

Cord Blood Manganese and ADHD-Related Behaviors Among 8-Year –Old Children



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Manganese Exposure

Sources of Mn:

- Ubiquitous element
- Diet, water
- Production of steel, batteries, catalysts, glass, ceramics; mining; welding
- Organic forms: fungicides, MMT



Kinetics:

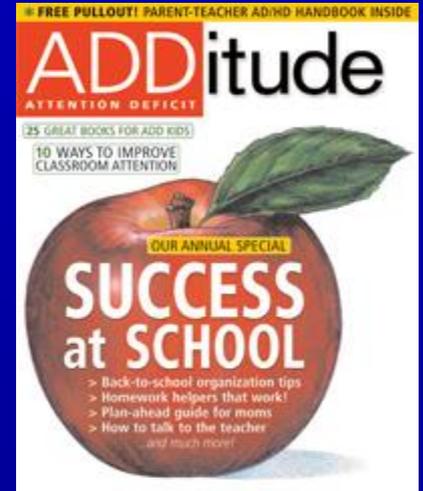
- Readily absorbed via inhalation, less so ingestion (Fe deficiency increases)
- $t_{1/2}$ blood short; longer in tissues
- Crosses placenta; potential enhanced fetal CNS uptake

Manganese and Neurological Function

- **Essential element required for healthy neurodevelopment**
- **Neurotoxicity with heavy occupational exposure (Parkinsonian, dementia, ↓memory, emotional lability, aggression)**
- **Animal models alterations in dopaminergic function with prenatal/early postnatal exposure, behavior (hyperactivity), learning/memory**
- **CNS neuropathology: degenerative changes especially in basal ganglia**

Attention Deficit-Hyperactivity Disorder

- Most common neurobehavioral disorder of children (6-12% worldwide)
- Risk factors poorly understood
- Clinical diagnosis (no specific test)
- Neuroimaging: ↓brain volume
- Mechanism: “dopamine deficit”
- Deficiencies:
 - vigilance-attention
 - cognitive control (working memory, impulse ctrl)
 - motivation



Biomarkers of Prenatal Mn Exposure and ADHD-Related Behavior

Preschool (3-5 yrs):

↑Behavioral disinhibition at 3 yrs (teeth)¹

↑Impulsive errors (CPT/Stroop) at 4.5 yrs (teeth)¹

↓Attention (McCarthy) at 3 yrs (cord blood)²

School age (6-17 years):

↓Prosocial (♀), ↑Conduct probs (♂ > ♀) (water)³

↑Internalizing, ↑Externalizing, ↑Hyperactivity (teeth)^{1,4}

No association clinical ADHD diagnosis (cord serum)⁵

¹Ericson et al. Neurotoxicol Teratol 2007; ²Tasker et al. Neurotoxicology 2003;

³Rahman et al. EHP 2016; ⁴Mora et al. Environ Int 2015 (prenatal in ♂);

