Current Epidemiology of Childhood Autrum Spectrum Disorder (ASD) and Study of Environmental Risk Factors

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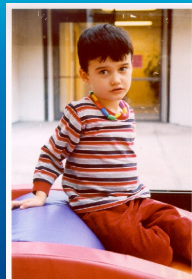Morgan Center Conference,
Science Panel 2014

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What are Autism Spectrum Disorders?

- No biologic "test" or marker, wide range of expression and severity

- Deficits in social communication and social interaction
- Restricted, repetitive patterns of behaviors, interests, or activities
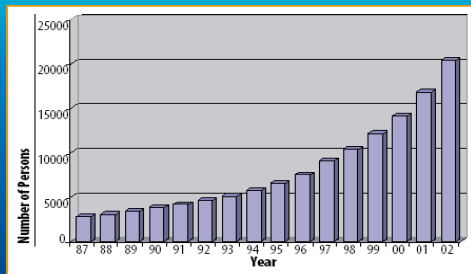
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How many people have Autism?

Department of Developmental Services, CA, 2003

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Best-estimate U.S. Prevalence

"*prevalence*" is the proportion of a population with the condition of interest at a given time

- First identified: 1 in 10,000 children
- 1970's-1980's: 1 in 2,000 children
- Mid '90's: 1 in 500
- Mid '00's: 1 in 150
- 2008 1 in 88 (8-yr olds)
- Most recent: 1 in 68 children (ASD) or 1.5%

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What is so hard about counting?

1. Finding or Defining Cases
   - Doctor Diagnosis or self-report?
   - What type of record (medical, school, lab) and access?
   - New case-finding by personal contact
2. What is the "population" and how many in it?
   - Specific place, time, group
   - Conduct a survey or count
   - Use existing data like census
3. Comparing 'rates'
   - Methods similar across time or place?
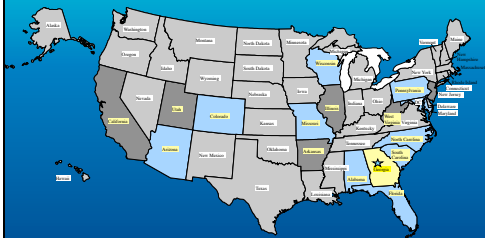   - Something else change?—like a new MD or service

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U.S.: Autism and Developmental Disabilities Monitoring (ADDM) Network

ADDM NET
Autism and Developmental Disabilities Monitoring Network

- CDC
- ADDM Phase 1 (2000-2006): 16 Sites
- ADDM Phase 2 (2006-2010): 11 Sites

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CA CADDRE Autism Surveillance

- Birth Prevalence—link to birth certificate to establish residency and birth year
- Single or multi-source ascertainment of ASD Cases

California CADDRE Surveillance

- Multi-Source Surveillance
- Single-Source Surveillanc

- Single source--statewide
  CA Dept of Developmental Services (DDS) client data base
- Multi-source—SF Bay Area
  DDS, Kaiser, clinics, specialists
  Dx before 9th (or 4th) birthday
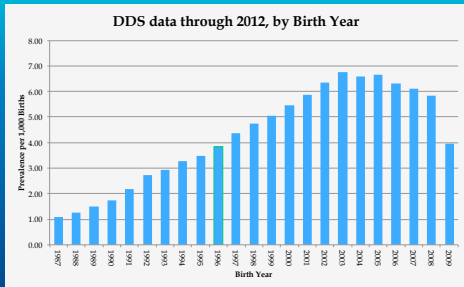 Review of health records (no Ed)

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Autism in California

DDS data through 2012, by Birth Year

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Autism in Santa Clara County

Autism Prevalence in DDS Data
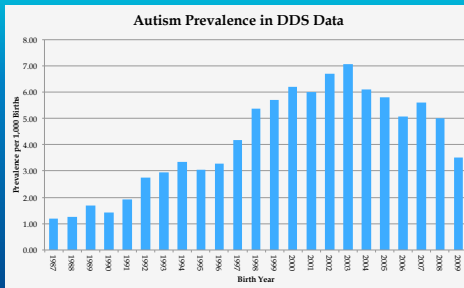
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ASD Prevalence by Maternal Race/Ethnicity, 1994 & '96 Births

Racial Group	#	Prev/1000 (95% CI)
White, non-hisp	362	5.6 (5.0 - 6.2)
Hispanic (any race)	**140**	**3.1 (2.6 - 3.6)***
Black	60	3.9 (2.9 - 4.9)
Asian	120	5.5 (4.5 - 6.5)
Other	75	5.2 (4.0 - 6.4)

Windham GC et al., JADD 2011

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ASD Prevalence by Parental Age, 1994 & 1996 Birth Years

*=p<0.05 from reference
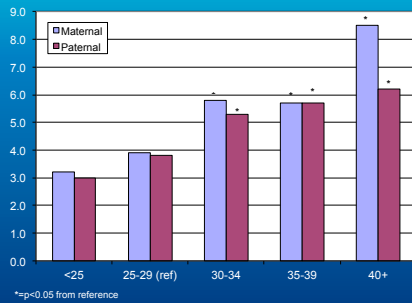
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Monitoring Early Childhood Autism (MECA)—Why?

