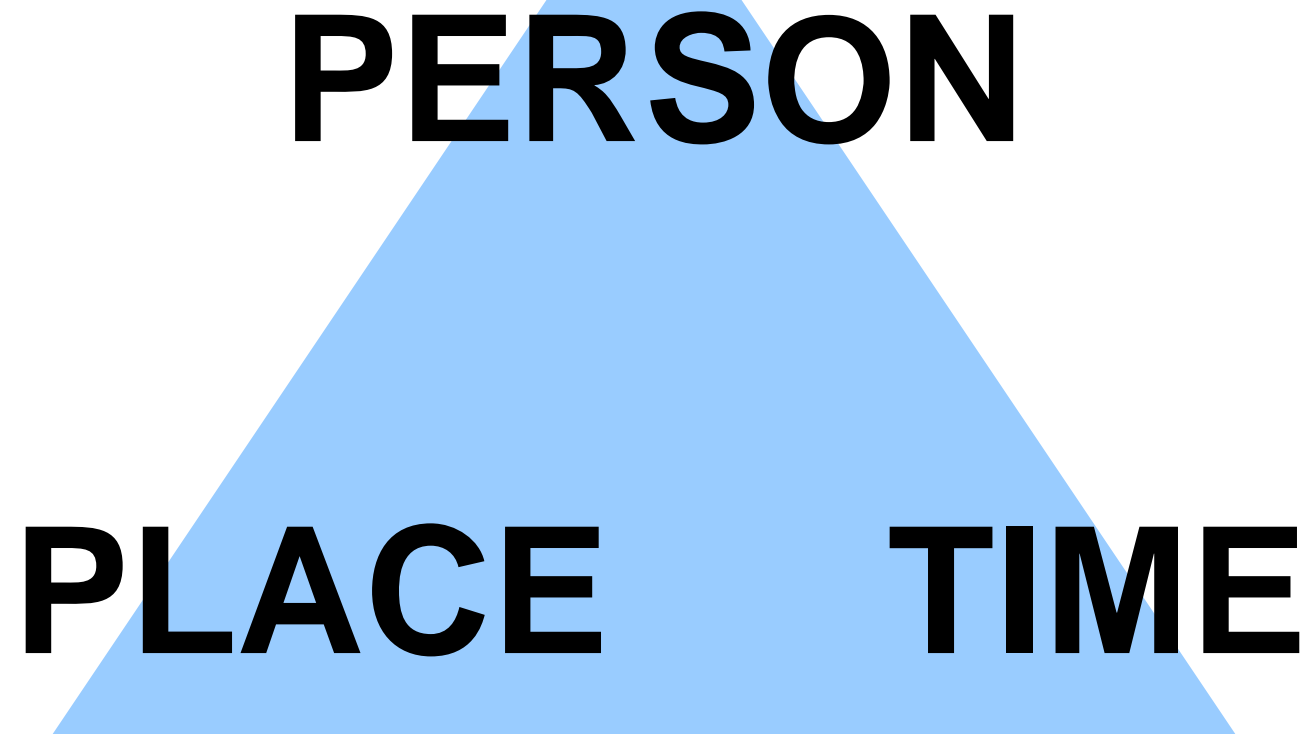


---

# **Environmental Exposures in Autism: International Studies**

**Craig J. Newschaffer, Ph.D.**  
**Department of Epidemiology and Biostatistics**  
**Drexel University School of Public Health**  
**Philadelphia, Pennsylvania**



---

## **“Place” in analytic epidemiology**

- w Classic application: environmental vs. genetic individual-level causes
- w Location-specific opportunities

---

## Classic application

- w Rule out bias
- w Consider extent and magnitude of variation
- w Genetic vs. environmental factors
  - Migrant studies
    - Change in risk post-migration suggests environmental contribution
    - External environment vs. sociocultural environment?
  - Ethnic variation
    - Difference in risk across ethnic groups within same location suggests genetic contribution
    - Genetics vs. sociocultural environment?
- w Cautious interpretation of ecologic associations

