AUTISM AND THE ENVIRONMENT: State of the Science

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What is Autism?

- Neurodevelopmental disorder with three defining domains of deficit:
  - Social reciprocity
  - Communication
  - Repetitive behaviors or restricted interests
- Symptoms present by 36 months of age
- Considered to be lifelong, no cure

Facts about Autism

- Prevalence in U.S.:
  1 in 110

- Sex ratio 4:1

- Neurobiologic basis: aberrant brain development
  - Post-mortem autopsy
  - Electrophysiologic
  - Magnetic Resonance Imaging and fMRI

- Highly heritable
  - Twin studies
  - Family recurrence
  - Candidate gene
  - GWAS (Genome-wide association studies)

What Causes Autism?

- Genes
- Advanced Parental Age (clues rather than causes)
- Obstetric/Perinatal factors
- Prenatal Infections (Reubella, Chess et al 1979)
- Medications (Thalidomide, SSRIs Croen et al 2011)
- Pesticides (Roberts et al 2007, Eskenazi et al 2007)
- Closely Spaced Pregnancies (Cheslack-Postava et al 2010)
- Month of Conception (Zerbo et al 2011)

The *CHARGE** Study

*CHildhood Autism Risks from Genetics and the Environment

PI: Irva Hertz-Picciotto

First comprehensive study
of environmental factors in autism

CCEH Center for Children's Environmental Health

The CHARGE Study Design:
Case-Control - 3 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

Eligibility for All 3 Groups

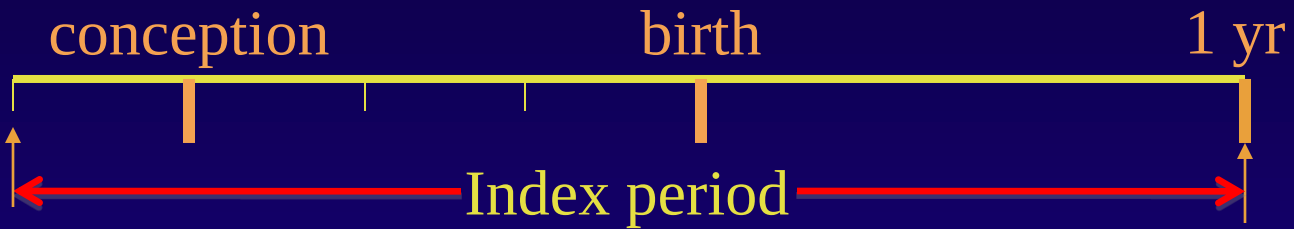
- 24-60 months
- Born in California
- English / Español
- Living in study catchment area

Diagnoses Confirmed

- Clinic visit:
  - Autism Diagnostic Observation Schedule (ADOS)
  - Autism Diagnostic Inventory – Revised (ADI-R)
- Medical examination and history
- Broad assessment of behavior, development, co-morbidities

Data Collection

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



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

CHARGE STUDY RESULTS

1. **Traffic-Related Air Pollution**

Residential Proximity to Freeways

- Proxy for Traffic-Related Air Pollution
- Calculated distance to nearest freeway from maternal address at time of delivery
- ArcGIS software

Volk et al, Environ Health Persp 2010

Residential Proximity to Freeways
(a proxy for air pollution exposure)

Distance to Freeway at Delivery	# Cases / # Controls	Adjusted OR	95% CI
<309m (closest 10%)	38 / 19	1.86	1.03, 3.45
309-647m (10th to 25th %)	43 / 41	0.96	0.58, 1.56
647-1419m (25th to 50th %)	77 / 63	1.11	0.73, 1.67
>1419m (farthest 50%)	146 / 136	reference	--

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

Volk et al, Environ Health Persp 2010

Comments

- Components of traffic-related air pollution (benzo(a)pyrene; diesel, O_3) induce neurodevelopmental deficits in rodents

- Polycyclic Aromatic Hydrocarbons (PAHs) → oxidative stress, inflammation, endocrine disruption, immunologic alterations

