NEURODEVELOPMENTAL EFFECTS

Health Effects Institute 2019 Annual Conference

Early-Life Exposure to Air Pollution

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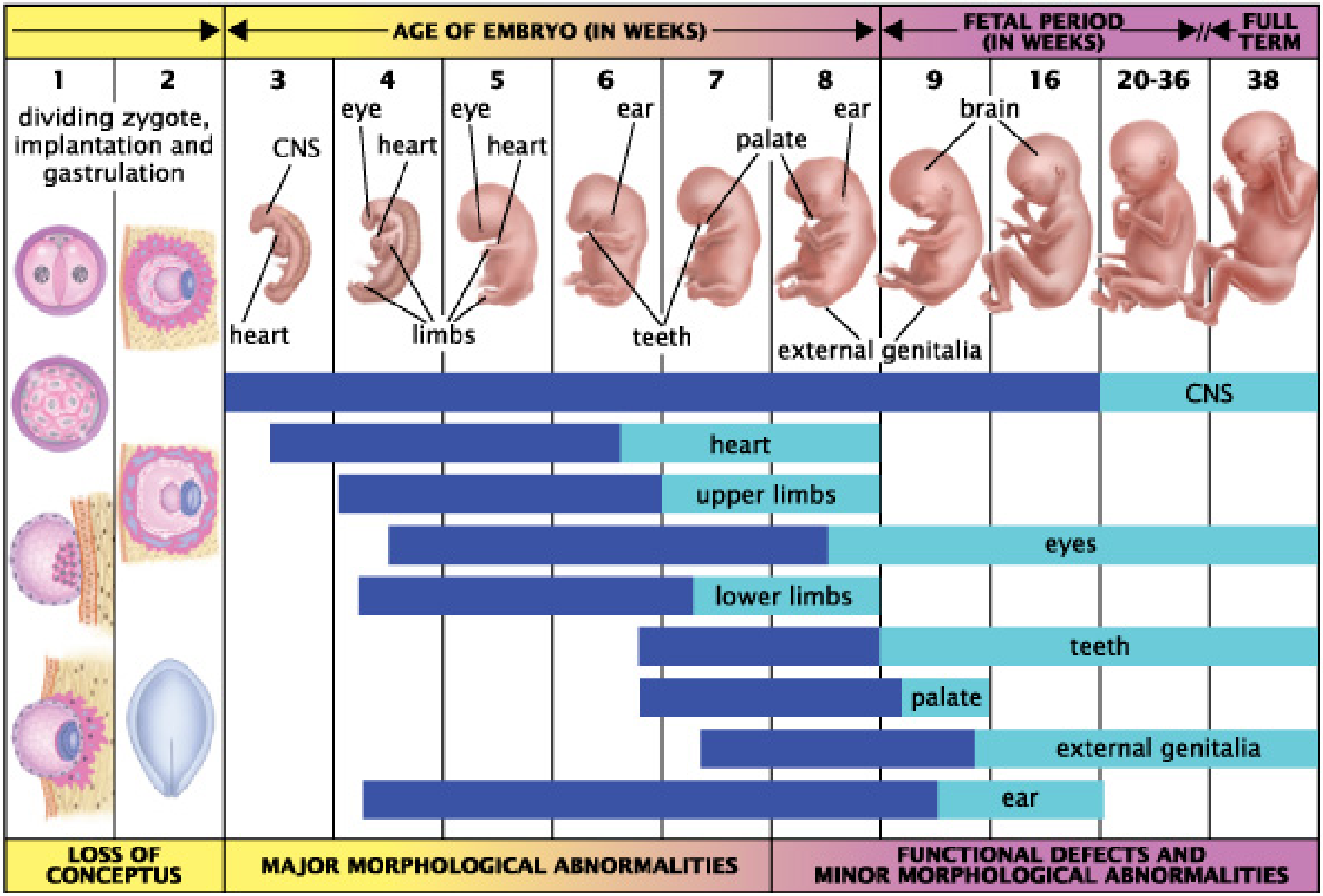
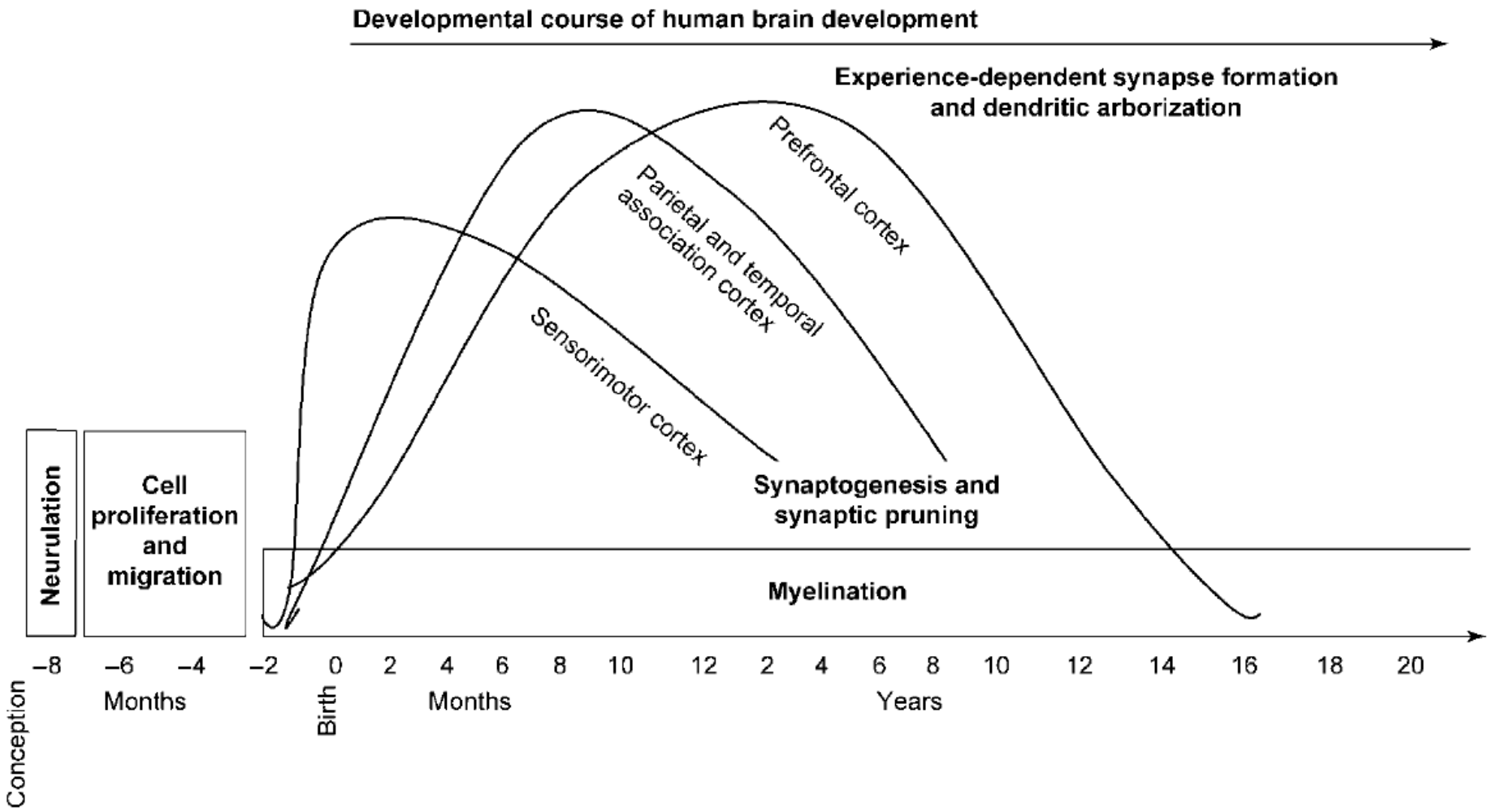
Overview

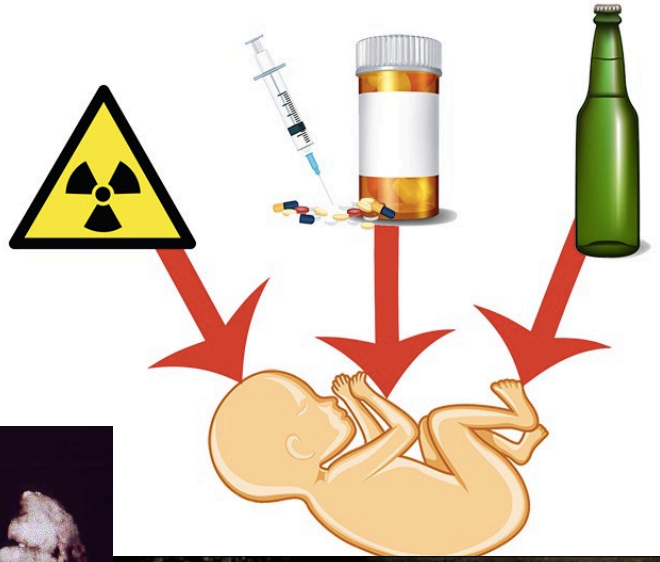
- Introduction to neurodevelopmental outcomes
  - Vulnerability of the developing brain
  - Neuropsychological assessment
- Air pollution and neurodevelopment
  - Prenatal exposure
  - Childhood exposure
- Discussion and future directions


AGE OF EMBRYO (IN WEEKS)
FETAL PERIOD (IN WEEKS)
FULL TERM
1
2
3
4
5
6
7
8
9
16
20-36
38
dividing zygote, implantation and gastrulation
CNS
heart
eye
heart
eye
heart
limbs
ear
teeth
palate
ear
external genitalia
brain
CNS
heart
upper limbs
eyes
lower limbs
teeth
palate
external genitalia
ear
LOSS OF CONCEPTUS
MAJOR MORPHOLOGICAL ABNORMALITIES
FUNCTIONAL DEFECTS AND MINOR MORPHOLOGICAL ABNORMALITIES

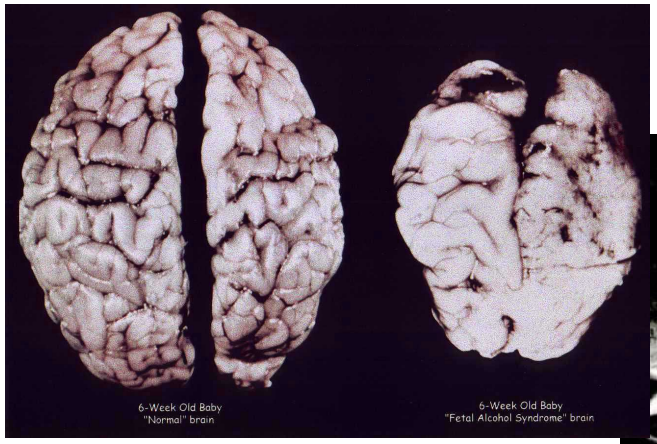
Brain development continues after birth



Neurotoxicants



Lead



Fetal alcohol syndrome

Mercury poisoning Minimata, Japan

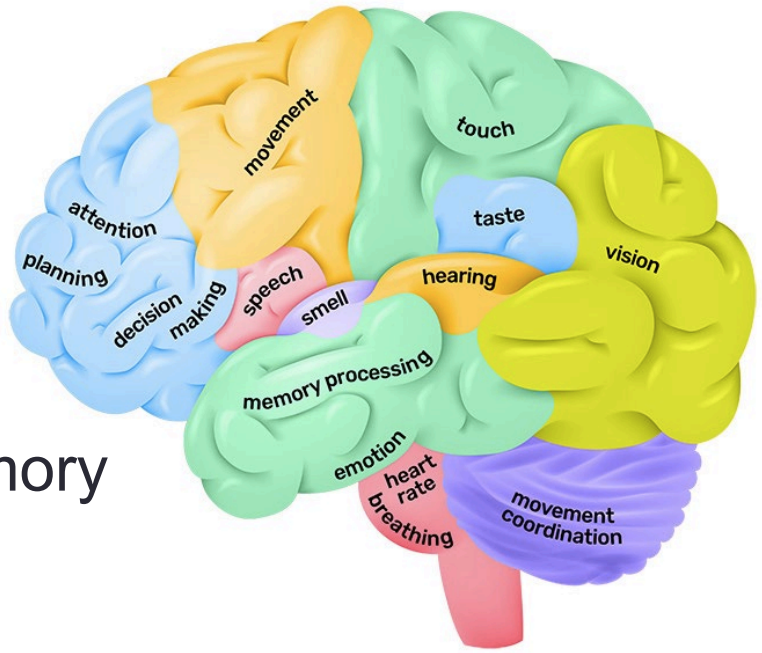
Environmental pollutants with known or potential neurotoxic effects

- Metals (arsenic, lead, mercury)
- Persistent organic pollutants (PCBs, PBDEs, PFASs)
- Solvents (ethanol, toluene)
- Pesticides (organophosphates)
- Consumer products chemicals
  - (e.g., phthalates, BPA, phenols)
- Air pollution, second hand smoke

PCB = Polychlorinated biphenyl
PBDE = Polybrominated diphenyl ethers
PFAS = Per- and polyfluoroalkyl substances
BPA = bisphenol A

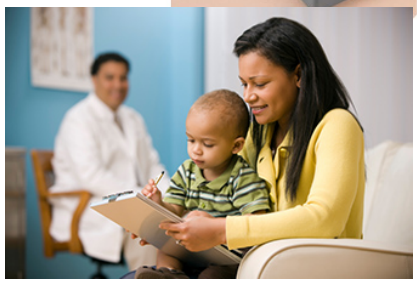
Neurodevelopmental domains

- Language/verbal skills
- Memory and learning
- Visuospatial abilities
- Motor function
- Attention
- Executive function/working memory
- Behavioral inhibition
- Social behavior