## Age standardized prostate cancer incidence and mortality rates per 100,000

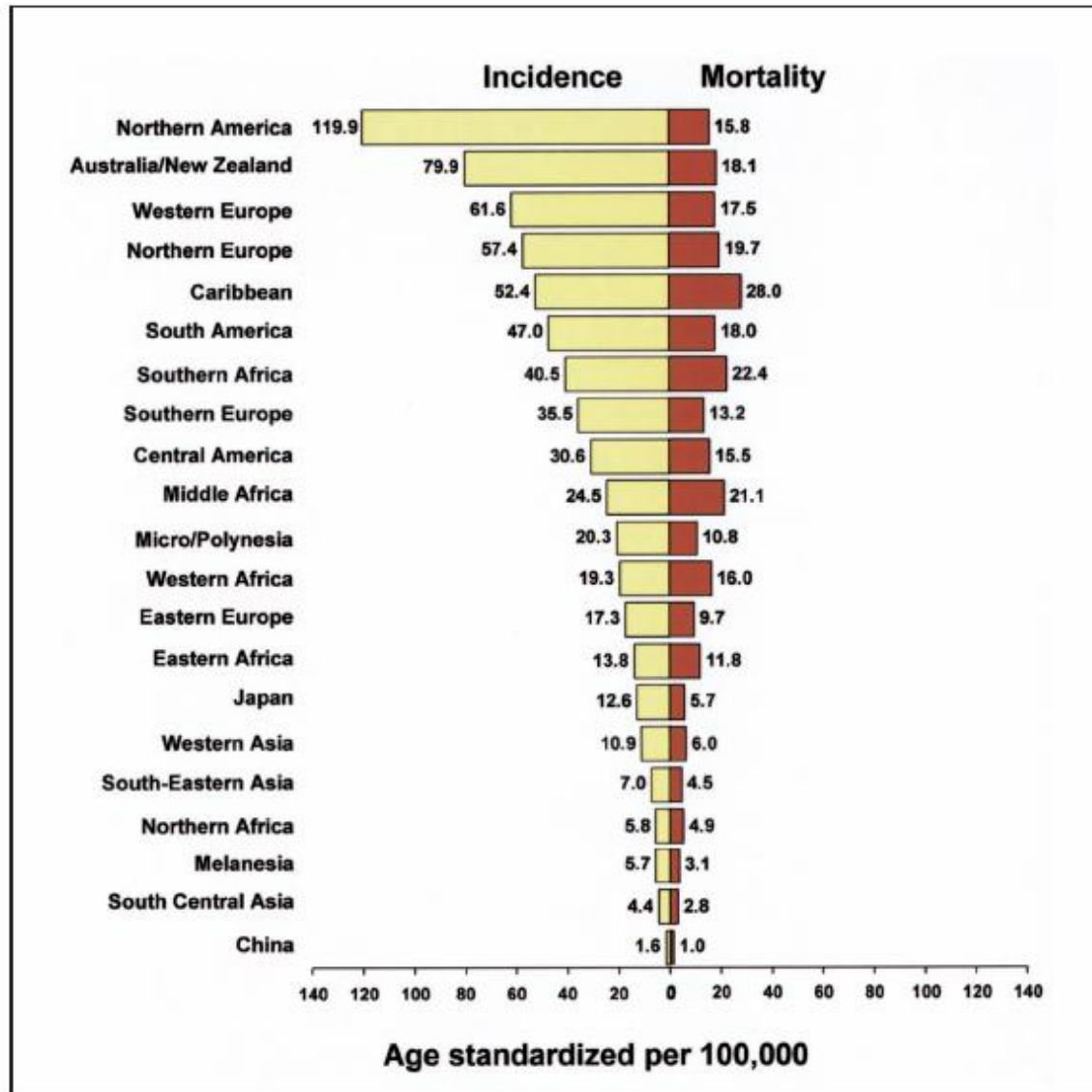
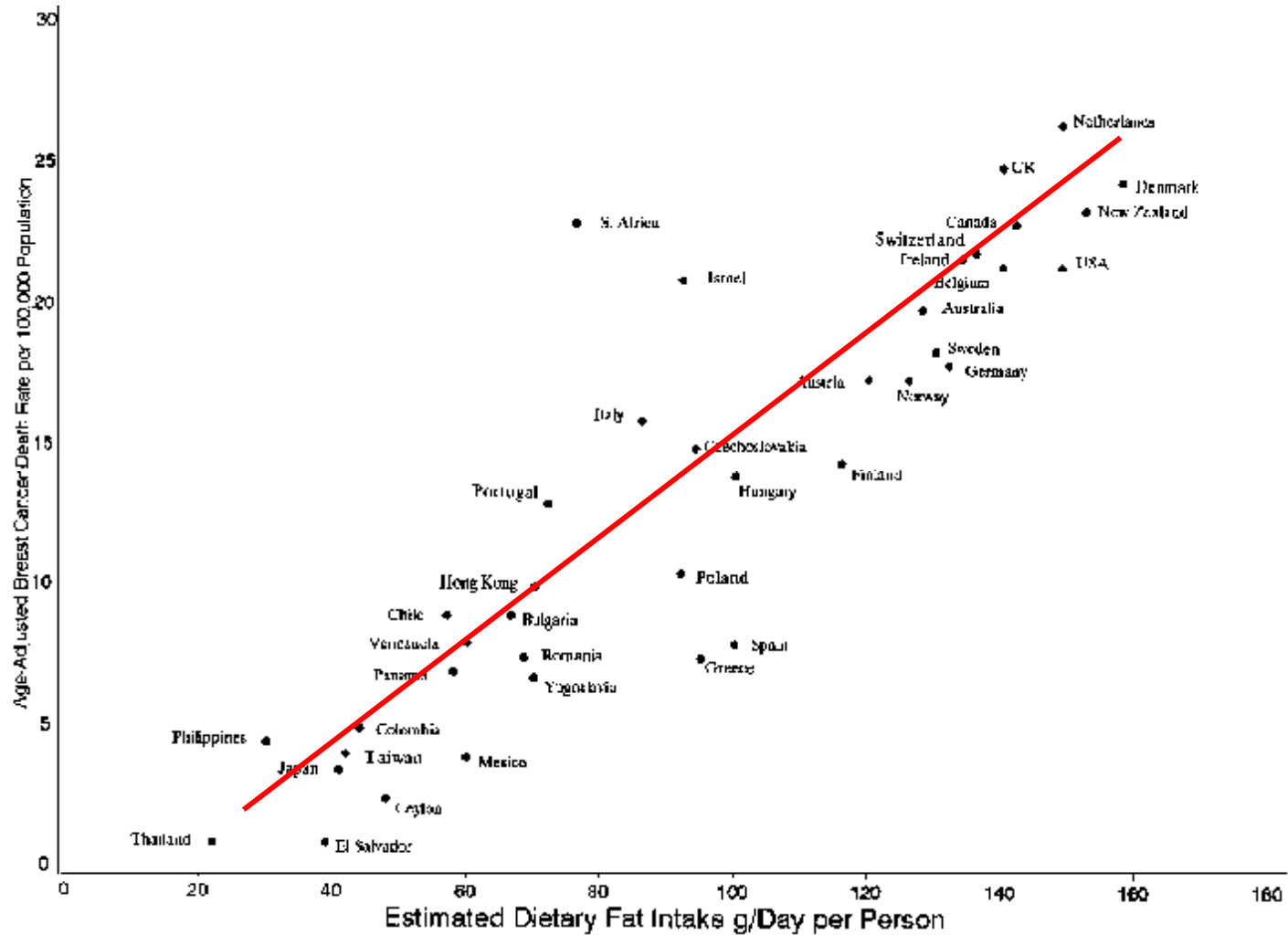