- By monitoring the # of <4 year olds with ASD we hoped to:
  - obtain accurate counts and rates of ASD in young children in SCC
  - learn more about their characteristics
  - provide reports to help in planning services

- By conducting early developmental screening of children we hoped to:
  - facilitate early diagnosis in under-served populations
  - determine acceptance and feasibility of using screening tools
  - improve the accuracy of our counts
  - examine why Hispanic children seem to have lower rates of ASD

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ASD Prevalence in 4 year olds, SCC, MECA

Confirmed Cases				
Birth Year	ASD Cases	Births	Estimated Prevalence (per 1,000)	95% CI
2005	200	26,453	7.6	(6.5, 8.6)
2006	226	26,839	8.4	(7.3, 9.5)
Confirmed Cases plus ASD Clients at another RC (e.g. moved)				
Birth Year	ASD Cases	Births	Estimated Prevalence (per 1,000)	95% CI
2005	213	26,453	8.1	(7.0, 9.1)
2006	230	26,839	8.6	(7.5, 9.7)

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Which Non-genetic Factors Involved?

- Male gender (4-5x)
  - Hormone env?
- Advanced Parental Age—Genes or Env?
- Higher SES
- Racial differences
- Preterm birth
- Short inter-pregnancy interval

- Medications
  - SSRIs
  - Valproate, Thalidomide
  - Infertility treatment
- Vaccines—MMR, thimerosol
- Infectious or autoimmune diseases
- Gestational Diabetes
- Smoking
- Vitamin deficiency: folate, Vitamin D
- Chemical exposures

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Why so few studies of Environmental Chemicals?

- **Perceptions**
  - Entrenched camps of genetics, psychiatry, neuroscience (Grant funders – reviewers)
  - Management—"oh, parental age is a factor, then that must explain it!"
  - Which chemicals have been increasing so much as to cause the "epidemic"?
  - Epidemiology is not a hard science, but observational; no good autism lab models

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Studying Environmental Chemicals, cont.

Data Issues

- Hard to ask people, may not know or remember
- Exposure monitoring--designed for other uses
  - can we link for appropriate time and place?
- Most people exposed to some extent, how tease apart from multiple exposures?
- Biomarkers—have stored specimens from susceptible periods?

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Link to Existing Environmental Databases

- Hazardous air pollutants (HAPs)
- Criteria Air Pollutants
- Traffic Density data
- Water monitoring, disinfection by-products
- Pesticide use or applications
- Toxic release inventories

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National Air Toxics Assessment

Characterization of air toxics by US EPA:
- Nationwide assessment of chemicals not measured
- ~177 hazardous air pollutants (HAPs), plus diesel particulate matter (PM)
- Emissions from:
  - Stationary sources (major and neighborhood)
  - Mobile sources (road and non-road)
- Estimate airborne concentrations from outdoor sources

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First Autism Studies using NATA

- Link to surveillance data—
  - CA multi-source (N. CA) and single-source (S. CA)
  - N. Carolina and W. Virginia ADDM
- Use of existing data, so no recall and minimizes drop-out
- Attempt to examine prenatal and early life exposure (vs. current or at diagnosis)
- Found associations, but chemicals varied by site

Windham GC et al, EHP 2006;114:1438-1444
Kalkbrenner AE et al., Epidemiology 2010;21:631-641

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Limitations of HAPs Studies

- Exposure *estimates*, so some misclassification
  - Concentrations are modeled not measured
  - Annual averages, not available every year
  - Census tract level
  - Only have birth residence, not other addresses
- Chemicals correlated so hard to tease apart
- Other sources of exposures not included, nor data on potential routes of exposure
- Limited info on other factors that could contribute

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Recent and New Studies using NATA

- ADDM Surveillance data in New Jersey
  - Elevated odds (~4) in most severe ASD cases
  - For aromatic solvents and PAHs
- Nurses Health Study
  - Self-report of any autism dx in children born 1987-2002
  - Increased odds for metals, solvents and diesel PM
  - Gender effect, higher in males
- *U.S.--Perinatal Exposure to Air Pollutants (PEAP)*
- *Pittsburgh-- Study of Environmental Risk Factors for Childhood Autism*

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Traffic-related Air Pollution

- Autism data from CHARGE
  - On-going study in N. CA
  - Used residential history: each trimester, first yr of life
- Traffic Proximity
  - Distance from home to nearest freeway or major road
- Increased odds of ASD close to freeways
- Added criteria APs; found 2xASD risk in high quartile of NO_2, $PM_{2.5}$ and PM_{10} (preg & infancy)
- Interaction of genotype and NO_2

Volk HE et al. EHP 2011;119(6):873-7. Ditto JAMA Psych 2012. Ditto Epidemiology 2014

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Have Others Studied Traffic-related Air Pollution?