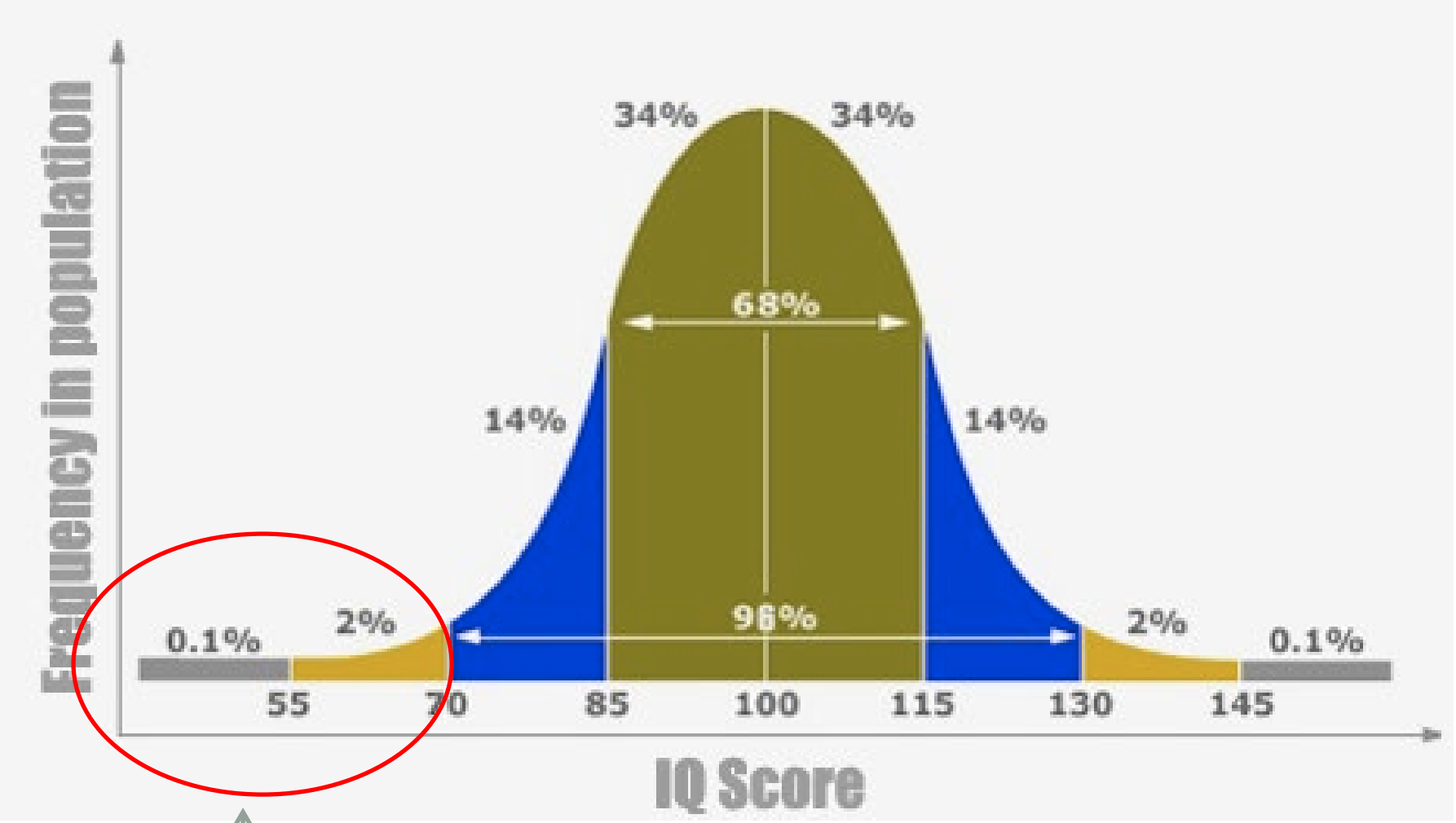
- Domains may be differentially sensitive to environmental exposures

Neuropsychological assessment

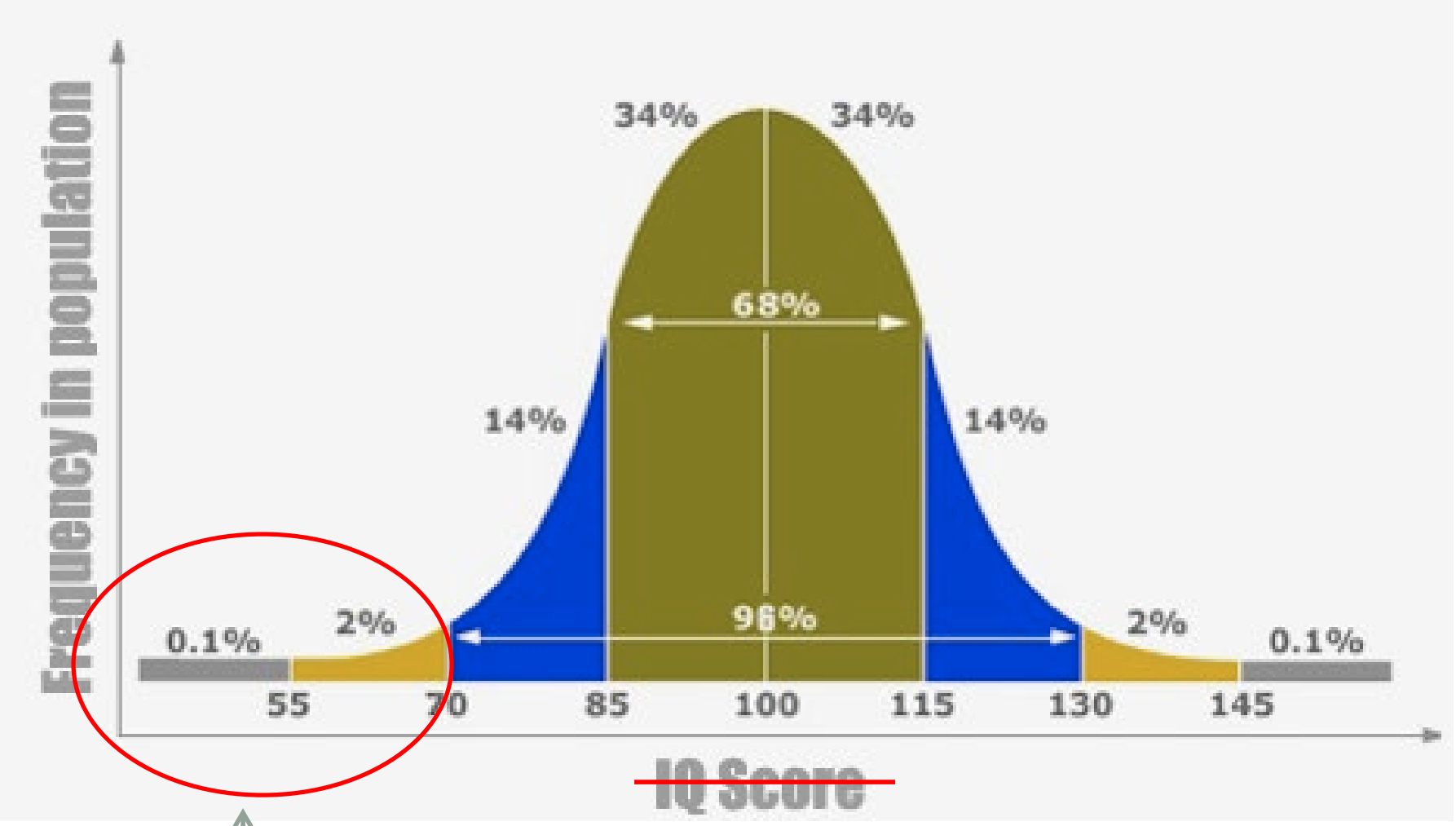


- Types of assessment
  - Neuropsychological performance
  - Reporting scales (parent, teacher, self)
- Battery of tests designed by a neuropsychologist
- Impairment measured on a continuum
  - Along dimensions/domains
- Diagnosis of developmental disorder
  - Extreme impairment can result in classification of a neurodevelopmental disorder, e.g. ADHD, autism spectrum disorder, intellectual disability

ADHD = Attention-deficit/hyperactivity disorder



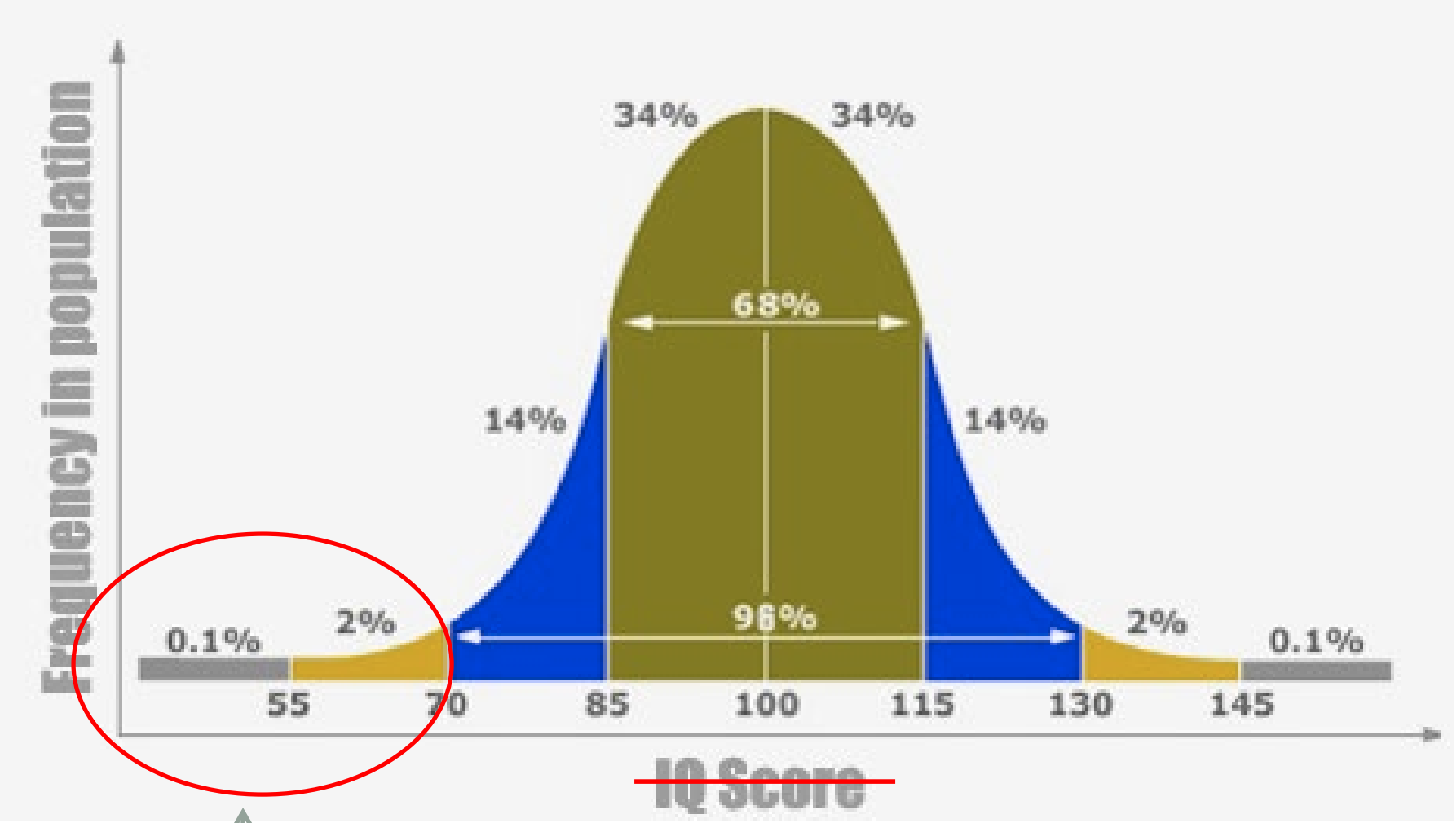
Intellectual disability



Attention, impulsivity/hyperactivity

ADHD

ADHD = Attention-deficit/hyperactivity disorder



Autism Spectrum Disorder

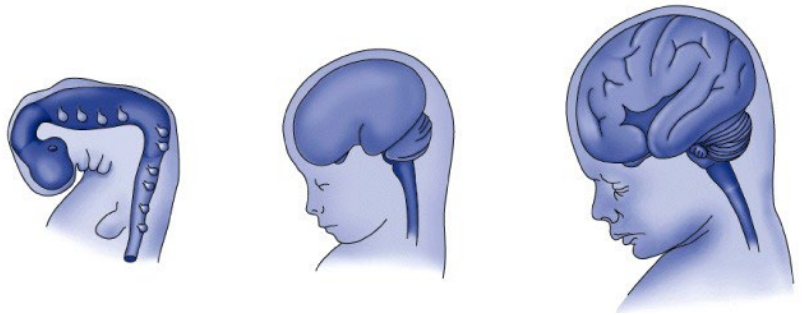
Social behavior
(social communication, restricted interests and repetitive behaviors)