Volk et al, Environ Health Persp 2010

CHARGE STUDY RESULTS

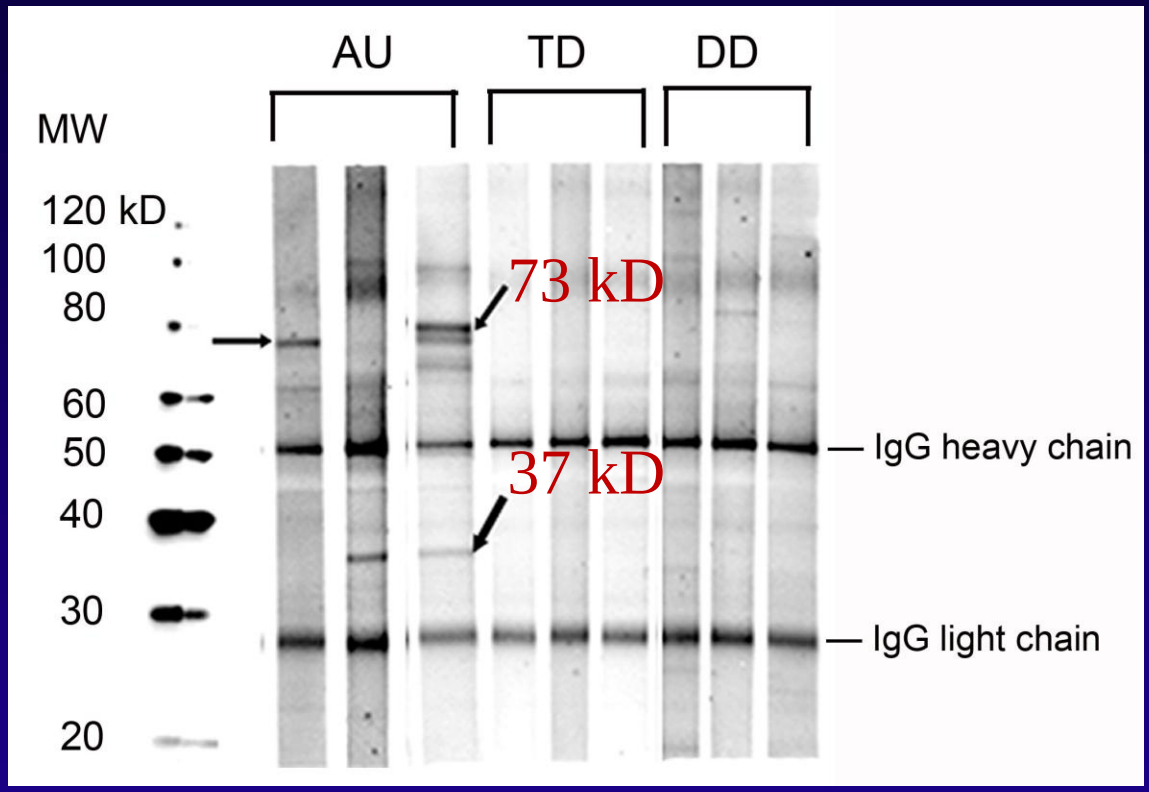
1. Air Pollution
2. **The Immune System**

Immunology Findings

- Elevated leptin levels in children with autism.
  (*Ashwood et al, J Autism Dev Dis 2008)*
- Lower overall IgG in children with autism
  (Heuer et al, Autism Res 2008)
- Higher concentrations of IgG4 subclass in peripheral blood
  (Enstrom et al, Brain, Behav Immun 2008)
- Reduced TGF-beta (regulates immune responses)
  (Ashwood et al, J. Neuroimmunol 2008)
- Abnormal NK (natural killer) cell functioning: over-stimulated, but less able to respond to specific challenge
  (Enstrom et al, Brain, Behav Immun 2008)
- Autoantibodies to cerebellum in children with ASD
  (Goines et al, Brain, Behav Immun 2011)

Immune dysregulation in children with autism

Maternal Antibodies to Fetal Brain Tissue



About 7% of mothers of children with autism produce specific antibodies to fetal brain tissue compared to 0% of mothers of children with TD

Braunschweig et al., JADD 2011

Comments

- Direction of connection to autism unclear:
  - immune aberrations could be downstream or upstream of neuropathology or neither
- Environmental factors could work through immune pathways (rather than direct effects)
- Not solely a disorder of the CNS