FIGURE 9 Age-standardized Incidence and Mortality Rates for Prostate Cancer. Data shown per 100,000.

Parkin DM et al *CA Cancer J Clin* 2005

# National age-adjusted breast cancer mortality rate by average dietary fat intake



Carroll et al. *Prog Biochem Pharmacol*, 1975

---

## Location-specific opportunities

- w Higher background exposure or outcome prevalences increase statistical power to detect comparable effect

## Demographic and exposure characteristics of mothers in three cohort studies of prenatal PAH exposure and fetal growth

Demographic variables	Krakow Caucasians ( <i>n</i> = 340)	NYC African Americans ( <i>n</i> = 168)	NYC Dominicans ( <i>n</i> = 212)
Maternal age (years)	28 ± 4 (18–36)*	24 ± 5 (18–36)	25 ± 5 (18–38)
Prepregnancy weight (kg)	58 ± 9 (40–118)	74 ± 20 (44–149)*	63 ± 13 (40–112)
Maternal height (cm)	165 ± 6 (144–180)	164 ± 9 (132–183)	161 ± 8 (127–178)*
Maternal education [ <i>n</i> (%)]			
< High school	36 (11)	54 (32)	71 (35)
High school graduate	90 (27)	74 (44)	87 (42)
> High school	214 (63)*	40 (24)	48 (23)
Frequent intake of PAH-containing foods [ <i>n</i> (%)]	49 (14)	54 (32)*	30 (14)
Maternal personal exposure to Σ8 c-PAHs (ng/m <sup>3</sup> )	39.05 ± 47.63 (1.80–272.18)*	3.34 ± 2.92 (0.52–22.10)	3.72 ± 3.90 (0.27–36.47)

## Characteristics of children in two cohort studies of lead exposure and IQ

Characteristic	Port Pirie (n = 324)	Rochester (n = 182)
Percent female <sup>a</sup>	174 (53.7)	89 (48.9)
Birth weight <sup>b</sup> (g)	3,393 ± 502	3,226 ± 506
Gestation at delivery <sup>b</sup> (weeks)	39.9 ± 1.7	39.1 ± 1.8
Birth order <sup>b</sup>	2.0 ± 1.1	2.4 ± 1.4
IQ test	WISC-R	WPPSI
IQ score <sup>b</sup>	106.0 ± 13.7	84.9 ± 14.4
Age at IQ testing (years)	7	6
Blood lead concentrations <sup>c</sup>		
Concurrent blood lead	13.0 (6.0–24.0)	4.0 (1.5–12.0)
Peak blood lead	27.0 (15.0–46.0)	9.0 (3.5–23.3)
Early childhood	20.5 (11.0–33.3)	5.8 (2.4–13.1)
Lifetime mean	18.6 (10.8–30.2)	5.5 (2.4–12.8)
Peak blood lead < 10 µg/dL <sup>a</sup>	0 (0.0)	103 (56.6)
Peak blood lead < 7.5 µg/dL <sup>a</sup>	0 (0.0)	69 (37.9)