Public health significance

- Prevalence of neurodevelopmental disorders is high and rising, e.g., ADHD (5-10%), autism (1.5-2%)
  - *Increasing incidence?*
- Features persist across the life course
- Impacts on long-term health and well-being *(among those with and without clinical diagnosis)*
  - Education and employment
  - Mental health, e.g., anxiety, depression
  - Behavioral health, e.g., substance use
  - Higher morbidity, risk for early mortality

ADHD = Attention-deficit/hyperactivity disorder

AIR POLLUTION AND NEURODEVELOPMENT



Air pollution: a complex mixture

- EPA criteria pollutants
- Traffic-related pollutants (PM, NO_2)
- Distance to roadways, traffic density
- Polycyclic aromatic hydrocarbons (PAHs)

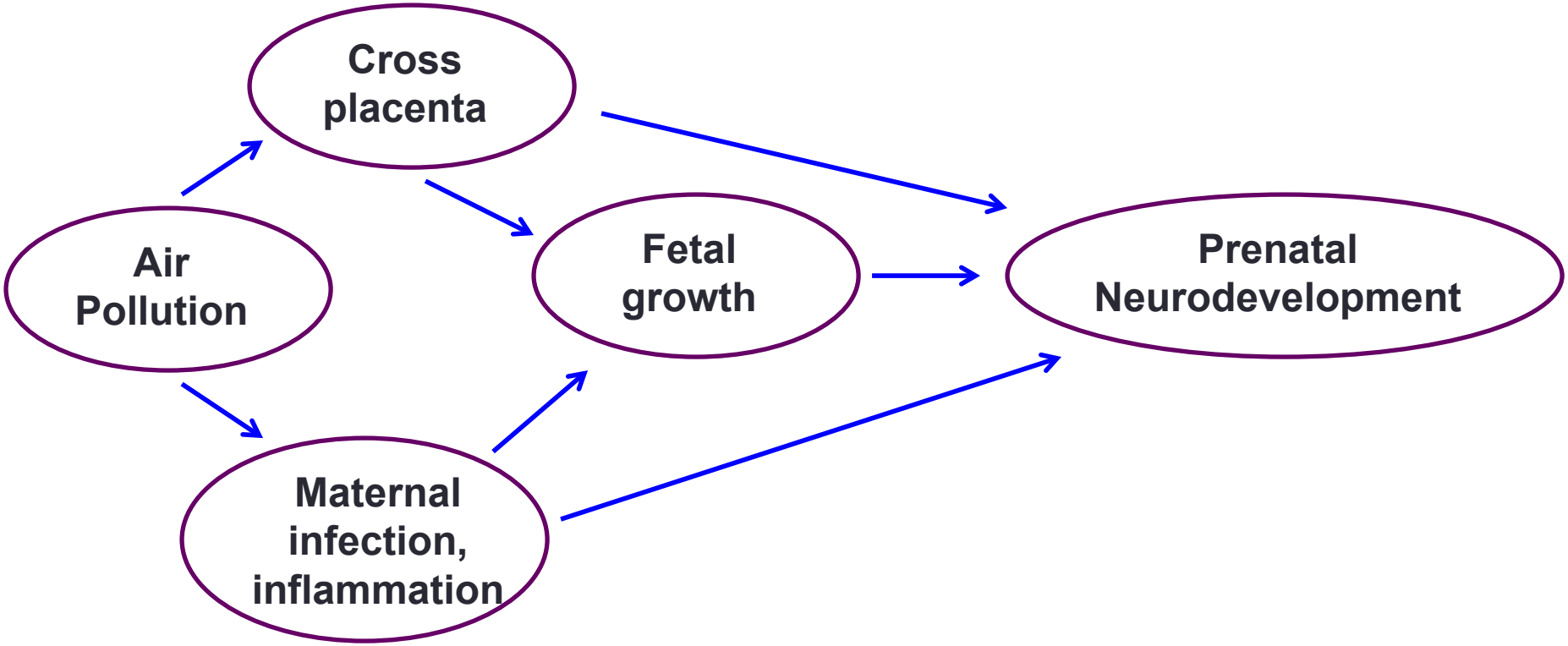
- 2 fractions of particulate matter most relevant to CNS:
  - $PM_{2.5}$: particles with a diameter < 2.5 μm
  - Ultrafine PM (UFPM): particles with a diameter < 100 nm

- PM as a vehicle for neurotoxicants
  - E.g., metals, organics

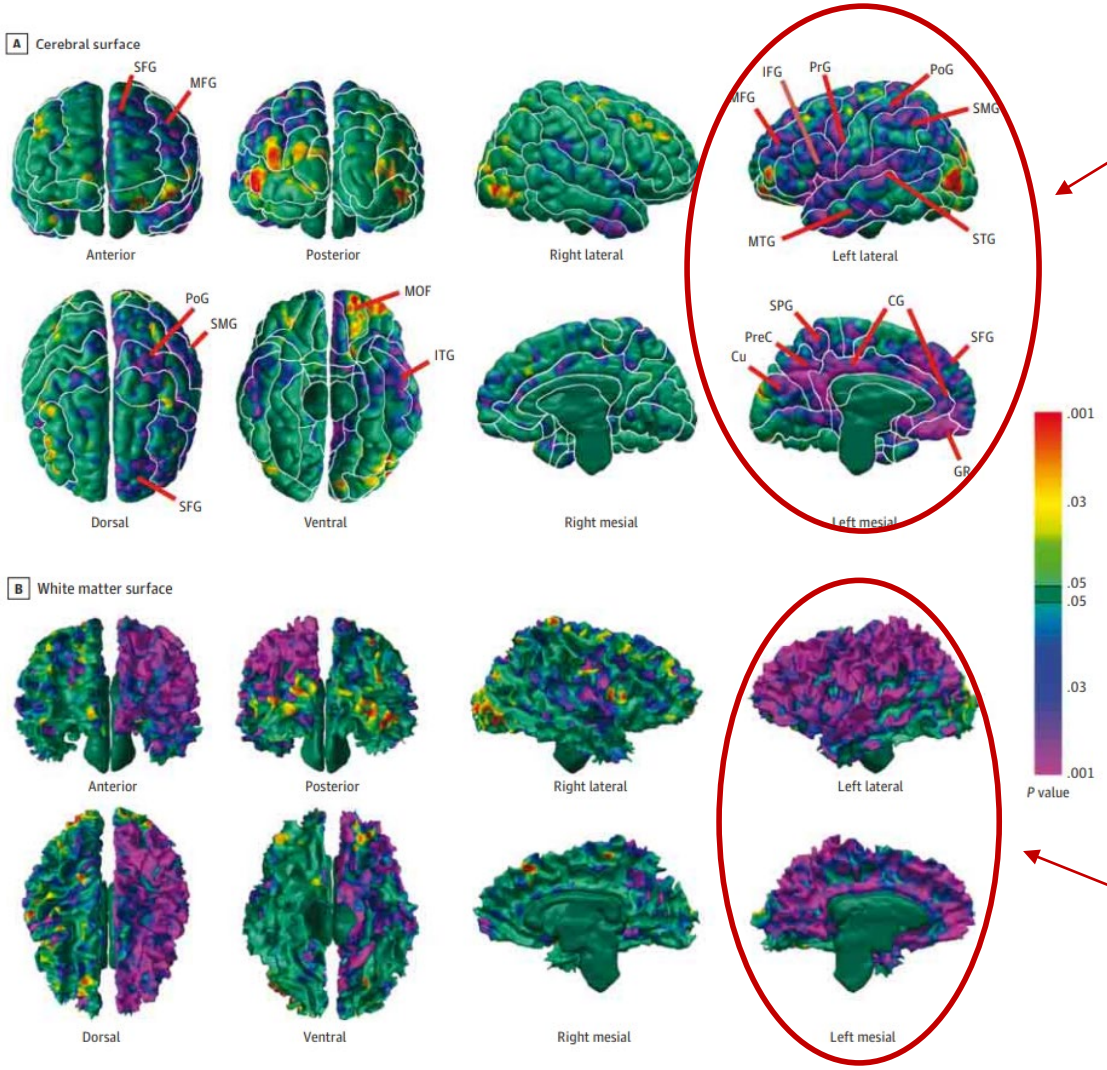
PM = particulate matter
NO_2 = nitrogen dioxide
CNS = central nervous system

PRENATAL EXPOSURE

Biologic plausibility



Prenatal PAHs and MRI (n=40, NYC)



Prenatal PAHs associated with lower volume of cerebral surface in left hemisphere

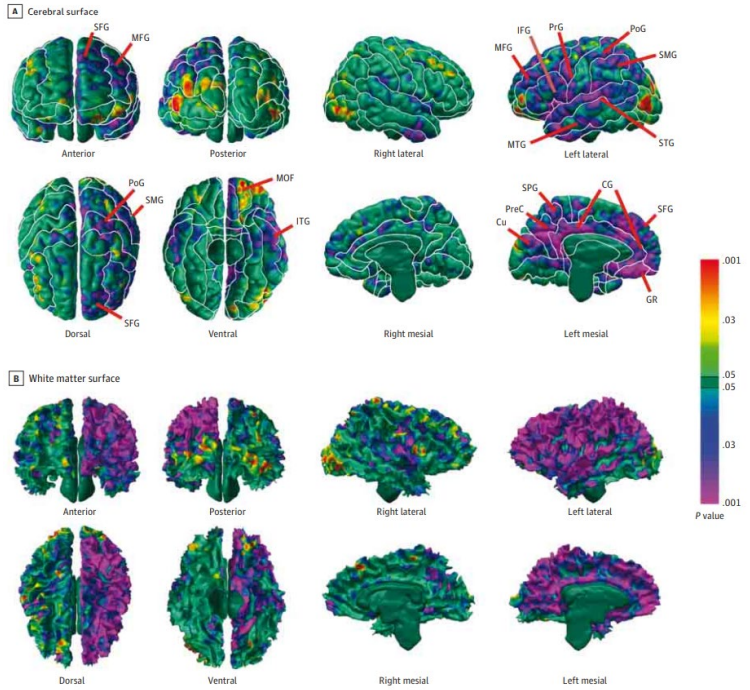
Derive from reductions in white matter

Peterson et al. JAMA Psychiatry 2015. 72(6): 531-40

PAHs = polycyclic aromatic hydrocarbons
MRI = magnetic resonance imaging

Mediated effects on performance/behavior

PAHs

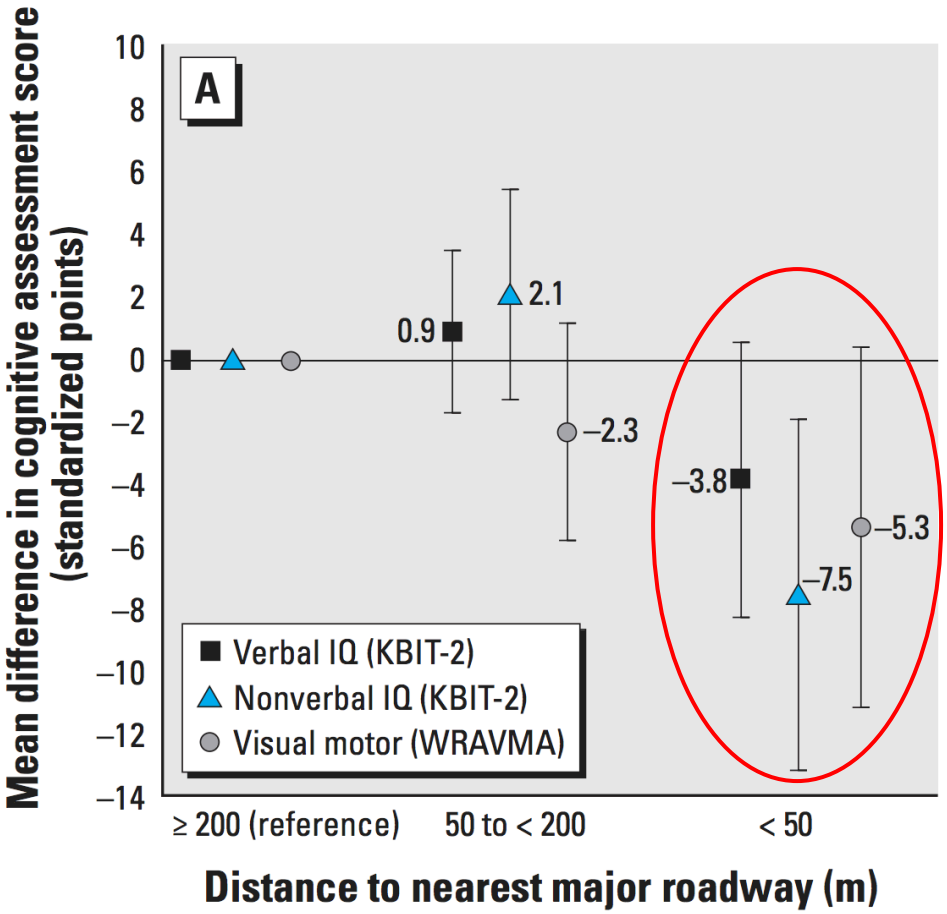


- Slower processing speed
- More ADHD-related behaviors

Peterson et al. JAMA Psychiatry 2015. 72(6): 531-40

PAHs = polycyclic aromatic hydrocarbons
ADHD = Attention-deficit/hyperactivity disorder

Roadway proximity & IQ, visual motor age 7-10y (Project Viva: Boston, MA, n=1,109)