CHARGE STUDY RESULTS

1. Air Pollution
2. The Immune System
3. **Maternal Metabolic Conditions**

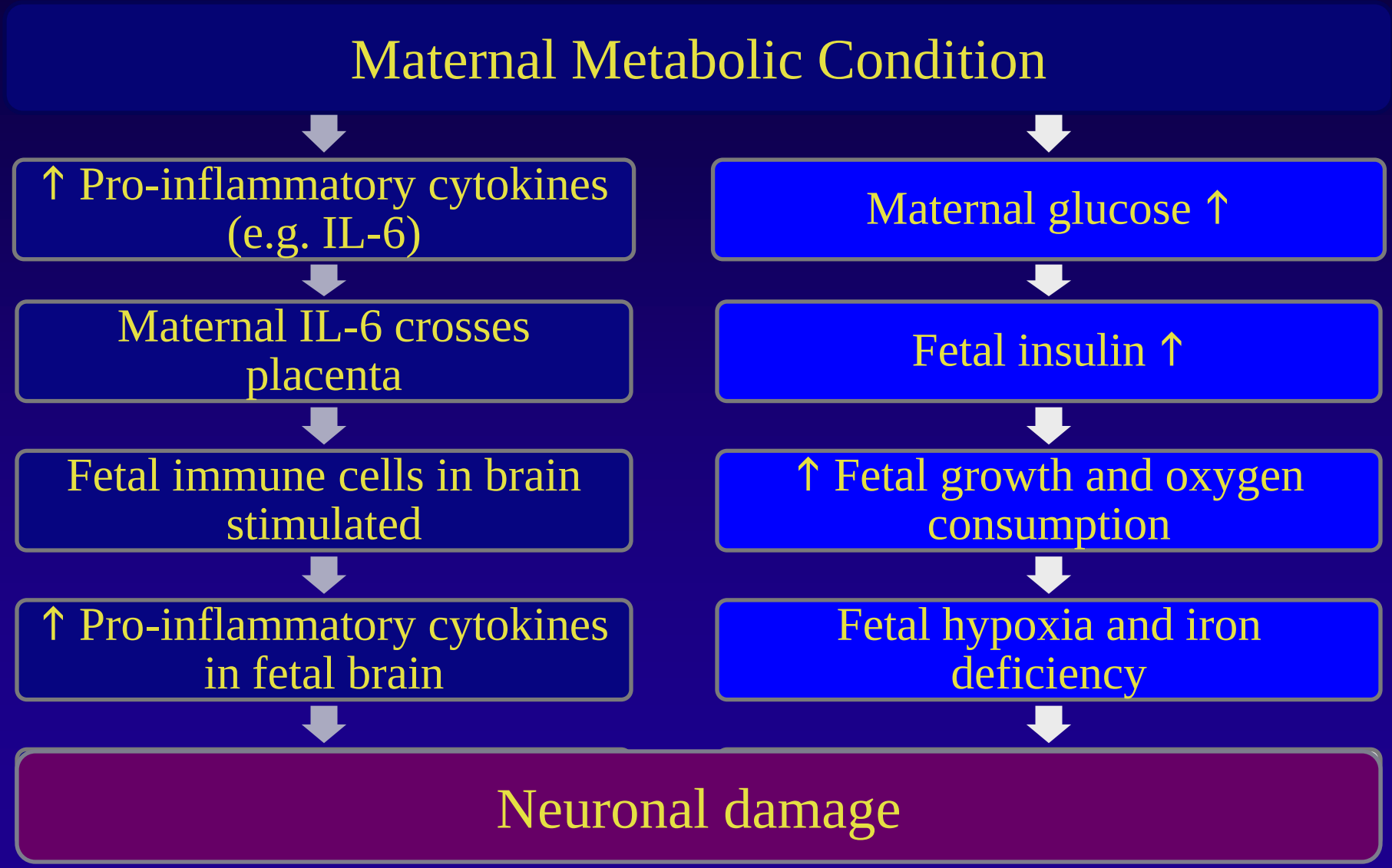
Maternal Metabolic Conditions

	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, and/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, in press Pediatrics

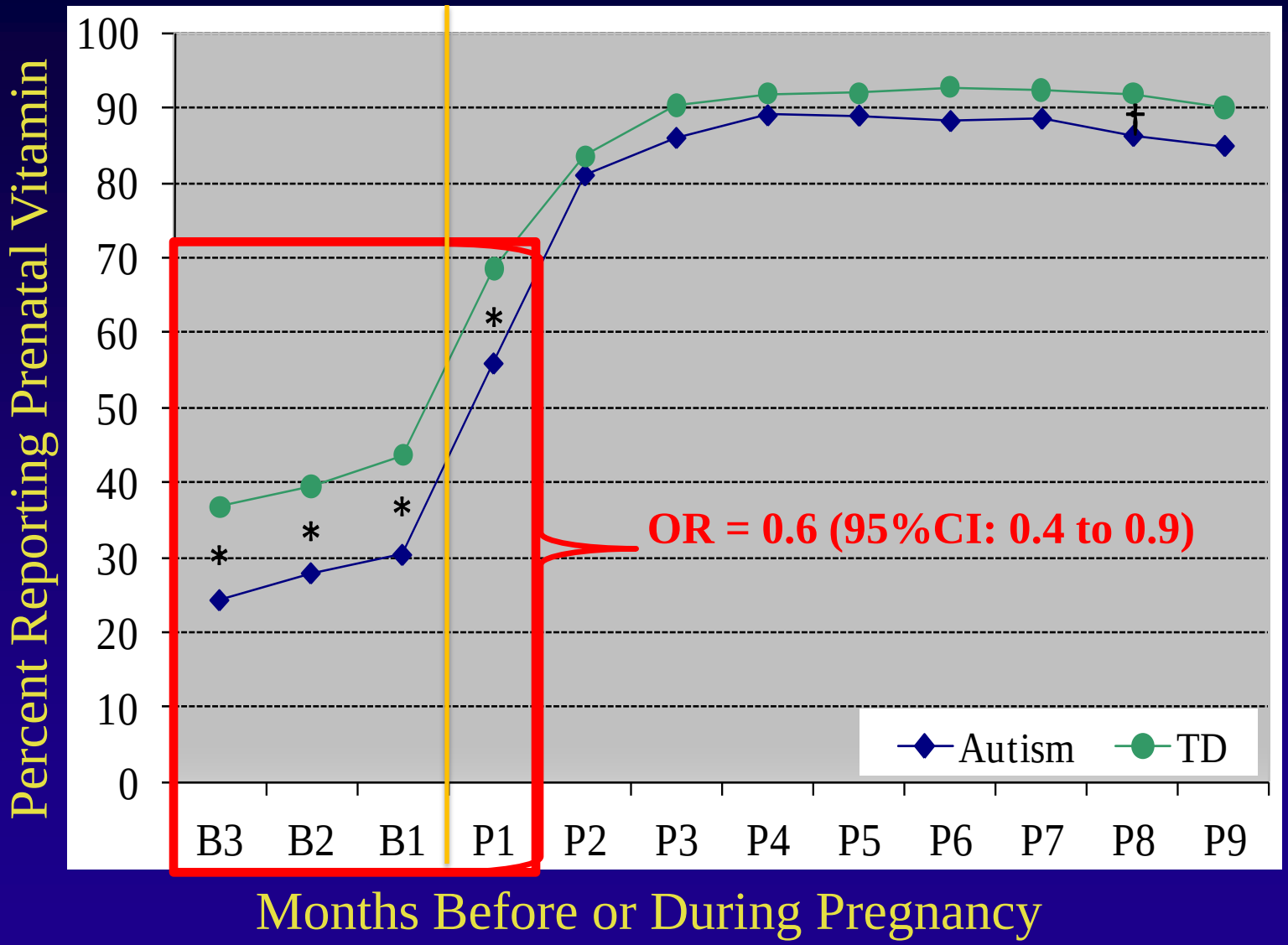
Insulin Resistance and Fetal Brain Damage