## Location-specific opportunities

- w Higher background exposure or outcome prevalences increased statistical power to detect comparable effect
- w Different genotype prevalences
  - Potential enhanced statistical power to identify genes
  - May allow for identification of full range genes
- w If there is GxE interaction...
  - Exposure main effect more detectable when background susceptibility is higher
  - Genetic main effect more detectable with higher background exposure
  - GxE interaction more detectable with higher genotype and exposure prevalence

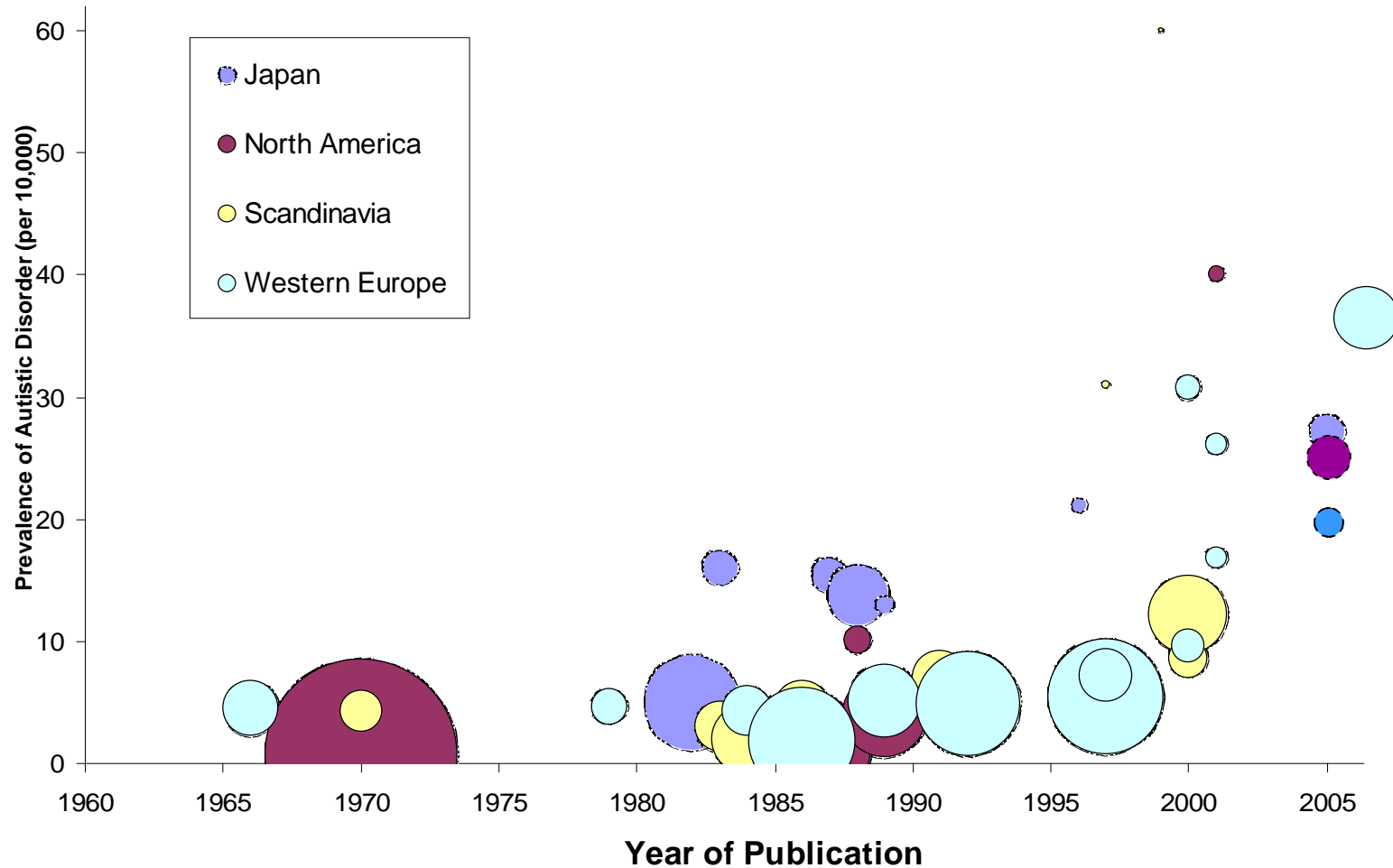
---

“We.. ...question the universality of Infantile Autism... Our research of the literature has convinced us that infantile autism appears to be an illness of Western Civilization... the illness seems to be quite infrequent in Latin American countries, Africa, and India...”