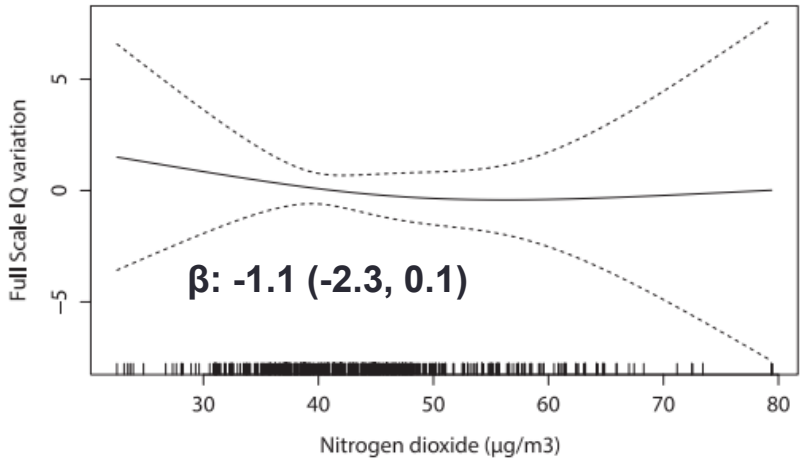
Null associations for $PM_{2.5}$ and black carbon

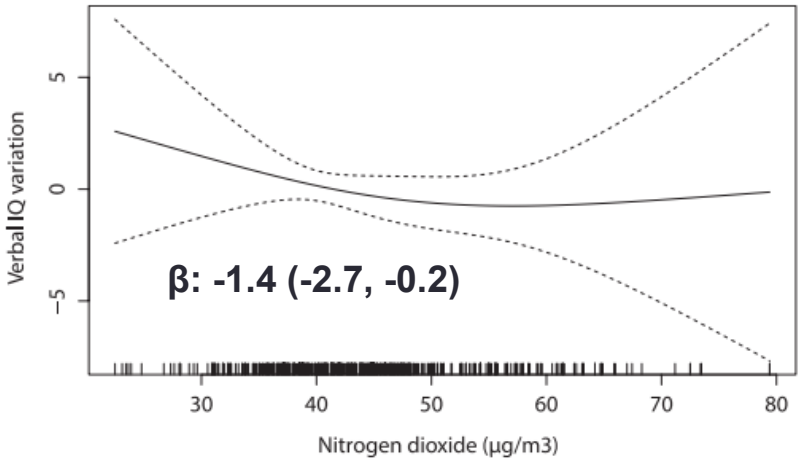
Harris et al. EHP 2015 123(10):1072-8.

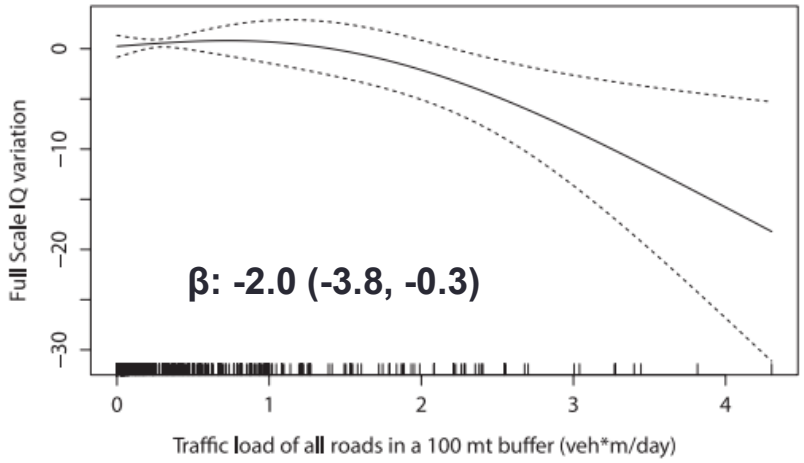
$PM_{2.5}$ = fine particulate matter

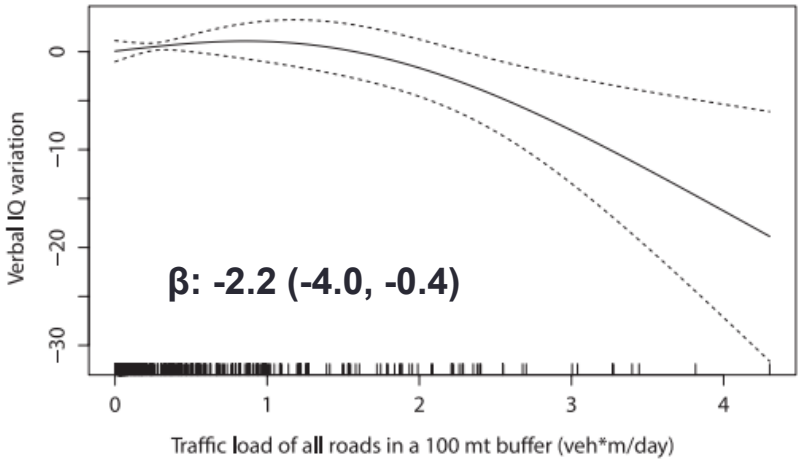
NO_2 & road traffic and Full Scale and Verbal IQ

(Gene and Environment Prospective Study on Infancy in Italy (GASPII), n=474)







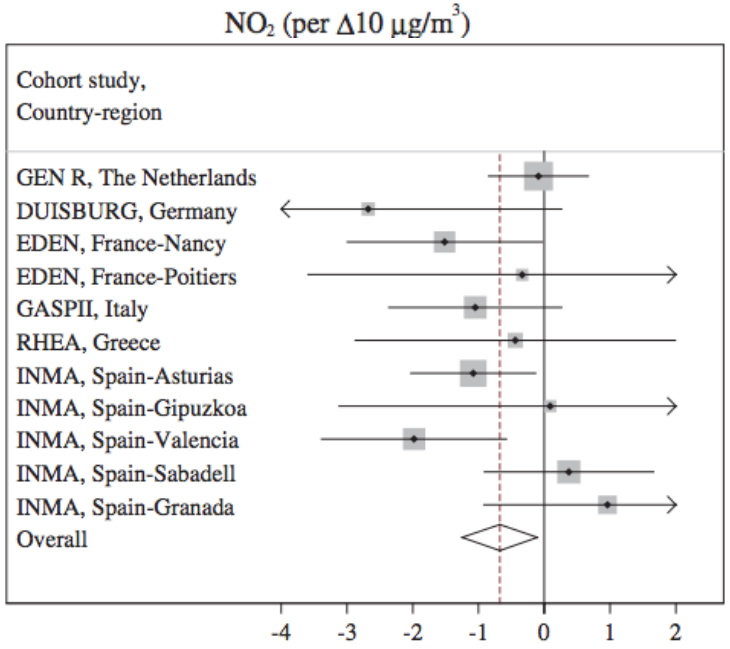


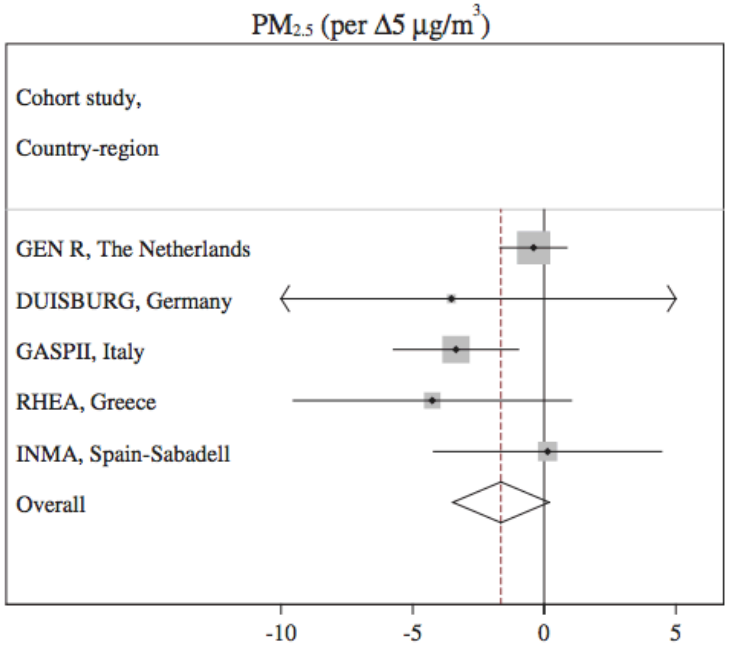
Porta et al. Epidemiology 2016 27(2): 228-236.

NO_2 = nitrogen dioxide

NO_2 & $PM_{2.5}$ and psychomotor age 1-6y

(European Study of Cohorts for Air Pollution Effects (ESCAPE): pooled analysis of 6 European Cohorts, n=9,482)





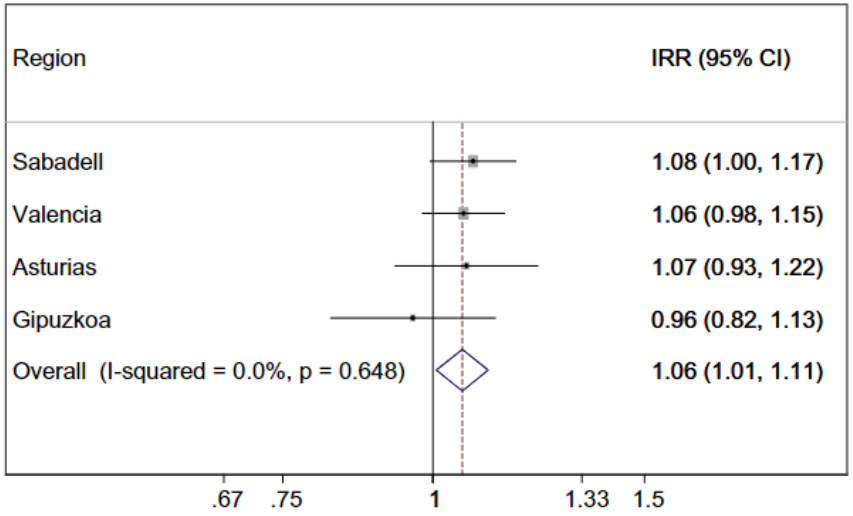
- ***BUT general cognition and language development not associated with any of the studied pollutant exposures (but most children assessed at age 2 or younger)***

Guxens et al. Epidemiology 2014. 25(5): 636-647.

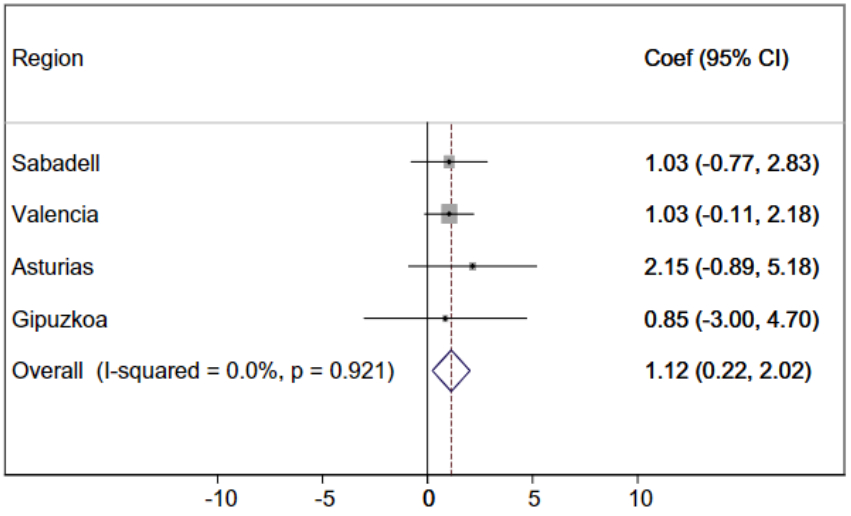
$PM_{2.5}$ = fine particulate matter
NO_2 = nitrogen dioxide

NO_2 and attention at 4-5y
(Spanish INMA Project n=1,298)

Omission Errors



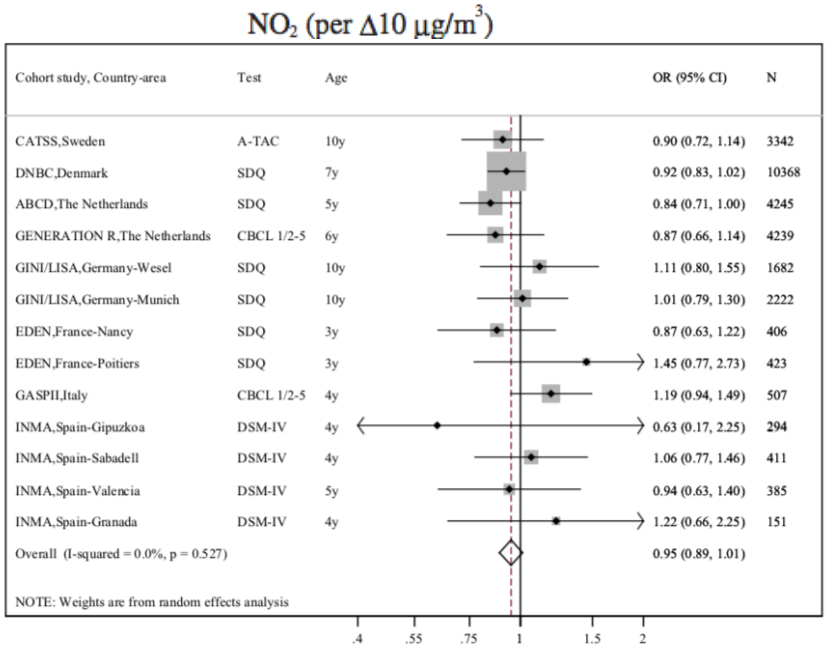
Response time variability

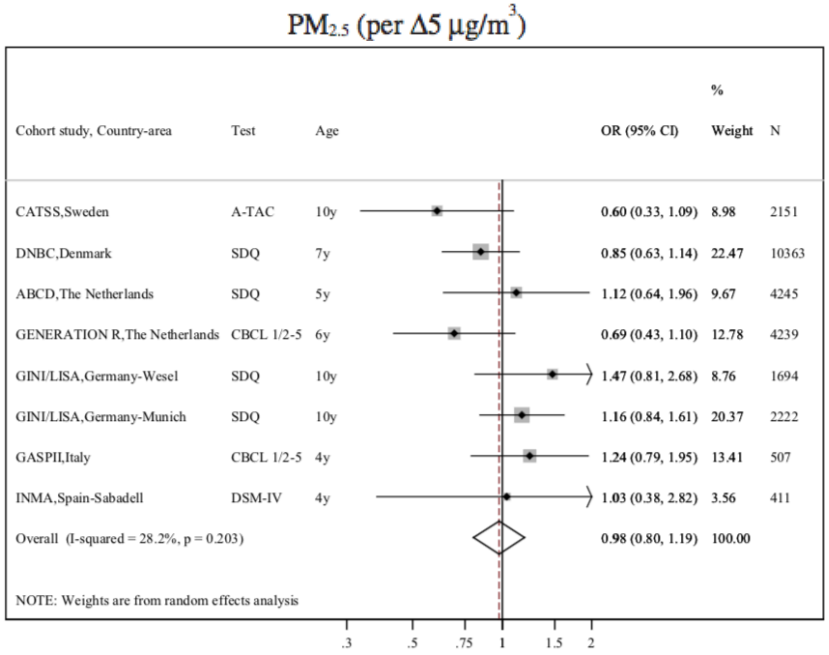


Sentis et al. Environment International 2017. 106:170-177.