CHARGE STUDY RESULTS

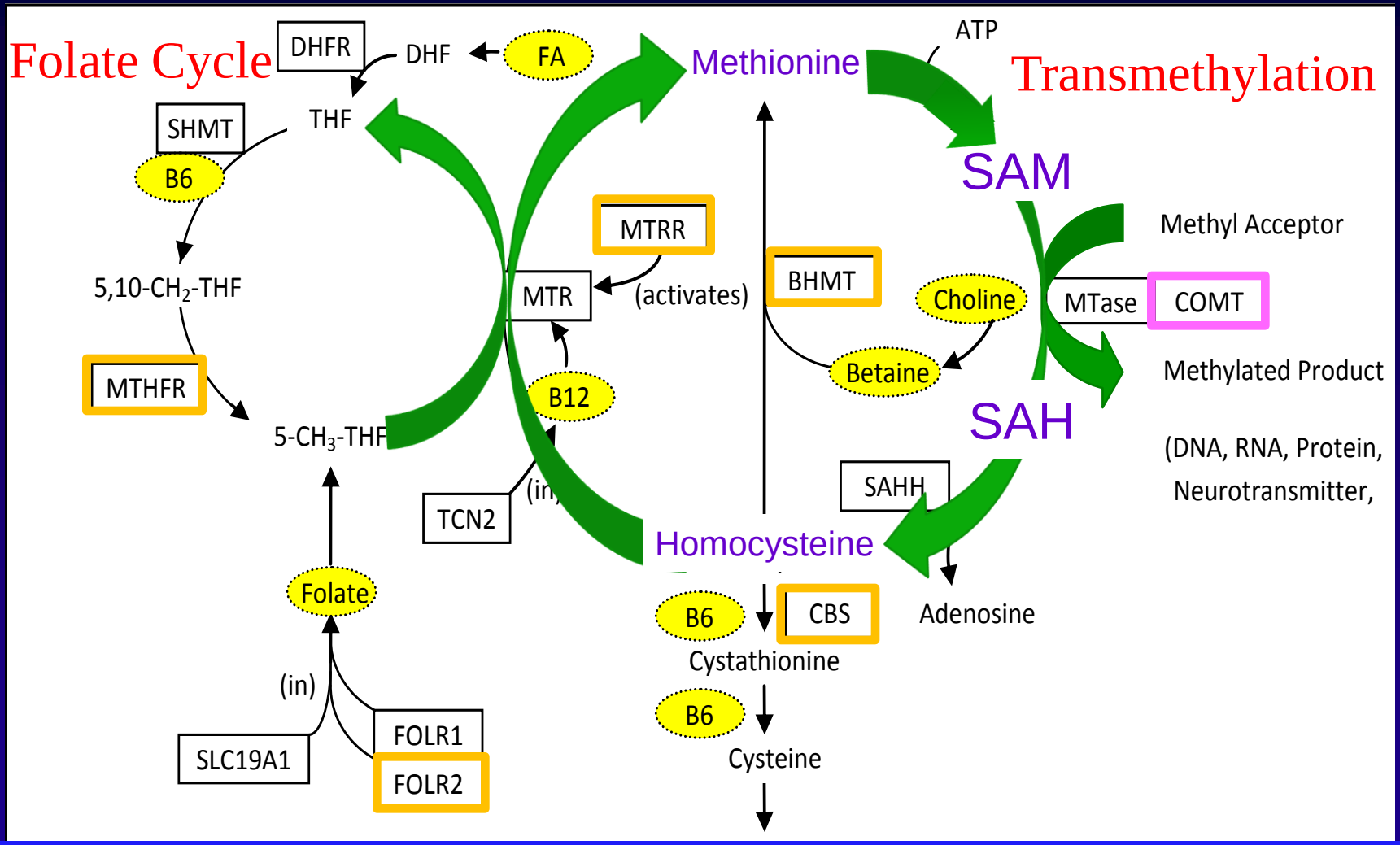
1. Air Pollution
2. The Immune System
3. Maternal Metabolic Conditions
4. **Maternal Vitamin Intake**

Prenatal Vitamin Use by Perinatal Month



Schmidt et al, Epidemiology 2011

Folate, Methionine, and Transmethylation Pathways



Maternal [Orange Boxes] and Child [Pink Boxes] Gene Variants Associated with Increased Autism Risk in Combination with No Prenatal Vitamin Intake

Gene x Environment (Vitamin) Interaction

Child *COMT 472* Genotype	Prenatal Vitamin B3-P1 YES	NO
GG+GA	REF	1.3
AA	1.8	7.2

Synergistic effect of child's COMT genotype with peri-conceptional supplementation

Maternal environment combined with child's genetic susceptibility could determine child's risk for autism

Schmidt et al, Epidemiology 2011

Interaction with Maternal Genes

Maternal Gene	Genotype	Prenatal Vitamin B3-P1 YES	Prenatal Vitamin B3-P1 NO
MTHFR 667	CC+CT	REF	1.2
	TT	0.7	4.5
CBS	GG	REF	1.0
	GT+TT	1.0	2.6
MTRR 66	AA	REF	0.9
	AG+GG	0.9	1.6
BHMT 716	GG	REF	1.1
	GA+AA	0.9	1.7
FOLR2	GG+GA	REF	1.1
	AA	1.0	1.9

Comments

- First to demonstrate gene/environment interactions in autism

- First to suggest a concrete step that may reduce the risk of having a child with autism

Significance of CHARGE: 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: recall can be faulty, or influenced by child's condition

