Lessons learned from the Seychelles Child Development Study

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MethylMercury Poisoning Episode in Iraq

- Fungicide containing MeHg in treated seed grain
- No fish consumed
- > 50,000 people exposed
- Prenatal exposures as low as 10 ppm may affect children's development
- Challenging environment for epidemiologic research
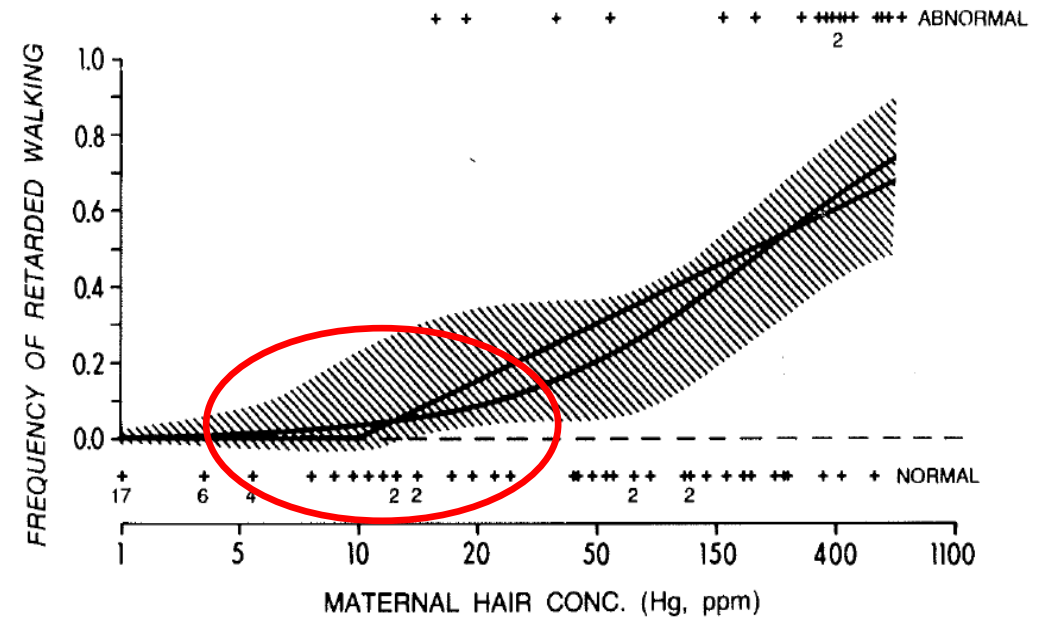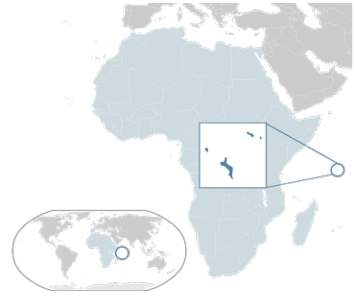

Cox et al. 1989

Epidemiologic Methods

- Important to consider the following factors when studying subtle associations:
    - Measurement of exposure
    - Measurement of outcome
    - Blinding
    - Control for confounding
    - Sample size
    - Follow-up retention
    - *A priori* analysis plans

Why the Seychelles?