- LA County (Becerra TA et al. EHP 2012)
  - DDS data & air monitoring (at birth),
  - 12-15% ↑ASD/IQR of O_3 and $PM_{2.5}$; 3-9% for NO_2
- Taiwan (Jung C-R et al. PLOS one 2013)
  - Health insurance data & monitored AP in prior 1-4 yrs
  - ↑ASD with CO, O_3, NO_2, and SO_2, not PM_{10}
- NC and CA (Kalkbrenner A et al, SER 2013, Epid 2014)
  - ASD surveillance & monitored AP (birth), geospatial
  - ↑ASD with PM_{10} in 3rd trimester
- Nurses Health Study (unpublished)
  - Positive associations

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Early Markers of Autism (EMA)

- Takes advantage of stored specimens
- DDS autism data in 2 counties compared to 2 control groups (DD and unaffected)
- Use biospecimens to measure:
  - Immune factors, hormones
  - Genetic markers
  - Chemicals—mercury, PBDEs, PCBs, DDE, PFCs
- Just added component to look at traffic and criteria air pollutants
- Expensive—multiple phases of funding with many collaborators (Croen LA, PI, Kaiser DOR)

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Exposures at Work

- CHARGE pilot study (McCanlies EC et al. JADD 2012)
  - Mothers and fathers combined, prenatal-breastfeed
  - IH assessment: ↑ ASD w/ lacquer, varnish, xylene
  - Self-report: ↑ ASD w/ solvents, asphalt
  - None significant when control for multiple comparisons
- CA CADDRE (Windham GC et al. Autism Res 2013)
  - SF Bay area multi-source ASD surveillance
  - Occupation at birth, 8 exp assigned
  - ASD ↑ 2x exposed mothers; exhaust and disinfectants
  - Paternal exp n.s. (High solvents OR=1.4)
  - No interaction of maternal and paternal exposures
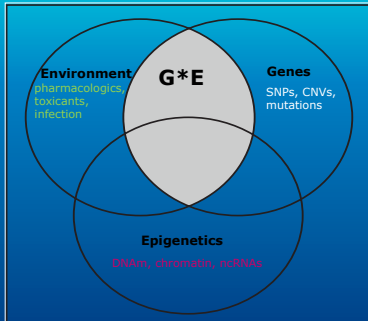
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No Smoking Gun ⟹
Gene-Environment Interactions

Environment
pharmacologics,
toxicants,
infection

G*E

Genes
SNPs, CNVs,
mutations

Epigenetics
DNAm, chromatin, ncRNAs

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Thank You!

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SEED Research Goals

Study to Explore Early Development

- Characterize autism behavioral phenotype and associated developmental, medical and behavioral conditions
  - Special focus on identifying distinct symptom profiles to guide etiologic analysis
- Investigate genetic and environmental risk factors
  - Infectious/Immunologic
  - Obstetric
  - Hormonal
  - Gastrointestinal
  - Socio-demographic

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SEED, cont.

Study to Explore Early Development

- Collection of **biospecimens**
  - blood and buccal DNA
  - Children and parents

- Comprehensive **phenotyping**
  - ADOS and ADI-R, Vineland, Mullen

- Prenatal environmental **exposures**
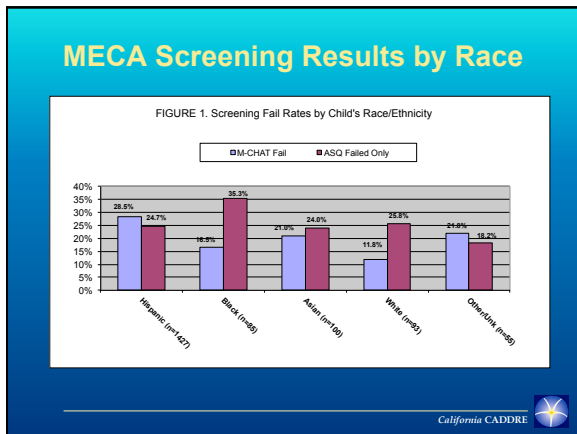 - Maternal interview
  - Medical records

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MECA Screening Results by Race

FIGURE 1. Screening Fail Rates by Child's Race/Ethnicity

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International Collaboration for Autism Registry Epidemiology (iCARE)

Population-based, national health registry data

To study prevalence and risk factors for autism

- Norway
- Sweden
- Finland
- Denmark
- Israel
- W. Australia
- *United States-- CA*

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