NO_2 = nitrogen dioxide

NO_2 & $PM_{2.5}$ and ADHD symptoms age 3-10y
(ESCAPE: pooled analysis of 8 European Cohorts, n=29,127)





Forns et al. Epidemiology. 2018. 29(5):618-626.

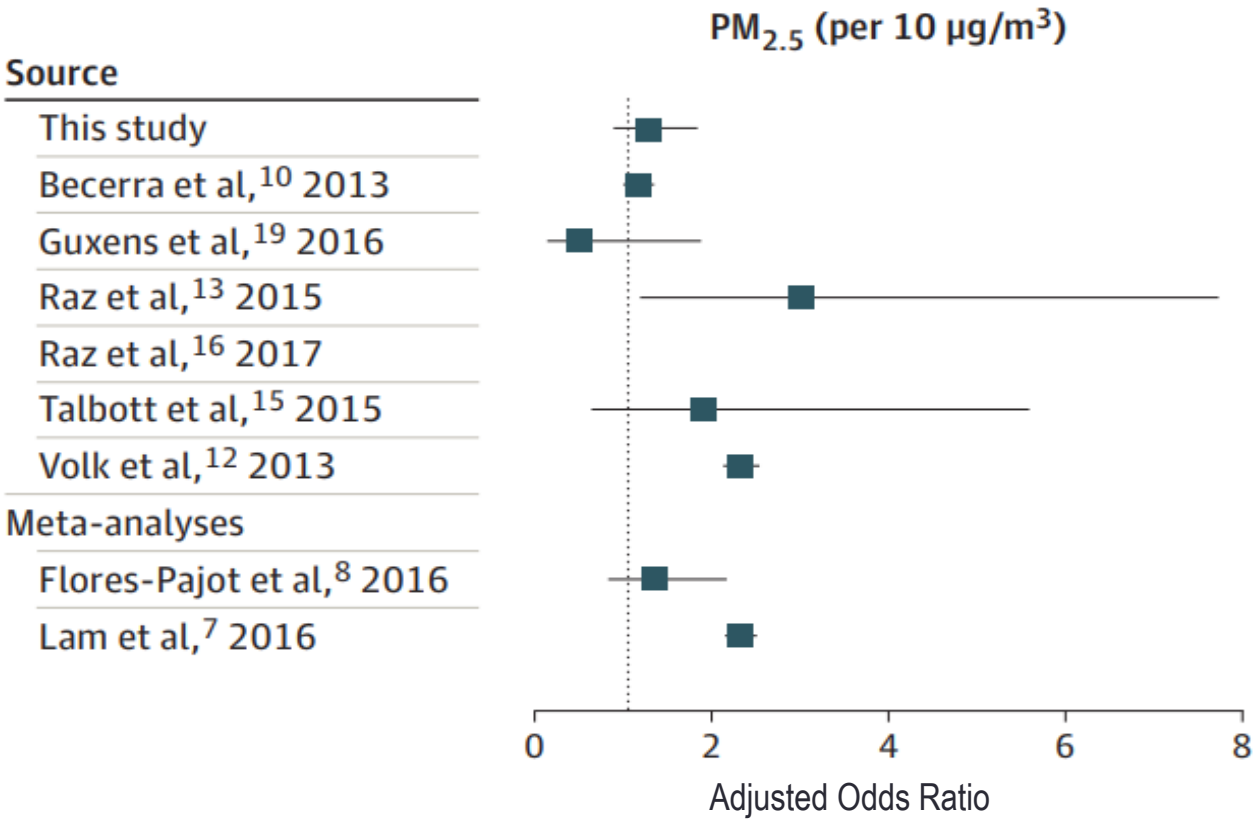
ADHD = Attention-deficit/hyperactivity disorder
$PM_{2.5}$ = fine particulate matter
NO_2 = nitrogen dioxide

Study design advantages of air pollution

- Prenatal exposures → prospective study design
  - Typically requires a birth cohort study to measure exposure during the relevant time period (pregnancy)
  - Underpowered to look at neurodevelopmental disorders (typically focus on quantitative traits)

- BUT: Air pollution less subject to these constraints
  - Exposure can be assessed via residential history
  - Adequate power to look at neurodevelomental disorders

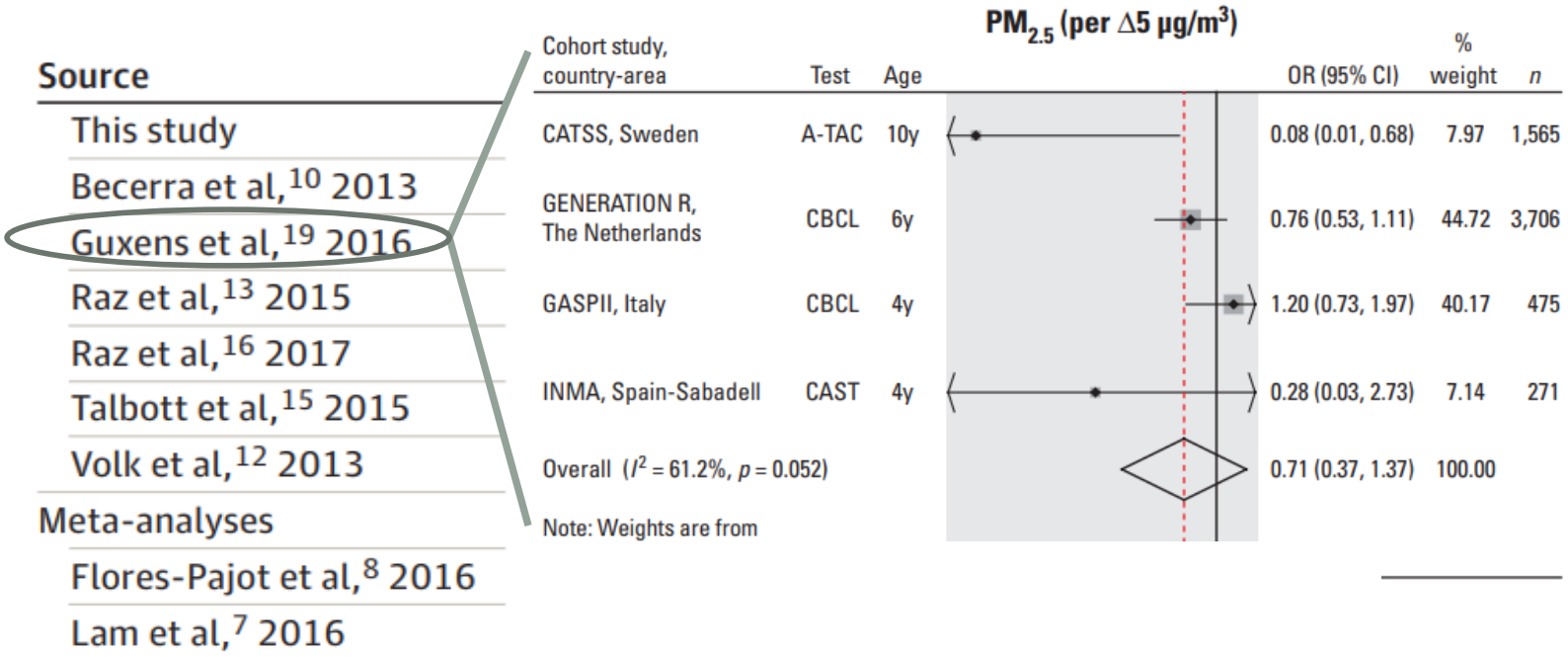
$PM_{2.5}$ and Autism Spectrum Disorders (ASD)



Pagalan L, et al. JAMA Pediatrics. 2019. 173(1): 86-92.

$PM_{2.5}$ and Autism Spectrum Disorders (ASD)

Associations with autistic traits



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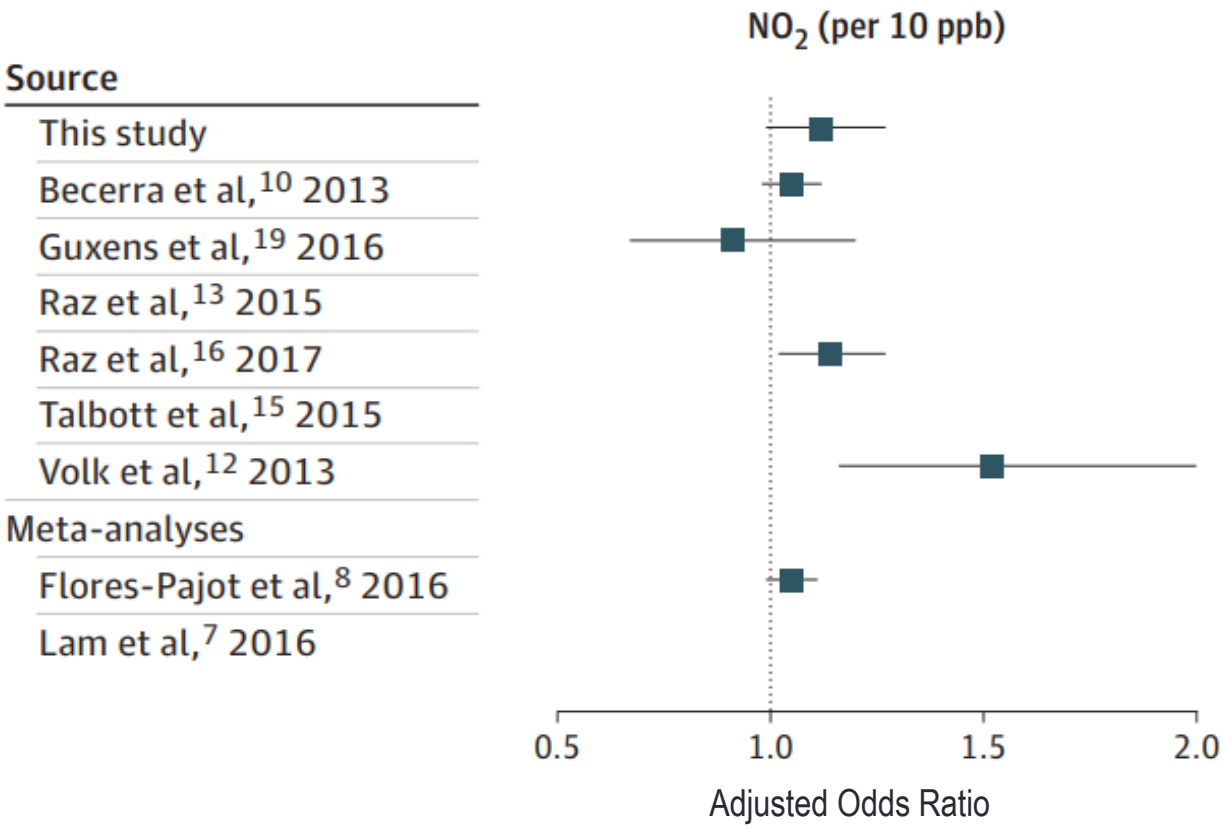
NO_2 and Autism Spectrum Disorder (ASD)



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NO_2 and Autism Spectrum Disorder (ASD)