-VD Sanuna

(Int J Soc Psychiatry, 1984)

## Autism/Infantile autism/autistic disorder prevalence estimates from published epidemiologic studies



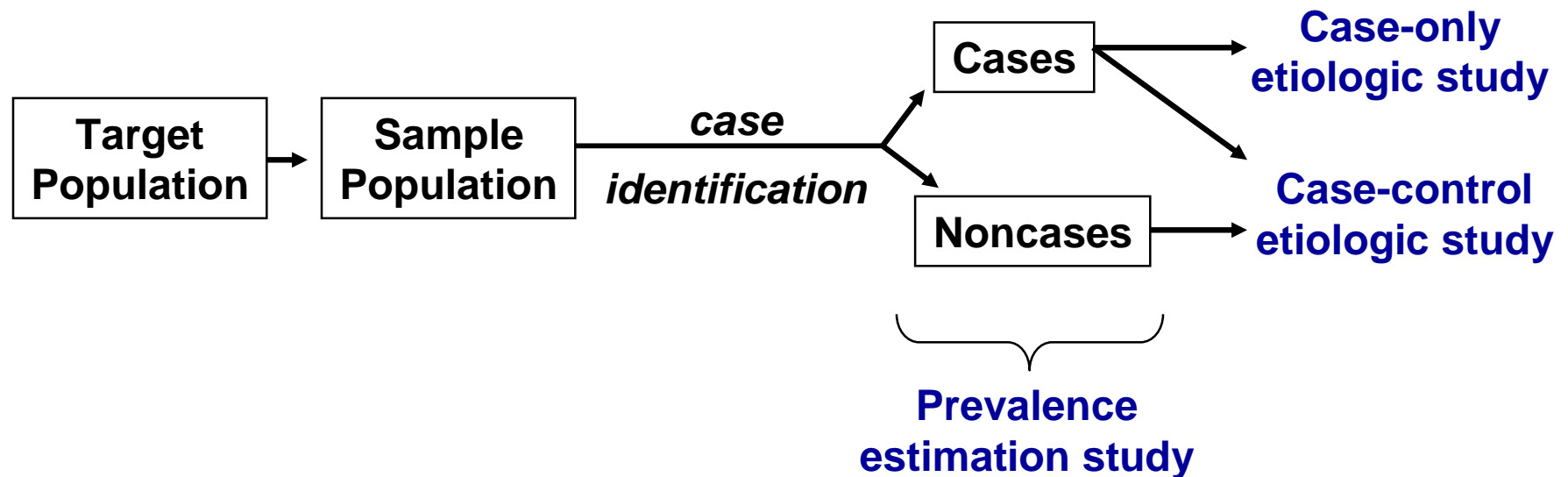
# Nations with autism prevalence estimation studies completed, in process, or in planning stages



