Wendy Klag Center for Autism
& Developmental Disabilities

at the Johns Hopkins Bloomberg School of Public Health

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Air Pollution and Autism Spectrum Disorder: What Do We Know and What Is Next?

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Today's Outline

- Review Air Pollution and ASD Findings To Date
- Emerging Areas of Research
  - Phenotypic Severity
  - Gene x Environment Interaction
  - Exposure Timing
- Suggestions for Next Steps

SOCIAL SKILLS
nonverbal interactions
friendship
joint attention
reciprocity

COMMUNICATION
language
conversation
play

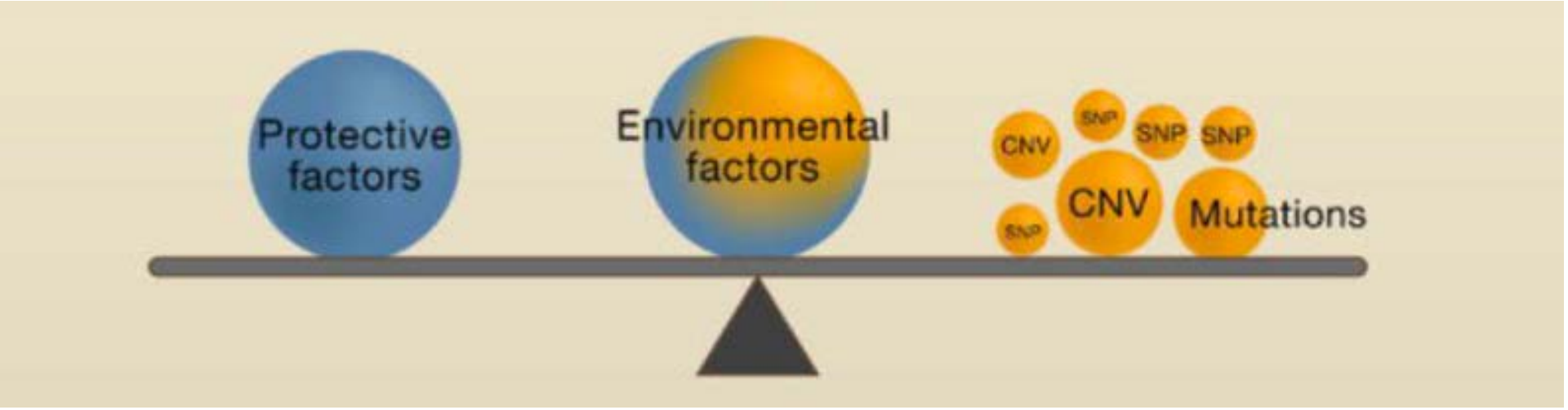
Autism Spectrum Disorder

UNUSUAL BEHAVIORS
obsessive interests
rigid rituals
preoccupation with
parts of objects

ASD Prevalence in the United States

Statistics from the Autism and Developmental Disabilities Monitoring Network (ADDM)				
Surveillance Year	Birth Year	Number Locations	Prevalence per 1,000 Children	~ 1 in X children…
2000	1992	6	6.7	1 / 150
2002	1994	14	6.6	1 / 150
2004	1996	8	8.0	1 / 125
2006	1998	11	9.0	1 / 110
2008	2000	14	11.3	1 / 88
2010	2002	11	14.7	1 / 68

Simple Model for Gene and Environment Effects



Adapted from Geschwind et al., 2008

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A CENTURY OF SAVING LIVES
100
MILLIONS AT A TIME
1916–2016

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Air Pollutants and ASD

Near Roadway and Regional Pollutants

- Roadway proximity in CA
  - 300m of freeway
  - Volk et al., 2011
- Modeled near roadway and regional pollution in CA
  - NRAP, $PM_{2.5}$, PM_{10}, NO_2
  - Volk et al., 2013
- Regional pollution across USA
  - $PM_{2.5}$
  - Raz et al., 2015
- Regional pollution in CA and NC
  - PM_{10}
  - Kalkbrenner et al., 2014
- Regional pollution in PA
  - $PM_{2.5}$
  - Talbott et al., 2015
- Modeled near roadway and regional pollution in LA County
  - NRAP, $PM_{2.5}$, NO_2
  - Becerra et al., 2013

