Emerging Knowledge about Environmental Exposures & Risk for Autism

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What Doesn’t Cause Autism?

Neurobiologic basis:
aberrant brain development

What Causes Autism?

- Genes
  - Syndromes
  - Single genes
  - Copy number variants

- Environmental factors

‘Root’ Causes

- Distinguish from factors that may exacerbate symptoms
- Occur prior to diagnosis

- Public health: ways to intervene

Goal is prevention

Genetics & Environment

- Heritability estimates

  35%-60%

Two largest studies of twins

Estimate the contribution of environment:

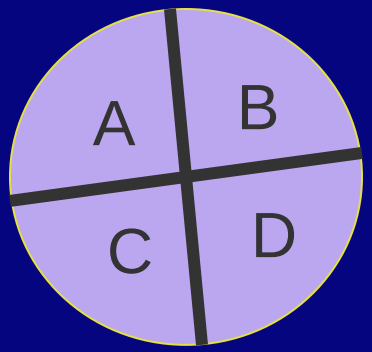
38%-57%

Hallmayer et al, Arch Gen Psychiatry 2010
Rosenberg et al, Arch Ped Adolesc Med 2009

Environment is modifiable

Multifactorial causation

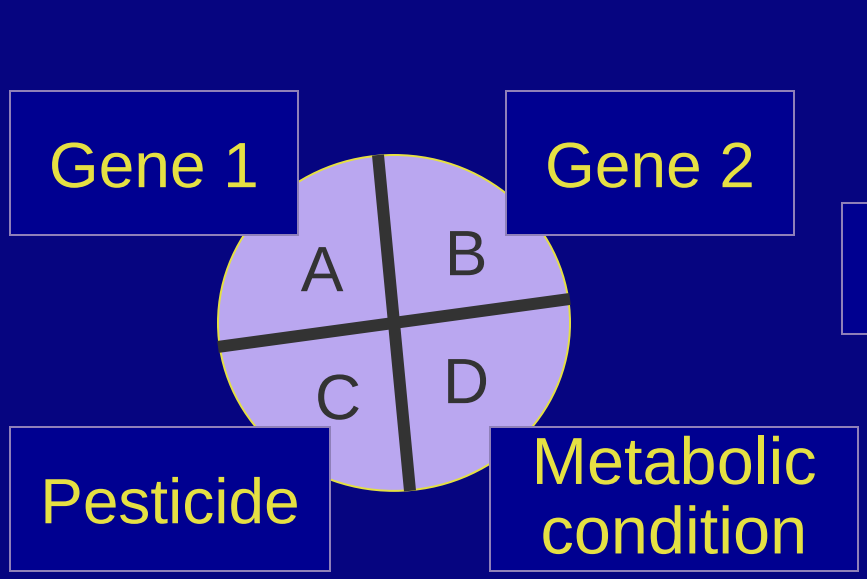
-across the population *and* within an individual