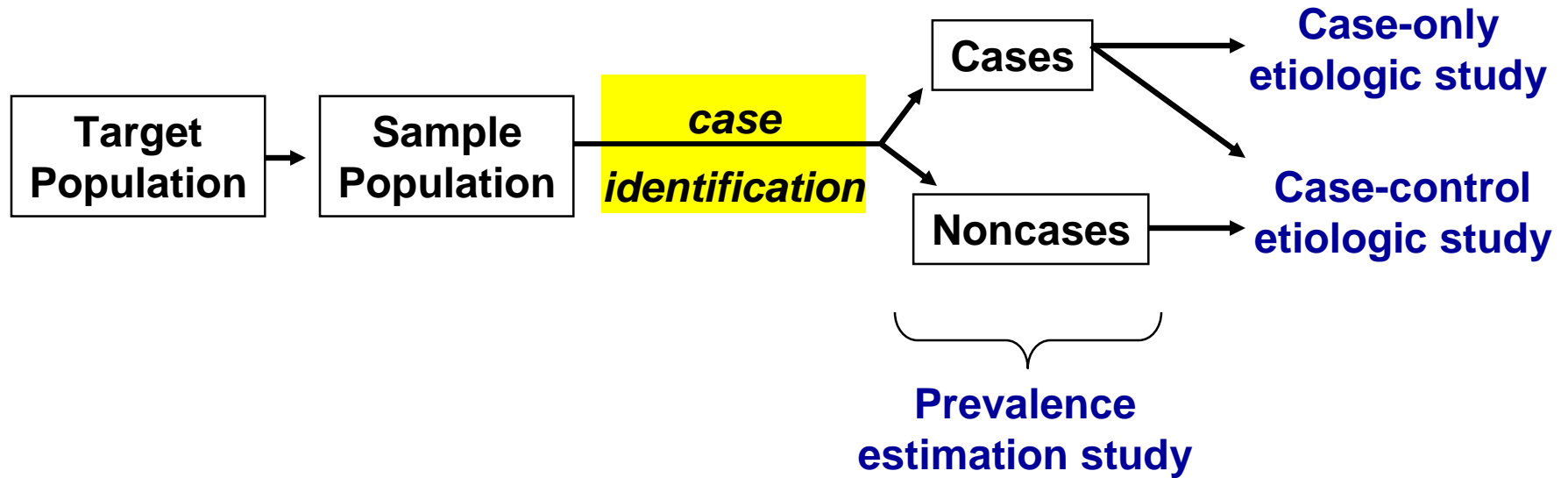
● High Income  
● Developing

# Study designs in international epidemiologic research on autism

- w Free-standing prevalence surveys
- w Free-standing etiologic studies
  - Retrospective (case-control, case-cohort)
  - Prospective (birth cohort)
- w Combined designs:



# Combined designs



## Case identification approaches

- Registries
- Service systems/records
- Population screening

**High income  
(some developing)**

**Developing  
(some high income)**

---

## The question of bias...

- w Will heterogeneity across case-identification approaches affect inferences?
- w Within case-identification approaches, are there substantive cross-national differences?
  - Registry and records-based approaches: community diagnostic tendency
  - Population screening approaches: language and cultural issues in adapting screening and diagnostic confirmation tools

## Language/cultural issues: examples from China pilot study

### w Language

- No distinction between singleton/plural or past/present tense
- Specific wording issues (e.g. “positively” = looking forward + appropriately + happily)



### w Cultural

- Child behavior:
  - Gestures are culturally discouraged
  - Persistence highly valued
- Objects: dinosaurs, traffic lights, drainpipes, timetables

---

## Moving forward...

- w In disease frequency studies, we need to maximize methods homogeneity, characterize methods heterogeneity
- w It is likely that initial analytic epidemiologic studies in developing countries will incorporate broad arrays of exposures
- w Leads from basic science, clinical science, or other epidemiologic work is needed to justify location-specific initiatives focused on specific exposures
- w Gene-finding studies will likely be motivated by the notion that important functional variants might be more common in populations of other nations
- w Assuming GxE interaction is important, there can be added motivation for gene-finding studies in nations where neurotoxic exposures differ or where levels are higher

# Thanks to:

## International Epi Symposia

- w Autism Speaks
- w CDC
- w Participating  
investigators

## China pilot: US

- w Li-Ching Lee
- w Rebecca Harrington
- w Angie David
- w Nora Lee
- w Rebecca Landa
- w Cathy Lord
- w WPS
- w NIH - FIC

## China pilot: China

- w Hong Wang
- w Yangqing Guo
- w Xiaoling Yang
- w YueQin Huang
- w AnNing Ma
- w ShaoYun Song
- w AiGuo Zhang
- w Township and Village  
Health and Family  
Planning Staff, Jun Bu  
Kou Township
- w Parents and children  
who participated

# Genetic vs.. environmental factors...

**TABLE 2. Estimated prevalence\* of autism spectrum disorders (ASDs) among children aged 8 years, by site and race/ethnicity — Autism and Developmental Disabilities Monitoring Network, 14 Sites, United States, 2002**