Hazardous Air Pollutants

- Mercury, cadmium, nickel, vinyl chloride, DEP in CA
  - Windham et al., 2006
- Methylene chloride, styrene, quinoline in NC and WV
  - Kalkbrenner et al., 2010
- Metals, DEP across USA
  - Roberts et al., 2013
- Traffic and industry emissions in LA County
  - Von Ehrenstein et al., 2014

Study Design

- Childhood Autism Risks From Genetics and the Environment (CHARGE) Study

- Autism Cases
  - First diagnosed by Regional Center (Department of Developmental Services (DDS))or clinical referral
  - Positive for autism on gold standard assessments

- Controls
  - Typically developing children from birth records

NIEHS R01 ES015359 , PI: Hertz-Picciotto

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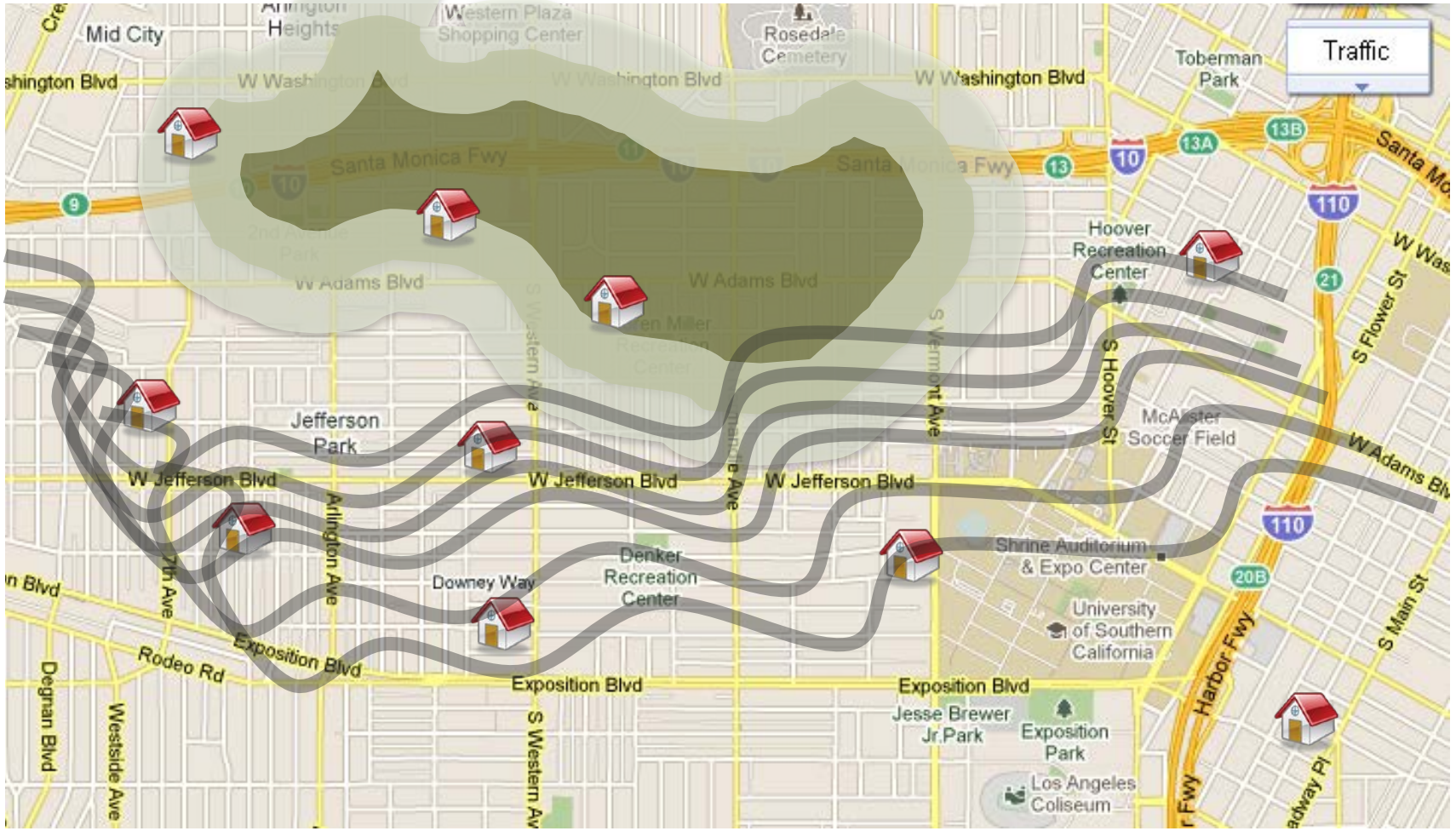
Measures of Air Pollution