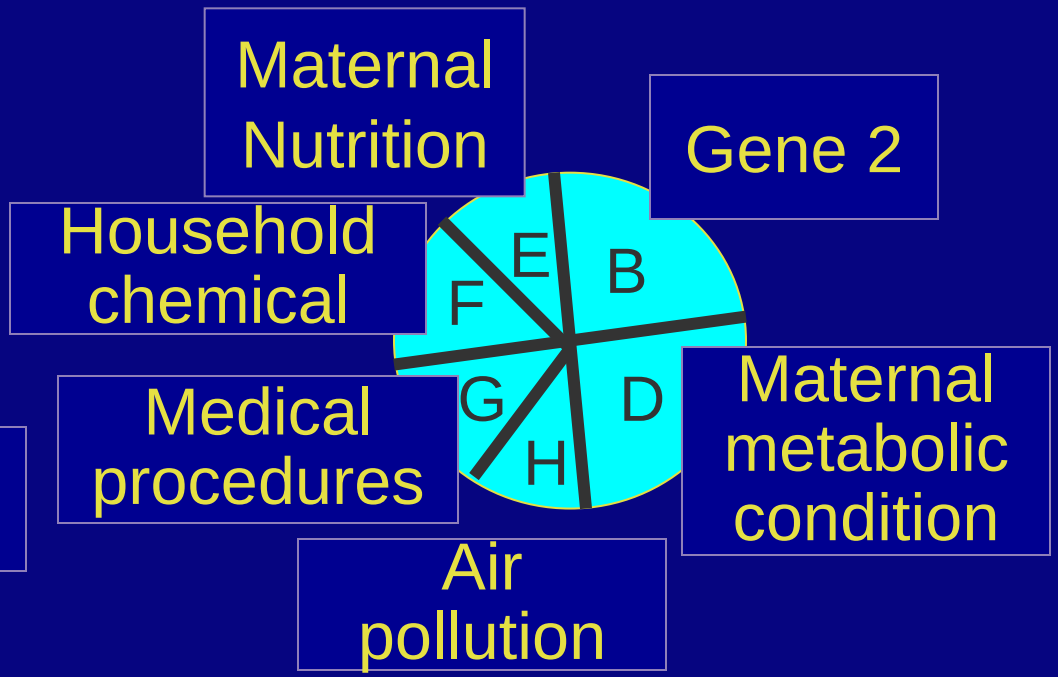


Sufficient Causes Model

Genes & Environment

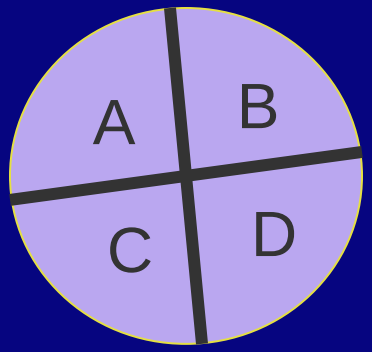
Multifactorial causation

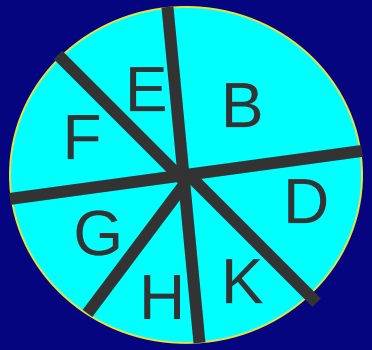


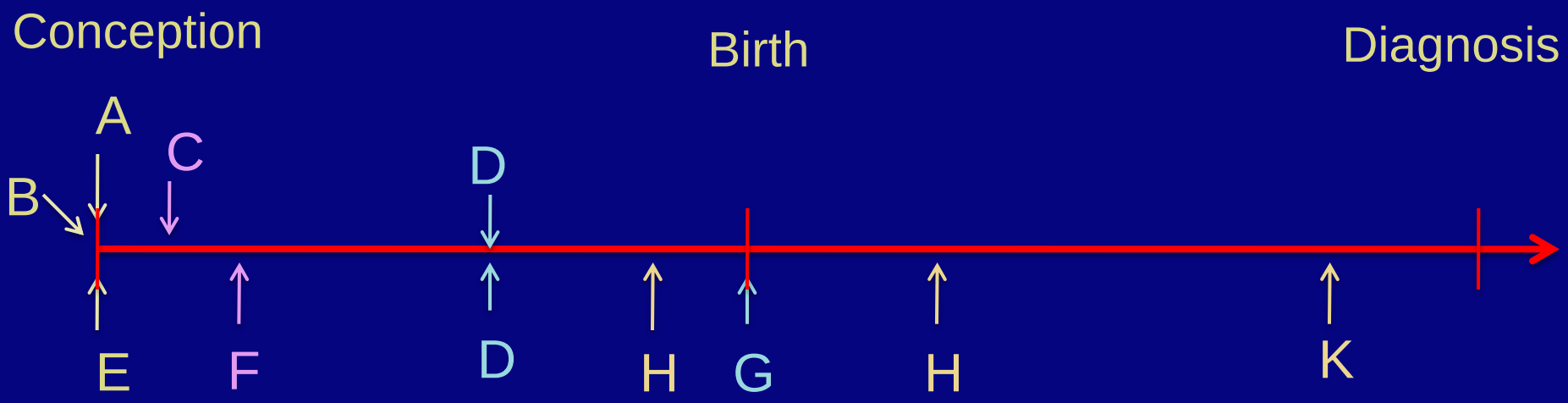


Timing matters!!

Developmental Biology Perspective:







Time Trends in Autism

Comparing 1990 births to 2001 births in California,

…autism incidence, by 5 years of age:

rose 7-fold (=600%)

How much of the 600% increase could have resulted from:

• Change in DSM criteria:	120%
• Trend towards younger age at diagnosis:	24%
• Broadening to include milder cases:	56%
• Older ages of mothers	4%
Total (from these 4):	204%

"…the possibility of a true increase in incidence deserves serious consideration."

Hertz-Picciotto & Delwiche, Epidemiol 2009; Shelton et al, Autism Res 2010

Time Trends of Other Conditions

- asthma, obesity, diabetes, ADHD, and mental health disorders (OCD, bipolar disorder)

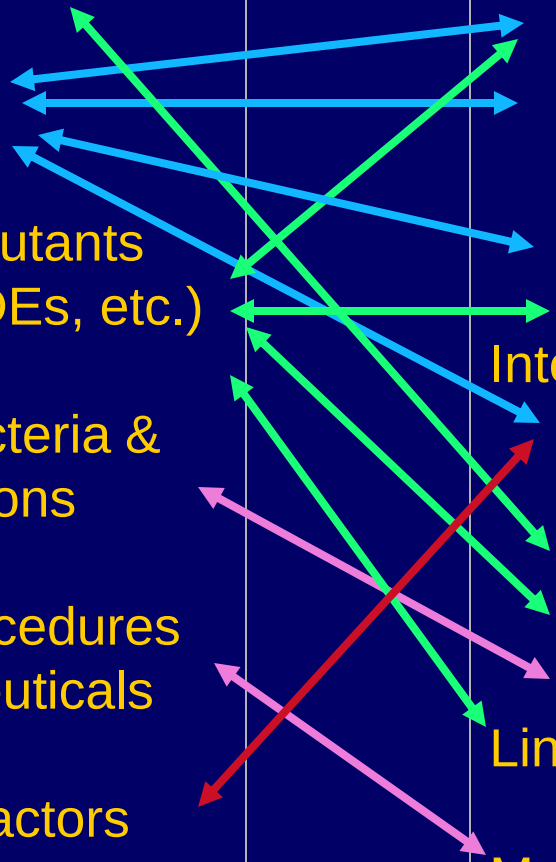
Is there a common set of environmental exposures that provides a unifying explanation for increased incidences of these conditions in recent decades?

*CHildhood Autism Risks from Genetics and the Environment

The CHARGE Study

Environmental Exposures & Ways to Assess

1. Pesticides
2. Metals
3. Organic pollutants (PCBs, PBDEs, etc.)
4. Viruses, bacteria & other infections
5. Medical procedures & pharmaceuticals
6. Nutritional factors



Biospecimens:
- Blood
- Baby lock (first year of life)
- Mother's hair
- Urine
- Newborn blood spot (prenatal)
- Teeth

Interviews:
- Diet
- Residential information
- Lifestyle
- Consumer products
- Medical history

Linkage to exposure databases
- Air, water, pesticides, haz waste

Medical records

CHARGE Study Goals

To identify causes and contributing factors for autism:

- Environmental exposures
- Genetic susceptibility
- Interactions of the two

CHARGE Study Design

Case-control - three groups

California DDS

1. Children with autism
2. Children with developmental delay

California Birth files

3. Children drawn from general population of births, frequency matched to projected distributions, in cases, of age, gender & geography

CHARGE Study Methods

Case-control sampling design

*Population-based recruitment

*Standardized clinical confirmation of dx

*Linkage to state-of-the-art laboratories

CHARGE Study Eligibility

All 3 groups:

- 24-60 months
- Born in California
- Live with biologic parent
- English / Español
- Reside in study catchment area

CHARGE Study: Child Assessment

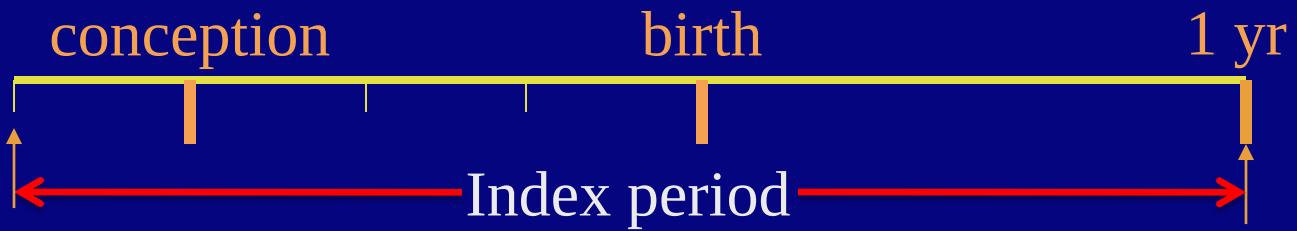
- Clinic visit:
  Autism Diagnostic Observation Schedule (ADOS)
  Autism Diagnostic Inventory – Revised (ADI-R)

- Medical examination and history

- Broad assessment of
  behavior, development,
  comorbidities

CHARGE Study: Exposure assessment

- Interview: lifestyle, demographics, medical conditions, repro hx, residential hx, etc.