- High fish consumption
- Free universal health care and education
- Minimal co-exposures
- No malnutrition
- Environment conducive to epidemiologic research
- Sentinel population:
  - Range of MeHg concentration in fish similar to US
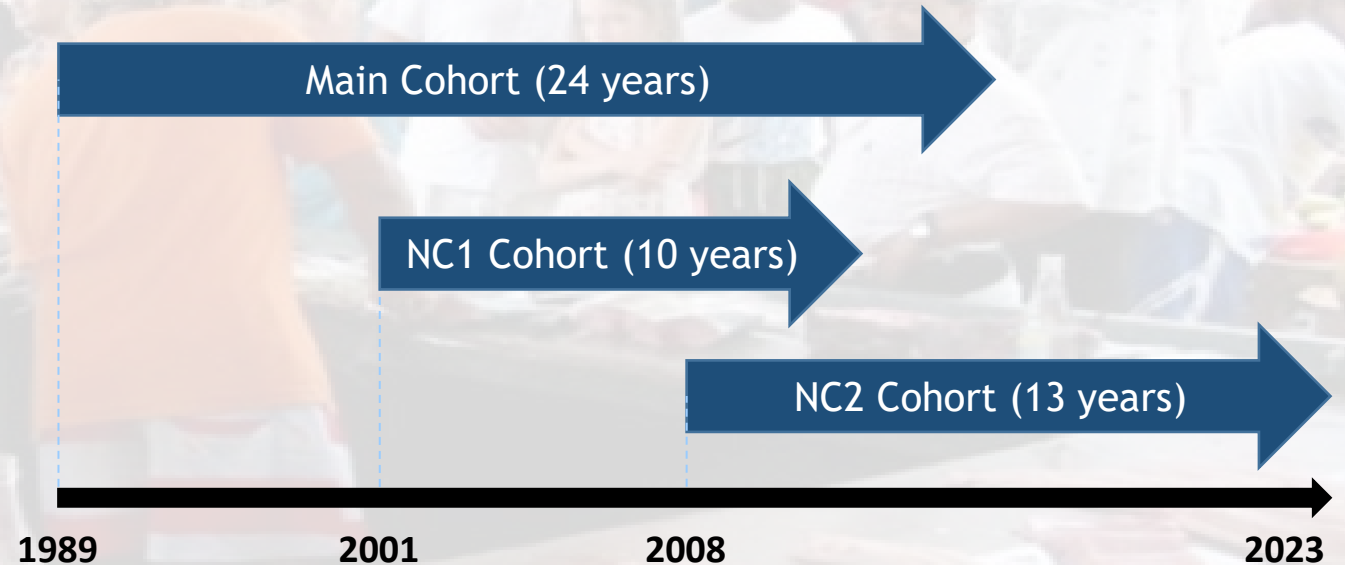 - Population has 10x the US exposure

Seychelles Child Development Study (SCDS)

- Originally Seychelles-Rochester collaboration
- Started out as methylmercury-centric study (mid-1980s)
  - Following up on findings from poisoning episodes in Japan and Iraq and toxicology studies
- Transitioned to nutrition-centric study (~2000)
  - Following up on SCDS findings suggesting that benefits of nutrients in fish can outweigh potential MeHg toxicity
  - Assessment of human and experimental genetics (~2011) has improved understanding of toxicokinetics and –dynamics
- Current and future efforts emphasizing fish as a whole food

Seychelles Child Development Study (SCDS)