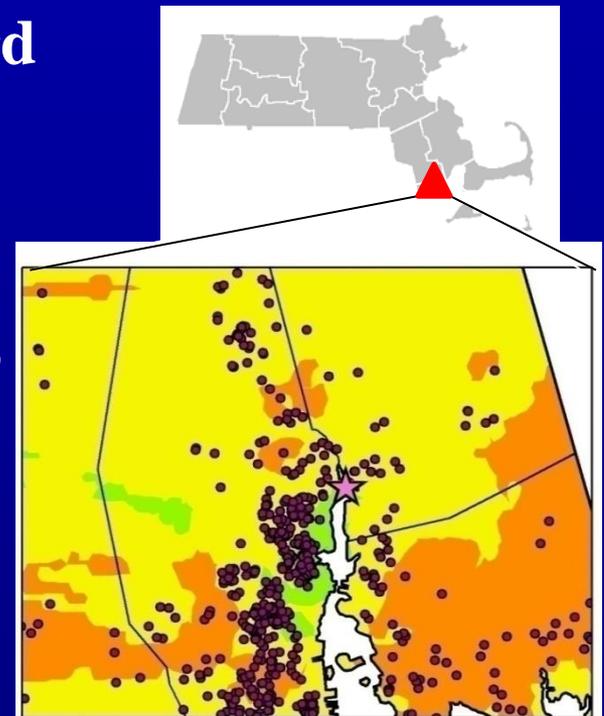
⁵Ode et al. Environ Res 2015

Study Goal

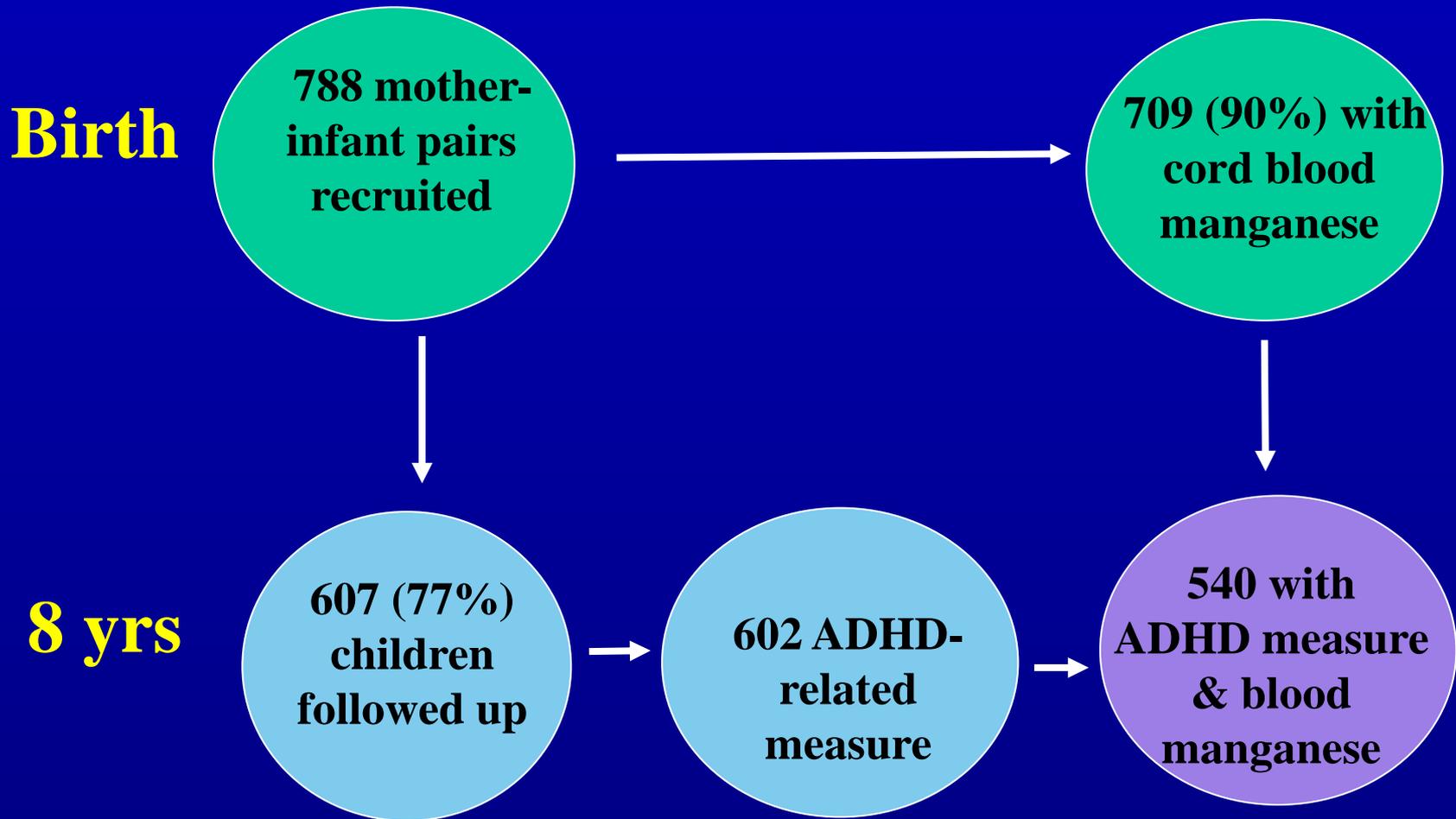
Assess associations of cord blood manganese levels (*in utero* exposure) with behaviors related to ADHD at age 8 years