- Specimens collected from family members:
  blood urine hair
- Permission to obtain medical charts:
  - prenatal
  - labor and delivery
  - pediatrician
  - fertility clinics

Be in *CHARGE !*

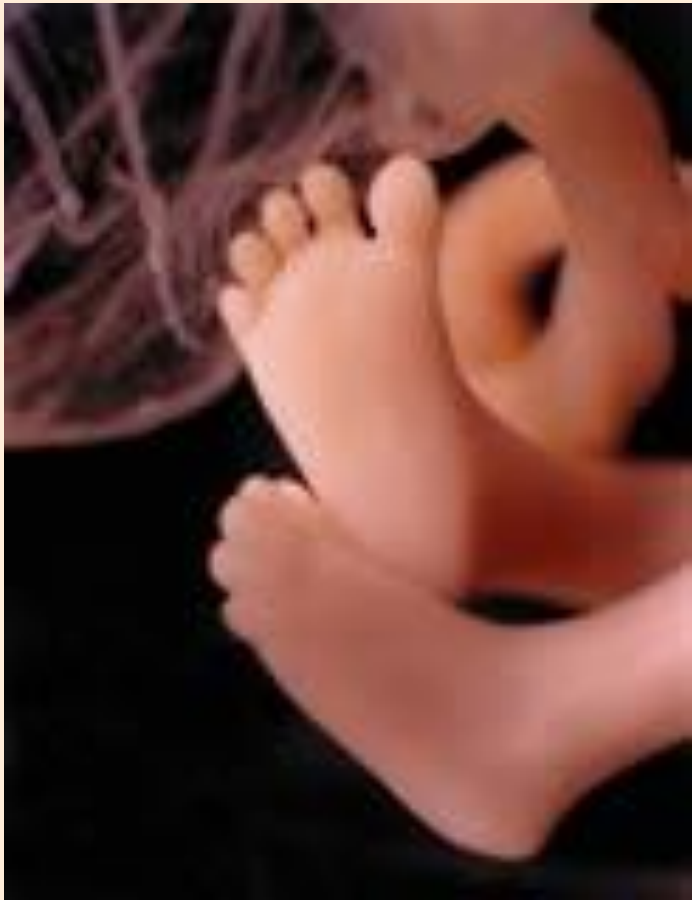
http://beincharge.ucdavis.edu/

State of the Science on Autism Etiology: 2013

- Genes ?
- Environmental pollutants? (air pollution)
- Household chemicals (pesticides, phthalates)
- Vitamins, nutritional deficiencies ?
- Maternal reproductive characteristics (IPI)?
- Obstetric, perinatal conditions (chronic & acute) ?
- Infections, inflammation, immune regulation ?
- Fertility treatments & other medical interventions ?
- Medications ?
- Modern technology ?

CHARGE Study Results

1. Maternal Metabolic Conditions



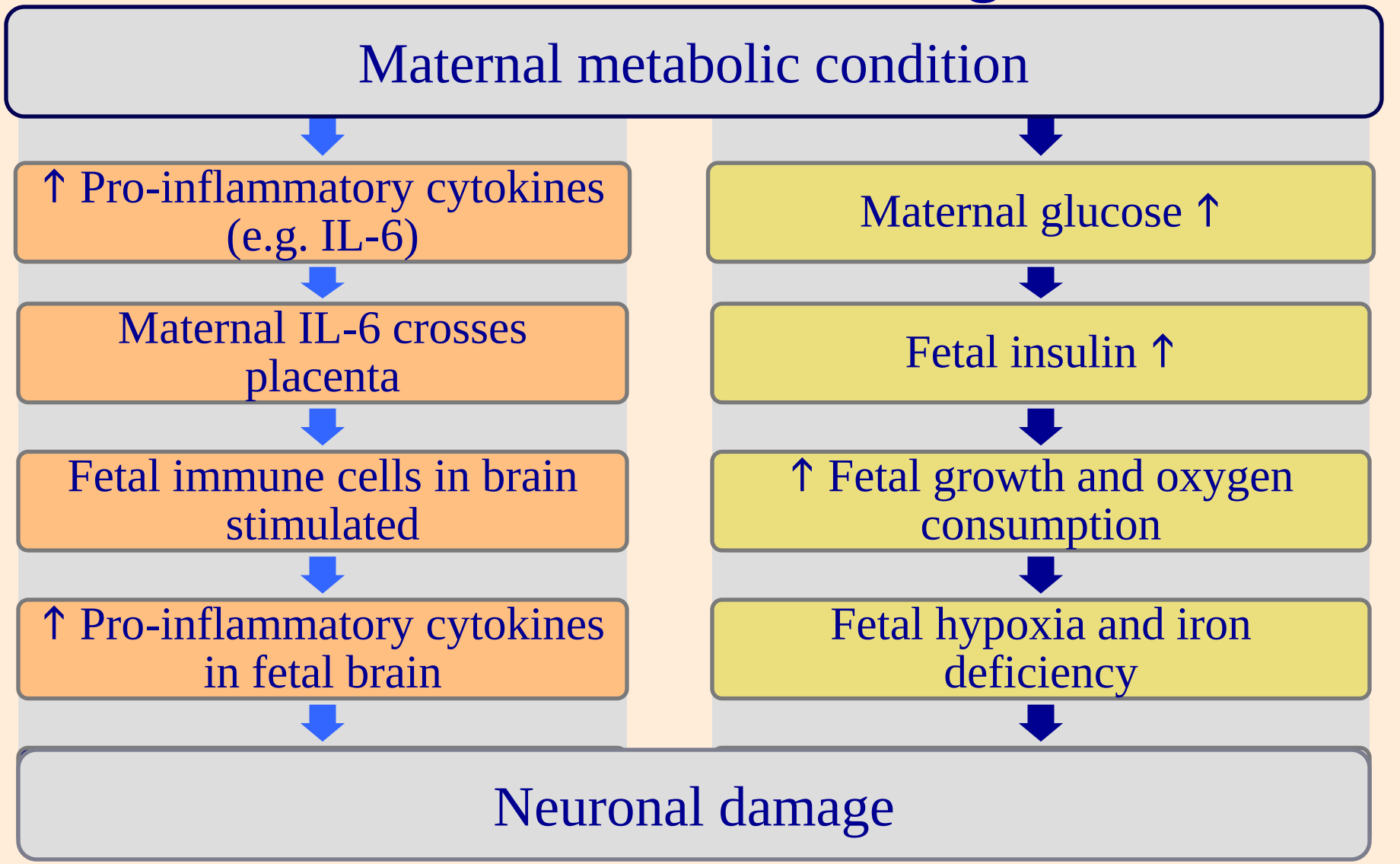
Maternal Metabolic Conditions

Goal:

To determine differences between mothers of children with typical development and those of children with autism or with developmental delay, in relation to:

* pre-pregnancy obesity,
* Type 2 or gestational diabetes, or
* underlying hypertension

Insulin resistance and fetal brain damage



Maternal Conditions and Child's Dx: ASD, Other Developmental Delay (DD)

	ASD *vs.* TD		DD *vs.* TD	
Conditions in index pregnancy:	OR†	95% CI	OR†	95% CI
Diabetes (type 2 or gestational)	1.5	(0.8, 2.9)	2.5	(1.1, 5.5)
Hypertension	3.1	(1.1, 8.8)	5.3	(1.5, 18.6)
Obesity	1.7	(1.1, 2.6)	2.1	(1.2, 3.7)
Diabetes, hypertension, or obesity	**1.6**	**(1.1, 2.4)**	**2.5**	**(1.5, 4.1)**

†Multinomial logistic regression models were adjusted for mother's age at delivery, race/ethnicity, and education, delivery payer, calendar time, and frequency-matching variables

Krakowiak et al, Pediatrics 2012

CHARGE Study Further Results

- Among ASD and among non-ASD, separately, maternal diabetes also associated with poorer:
  - Receptive language
  - Expressive language
- Among non-ASD maternal diabetes also associated with reduced:
  - Socialization

Krakowiak et al, Pediatrics 2012

Discussion

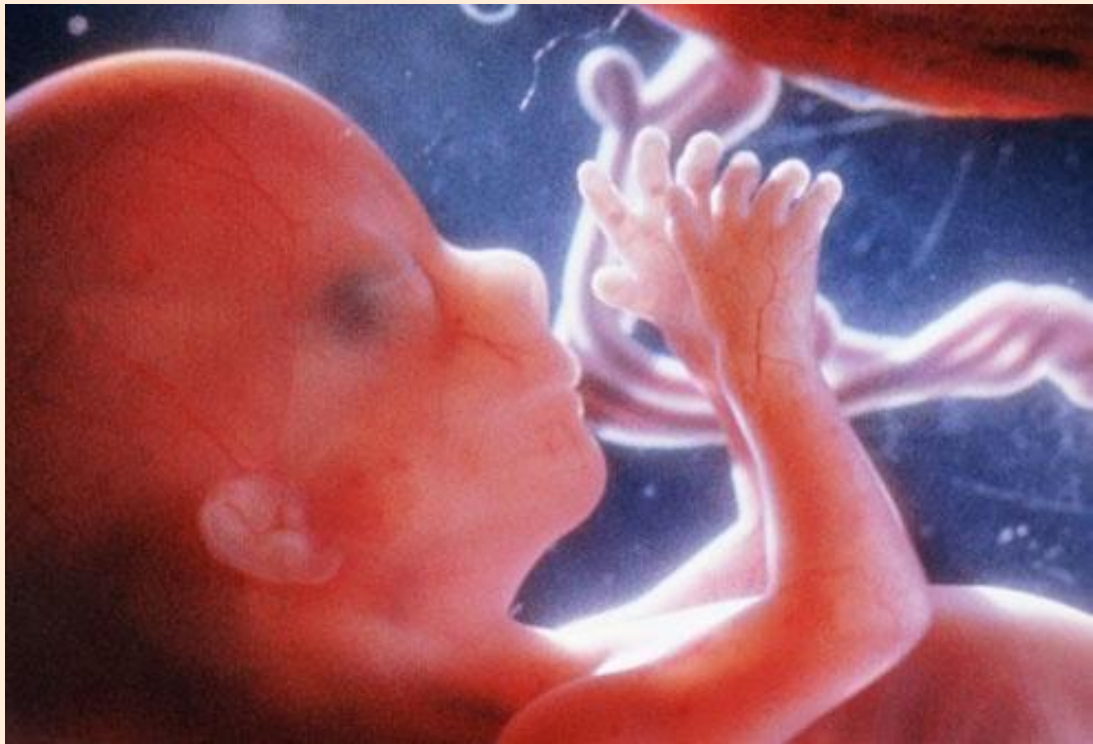
- Prior studies of diabetes show associations with intellectual disability

What influences metabolic conditions??

- Cross-sectional studies show associations of several endocrine disruptors with diabetes/obesity (bisphenol A, anti-bacterials)
- High fructose corn syrup *(Stanhope et al 2012)*

CHARGE Study Results

1. **Maternal Metabolic Conditions**
2. **Maternal Nutrition**



Maternal Nutrition

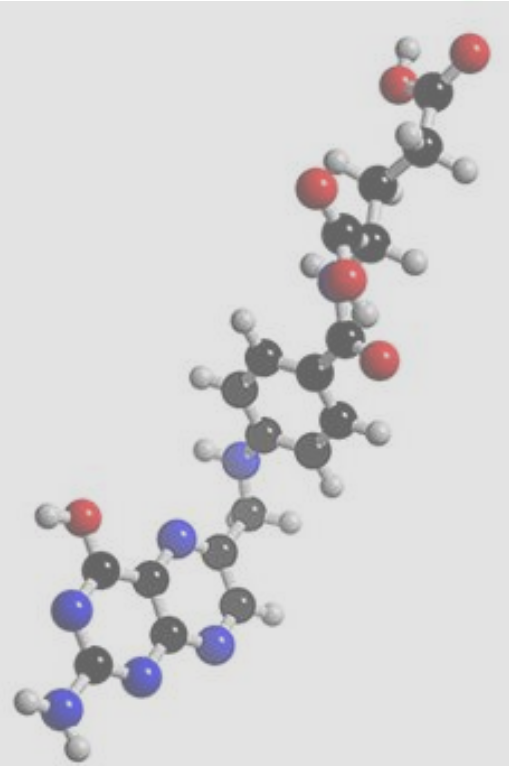
Goals:

To determine whether mothers of children with typical development differed from those of children with autism or with developmental delay

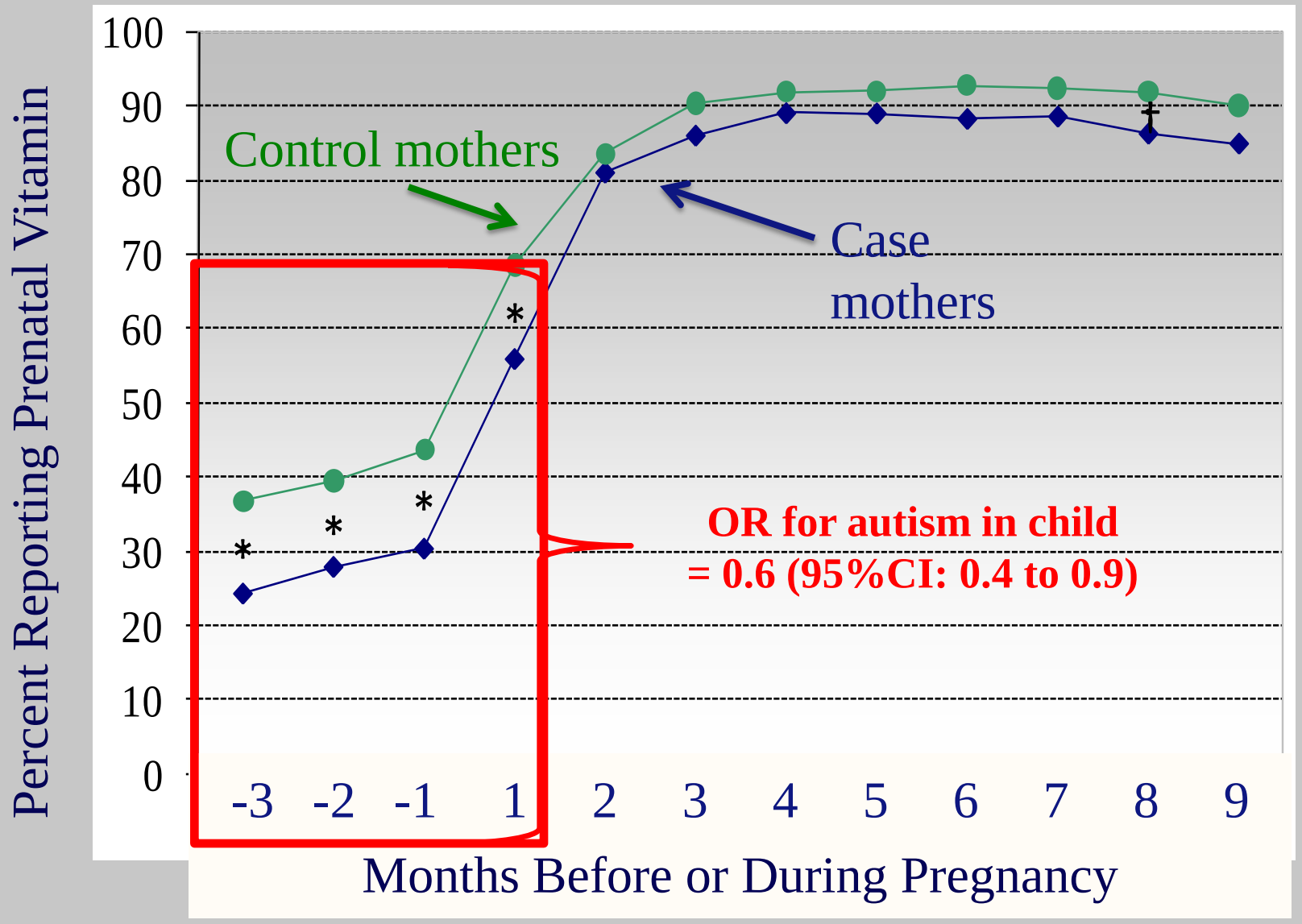
* intake of prenatal vitamins
* timing of intake
* combination of genes and prenatal vitamin intake

Folic Acid

- Required for DNA:
  synthesis, repair, and methylation
- Supplementation prevents 50-70% of neural tube defects (NTDs)
- Prenatal supplements recommended before and during early pregnancy
- Folic acid fortification mandated for cereal grains by 1998
- Several studies have since shown declining prevalence of NTDs in US



Prenatal Vitamin Supplements



Schmidt et al, Epidemiology 2011; Amer J Clin Nutrition 2012

Average Daily Folic Acid Intake

Folic Acid P1	OR (95% CI)
0	Reference
< 500	0.73 (0.31, 1.69)
500 – 800	0.64 (0.24, 1.71)
800 – 1000	0.57 (0.24, 1.35)
1000+	0.41 (0.17, 0.96)

$P_{trend} = 0.001$

Maternal Nutrition

- Estimated intake from diet and supplements → similar results
- Inter-pregnancy interval