MARBLES

Markers of Autism Risk in Babies—Learning Early Signs

EARLI

Early Autism Risk Longitudinal Investigation

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

Investigators & Collaborators

- UC Davis CCEH
  - Isaac Pessah
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  - Rebecca J. Schmidt
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- Over 250 families who invited us into their homes & lives (repeatedly!) for the MARBLES Study
- Families participating in EARLI

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- Autism Speaks
- Cure Autism Now
- The Allen Foundation
- National Institute for Occupational Safety and Health

End

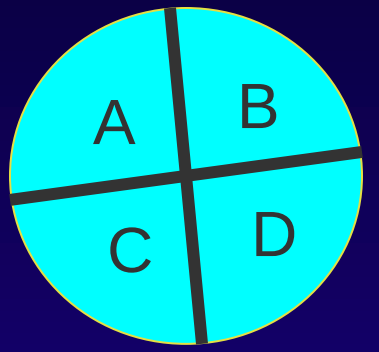
Thank you!

Multifactorial Causation

- Genetics: ~38-90% (twin studies)
- Environment: 10-62% = minimum

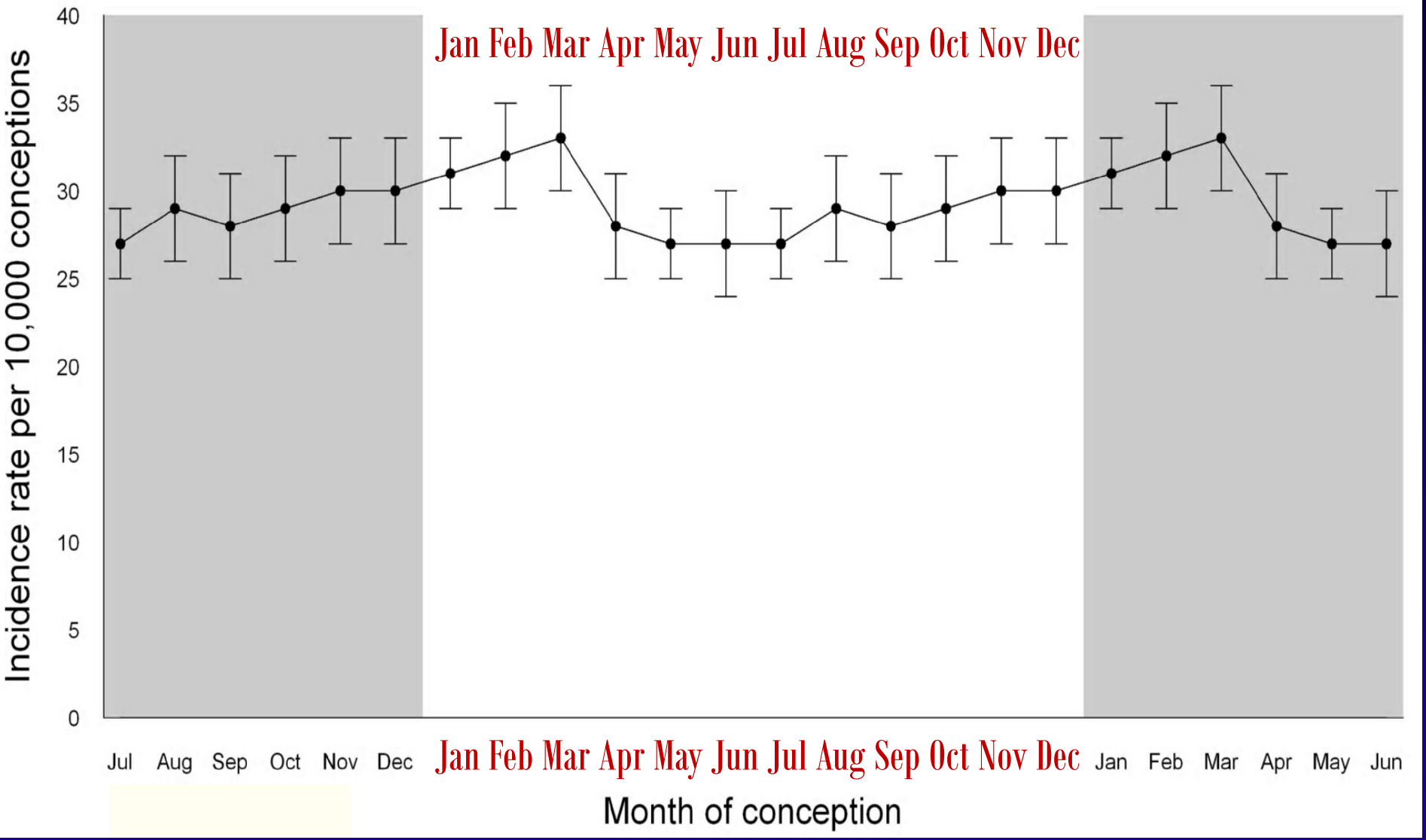
…Sum not 100%

Assumes *no interaction with environment*



- across populations *and* within each individual

Seasonality in Autism



Zerbo et al, Epidemiology 2011

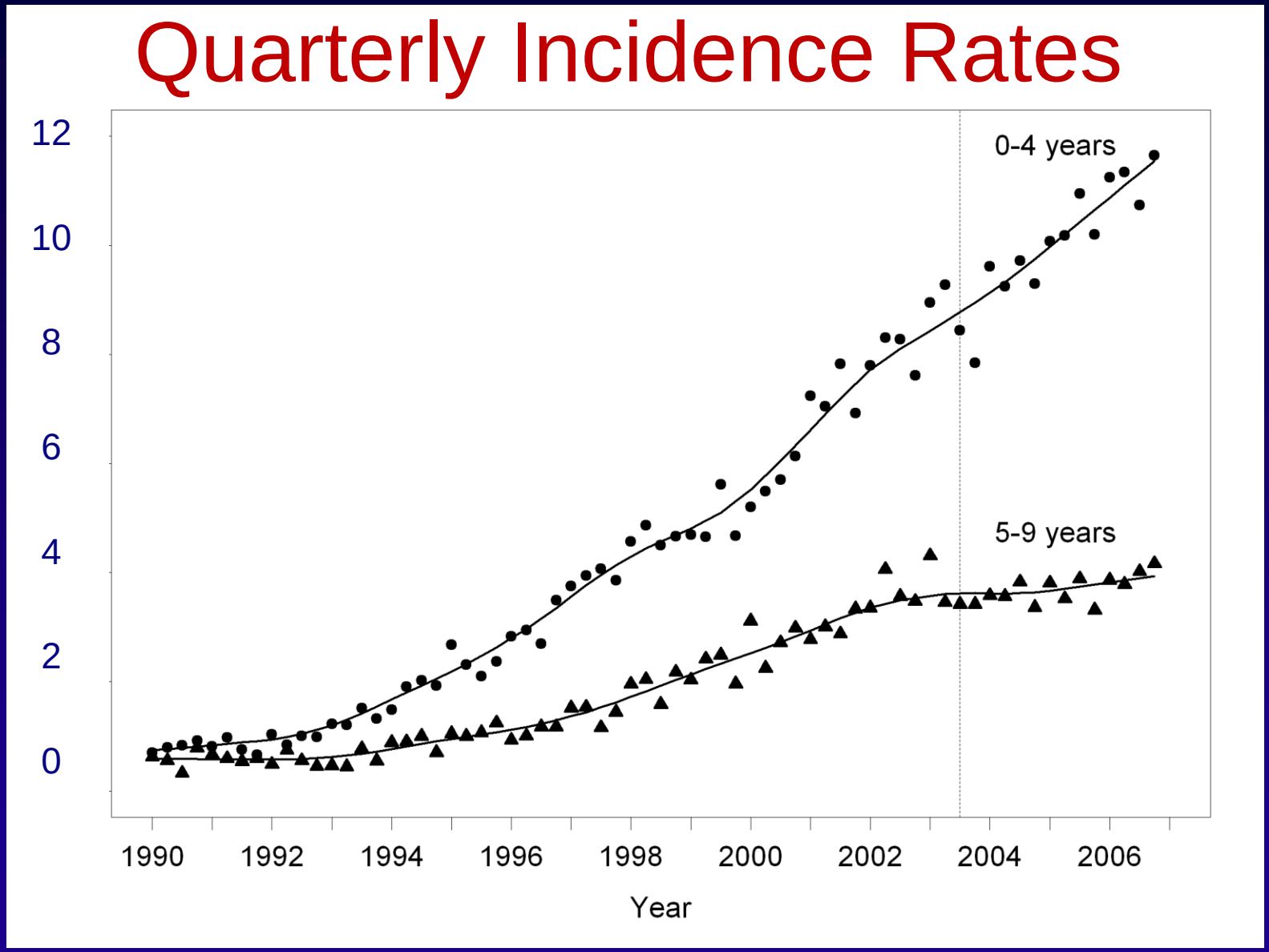
Seasonal Variation in Month of Conception

- Implies seasonality of causes
- Time of conception not necessarily critical window
- Potential seasonal causes include:
  - Infectious diseases such as influenza
  - Pesticide exposures
  - Deficiencies: vitamin D, other nutrients