New Bedford Cohort (NBC) Study

- 788 newborns enrolled at birth 1993-1998
- Maternal residence in towns next to PCB-contaminated New Bedford Harbor
- Assess relation early life exposure to PCBs, OC pesticides and metals with child neurodevelopment and growth



Analysis Population



Manganese Exposure Assessment

- **Assessed in cord blood**
 - **Collected at delivery (Vacutainer™ trace metal tubes)**
 - **Whole blood analyzed with Inductively Coupled Plasma Mass Spectrometry (ICP-MS) at Harvard Trace Metals Laboratory**
 - **LOD 0.2 µg/L**

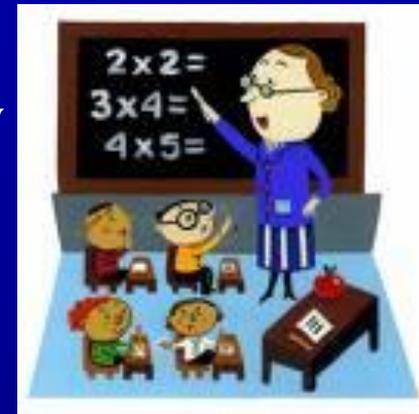
Data Analysis

- **Multivariable linear regression models (linear dose-response in penalized splines)**
- **Covariates:**
 - **Child:** age, sex, and race
 - **Mother:** age, education, marital status, IQ, depression, prenatal smoking, prenatal alcohol consumption, illicit drug use
 - **Household:** income, HOME score, paternal education
- **Sensitivity analyses:**
 - **Lead (cord blood, peak @ 12-36 months)**
 - **PCBs (cord serum sum of 4 congeners 118,138,153,180)**

Unpublished Preliminary Findings Removed

Outcome: Behavioral Rating Scale

- **Conners Rating Scale – Teachers (CRS-T)**
 - 59 item questionnaire, problem behaviors
 - Used in clinical dx, monitoring, research
 - Analyzed 4 subscales:
 - Conners' ADHD Index
 - DSM-IV Inattention
 - DSM-IV Impulsivity-Hyperactivity
 - DSM-IV Combined



Unpublished Preliminary Findings Removed

Outcome: Continuous Performance Test

- **Conners Rating Scale – Teachers (CRS-T)**

- 59 item questionnaire, problem behaviors
- Used in clinical dx, monitoring, research
- Analyzed 4 subscales



- **Continuous Performance Test (CPT)**

- Inattention and impulsivity assessed as:

- Errors of omission (non-response, inattention)
- Errors of commission (false response, impulsivity)
- Mean response time
- Response time variability

Unpublished Preliminary Findings Removed

Outcome: Psychometric Test

- **Conners Rating Scale – Teachers (CRS-T)**
 - 59 item questionnaire
 - Assesses problem behaviors in children
 - conduct, cognitive, emotional, ADHD
 - Used in clinical diagnosis (DSM-IV), treatment monitoring, research
- **Neurobehavior Examination System 2 Continuous Performance Test (CPT)**
 - Computer assisted test system
 - Inattention and impulsivity assessed with 3 outcomes:
 - Errors of omission (non-response)
 - Errors of commission (false response)
 - Response time
- **Wechsler Intelligence Scale for Children 3rd Edition (WISC-III)**
 - IQ Test
 - Components associated with ADHD (*a priori*):
 - Processing Speed
 - Freedom from Distractibility



Unpublished Preliminary Findings Removed

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The children and families of the NBC

Thank you!



New Bedford Harbor