

***Environmental Epidemiology:
Centers for Autism and Developmental
Disabilities Research and Epidemiology
(CADDRE)***

**Autism and the Environment:
Challenges and Opportunities for Research – A
Workshop
April 18-19, 2007**

**Forum on Neuroscience and Nervous System Disorders
Institute of Medicine**

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Congressional Guidance

Children's Health Act of 2000

“establish autism surveillance and research programs to address the number, incidence, correlates, and causes of autism and related developmental disabilities”

- u “National Autism and Pervasive Developmental Disorders (PDD) Surveillance Program”
- u “Centers of Excellence in Autism and PDD Epidemiology”



CDC's Autism Programs

- n Autism and Developmental Disabilities Monitoring Network
Surveillance



- n Centers for Autism and Developmental Disabilities Research and Epidemiology
Research



- n "Learn the Signs Act Early"
Prevention

Learn the Signs. Act Early.





Surveillance Goals:

- n Accurate and comparable **population-based estimates of the prevalence** of autism spectrum disorder (ASD) in selected regions of U.S.
- n **Describe the characteristics of** children with autism
- n Examine **trends** in prevalence



ADDM Strengths

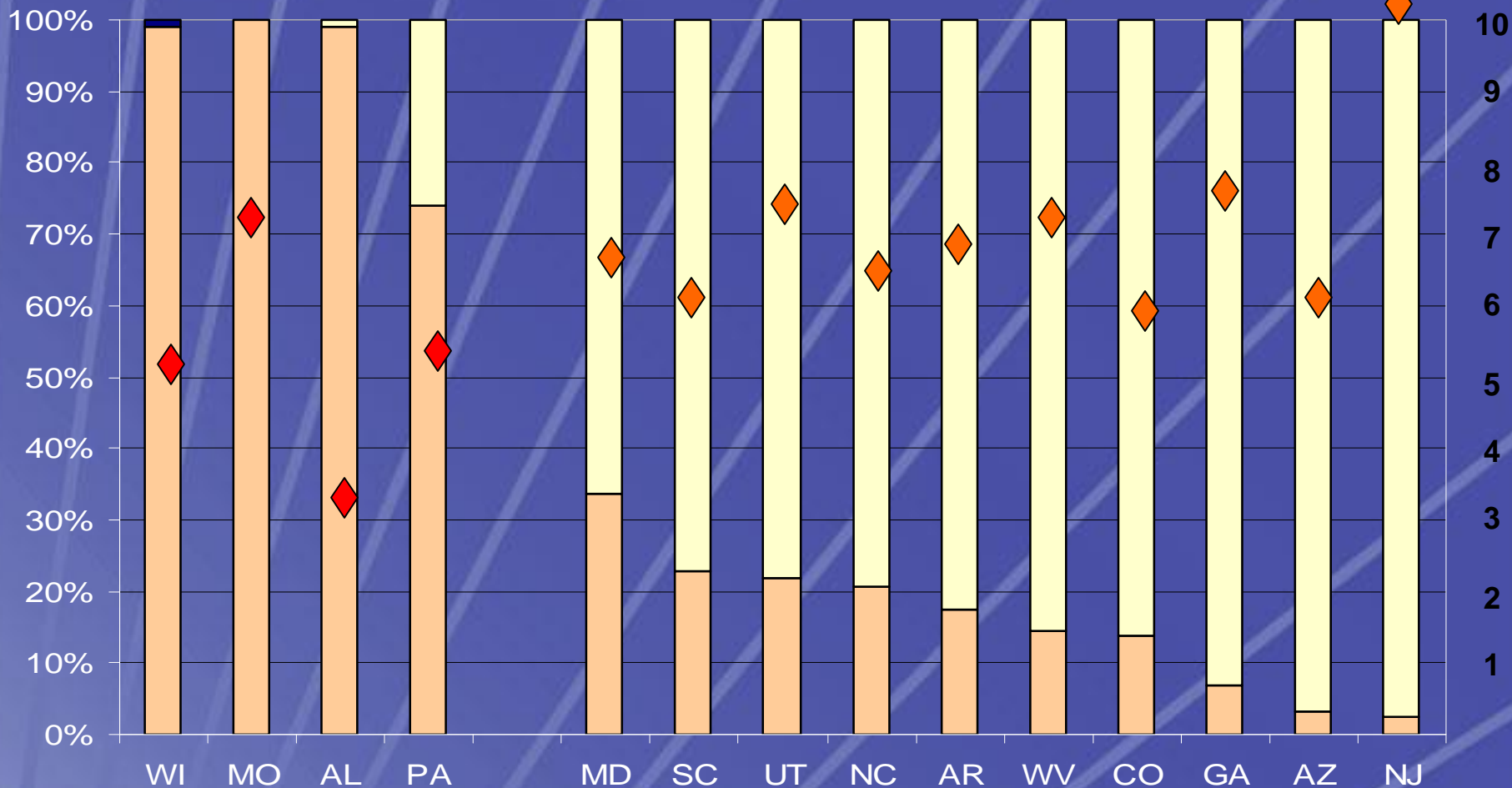
- n Common case definition
- n Common case identification approach in majority of sites
- n Multiple sites: geographic and community diversity
- n Large population base
 - u 10% of US 8-year olds in 2002*
 - *varies by study year
- n Ongoing