- Study has recruited >3,000 children
- Comprehensive exams
  - Neurodevelopment and neurobehavior
  - Demographic and medical questionnaires
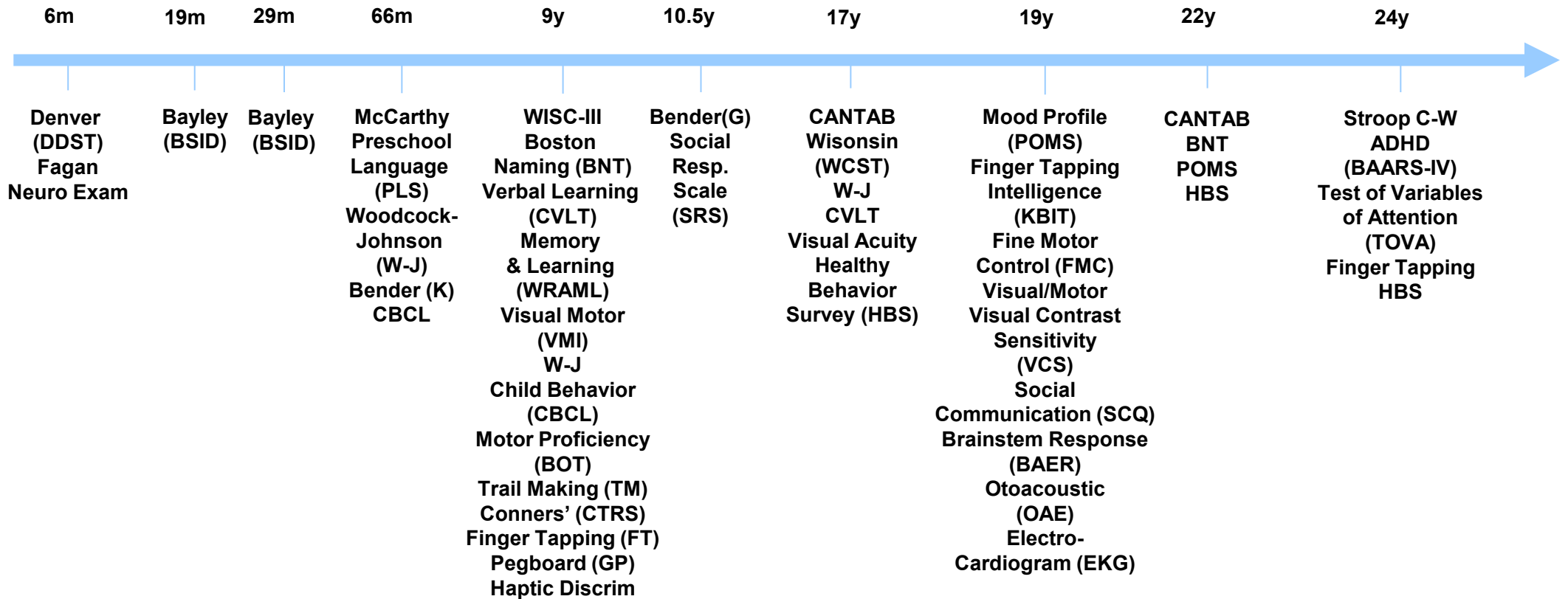 - Biospecimens
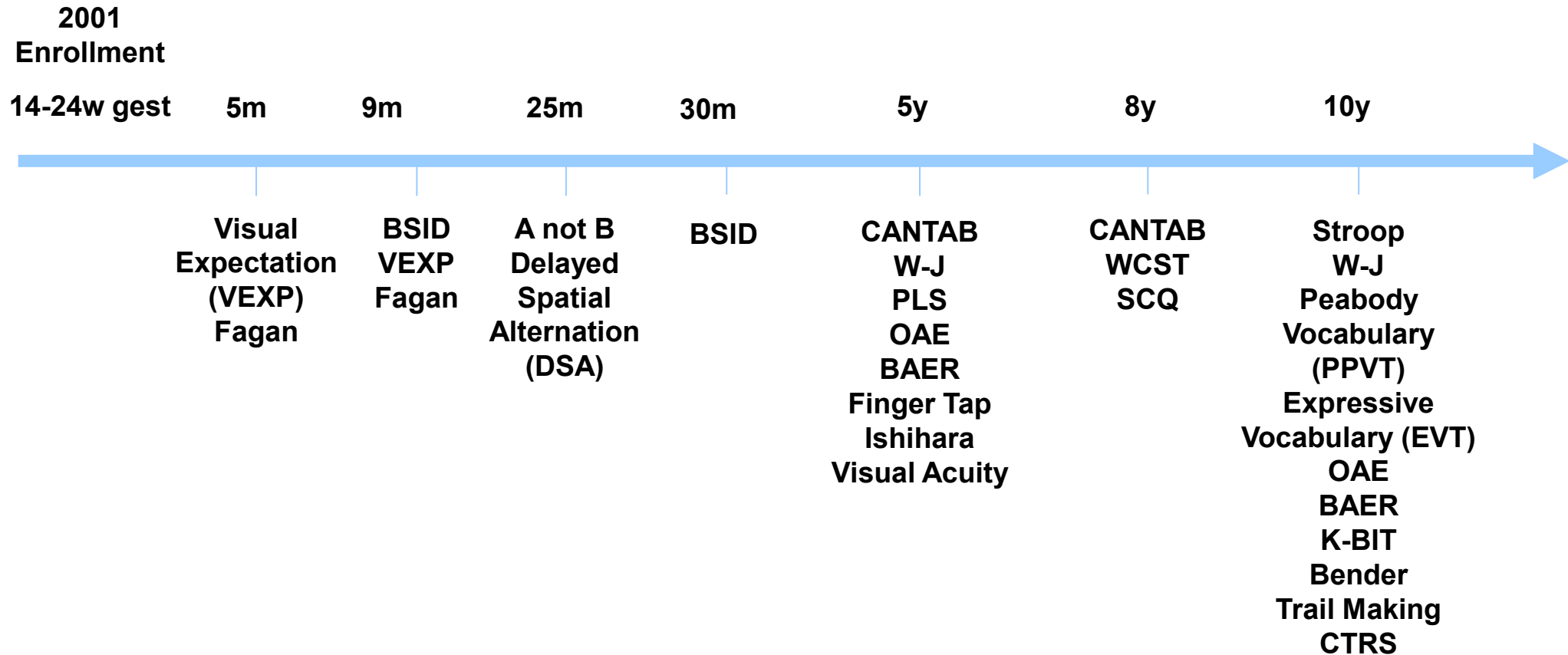 - Dietary data