Distance From Freeway at Birth
(304 Cases and 259 Controls)

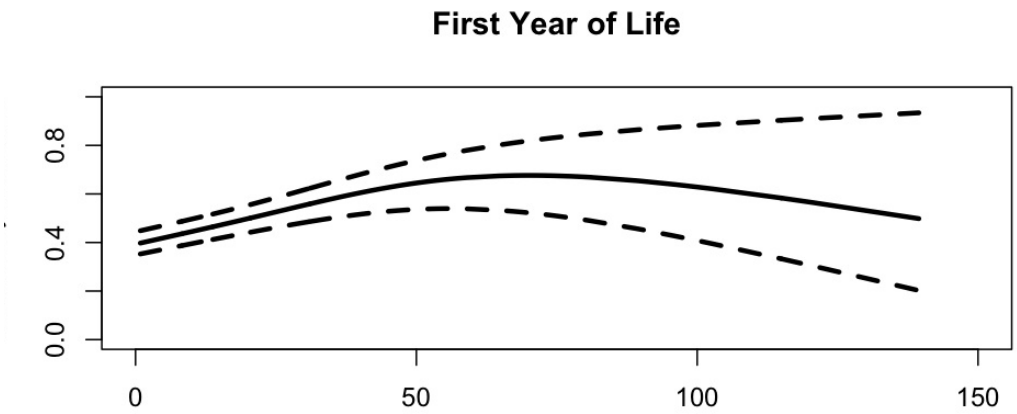
	Crude OR	Adjusted OR*
Birth Address <309m	1.86 (1.04-3.45)	1.86 (1.03-3.45)
Birth Address 309-647m	0.98 (0.60-1.59)	0.96 (0.58-1.56)
Birth Address 647-1419m	1.14 (0.76-1.71)	1.11 (0.73-1.67)
Birth Address >1419	Reference	Reference

*Model adjusted for child male gender, child ethnicity (Hispanic vs. White, Black/Asian/Other vs. White), maximum education in home (college degree or more), maternal age > 35 years, and prenatal smoking

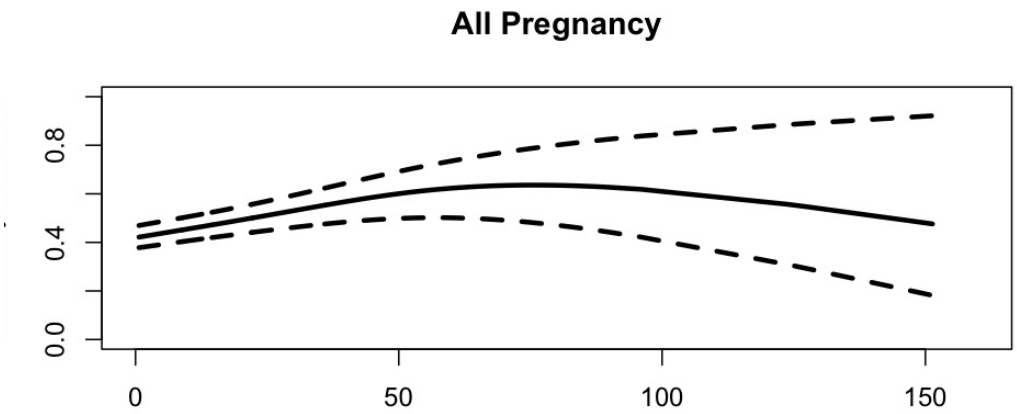
SCEHSC Pilot Project, PI: Volk

Volk, et al., 2011

Near Roadway Air Pollution (279 Cases and 245 Controls)



Near Roadway Air Pollution



Probability of ASD Increases as NRAP Increases

Volk, et al., 2013

Regional Pollutant Exposure
(279 Cases and 245 Controls)