Role of ADDMM Surveillance in Environmental Epidemiology

- n Better understanding of occurrence patterns
 - u Sources of variation in prevalence:
 - « “Environmental”
 - Geography/community
 - Sociodemographic factors
 - Race/ethnicity
 - Sex
 - parental age, education
 - « Methodologic
 - source of information on cases

ASD Prevalence in 8-yr olds: 6.6 per 1000 ADDM 2002



nHealth Sources Only: 5.1 per 1000

nEducation Sources: 7.2 per 1000



Role of ADDM Surveillance in Environmental Epidemiology

- n Baseline reference rates
 - u Comparative data for:
 - « Time/space trends
 - « Evaluation of intervention/prevention
 - « “Cluster” investigations
 - u Inform health policy
 - « Public health burden
 - « Vulnerable “at risk” groups

Role of ADDMM Surveillance in Environmental Epidemiology

- n Provide clues regarding potential “environmental” factors
 - u Social/economic class gradients?
 - u Demographic gradients?
 - u Geographic gradients?
 - u Race/ethnic group gradients?

Gradient may be marker for associated environmental exposure (e.g., due to lifestyle, other exogenous factors), assuming methodologic biases are accounted for

“Environment” is a complex mixture to disentangle:

Which components cause disease

- ┆ Physical
 - « Features: air, water, terrain
 - « Venue: community, home, workplace
- ┆ Biologic
 - « Exogeneous
 - « Endogenous
- ┆ Lifestyle
 - « Diet
 - « Activity

⇒ Not single components, but combined in pathways

ASD phenotypic variation ⇒ multiple outcomes

Contributions by genetic factors

- ┆ Susceptibility (or resistance) to environmental factors



To address these analytic challenges:

- ┆ Well designed population based studies
 - « Minimized biases in participant selection and information
 - « Adequate sample size and study power
 - « High quality data collection
 - phenotype
 - “environment”
 - biologic sampling



CADDRE Goals

First Funding Cycle (2001-06)