Main Cohort (24 years)

NC1 Cohort (10 years)

NC2 Cohort (13 years)

1989   2001   2008   2023

NC1 = Nutrition Cohort 1; NC2 = Nutrition Cohort 2

SCDS Main Cohort Timeline

1989-1990 Enrollment

6m	19m	29m	66m	9y	10.5y	17y	19y	22y	24y
Denver (DDST) Fagan Neuro Exam	Bayley (BSID)	Bayley (BSID)	McCarthy Preschool Language (PLS) Woodcock-Johnson (W-J) Bender (K) CBCL	WISC-III Boston Naming (BNT) Verbal Learning (CVLT) Memory & Learning (WRAML) Visual Motor (VMI) W-J Child Behavior (CBCL) Motor Proficiency (BOT) Trail Making (TM) Conners' (CTRS) Finger Tapping (FT) Pegboard (GP) Haptic Discrim	Bender(G) Social Resp. Scale (SRS)	CANTAB Wisonsin (WCST) W-J CVLT Visual Acuity Healthy Behavior Survey (HBS)	Mood Profile (POMS) Finger Tapping Intelligence (KBIT) Fine Motor Control (FMC) Visual/Motor Visual Contrast Sensitivity (VCS) Social Communication (SCQ) Brainstem Response (BAER) Otoacoustic (OAE) Electro-Cardiogram (EKG)	CANTAB BNT POMS HBS	Stroop C-W ADHD (BAARS-IV) Test of Variables of Attention (TOVA) Finger Tapping HBS

SCDS NC1 Timeline

**2001
Enrollment**

| 14-24w gest | 5m | 9m | 25m | 30m | 5y | 8y | 10y |

Visual Expectation (VEXP) Fagan (5m)

BSID VEXP Fagan (9m)

A not B Delayed Spatial Alternation (DSA) (25m)

BSID (30m)

**CANTAB
W-J
PLS
OAE
BAER
Finger Tap
Ishihara
Visual Acuity** (5y)

**CANTAB
WCST
SCQ** (8y)

**Stroop
W-J
Peabody Vocabulary (PPVT)
Expressive Vocabulary (EVT)
OAE
BAER
K-BIT
Bender
Trail Making
CTRS** (10y)

*Additional outcomes include gestational age, birth weight and length, and head circumference from the maternity registry

NC2 Timeline

2008-2011
Enrollment
1st prenatal
visit (>14w gest)

20m

7y

13y (in progress)

Bayley Scales Infant Dev
Infant Behavior (IBQ-R)
Dunn Sensory Profile
MacArthur-Bates
Communicative
Development (CDI)

K-BIT
Language Fundamentals
(CELF-5)
Woodcock-Johnson
Finger Tapping
Trail Making
Boston Naming Test
Stroop Color-Word
Social Communication Q
Social Responsiveness Scale
Child Behavior Check List
Asthma & Allergies (ISAAC)