	First Year of Life OR*	All Pregnancy OR*
$PM_{2.5}$	2.12 (1.45-3.10)	2.08 (1.93-2.25)
PM_{10}	2.14 (1.46-3.12)	2.17 (1.49-3.16)
Nitrogen Dioxide	2.06 (1.37-3.09)	1.81 (1.23-2.65)
Ozone	1.15 (0.72-1.86)	1.09 (0.76-1.55)

***Regional pollution effects reflect risk of autism based on 2 standard deviations from the mean value, specifically per increase of 8.8 mg/m3 $PM_{2.5}$, 12.4 mg/m3 PM_{10}, 9.0 ppb NO_2, and 13.6 ppb ozone. The top TRP quartile refers to estimated exposure levels of 30.4ppb or greater.**

Models adjusted for child male gender, child ethnicity (Hispanic vs. White, Black/Asian/Other vs. White), maximum education of parents (parent with highest of four levels: college degree or higher vs. some high school, high school degree, or some college education), maternal age (>35 years vs. 35years), prenatal smoking, population density.

NIEHS R21 ES19002, PI: McConnell, Co-I: Volk

Volk, et al., 2013

Is Increasing Air Pollution Exposure Associated with Worse Outcomes?

- Autism and ASD Cases (N=327)
  - Broad Neurodevelopmental Assessments
    - Mullen Scales of Early Learning (MSEL)
    - Vineland Adaptive Behavior Scales (VABS)
  - ASD-specific Assessments
    - ADOS
    - ADI-R
    - Autism Severity Score

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Increased Language Deficits with Increasing Prenatal Air Pollution Exposure*

	NO_2	Ozone	PM_{10}	$PM_{2.5}$
MSEL Expressive Language				
High MSEL	Reference	Reference	Reference	Reference
Middle MSEL	2.08(0.96-4.51)	1.07(0.41-2.74)	1.26(0.47-3.41)	1.67(0.67-4.10)
Low MSEL	3.33(1.63-6.80)	0.95(0.41-2.20)	0.72(0.57-3.52)	2.40(1.06-5.37)
MSEL Receptive Language				
High MSEL	Reference	Reference	Reference	Reference
Middle MSEL	3.81(1.66-8.71)	1.03(0.38-2.79)	1.23(0.45-3.41)	4.30(1.62-11.47)
Low MSEL	3.52(1.72-7.31)	1.22(0.52-2.83)	1.23(0.52-2.96)	3.24(1.40-7.51)

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Kerin et al., In Preparation

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Increased Adaptive Deficits with Increasing Prenatal Air Pollution Exposure*

	NO_2	Ozone	PM_{10}	$PM_{2.5}$
VABS Composite	-11.08%, p=0.02	-3.54%, p=0.55	5.52%, p=0.37	-5.58%, p=0.32
Communication	-14.05%, p=0.01	0.56%, p=0.94	4.19%, p=0.55	-5.43%, p=0.39
Socialization	-8.79%, p=0.06	-3.43%, p=0.56	6.63%, p=0.27	-2.73%, p=0.62

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Kerin et al., In Preparation