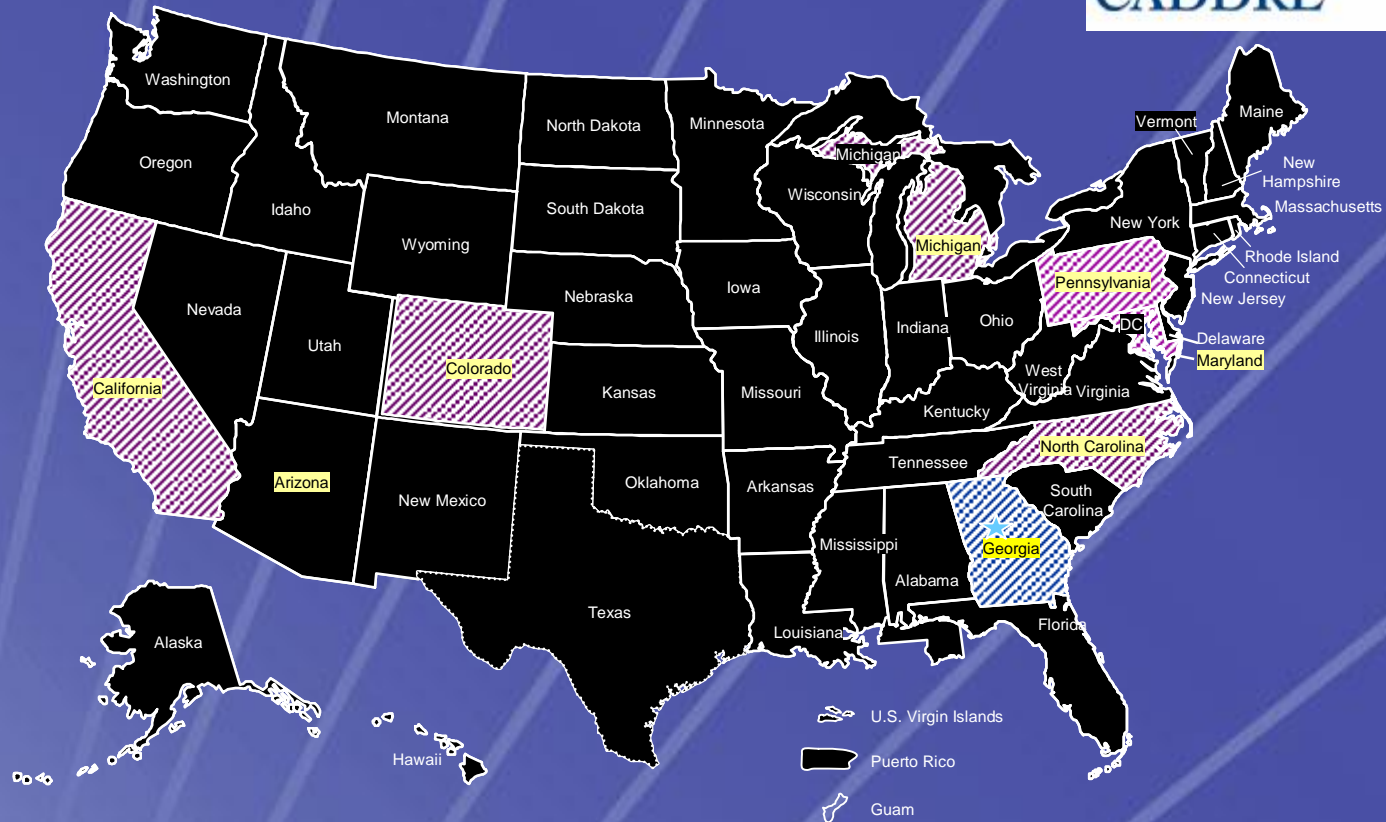




- n Collaborative epidemiologic study:
Study to Explore Early Development (SEED)
 - u Designed to fill gaps:
 - « Understanding of autism epidemiology
 - « Federally-funded autism programs with an **explicit population-based epidemiologic focus**

- n Surveillance (members of ADDM network)

- n Site-specific research





-  CADDRE grantees, including Data Coordinating Center
-  CDC, 6th CADDRE site



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SEED



- n Main research areas
 - u ASD phenotypic variation
 - « Subgrouping for etiologic analysis
 - u Infection and immune function, including autoimmunity
 - u Reproductive and hormonal features
 - u Gastrointestinal features
 - u Genetic features
 - u Sociodemographic features



SEED



u Other areas of interest:

- « Lifestyle in pregnancy: smoking, alcohol, illicit drug use
- « Select mercury exposures
- « Occupational exposures
- « Sleep features
- « Hospitalizations
- « Injuries