Zerbo et al, Epidemiology 2011

Time Trends in Autism

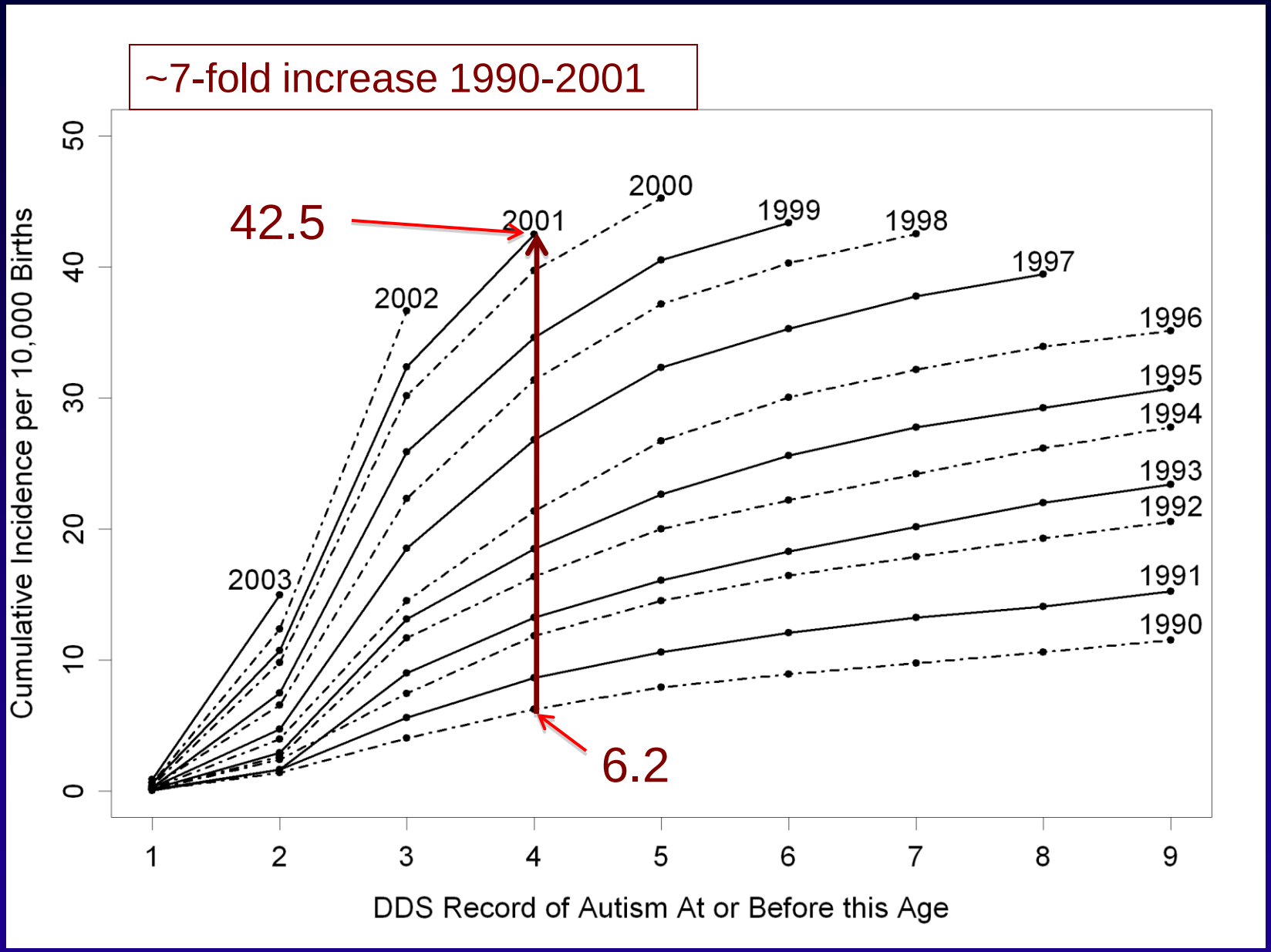
Quarterly number of new cases per 10,000 Children



