vehicular pollution. Eur J Pediatr 170: 923–929. doi: 10.1007/s00431-010-1379-0

* This cross sectional study from New Delhi India considered 969 urban children compared to 850 rural children, with PM10 levels measured from municipal measurements in neighborhoods involved. ADHD was measured by DSM IV criteria, and ambient PM10 was associated with increased risk for ADHD, primarily inattentive type, with OR 2.7, P<.05 mostly in boys, 4.5 to 1.

14. Weiland, K J Health Care Poor Underserved. 2011 February ; 22(1): 320–329. doi:10.1353/hpu.2011.0012. Cost of Developmental Delay from Prenatal Exposure to Airborne Polycyclic Aromatic Hydrocarbons

This paper is linked to the CCCEH cohort studies of Perera et al which showed Developmental Delay in children exposed to the highest quartile of PAH exposure prenatally. It estimates the cost of preschool for the entire Medicaid population who may be similarly affected in NYC. It calculates 13.7 million dollars per year cost, using a calculation by the “Environmental Attributable Fraction” method, developed by the Institute of Medicine to estimate effects of the environment on disease prevalence ( as opposed to genetic influence for example)

15. Calderón-Garcidueñas L, Engle R, Mora-Tiscareño A, et al. Exposure to severe urban air pollution influences cognitive outcomes, brain volume and systemic inflammation in clinically healthy children. *Brain and cognition*. 2011;77(3):345–355. [[PubMed](http://www.ncbi.nlm.nih.gov/pubmed/22032805)]

This small cohort (N ==20. Controls 10) prospective study measured the effect over a year of severe traffic pollution in Mexico City children compared with matched controls in a low traffic city, with three biological parameters – brain volume by MRI, WISC scales for cognitive development, and measured serum concentration of an inflammatory marker. They found significant deficits in Vocabulary and Digit Span scales on the WISC which correlated with white matter deficits in the parietal and temporal brain regions ! Although N is small, it was an expensive study and will necessarily be limited. We argue that although prefrontal WMH characterized highly exposed children and translated in cognitive deficits, hyperintensi- ties likely only partially identified underlying white matter pathol- ogy. Moreover, systemic inflammation and endothelial activation likely play a key role in the detrimental structural and cognitive ef- fects in keeping with the literature suggesting that up-regulation of serum inflammatory markers, microglial and endothelial cell activation and BBB abnormalities are key CNS pathology factors associated with air pollution (

16. [Green and Blue Spaces and Behavioral Development in Barcelona Schoolchildren: The BREATHE Project](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4256702/)

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Environ Health Perspect. **2014** December; 122(12): 1351–1358. Published online **2014** September 9. doi: 10.1289/ehp.1408215

PMCID: PMC425670

This very complicated cross sectional retrospective paper reports on a cohort of N =2111 schoolchildren from 36 schools and attempts a modeled spatiotemporal estimate of air pollution in various areas of Barcelona where the children live, play and go to school. They designated and stratified green spaces by distance from air polluting sources- living and playing 100, 250, 300 and 500 meters from a more polluted area, . In retrospective questionairres by teachers and parents, they found more symptoms of ADHD in children who lived and played closer to sources of pollution. They also modeled outdoor playing time and time near Blue spaces ( Beaches) The statistical analyses are different than what one usually finds in the US and I can not decipher the strength of the correlations but this is a very interesting and unusual approach to spatiotemporal modeling. The EU has suggested 300 meters as the desirable distance ( green space)

17. Rauh VA, Garfinkel R, Perera FP, et al. Impact of prenatal chlorpyrifos exposure on neurodevelopment in the first 3 years of life among inner-city children., *Pediatrics.* 2006 December; 118(6): e1845–e1859.

18. Kalkbrenner , et al. Particulate Matter Exposure, Prenatal and Postnatal windows of susceptibility and Autism Spectrum Disorder. Epidemiology . 2015, 26:30-42

Two cohorts in North Carolina and San Francisco born from 1994-2000, N = 645 in NC and 334 in SF, with randomly sampled controls. Retrospective records based on PM10 measurements and birth address. Analysis showed increased susceptibility associated with third trimester exposure. OR 1.38, 95% CI.

19.Becerra TA, et al. Ambient Air Pollution and Autism in Los Angeles County. (2013) Environmental Health Perspectives.121: 380-386

This study in Los Angeles retrospective with data from California Health Records, and spatiotemporal modeling of exposure from residential birth records, N =7603 at age 3-5 found modest increase in risk of ASD diagnosis for children living close to a freeway with increased PM 2.5 and ozone, OR 1.15,

20. Peterson BS. Et al. (2015) Effects of Prenatal Exposure to Air Pollutants ( Polycyclic Aromatic Hydrocarbons ) on the Development of Brain White Matter, Cognition and Behavior in Later Childhood. JAMA Psychiatry (2015) doi:10.1001 2015.57

From the CCEHS cohort at Columbia, a sample N=40 aged 7-9, measured decrease in local volumes of the surface of the left side of the brain ( the white matter ), slower information processing subscale on WISC, externalizing behavior problems and ADHD all correlated with third trimester prenatal exposure to PAHs ( with postnatal exposure contributing to additional disturbance in the development of white matter in dorsal prefrontal regions of the brain, associated with executive functioning.)