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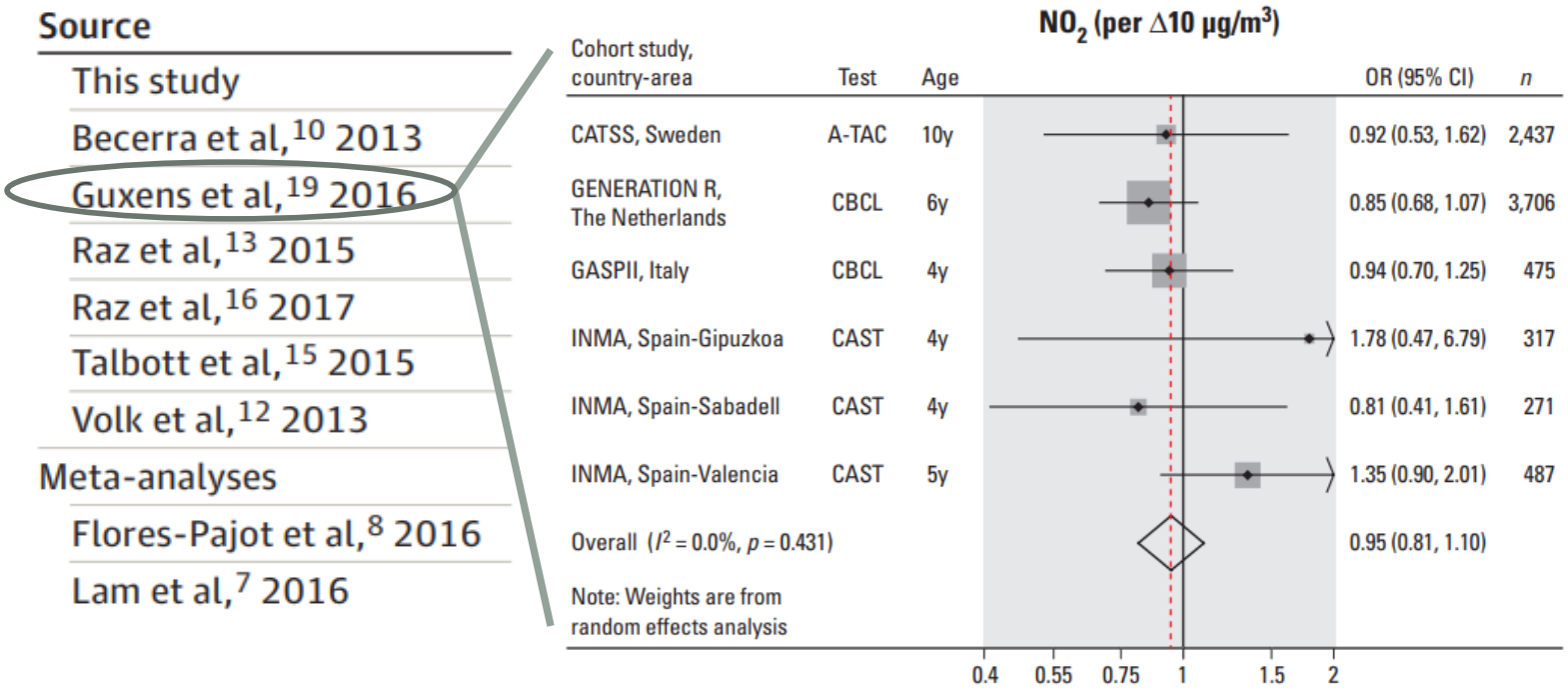
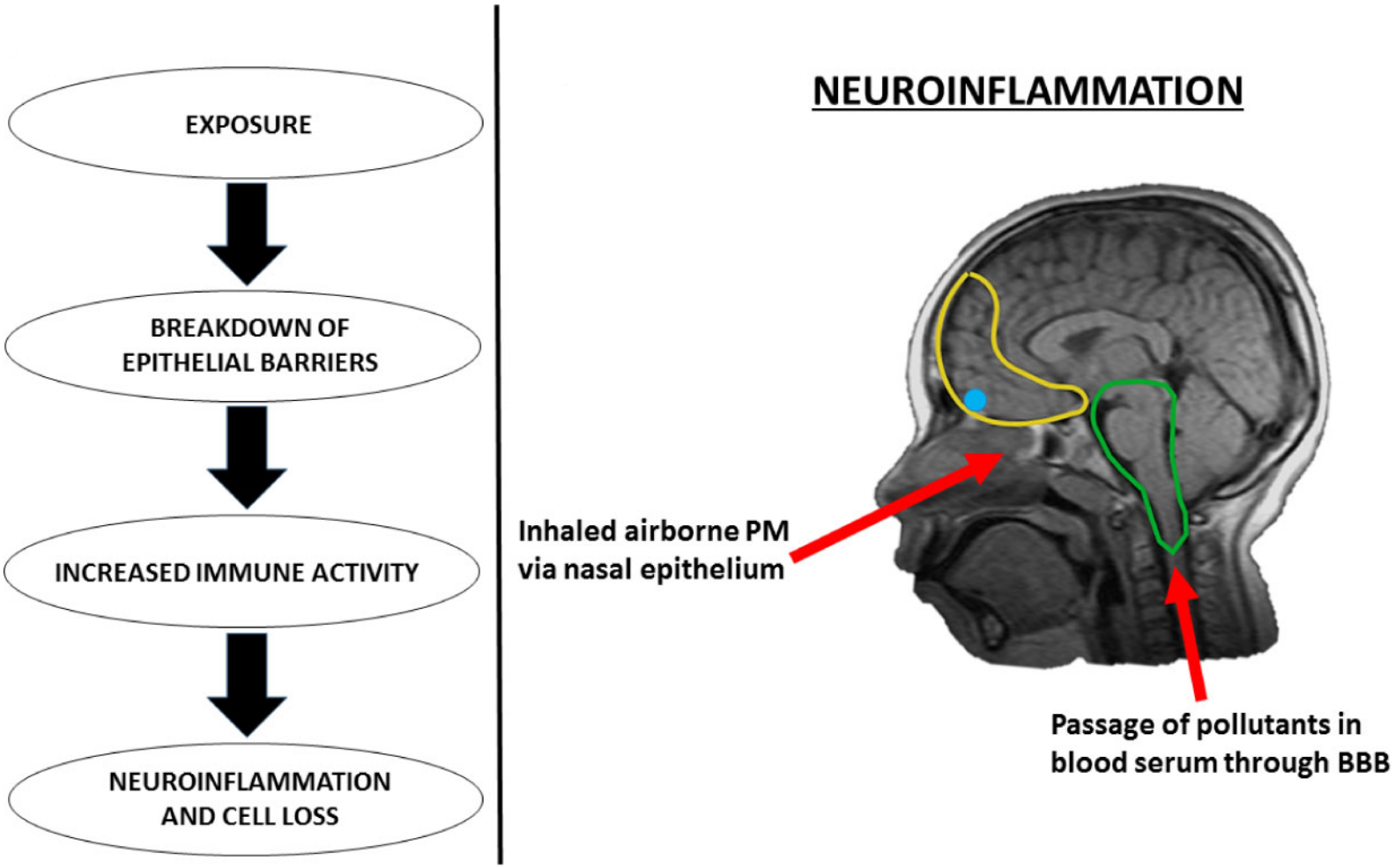


Pagalan L, et al. JAMA Pediatrics. 2019. 173(1): 86-92.

CHILDHOOD EXPOSURE

- immature blood brain barrier
- rapid brain development
- higher breathing rate to body size ratio
- ↑ time spent outdoors



Brockmeyer S, et al. Translational Neuroscience. 2016. 7(1): 24-30.

BBB = blood brain barrier
PM = particulate matter

Black carbon and cognition at age 9y

(Maternal-Infant Smoking Study of East Boston, n=202)

TABLE 2. Relation of predicted black carbon levels (average of summer and winter) at children's residences to scores on subscales of the Kaufman Brief Intelligence Test in linear regression models ($n = 202$), Maternal Infant Smoking Study of East Boston, 1986–2001†

Black carbon model	Vocabulary		Matrices		Composite	
	Estimate	95% CI‡	Estimate	95% CI	Estimate	95% CI
Adjusted for demographic factors§	−2.0	−5.3, 1.3	−4.2	−7.7, −0.7*	−3.4	−6.6, −0.3*
Adjusted for above factors + in-utero tobacco smoke + secondhand smoke	−2.0	−5.3, 1.4	−4.0	−7.5, −0.4*	−3.3	−6.4, −0.1*
Adjusted for above factors + birth weight	−2.0	−5.4, 1.3	−4.0	−7.6, −0.5*	−3.3	−6.5, −0.2*
Adjusted for above factors + blood lead level	−2.2	−5.5, 1.1	−4.0	−7.6, −0.5*	−3.4	−6.6, −0.3*

* $p < 0.05$.

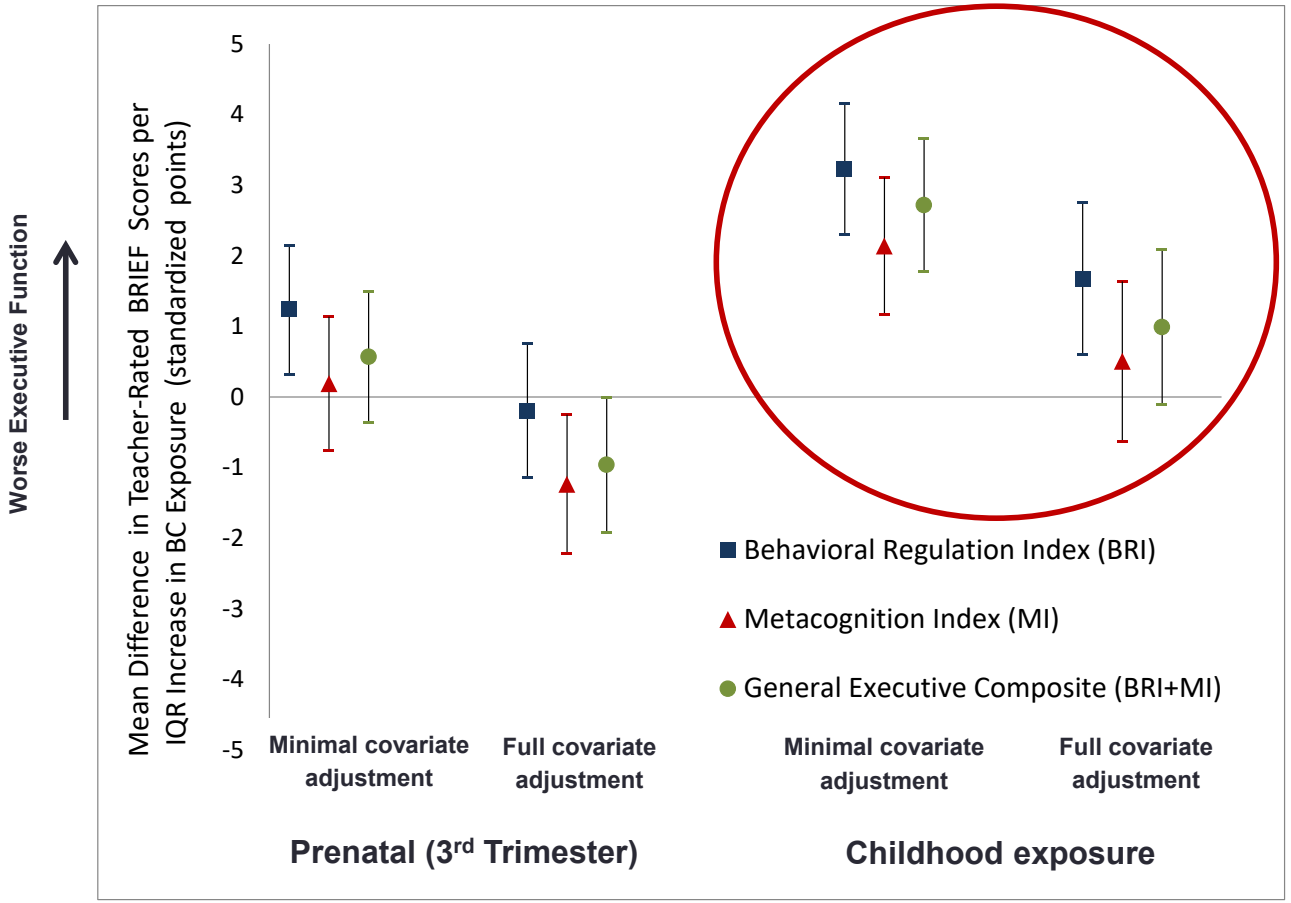
† Change in subscale score per interquartile-range (0.4-μg/m^3) increase in log black carbon level.

‡ CI, confidence interval.

§ Adjusted for age, gender, primary language spoken at home, and mother's education.