SEED



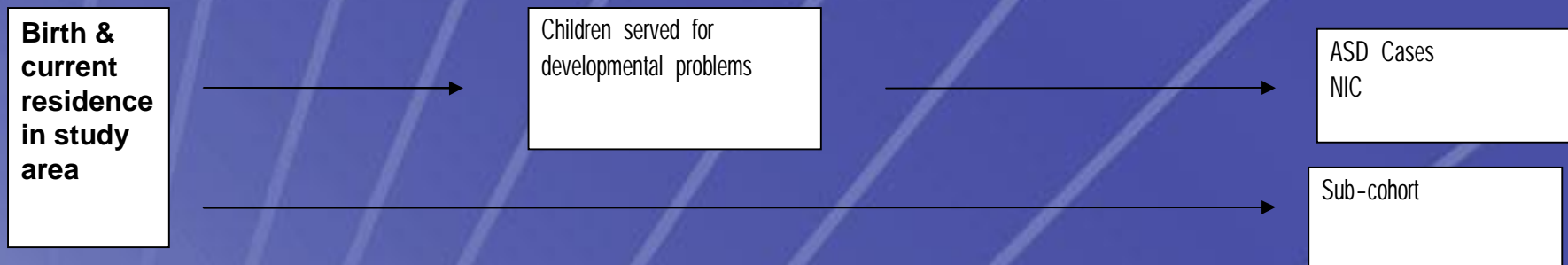
- n Case-cohort study design: population-based ascertainment
 - u ASD cases
 - u Neurodevelopmentally Impaired Comparison Group (NIC)
 - u Sub-cohort