  <12 months: 3.7-fold

  12-24 months: 2.1

  24-36 months: 1.4

- Replication of prenatal supplement result in Norway

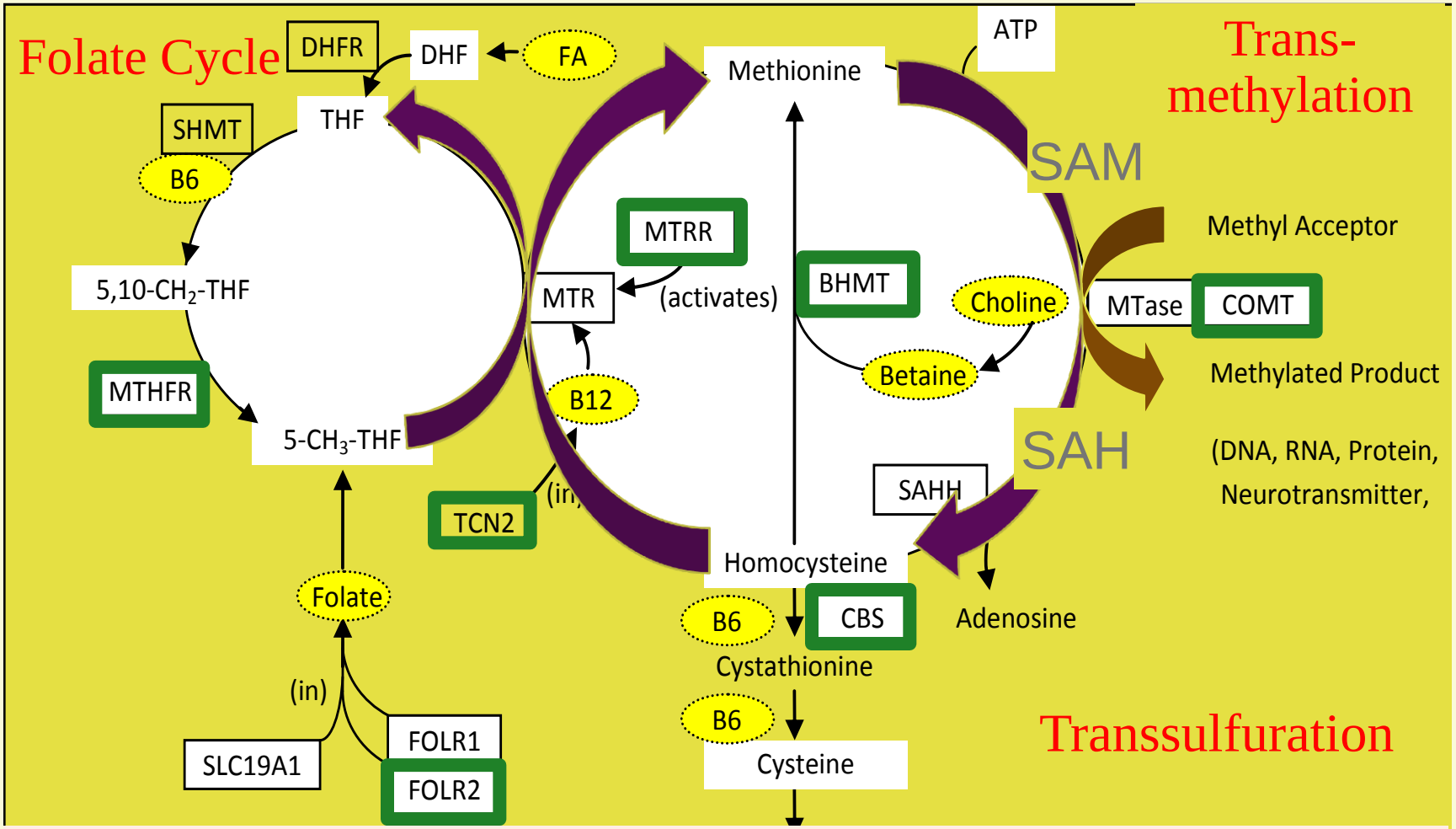
Schmidt et al, Epidemiology 2011; Amer J Clin Nutrition 2012
Cheslack-Postava Pediatrics 2011
Suren et al JAMA 2013

Confirmation in a prospective study

- Norwegian mother-baby cohort: MoBa Study
- 85,000 children followed to mean age of 6.4 years (Range= 3.3 to 10.2 years)
- Recruited during pregnancy, children born 2002-2008
- Asked about dietary supplements at 18 weeks gestation for the period 4 weeks before LMP to 8 weeks post LMP
- Also found a 40% reduction in risk for ASD for folic acid consumers
- Rate for autism was substantially lower than in the U.S., and prenatal supplements were 400 mcg folic acid.

Suren et al JAMA 2013

Folate, Methionine, and Transmethylation Pathways



Maternal and Child Gene Variants
Associated with Increased Autism Risk
in Combination with No Intake of Prenatal Vitamins

Gene x Nutrition Interaction

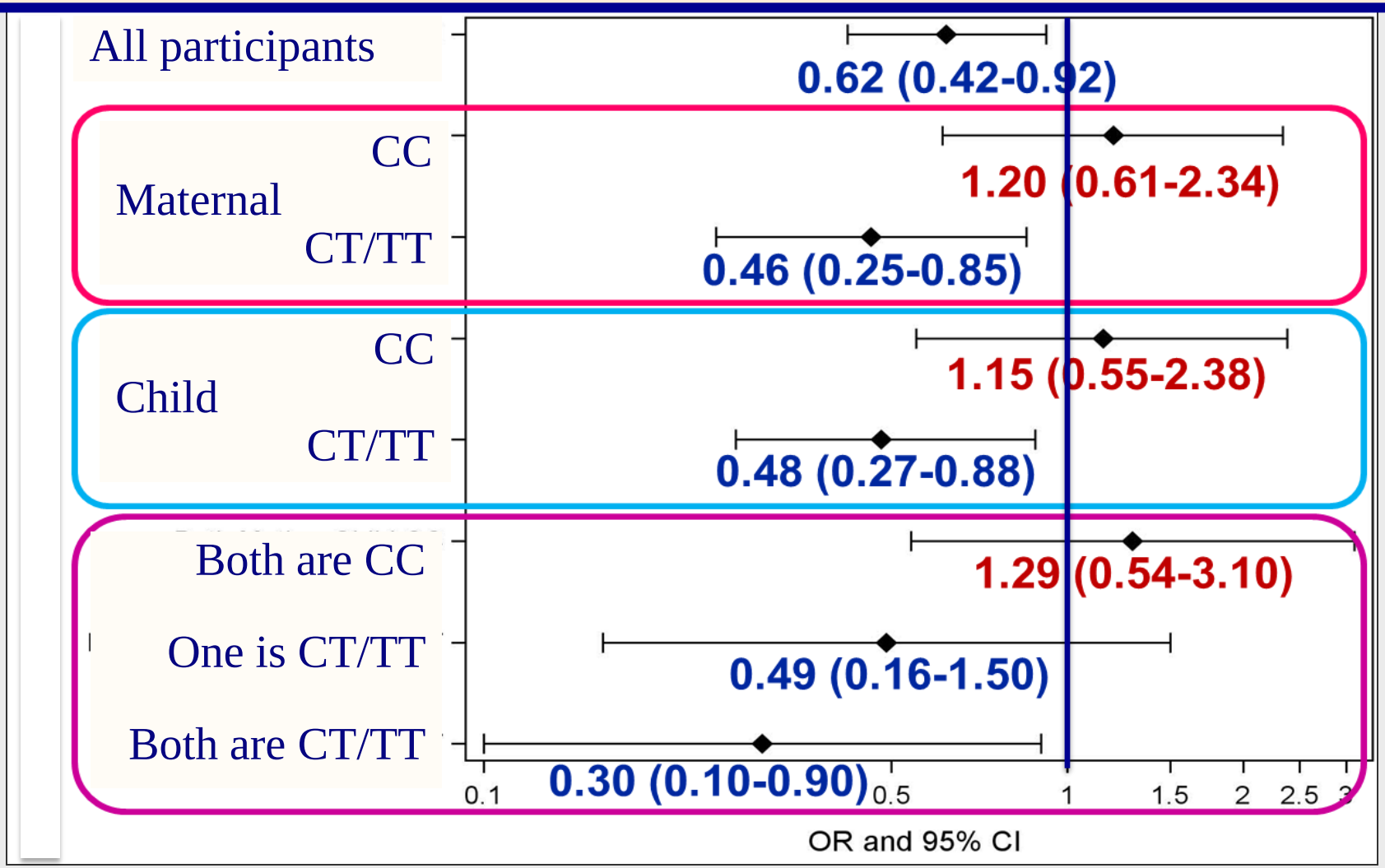
ODDS RATIOS	Periconceptional supplementation:	
COMT genotype	Yes	No
GG+GA	Referent	1.8
AA	1.3	7.2