Site	Total no. in study area	Total no. with ASDs	Prevalence										
			Overall†		White, non-Hispanic		Black, non-Hispanic		Hispanic		A/AN§		A/PI¶
			Rate (95% CI)**	Rate (95% CI)	Rate (95% CI)	Rate (95% CI)	Rate (95% CI)	Rate (95% CI)	Rate (95% CI)	Rate (95% CI)	Rate (95% CI)	Rate (95% CI)	Rate (95% CI)
<b>Sites with access only to health records</b>													
Alabama	35,472	116	3.3 (2.7–3.9)††	3.3 (2.6–4.1)	3.4 (2.4–4.8)	1.9 (0.5–7.7)	—§§	—					
Missouri¶¶	28,049	205	7.3 (6.4–8.4)	7.7 (6.5–9.0)***	4.7 (3.4–6.5)***	1.8 (0.3–13.0)	—	7.1 (2.7–19.0)					
Pennsylvania	21,061	111	5.3 (4.4–6.4)	7.6 (5.7–10.2)****	4.2 (3.2–5.6)***	4.7 (2.8–8.0)†††	—	1.2 (0.2–8.2)					
Wisconsin	35,126	181	5.2 (4.5–6.0)	5.9 (5.0–6.9)****	3.7 (2.5–5.5)***	0.3 (0.0–2.1)†††	5.2 (0.7–36.8)	3.8 (1.4–10.1)					
<b>Sites with access to both education and health records</b>													
Arizona	45,113	280	6.2 (5.5–7.0)	7.7 (6.7–8.9)†††	6.3 (3.8–10.5)	3.4 (2.6–4.5)†††	3.1 (1.0–9.6)	2.6 (0.8–8.0)					
Arkansas	36,472	251	6.9 (6.1–7.8)	7.4 (6.5–8.6)	5.8 (4.3–7.8)	2.9 (1.3–6.4)	3.5 (0.5–24.7)	—					
Colorado	11,020	65	5.9 (4.6–7.5)	6.4 (4.8–8.5)†††	6.4 (2.9–14.3)	2.0 (0.7–5.3)†††	14.9 (2.1–106.0)	6.3 (2.0–19.6)					
Georgia	44,299	337	7.6 (6.8–8.5)	8.9 (7.7–10.4)****	6.8 (5.7–8.0)***	4.6 (3.0–7.1)†††	—	5.0 (2.7–9.3)					
Maryland	29,722	199	6.7 (5.8–7.7)	7.0 (5.8–8.3)	6.2 (4.9–7.8)	1.4 (0.2–9.7)	—	3.2 (1.0–9.9)					
New Jersey	29,748	316	10.6 (9.5–11.9)††	12.5 (10.7–14.6)***	7.7 (6.0–9.9)***	9.7 (7.7–12.3)	—	14.0 (9.2–21.2)					
North Carolina	20,725	135	6.5 (5.5–7.7)	6.4 (5.2–8.0)	7.2 (5.4–9.6)	4.10 (2.0–8.6)	12.5 (1.8–88.7)	1.9 (0.3–13.7)					
South Carolina	23,191	140	6.0 (5.1–7.1)	6.0 (4.8–7.6)	5.5 (4.2–7.1)	4.4 (1.4–13.6)	—	4.5 (0.6–32.0)					
Utah	26,108	196	7.5 (6.5–8.6)	8.0 (6.9–9.3)††	5.5 (1.4–22.0)	4.4 (2.6–7.2)†††	—	2.2 (0.6–8.8)					
West Virginia	21,472	153	7.1 (6.1–8.4)	6.8 (5.7–8.0)	6.4 (2.9–14.2)	—	—	—					

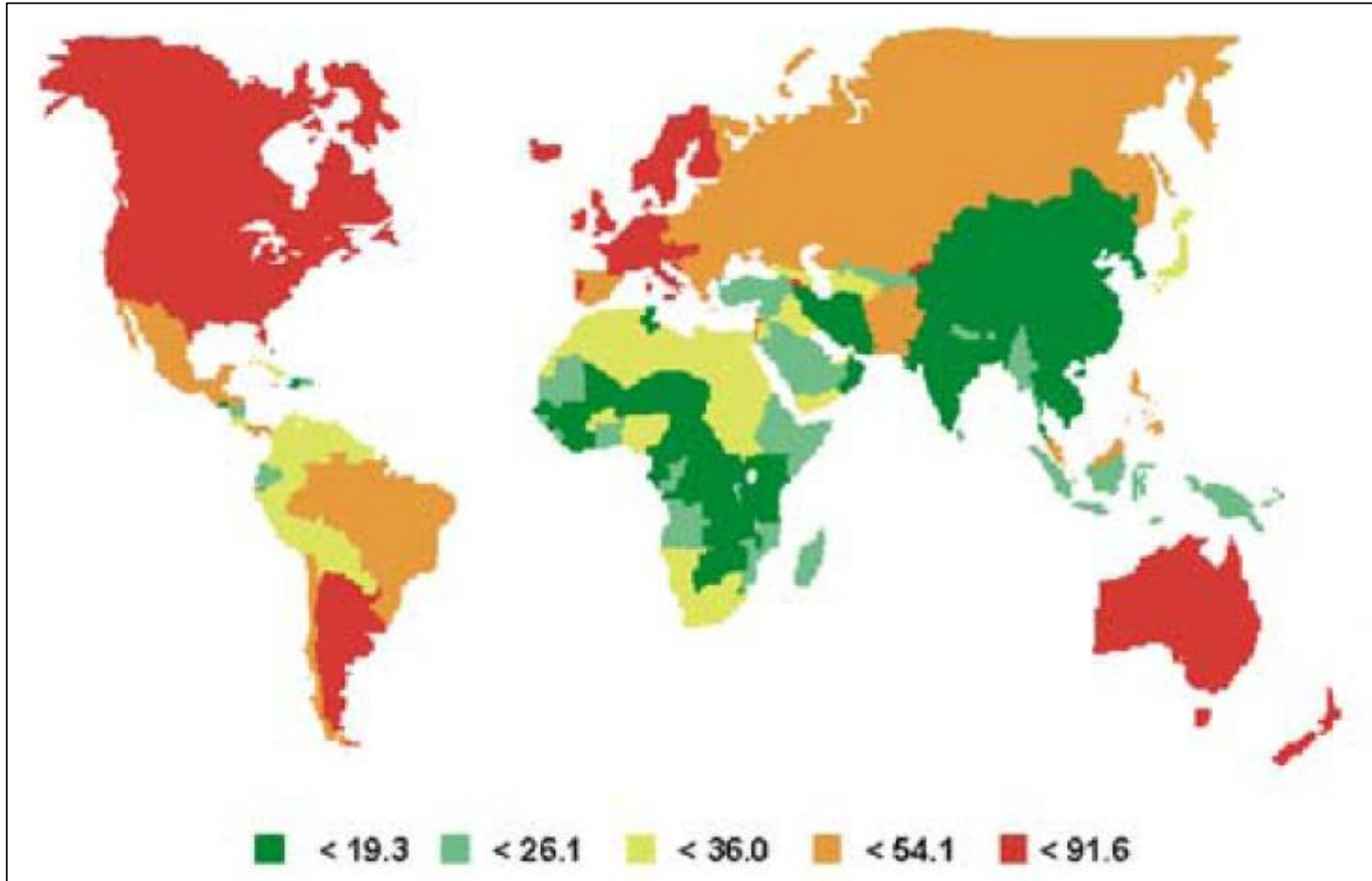
Source: Population data were obtained from CDC's National Center for Health Statistics vintage 2004 postcensal population estimates (13).