SEED



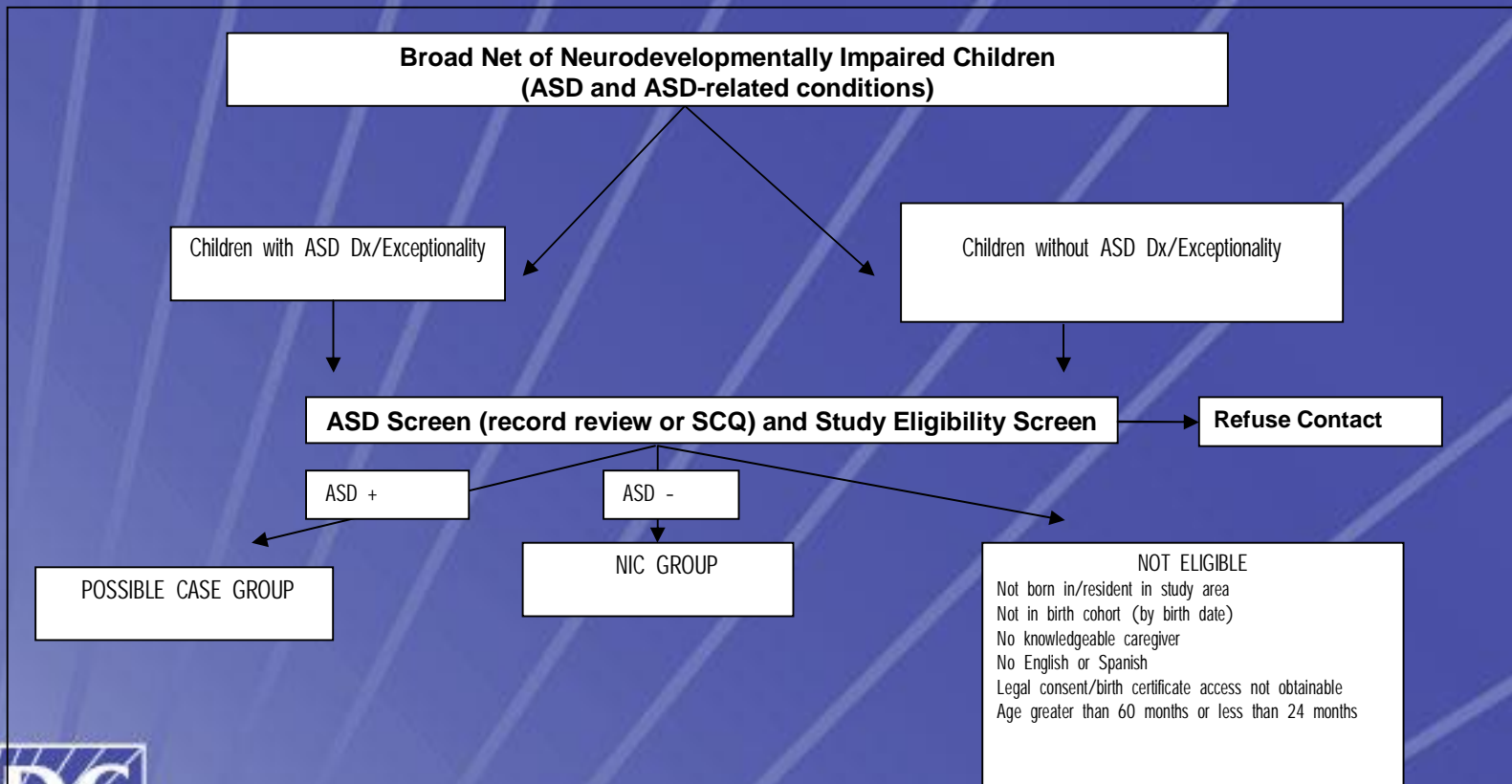
Overview of study design



SEED



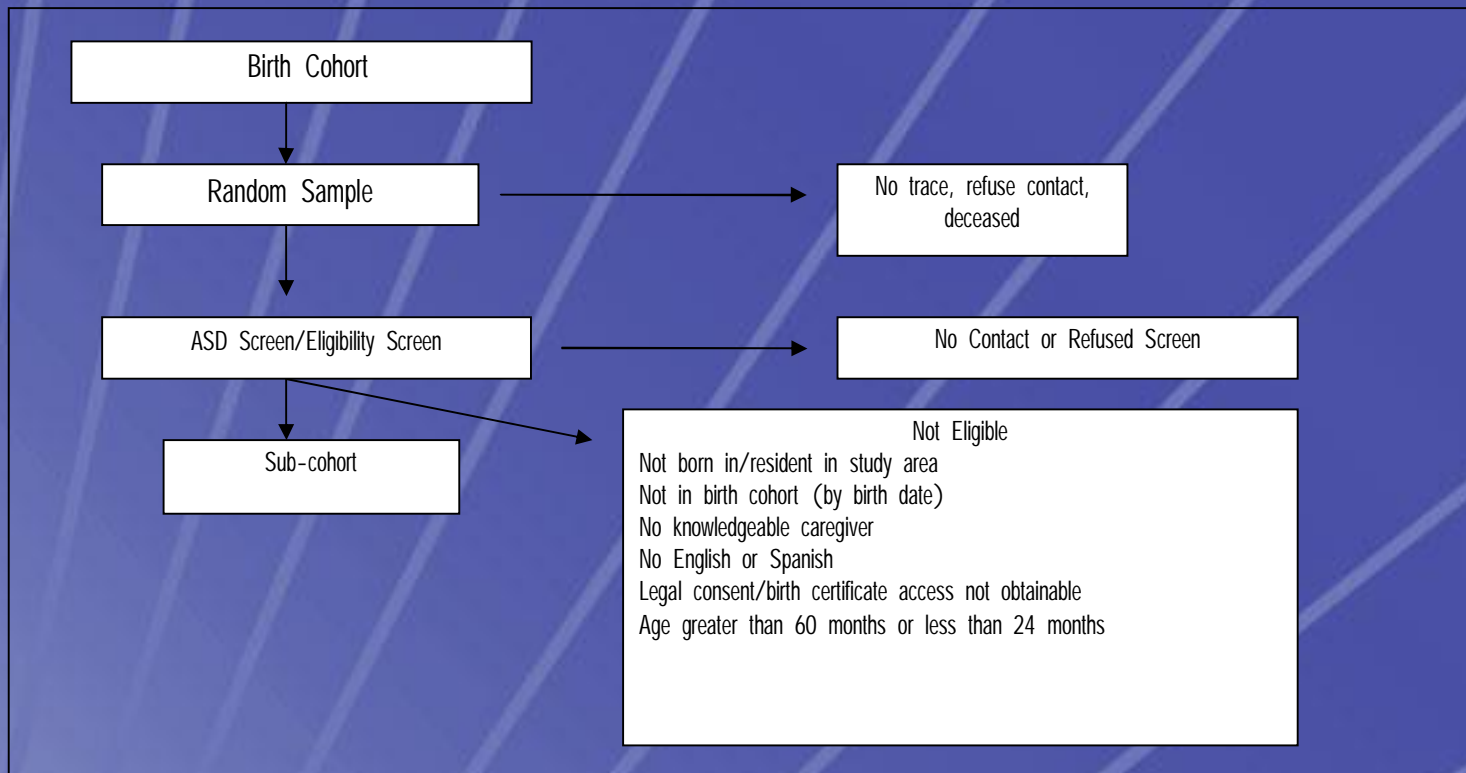
Identification of possible Cases and NIC