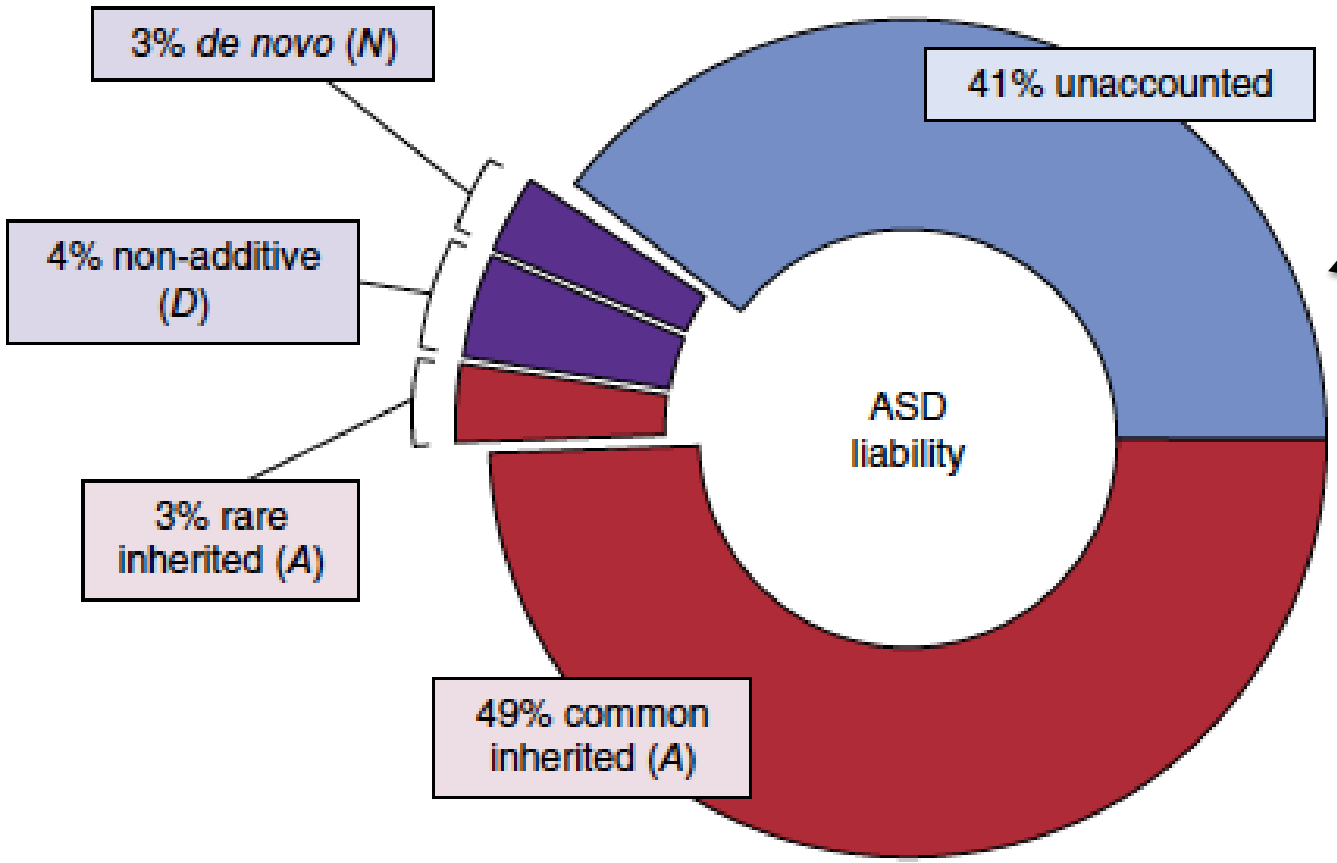
No Associations With Autism Severity Score

	NO_2	Ozone	PM_{10}	$PM_{2.5}$
Autism Severity Score	8.44%, p>0.05	6.81%, p>0.05	10.76%, p>0.05	0.61%, p>0.05

Limited Correlation Between Assessments

	MSEL-Total	MSEL- Exp Lang	MSEL- Rec Lang	VABS Total	VABS-Comm	VABS-Social
Autism Severity Score	-0.22	-0.18	-0.23	-0.12	-0.16	-0.11