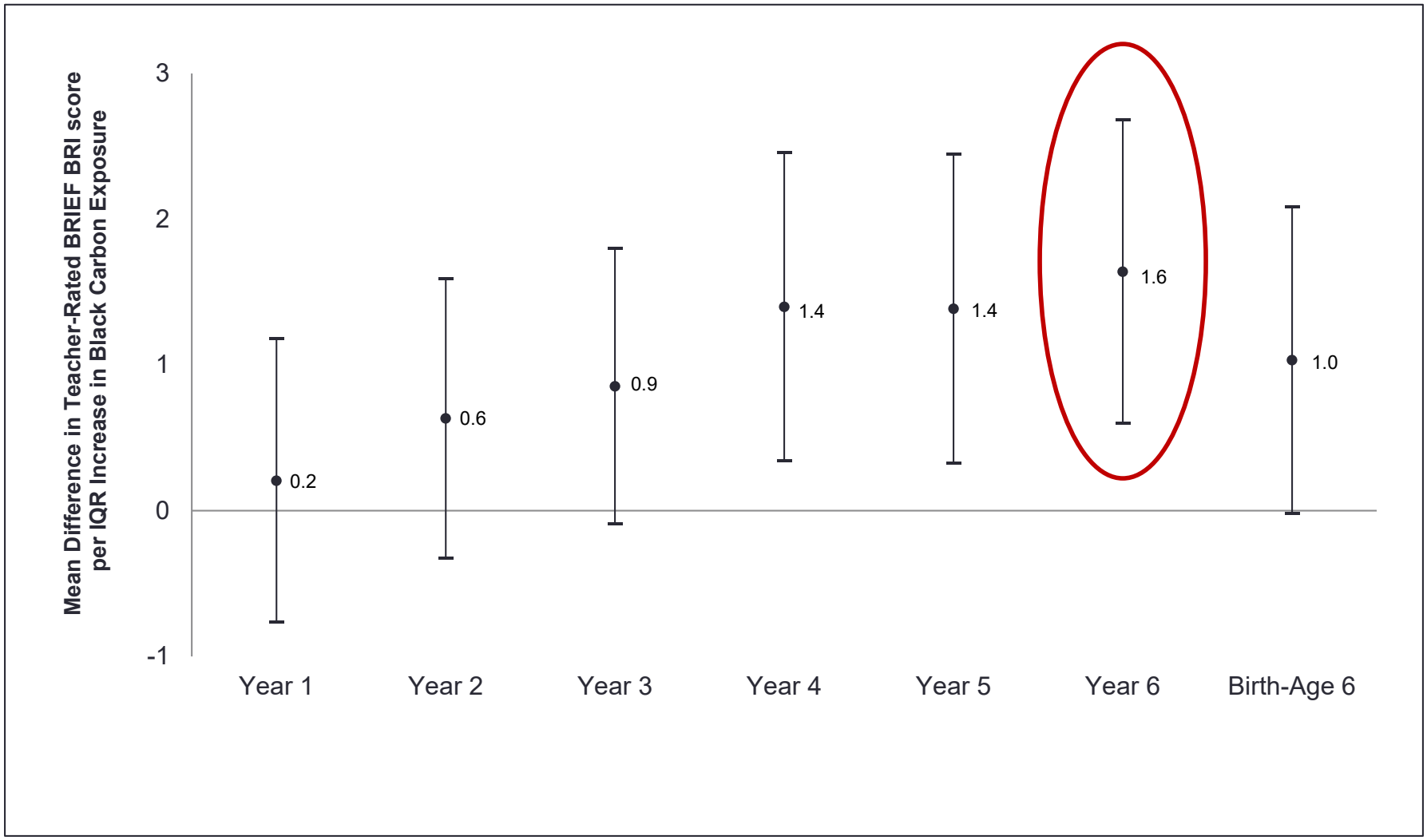
Franco Sulgia et al. Am J Epidemiol 2008. 167:280-286

Black carbon executive function at 7y (Project Viva, Boston, MA, n=1,212)



Harris et al. Neurotox and Teratology 2016. 57:60-70

Postnatal



Harris et al. Neurotox and Teratology 2016. 57:60-70

IQR = interquartile range

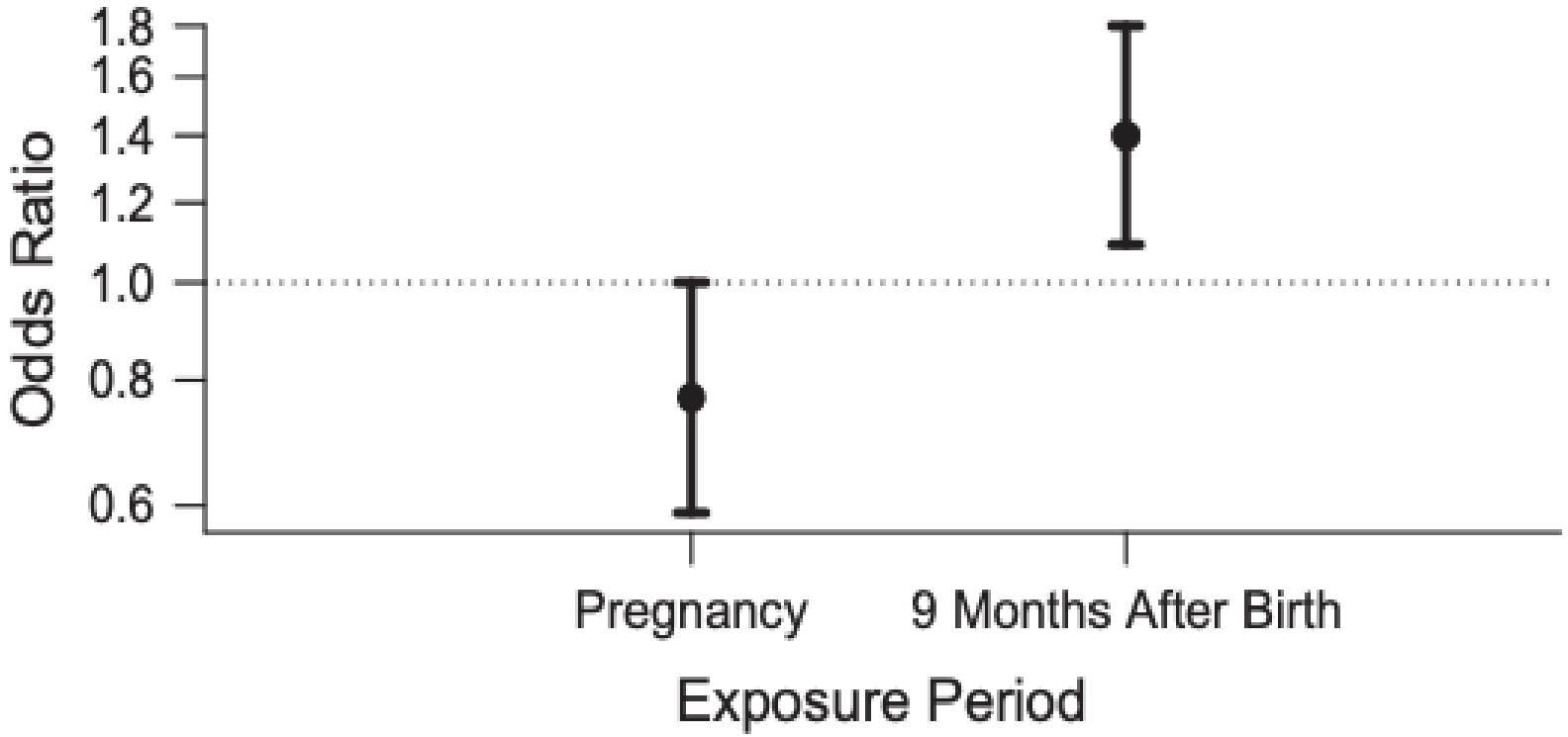
Prenatal vs. infant AP exposure and ASD (Denmark nation-wide (ca=15,387;co=68,139))

Exposure (IQR ↑)	Exposure period	OR (95% CI)		
		Unadjusted[a]	Adjusted[b]	Mutually adjusted[c]
NO_2	Pregnancy	1.19 (1.16, 1.22)	1.10 (1.06, 1.13)	1.00 (0.93, 1.08)
	9 months after birth	1.20 (1.17, 1.23)	1.11 (1.07, 1.14)	1.08 (1.01, 1.15)
SO_2	Pregnancy	1.29 (1.23, 1.35)	1.12 (1.07, 1.18)	0.96 (0.90, 1.04)
	9 months after birth	1.38 (1.31, 1.45)	1.21 (1.15, 1.28)	1.21 (1.13, 1.29)
PM_{10}	Pregnancy	0.99 (0.95, 1.02)	0.97 (0.94, 1.01)	0.95 (0.91, 1.00)
	9 months after birth	1.03 (0.99, 1.06)	1.01 (0.97, 1.05)	1.04 (1.00, 1.09)
$PM_{2.5}$	Pregnancy	1.06 (1.02, 1.11)	1.00 (0.96, 1.04)	0.96 (0.91, 1.02)
	9 months after birth	1.11 (1.07, 1.15)	1.04 (1.00, 1.09)	1.06 (1.01, 1.11)

Ritz et al. Environ Epi 2018. 2(4): e028

AP = air pollution
ASD = Autism Spectrum Disorder
OR = odds ratio
CI = confidence interval

Prenatal vs. infant NO_2 and ASD (Israel nation-wide (ca=2,098; co=54,191))



Raz et al. AJE 2018 187(4): 717-725.

- Negative birth bias? Raz et al. AJE 2018 187(11): 2292-2296.

NO_2 = nitrogen dioxide
ASD = Autism Spectrum Disorder

BREATHE Study

Brain Development and Air Pollution Ultrafine Particles in School Children

- 39 schools in Barcelona
- High vs. low traffic
- Matched on socioeconomic status
- N=2,897 age 7-10y

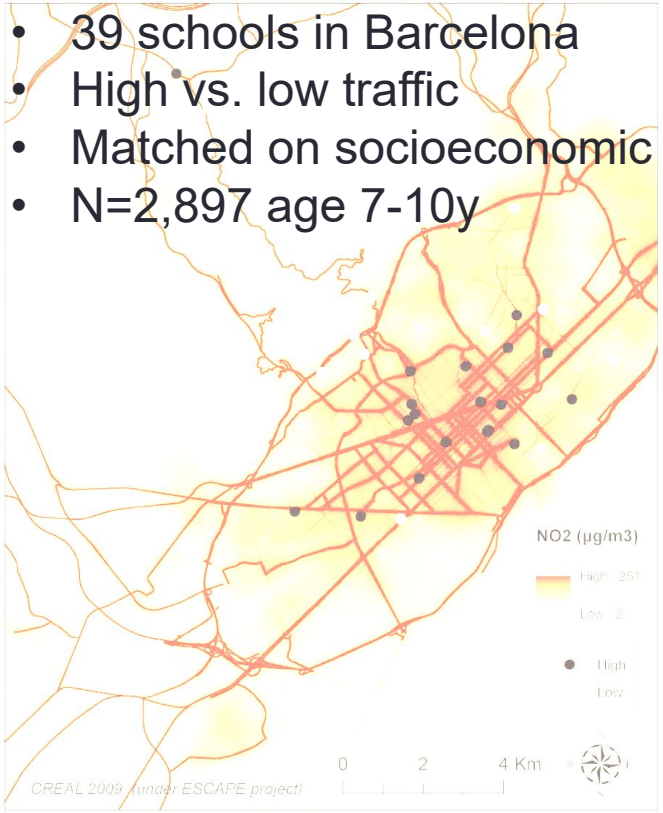
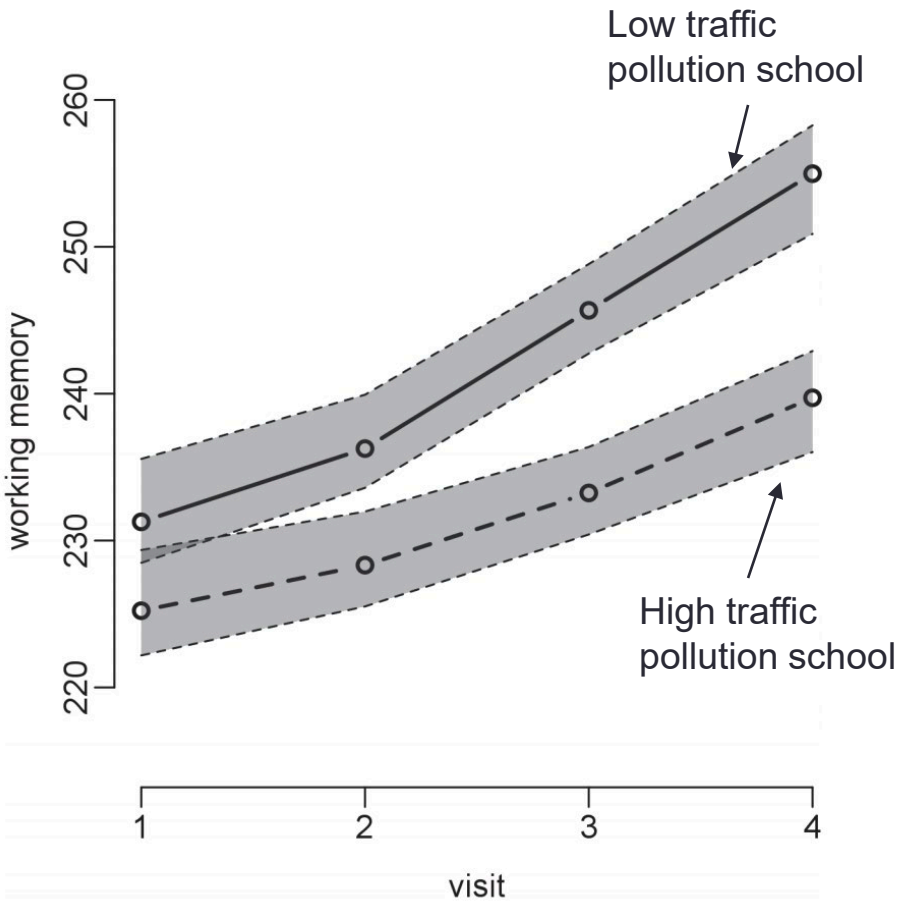


Fig 1. Map of Barcelona and the schools by high or low air pollution by design. Black dots indicate the locations of schools with high air pollution, and white dots indicate the locations of schools with low air pollution, based on NO_2 levels.