SEED



Identification of Sub-cohort



SEED



Case Sample Size Estimates

n	Birth cohort (2 years)	485,000
n	Expected min prevalence	3.2 per 1000
n	N of ASD (w/wout prev dx)	1550
n	1550 cases x 80% contacted/eligible =	1240 invited ASD cases
n	1240 invited x 73% participation =	900 enrolled ASD cases
n	900 enrolled x 72% complete data =	650 ASD cases with complete data

Comparable sample size of NIC and Sub-cohort (1:1 ratio with cases)

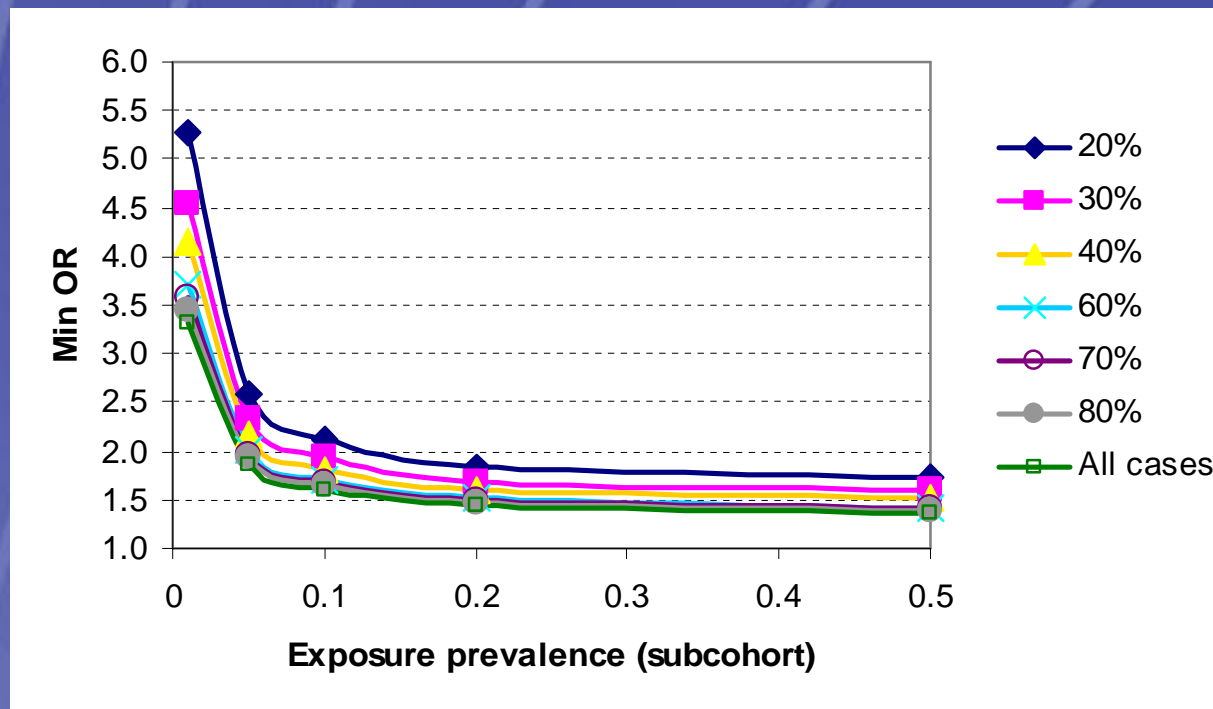
2700 enrolled families

1950 enrolled children (families) with complete data collection



SEED

Study Power Estimates



SEED Data Collection



- Caregiver Interviews
- Self-administered questionnaires
- Medical record abstraction
 - Prenatal, L&D
 - Select records: 3 yrs preconceptional
 - Neonatal, 3-yrs postnatal
- Child clinical evaluation and physical exam
- Biologics:
 - Buccal cells, blood (parents, child)
 - Hair (child)