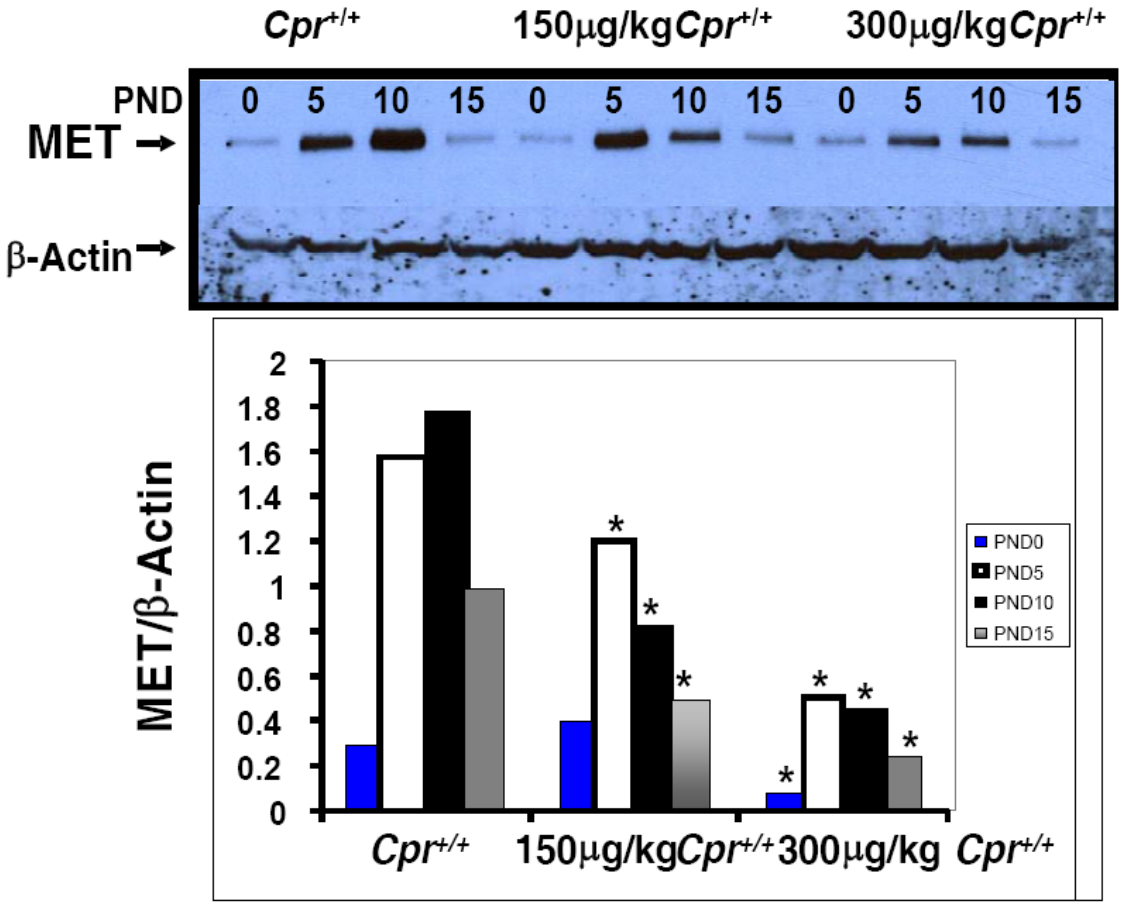
Where Do Genes Fit In?



Environmental Effects and GxE Interactions

Adapted from Gaugler et al., 2014

Prenatal PAH Exposure Reduces MET Protein Expression in Mouse Cortex (Benzo(a)Pyrene)



Sheng et al., 2010

Replications of *MET* rs1858830 Variant Association with Autism

	Reference	Study Design	Sample Source
1	Campbell et al. 2006. *PNAS*.	Family-based and case-control	Italy (Rome 1)
2	Campbell et al. 2006. *PNAS*.	Family-based and case-control	NIMH
3	Campbell et al. 2008. *Autism Res*.	Family-based	Vanderbilt
4	Sousa et al. 2009. *Eur J Hum Genet.*	Family-based and case-control	Europe (UK)
5	Sousa et al. 2009. *Eur J Hum Genet*.	Case-control	Italy (Bologna)
6	Jackson et al. 2009. *Autism Res*.	Case-control	South Carolina
7	Jackson et al. 2009. *Autism Res*.	Case-control	Italy (Rome 2)
8	Thanseem et al. 2010. *Neurosci Res*.	Family-based	Japan
9	Thanseem et al. 2010. *Neurosci Res.*	Family-based	AGRE
10	Rajamma et al. 2011. SfN poster	Family-based	India

Joint Effect of *MET* rs1858830 and Air Pollution

Near Roadway Air Pollution		
	MET rs1858830 Genotype	
	C/C	C/G or G/G
Exposed	2.9 (1.0-10.4)	1.3 (0.73-2.2)
Unexposed	0.80 (0.47-1.4)	reference
Regional Nitrogen Dioxide		
	MET rs1858830 Genotype	
	C/C	C/G or G/G
Exposed	3.6 (1.3-12.7)	1.2 (0.71-2.1)
Unexposed	0.72 (0.41-1.3)	reference

Volk et al, 2014

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What About Timing?