Child's COMT gene exerts a ***synergistic*** effect
in combination with prenatal vitamin supplements taken around the time of conception

Schmidt et al, Epidemiology 2011, Amer J Clin Nutrition 2012

Impact of Folic Acid Intake according to genotype for MTHFR 677

MTHFR677 gene regulates folate metabolism



CHARGE Study Results

1. **Maternal Metabolic Conditions**
2. **Maternal Nutrition**
3. **Medications**

CHARGE Study Results

1. **Maternal Metabolic Conditions**
2. **Maternal Nutrition**
3. **Medications**
4. **Air Pollution**

Air Pollution

Goal

- To determine whether mothers of cases were more likely during pregnancy to have greater exposures to ambient air pollution.
- Distance to freeway
- Estimated ambient concentrations of pollutants in air

Residential Proximity to Freeways

Distance to freeway		Adjusted Odds Ratio	**95% CI**
<2/10 mile	closest 10 %	1.86	1.03, 3.45
2/10 – 4/10	10th to 25th %	0.96	0.58, 1.56
4/10 – 9/10	25th to 50th %	1.11	0.73, 1.67
>9/10 mile	farthest 50%	reference	--

*Adjusted for child's sex and ethnicity, parental education, and maternal age and smoking

Volk et al, Environ Health Persp 2010

Biologic Plausibility

- Particle concentrations in ambient air *high* near freeways, and drop to background at about 300m
- Objective exposure measure for prenatal period
- Proximity to traffic ~ asthma
- Components of traffic-related AP (benzo(a)pyrene, diesel, ozone) induce neurodevelopmental deficits in rodents
- PAHs → oxidative stress, inflammation, endocrine disruption

Early Life Air Pollution

- Windham et al 2006, San Francisco
- Kalkbrenner et al 2010, North Carolina & West Virginia
- Roberts et al 2013, Nurses Health Study II
- Volk et al 2011, 2012, northern & southern Calif selected areas
- Becerra et al 2013, Los Angeles County
- Jung et al 2013, Taiwan

Discussion

- PAHs (polycyclic aromatic hydrocarbons), chlorinated semi-volatile compounds, fine and coarse particles, ozone, metals, nitric oxide, nitrogen dioxide,
- Most components of cigarette smoke and ambient air pollution are in both
- Cigarette smoking literature
- How to explain discrepancy?

CHARGE Study Results

1. **Maternal Metabolic Conditions**
2. **Maternal Nutrition**
3. **Medications**
4. **Air Pollution**
5. **Infection/Inflammation/Immune Responses**

CHARGE Study Results

Adjusted OR[1] (95% CI) associated with Fever During Pregnancy stratified by use of anti-fever or anti-inflammatory medication

	Autism/ASD	Developmental Delay
Had fever, took anti-fever medication	1.30 (0.59 – 2.84)	2.05 (0.78 – 5.36)
Had fever, did not take anti-fever medication	2.55 (1.30 – 4.99)	2.73 (1.19 – 6.28)
Did not have fever, took no anti-fever med.	Referent group	Referent group

[1]Adjusted for maternal report of flu, private vs. public health insurance for delivery, race/ethnicity, and the matching variables (child age, sex, and maternal place of residence at child birth)

Zerbo et al 2011

Interpretation of fever results

Self reports – recall bias?

Results are consistent with a role for an acute inflammatory reaction

Influenza rodent model

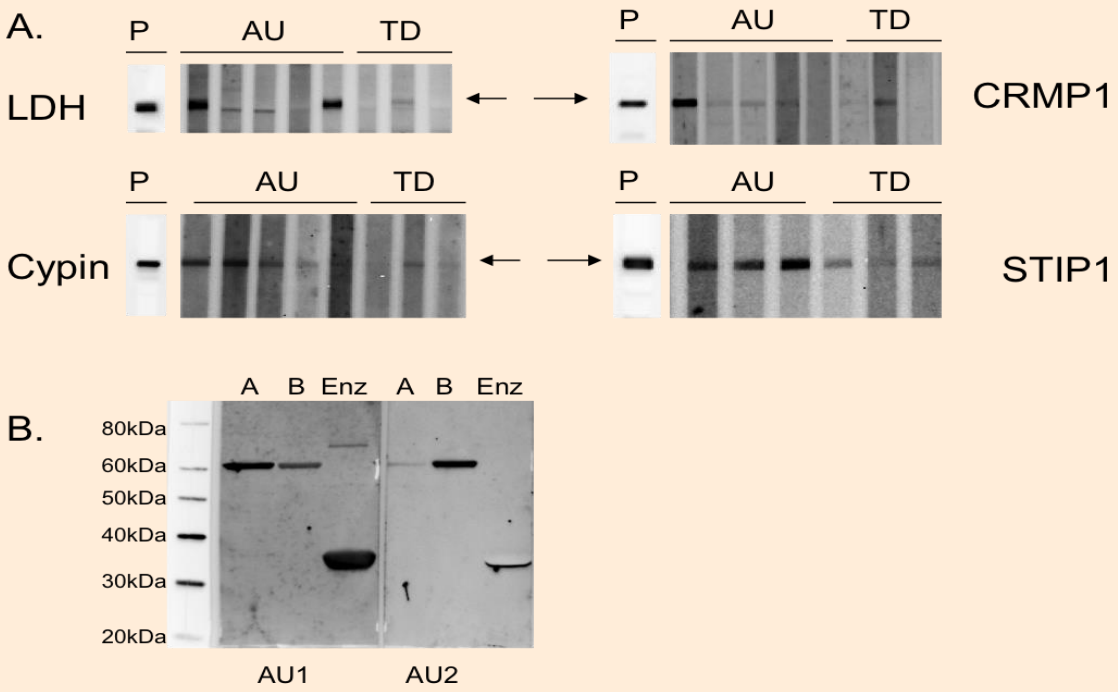
Is autism a neuroinflammatory condition?