Sunyer et al. PLoS Medicine 2015. 12(3); Forns et al. Environ Res 2017 159:416-21.

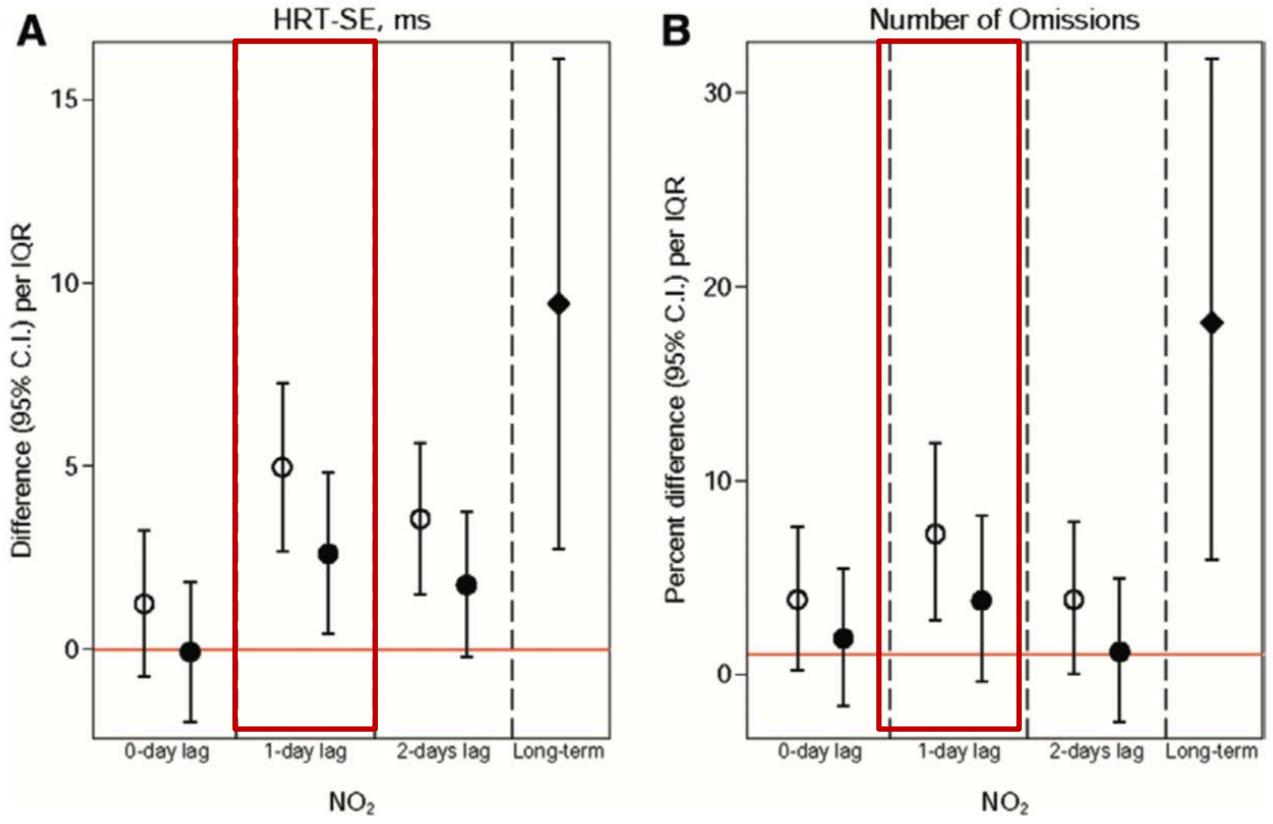
Elemental carbon and behavior (BREATHE Study, n=2,714)

Variable	EC indoor IQR = 1.01 μg/m^3 EC outdoor IQR = 0.86 μg/m^3	NO_2 indoor IQR = 21.01 μg/m^3 NO_2 outdoor IQR = 22.26 μg/m^3
Total difficulties score (SDQ)[a]		
Indoor		
Single-exposure	1.07 (1.01, 1.12)*	1.02 (0.96, 1.08)
Multi-exposure	1.08 (1.02, 1.14)**	1.02 (0.95, 1.10)
Outdoor		
Single-exposure	1.07 (1.03, 1.12)**	1.07 (1.01, 1.14)*
Multi-exposure	1.08 (1.03, 1.13)**	1.08 (1.01, 1.16)*

Forns et al. EHP 2016. 124(4): 529-535

NO_2 = nitrogen dioxide
IQR = interquartile range

"Acute" associations of NO_2 with attention (BREATHE Study)

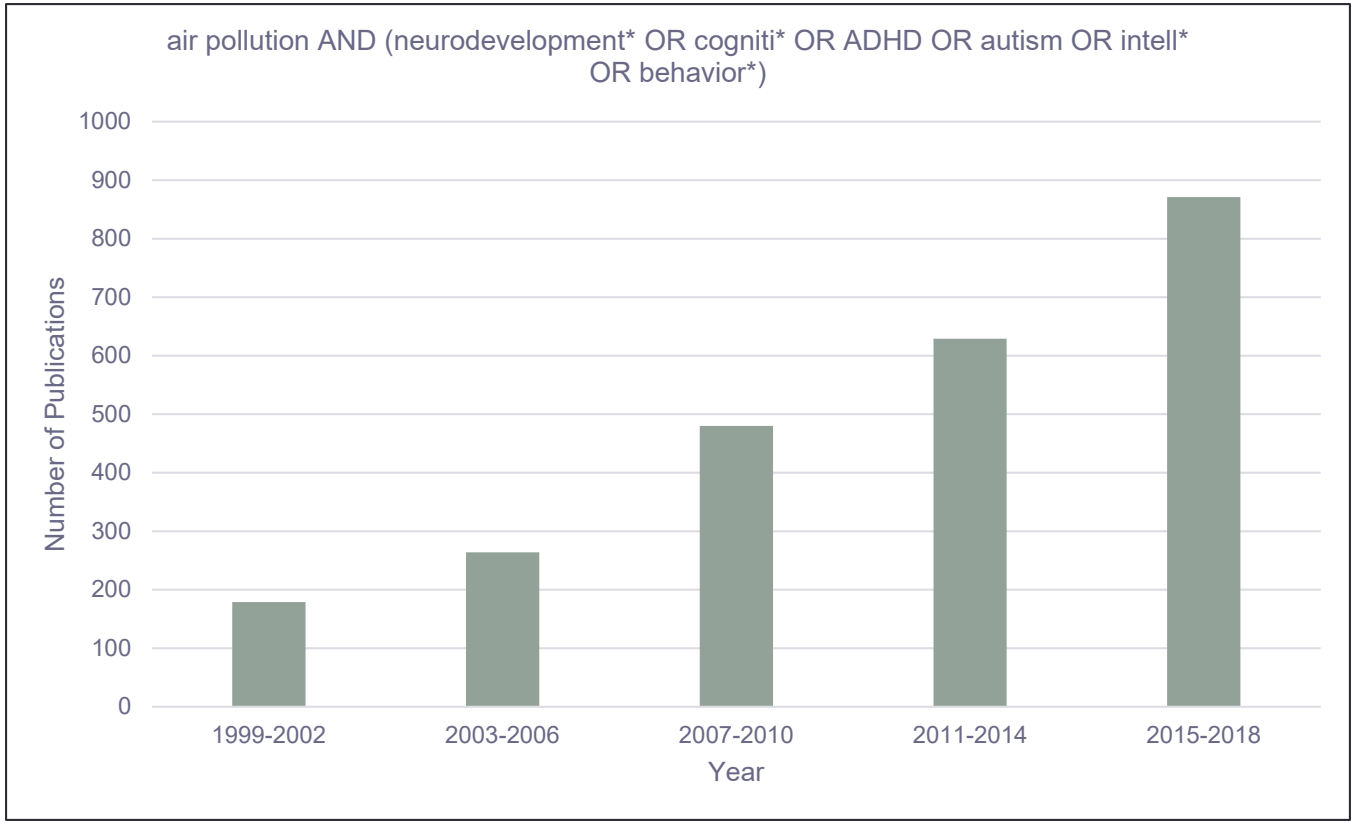


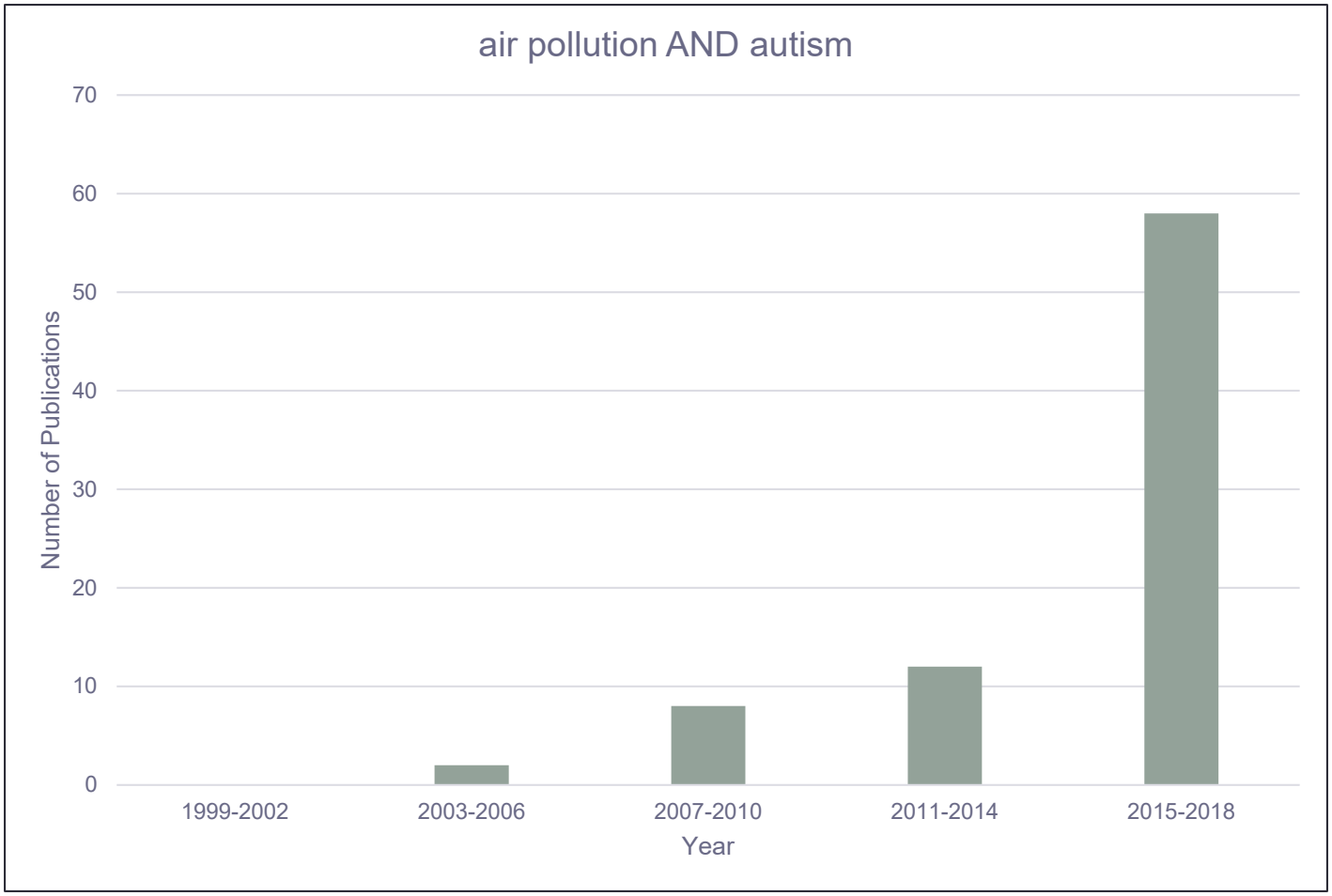
Sunyer et al. Epidemiology 2017. 28(2): 181-189

NO_2 = nitrogen dioxide

Discussion

- Neurodevelopmental outcomes: complex, sensitive and important
- Number of studies on air pollution and neurodevelopment have exploded in the last 5-10 years


air pollution AND (neurodevelopment* OR cogniti* OR ADHD OR autism OR intell* OR behavior*)
Number of Publications
1000
900
800
700
600
500
400
300
200
100
0
1999-2002
2003-2006
2007-2010
2011-2014
2015-2018
Year


air pollution AND autism
70
60
50
40
30
20
10
0
Number of Publications
1999-2002
2003-2006
2007-2010
2011-2014
2015-2018
Year

Discussion

- Neurodevelopmental outcomes: complex, sensitive and important
- Number of studies on air pollution and neurodevelopment have exploded in the last 5-10 years
- Literature shows associations of ***both prenatal and childhood*** air pollution exposure with adverse cognitive and behavioral function
  - *Child exposure associated with higher risk for some endpoints?*
- Regulatory implications
  - Fetuses and children more vulnerable to neurodevelopmental impacts of air pollution

Thoughts on Future Directions

- Cognitive/behavioral domains vulnerable to air pollution
- Critical time windows during prenatal AND postnatal periods
  - More investigation of childhood exposure and “acute” effects
- Autism Spectrum Disorder (ASD) associations: inconsistency between U.S. and European studies
- Residual confounding (e.g., socioeconomic status, noise)
- Accounting for air pollution mixtures
  - Particulate matter → chemical composition
- Ultra fine particles
- Neuroimaging

Thank you for your attention!

*Thanks to Maria Harris for providing some of the slides for this talk