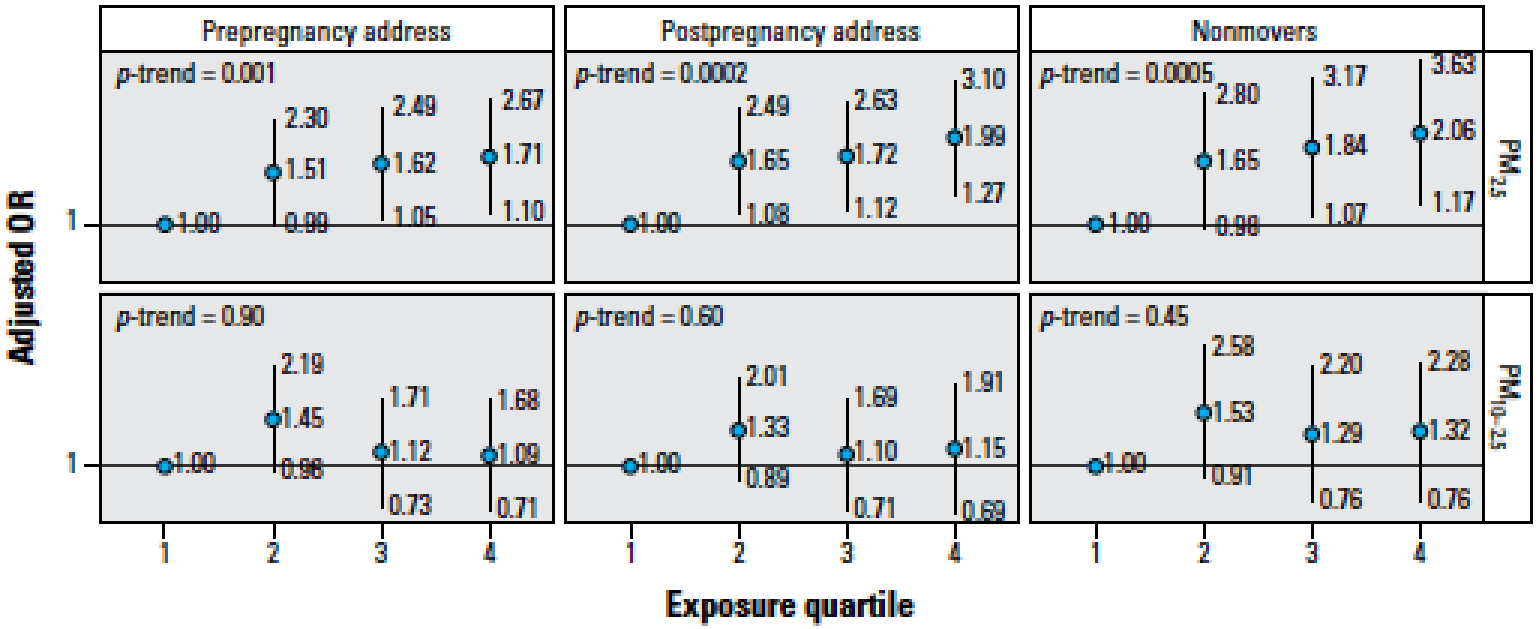

Figure 1. ORs (95% CIs) for ASD by quartile of PM exposure. ORs are adjusted for child sex, year of birth, month of birth, maternal age at birth, paternal age at birth, and census income. There were 245 cases and 1,522 controls in analyses using pre- and postpregnancy addresses. Prepregnancy address is the last known residential address before conception. Postpregnancy address is the first known residential address after birth. Nonmovers are those participants for whom prepregnancy and postpregnancy addresses were the same [cases = 160 (65%), controls = 986 (65%)]. *p*-Trend, *p*-values from models of exposures as continuous variables. The number of cases (including movers) by quartiles from low to high: 45, 66, 66, 68; controls: 397, 376, 375, 374. $PM_{2.5}$ quartile ranges ($\mu g/m^3$): 5.24–12.3, 12.4–14.5, 14.6–16.7, 16.7–30.8; $PM_{10-2.5}$ quartile ranges ($\mu g/m^3$): 1.9–6.7, 6.8–8.9, 9–11.9, 12–49.4.

Raz et al, 2015

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Future Goals and Directions

- Define Specific Air Pollutant – ASD Relationships
  - Timing!
  - One pollutant or a mixture?
- Evaluate Air Pollutant Effects on Trajectories
  - Broad Cognitive Phenotypes / Domains of ASD
  - Neuroimaging
- Study the Potential Mechanisms of Air Pollution on the Brain
- Gene-Environment Interaction Studies
  - Consortium for Integrative Research
  - Common Air Pollution Assessment Methods in Epidemiologic Samples (GEWIS)

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