Also consistent with seasonality data

Infection, Fever, Inflammation

- Atladottir et al 2010a, 2010b: Maternal hospitalizations for infection, Denmark
- Zerbo et al 2012, Fever in pregnancy
- Vargas et al, 2005: Neuroinflammation and autism
- Hornig et al 2002, Shi et al, 2003, Meyer et al 2006: Animal models of inflammation
- Patterson et al 2011, Huang et al

Infection/Inflammation/Immune Responses



Up to 23% of mothers of children with autism may produce specific antibodies to fetal brain tissue

Braunschweig et al. Neurotoxicology 2008,
J Autism Dev Dis 2012,
Transl Psychiatr 2013

CHARGE Study Results

- Direction of connection to autism unclear:
  - immune aberrations could be downstream or upstream of neuropathology
    …or neither
- Possibility that environmental chemicals may influence neurodevelopment indirectly, through immune dysregulation

Take-home messages from the CHARGE & other studies

Take prenatal vitamin supplements – before pregnancy (best: 3 months prior)!

Space pregnancies (best: 36 months or more from conception to next conception)

Consult with your physician regarding risks & benefits from SSRI use

Limit exposure to air pollutants from traffic, cigarettes, and other sources

Reduce weight, control blood glucose, exercise moderately to reduce blood pressure

Avoid flu/prolonged fever, take anti-fever meds

The CHARGE Study

First comprehensive study of environmental factors in autism

Our focus is on **modifiable** risk and protective factors
- goal is to intervene and prevent autism!

Limitation is retrospective data collection

MARBLES

Markers of Autism Risk in Babies—Learning Early Signs

A study of pregnant moms, who already have a child with autism, following their pregnancies and new child

Prospective Studies of Younger Siblings Starting in Pregnancy

- Complement case-control studies
- Eliminate problem of differential reporting
- Permit examination of temporally relevant exposures

Prospective Studies of Large Populations

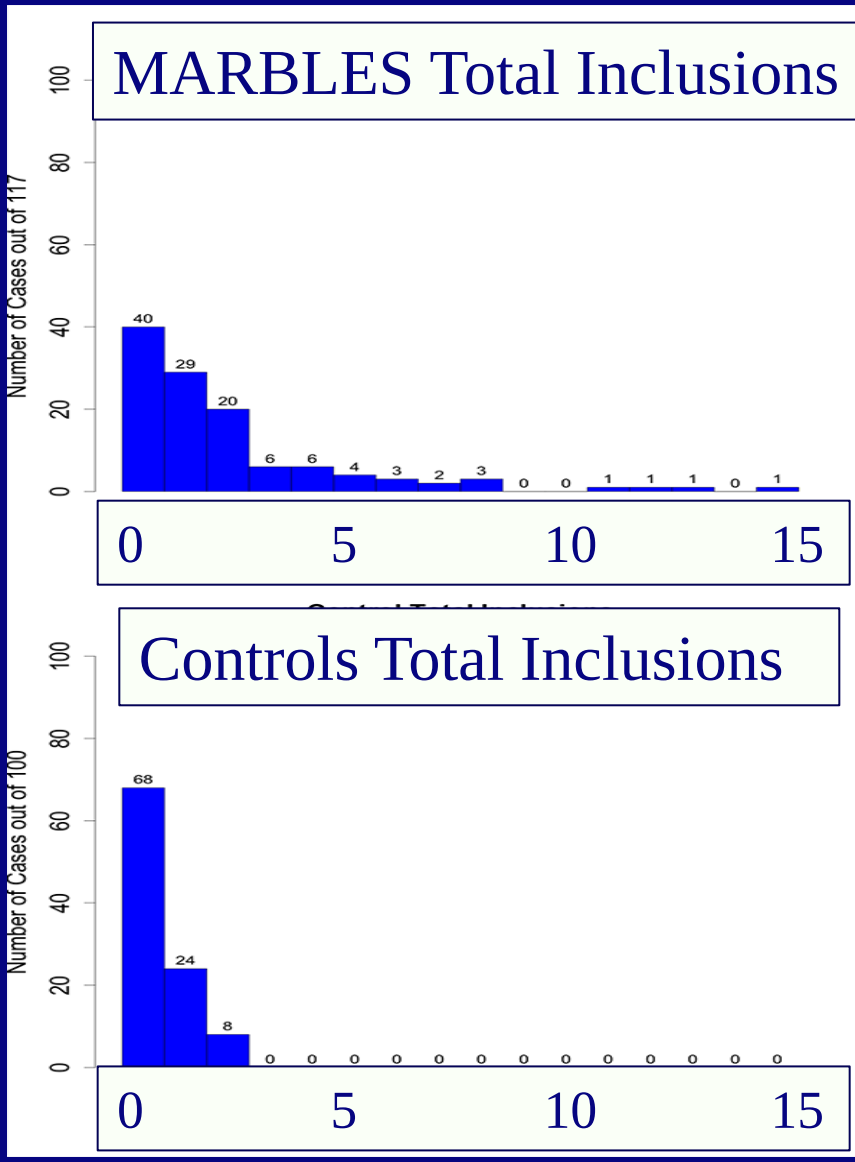
NCS, Danish NCS, MoBa

Results from MARBLES

- Trophoblastic inclusions

Results from MARBLES

- Trophoblastic inclusions



Walker et al, Molecular Psychiatr 2013

Postnatal influences?

Early childhood exposures

- Air pollution?
- Nutrition?
- Breastfeeding?

Post-diagnosis influences?

- Behavioral
- Nutritional
- Environmental
  - Address core symptoms
  - Address co-morbidities
- ReCHARGE Study

Investigators & Collaborators

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Thank you!

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End