Hertz-Picciotto and Delwiche, Epidemiology 2009

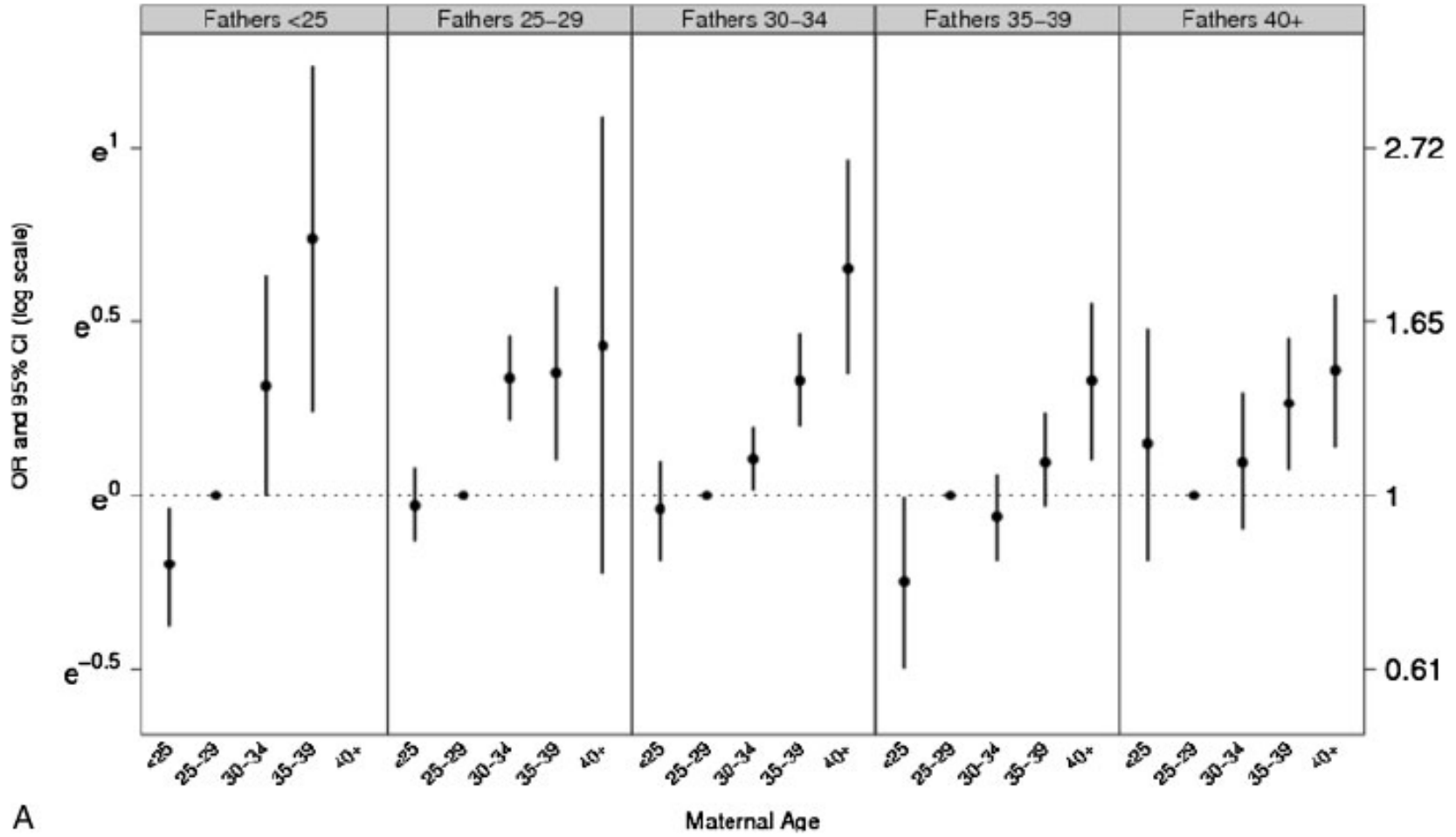
Time Trends in Autism

Cumulative Incidence by Birth Cohort



Hertz-Picciotto & Delwiche, Epidemiology 2009

The effect of maternal age across strata of paternal age



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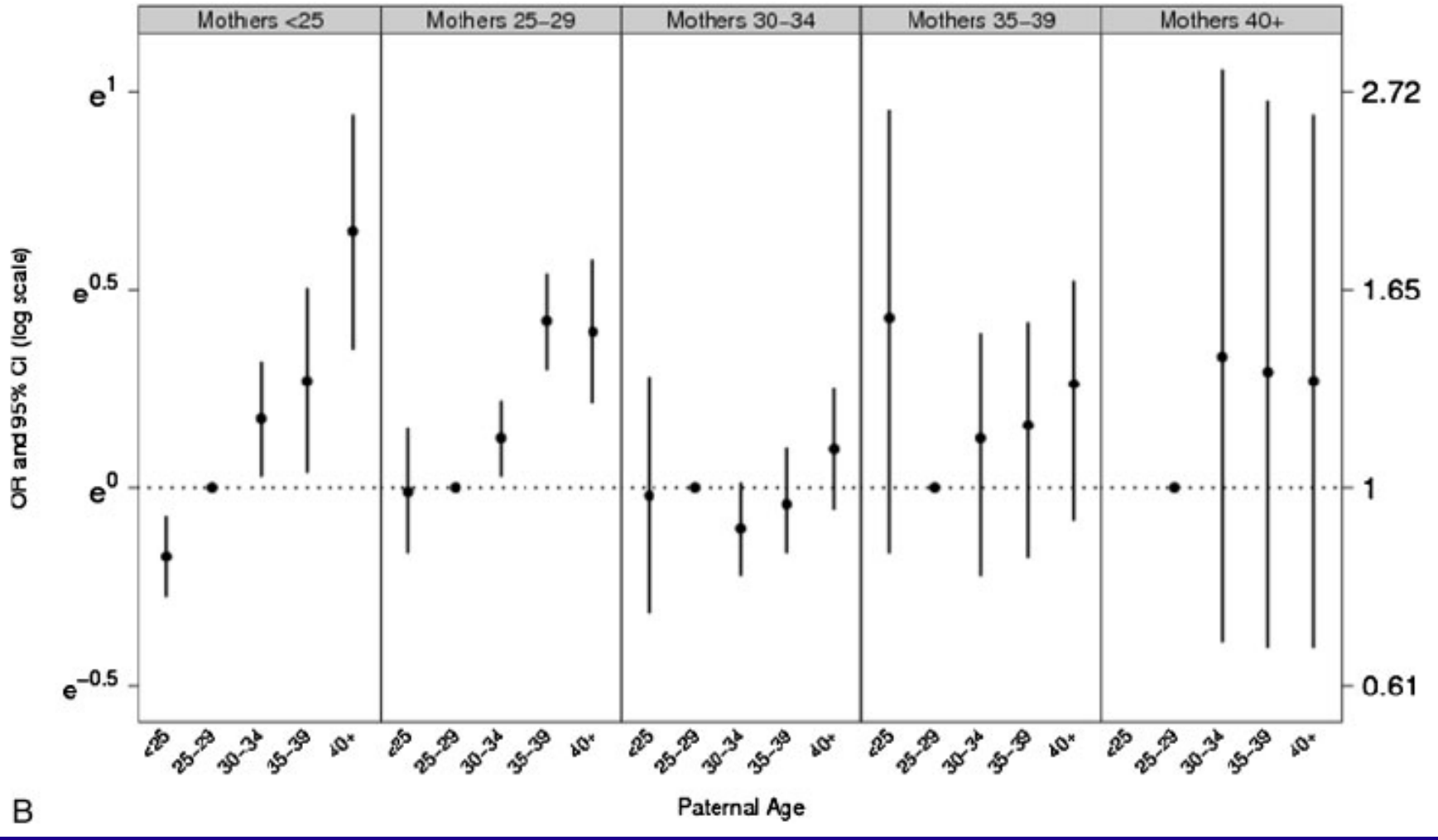

Goal

- To determine whether current blood Hg levels differ in children with autism or ASD as compared with typically developing (TD) children

Proportions exposed by case status

	Autism/ ASD N=249	Dev Delay (DD) N=60	Typical Dev (TD) N=143
Ate any fish	43%	68%	76%
Dental amalgams and chew or grind teeth	1.5%	2.4%	1.9%
Thimerosal-containing vaccine in last 90 days	3%	8%	5%
Nasal spray or earwax removal	19%	23%	13%

Hertz-Picciotto et al, Environ Health Persp 2009