Trail Making
Boston Naming Test
Stroop Color-Word
Strength & Difficulties Q
SCARED Anxiety
Asthma & Allergies (ISAAC)
BP and Body Composition
Health Behaviors

Main Cohort: Associations between the 5.5-year Preschool Language Scale score and maternal hair mercury

p=0.02

Davidson et al. 1998

NC1: Associations between the 5-year Preschool Language Scale score and maternal DHA status (A), maternal AA status (B), and maternal hair mercury (A)
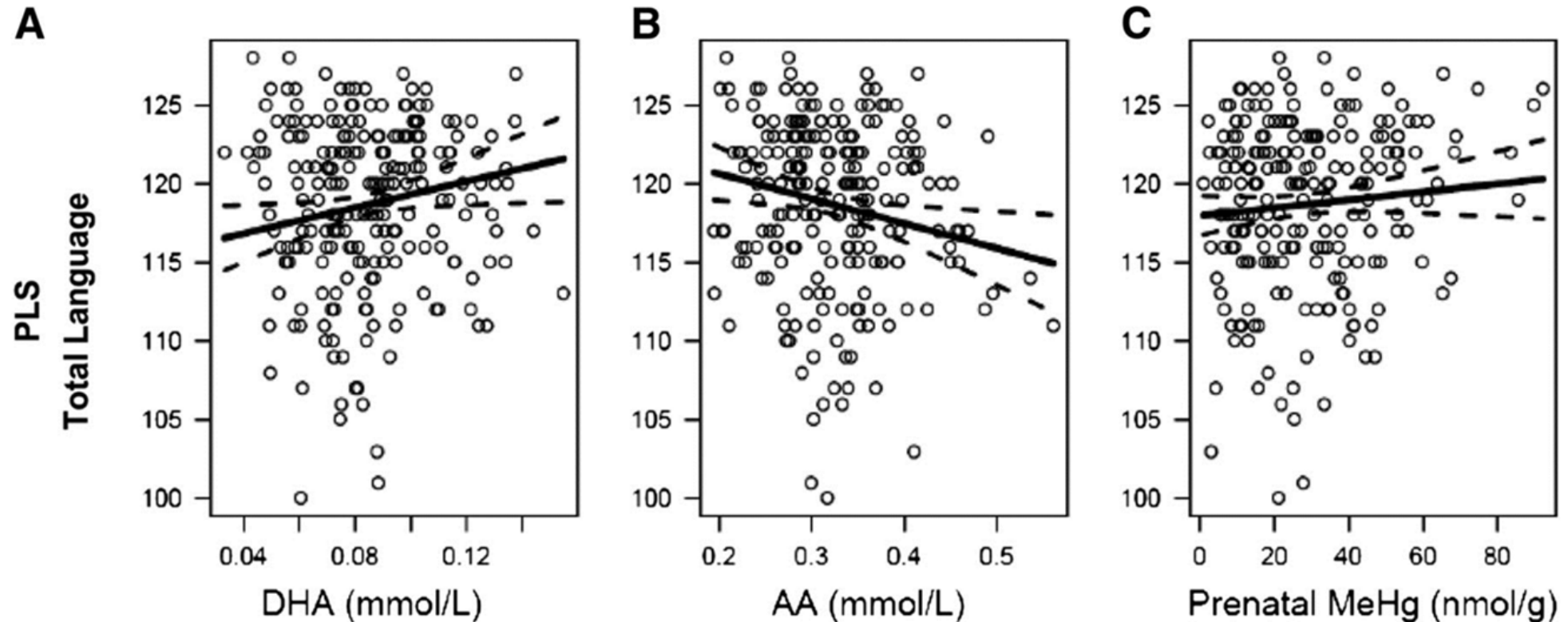
Strain J J et al. J. Nutr. 2012;142:1943-1949