TOTAL PARTICIPANT BURDEN

Case: 11 hours

NIC/Sub-cohort: 7 Hours



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Biologics: buccal, blood, hair



- n Proteins, genes, mercury
- n No specific a priori candidate proteins/genes
 - u Accommodate new discoveries/hypotheses
 - u Peripheral blood collection protocol allows a variety of analytes to be tested
 - « four 5 ml tubes of different types (EDTA purple top, SST red top, ACD yellow top) to permit analyses of serum, plasma, and cell line immortalization
 - « 1 ml of residual specimen from the butterfly tube placed on filter paper cards
 - u Informed consent form includes provisions for retaining sample and future testing of biomarkers



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Biologics: buccal, blood, hair



Protein and gene candidates:

- u Immune and hormone function, including autoimmunity
 - « e.g. auto antibodies to CNS proteins
- u Specific biomarkers involved in CNS, immune, and endocrine development and regulation
 - « e.g., immunoglobulins, cytokines, neuropeptides, neurotrophins, and neurotransmitters
- u Epigenetic influences



may modify, or be modified by, environment



SEED Strengths



#1

Only ASD multi-site study focusing on etiology

↳ **Diverse communities and populations**



Enhance generalizability to US population



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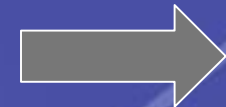
SEED Strengths



#2

Population-based identification of subjects

- u Multiple sources within each study area
- u Diagnosed AND undiagnosed cases
 - « important consideration given target age



Enhance representativeness of sample

Reduce ascertainment biases

(cases and sub-cohort)



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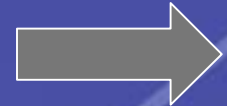
SEED Strengths



#3

Two comparison groups

- u Affected (NIC) and Unaffected (sub-cohort) individuals



Detect biases due to differential recall
reduce exposure misclassification



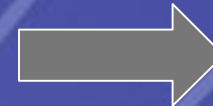
SEED Strengths



#4

Uniform protocol

- u Subject inclusion criteria
- u Data collection protocols
- u ASD confirmation



Can pool data across sites

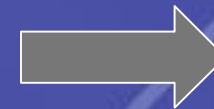


SEED Strengths



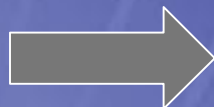
#5

Largest sample size planned to date



Enhanced study power

Permits phenotypic subgroup stratification for etiologic analyses



reduce imprecision due to outcome misclassification



SEED Strengths



#6

Research domains

- u Multiple domains
- u Overlapping and non-overlapping domains with other epi studies, e.g., CHARGE Study



Can explore multiple causal pathways

Can explore multiple points in single pathway, e.g., economic status and ART

Can replicate analyses from prior studies



SEED



Primary Roles in Environmental Epidemiology

Better understanding of role of a variety of “environmental” and genetic factors in ASD

- Referent for studies focused on other specific toxicologic factors
- Potential to expand array of environmental factors through data linkages or added data collection

Both hypothesis-testing and hypothesis-generating

- Inform data collection and analysis in other studies, e.g., National Children’s Study



Beyond ADDM and SEED: single studies can't meet all environmental epi needs

Data pooling/coordination across studies: new and existing studies, in the US and abroad

- ┆ Enhance sample sizes (meta-analyses, raw data)
 - ┆ Gene/Environment main effects, interaction
 - ┆ e.g., relatively low risk but widespread exposure may have public health significance but difficult to detect association
- ┆ Data collection at multiple points
 - ┆ During development – prospective studies (US/NCS, Denmark/Norway cohorts)
 - ┆ Over time (Scandinavian registries)

Statistical methods to handle data quantity



Thank you!



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