\* Per 1,000 children aged 8 years.

## Research models by country

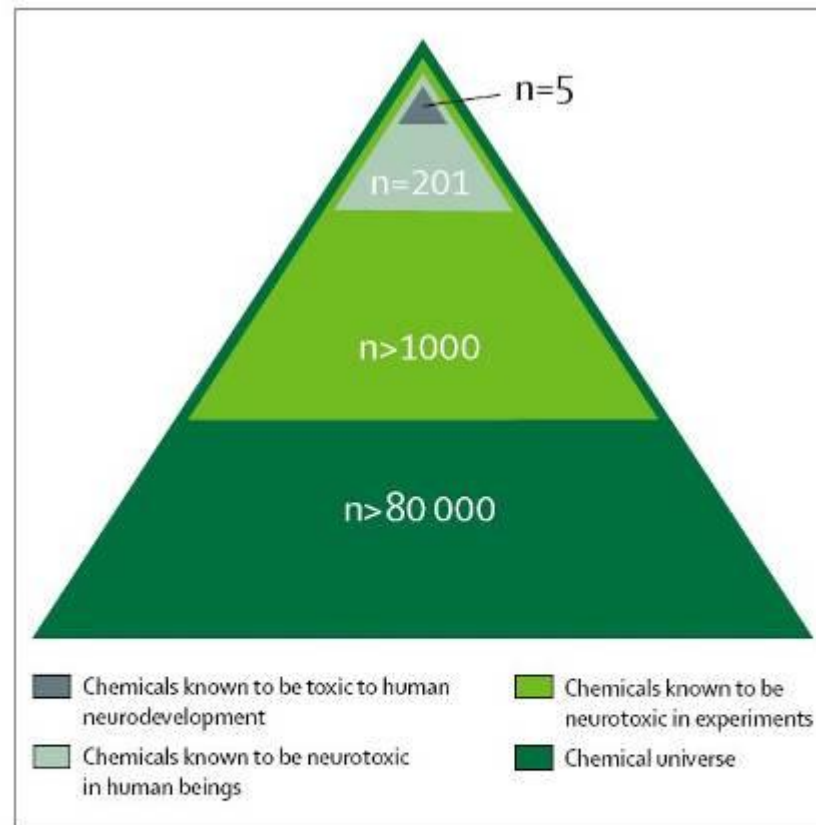
Prevalence Surveys	Freestanding Etiologic Studies		Combined Designs
	Retrospective	Birth Cohort	
w UK	w US	w Denmark	w Australia
w US	w Denmark	w Scotland	w UK
w Aruba		w Norway	w Norway
w Canada		w US	w Denmark
w Sweden		w Bangladesh	(Faroe Islands)
w Finland			w South Korea
w Portugal			w India
			w China

## Age standardized breast cancer incidence rates per 100,000



Parkin DM *Oncogene*, 2004

# Location specific opportunities...



**Figure 2: Diagram of the extent of knowledge of neurotoxic chemicals**  
Of the thousands of known chemicals, only a small fraction have been proven to cause developmental neurotoxicity in humans. Although this evidence does not represent the true potential for industrial chemicals to cause neurodevelopmental disorders, assessments of need for preventive measures nonetheless rely on that information.

Grandjean and Landrigan. *Lancet* 2007