NC2: Associations between the 20-month McArthur-Bates CDI total gestures score and maternal hair mercury (A), maternal DHA status (B), and maternal n-6/n-3 ratio (C)
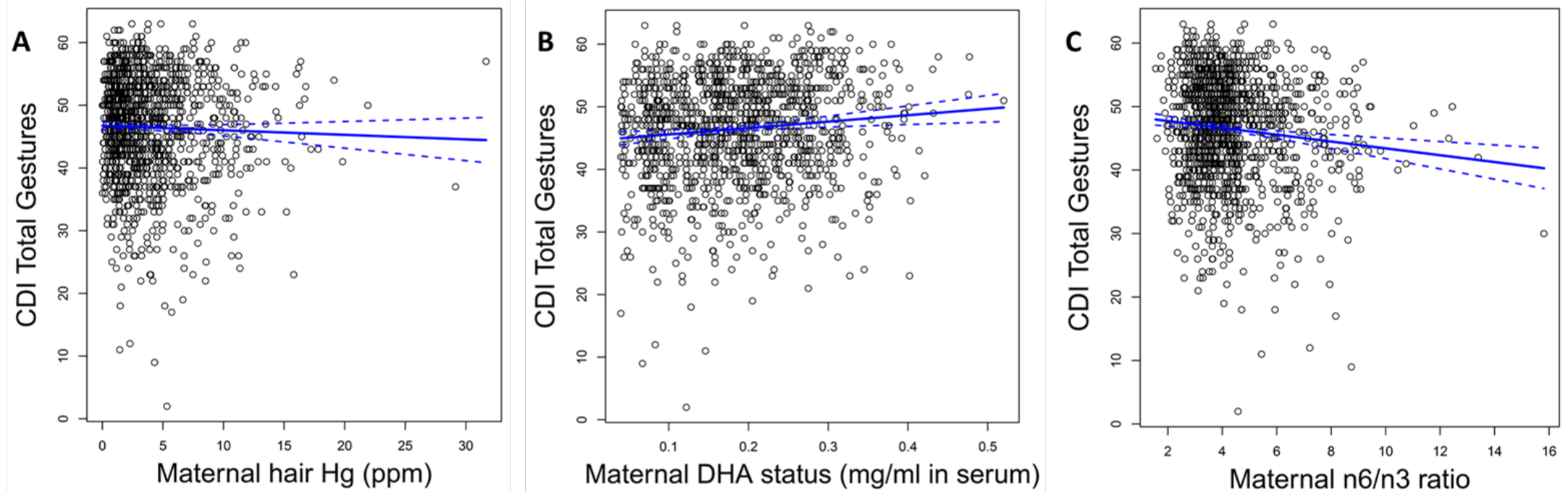
Strain JJ et al. Am J Clin Nutr 2015;101:530-537

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Maternal fish consumption and child neurodevelopment in Nutrition 1 Cohort: Seychelles Child Development Study

Marie C. Conway[1]*, Alison J. Yeates[1], Tanzy M. Love[2], Daniel Weller[2], Emeir M. McSorley[1], Maria S. Mulhern[1], Maria Wesolowska[1], Gene E. Watson[2], Gary J. Myers[2], Conrad F. Shamlaye[3], Juliette Henderson[3], Philip W. Davidson[2], Edwin van Wijngaarden[2] and J. J. Strain[1]

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[3]The Ministry of Health, Mahé, Republic of Seychelles

"In this cohort, where fish consumption is substantially higher than current global recommendations, maternal fish consumption during pregnancy was not beneficially or adversely associated with children's neurodevelopmental outcomes."

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Prenatal MeHg Neurotoxicity: SCDS Findings

No overall association between prenatal MeHg exposure and neurodevelopmental outcomes

Maternal n-3 PUFA are beneficial for early child neurodevelopment

Van Wijngaarden E et al. Neurotoxicol Teratol 2017;59:35-42; Strain JJ et al. J Nutr 2012;142:1943-1949; Strain JJ et al. Am J Clin Nutr 2021;113:304-313

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Variation in Studies of Prenatal MeHg Exposure

Mercury exposure source

Geographic variability in nutritional content and co-exposure to contaminants

Epidemiologic Methods

Variability in neurodevelopmental tests, exposure measures, covariates, statistics

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