

The Navigation Guide Systematic Review Methodology: Evaluating Neurodevelopmental Outcomes

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PBDE/IQ-ADHD case study

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Health and the Environment

Clinical sciences have faced and addressed these same challenges

Evidence-Based Medicine (EBM)

EBM aims to apply the best available evidence gained from the scientific method to clinical decision making

- Developed to prevent harm from treatment decisions being made without strong basis in the evidence
- Transparent and systematic approach to evaluating evidence



Models for Navigation Guide



The Navigation Guide (2011)

Developed in 2009 by UCSF's Program on Reproductive Health and the Environment in collaboration with

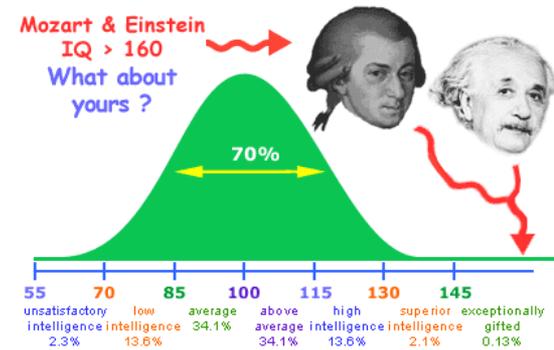
22 clinicians and scientists from:

- Federal and state government agencies
- Other academic institutions
- Non-governmental organizations



GOAL: Establish a systematic and transparent method to evaluate the quality of evidence and to support evidence-based decision making, bridging the gap between clinical and environmental health

PBDES & Neurodevelopmental Outcomes

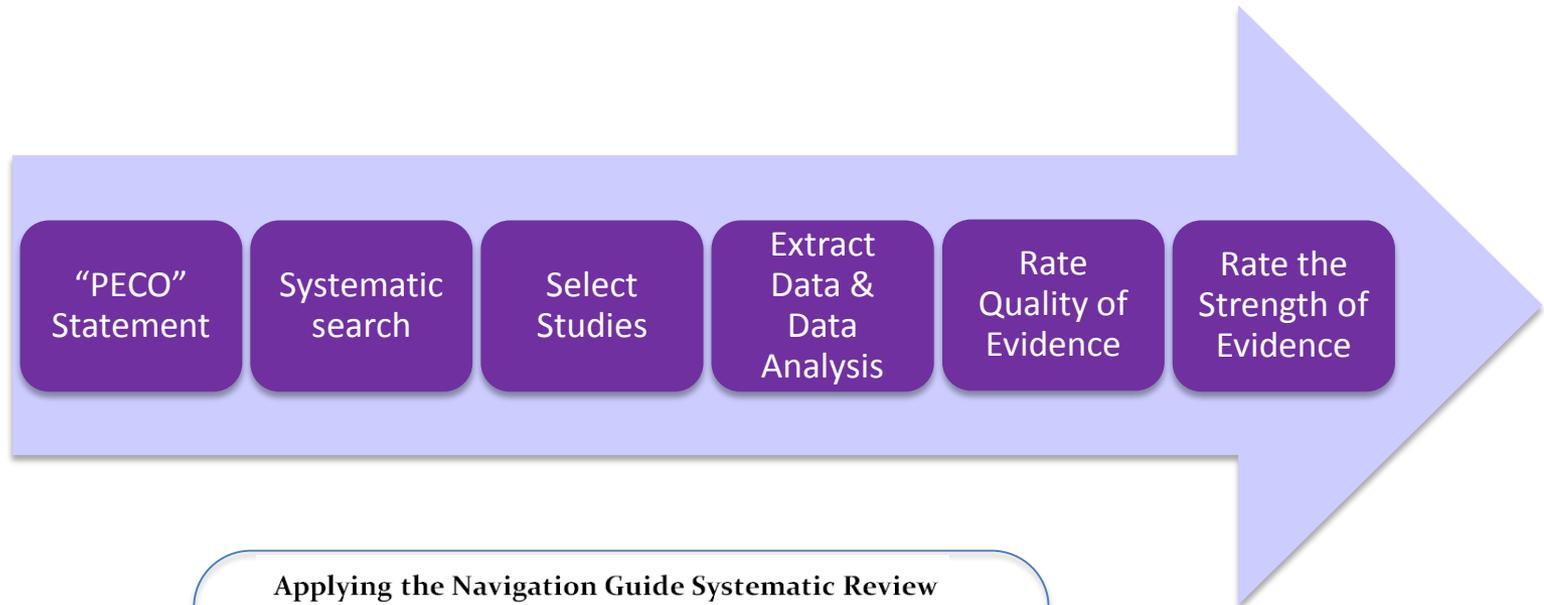


Does developmental exposure to PBDEs in humans affect:

- Quantitative measures of intelligence; or*
- ADHD and attention-related behavioral conditions?*

Systematic Review Approach

A pre-specified analytic plan (protocol) is developed and applied consistently to the evidence.



Applying the Navigation Guide Systematic Review
Methodology
Case Study #5

Association between Developmental Exposures
to PBDEs and Human Neurodevelopment

A Systematic Review of the Evidence
Protocol
March 2015

Overall Conclusion

Protocol is registered in PROSPERO: University of York's Center for Reviews and Dissemination.

PBDE case study: PECO statement



Population: *Humans*

Exposure: Any *developmental* exposure to **PBDEs** that occurred prior to the assessment of 1) quantitative measure of intelligence or 2) ADHD and attention-related behavioral problems.



Comparator: Humans exposed to lower levels of PBDEs than the more highly exposed humans.



Outcome: Any clinical diagnosis or other continuous or dichotomous scale assessment of 1) *quantitative measures of intelligence* or 2) *ADHD and attention-related behavioral problems*.

PBDE case study: PECO statement

- **Exposures:** *“PBDEs” refers to any single PBDE congener, or combination of grouped congeners.*
 - *“Any developmental exposure” is defined as maternal or paternal exposure incurred any time in proximity to conception (as defined by authors of the included study), or exposures to the offspring incurred in utero or in the perinatal or childhood period.*
 - *Exposures “prior to the assessment of quantitative measure or intelligence or ADHD and attention-related behavioral problems” include exposures measured in human biological samples prior to or concurrent with outcome assessment. Measures of exposure (PBDE congener levels) will be limited to only concentrations measured in human biological samples*

PBDE case study: PECO statement

- **Comparator:** *This definition is intended to include groups defined by case-control studies; for instance comparing the PBDE exposure levels for people with ADHD versus those without. In the event that these exposure levels turn out to be not statistically different, for the purposes of this case study this is still considered a sufficient definition of a comparator group.*

PBDE case study: PECO statement

Outcome:

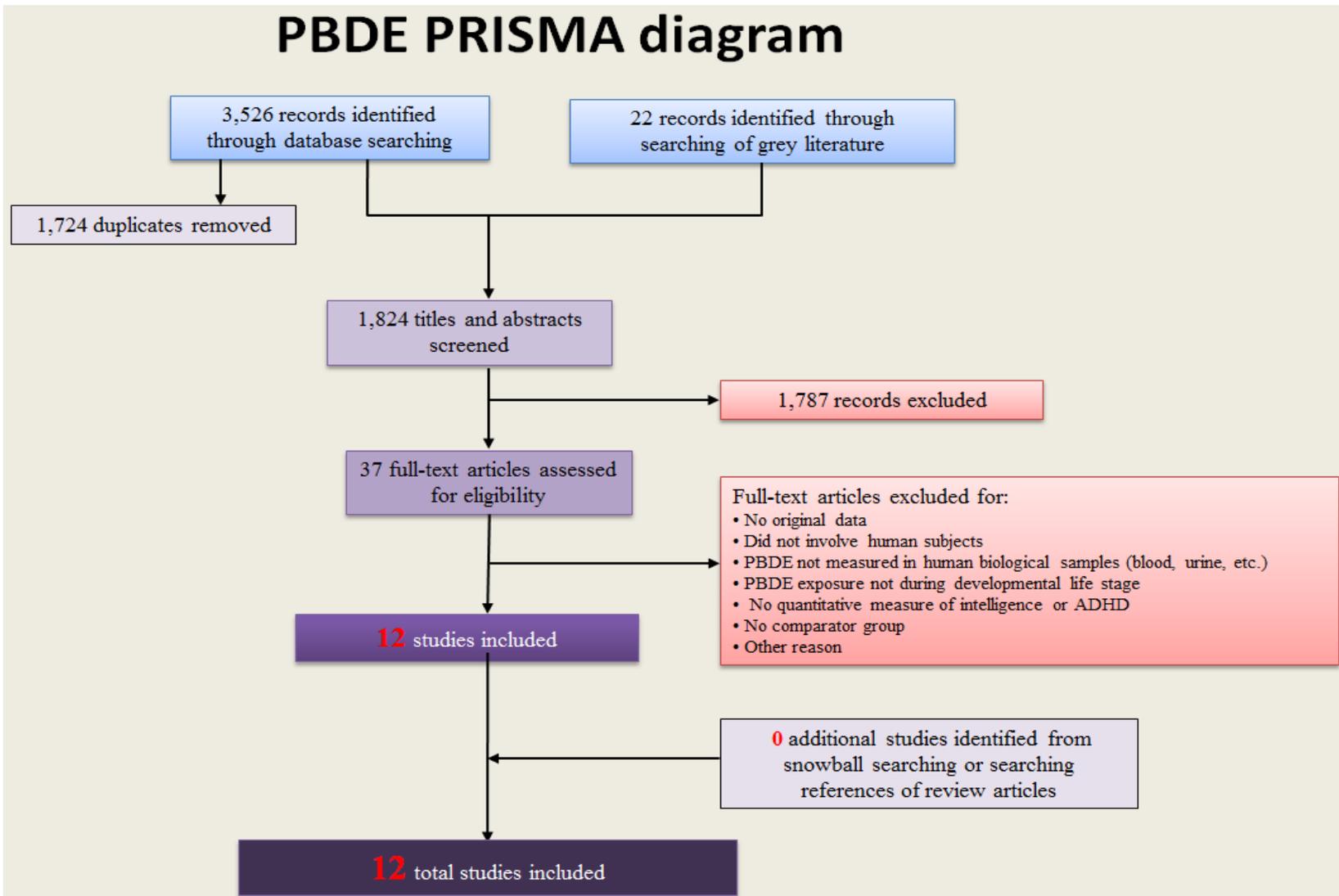
- *Quantitative measures of intelligence include:*
 - *Wechsler Preschool and Primary Scale of Intelligence (WPPSI), Wechsler Intelligence Scale for Children (WISC), Stanford-Binet Intelligence Scale, or the McCarthy Scales of Children's Abilities (MSCA).*
- *Outcome measures of ADHD and attention-related behavioral problems include:*
 - *the Child Behavior Checklist (CBCL)/1.5-5, Conners' Kiddie Continuous Performance Test (K-CPT), Conners' Rating Scale-Teachers (CRS-T), Conners' Parent Rating Scale-Revised (CPRS), WISC-III (selected subscales), the Disruptive Behavior Disorders Rating Scale (DBD), or Continuous ADHD Confidence Index score.*

Systematic literature search

- Systematic search developed and implemented by a Cochrane-trained librarian.
- *A priori* exclusion criteria:
 - No original data;
 - Did not involve human subjects;
 - Did not quantify developmental PBDE exposure in biological samples;
 - Did not report outcomes of quantitative measures of intelligence or ADHD and attention-related behavioral problems;
 - No comparator group; or
 - Study reported pre-existing conditions of genetic origin (e.g., fragile X syndrome)
- Snowball searching & searching references of review articles to identify additional studies

Systematic literature search

PBDE PRISMA diagram



Included studies

12 total studies (2009-2014)

9 Intelligence

7 ADHD

- Sample size: 35-309
- Exposure: breast milk, maternal/child serum, cord blood
- Timing: gestation, at birth, postpartum
- Outcome: MSEL composite, Bayley-II, Bayley-III, Full scale IQ, MSCA, WPPSI-R

- Sample size: 43-309
- Exposure: breast milk, maternal/child serum and whole blood, cord blood
- Timing: gestation, at birth, postpartum
- Outcome: BASC-2, CBCL, K-CPT, DSM-IV, Conner's Rating Scale, Parental Strength and Difficulties Questionnaire, ITSEA

PBDE & IQ (9 studies)



- Prospective birth cohorts
- 3 potentially related (Chao, Shy, Ding-Yan)
- Child Age : 8-72 months
- Confounders adjusted for: varying (child's sex, age at testing, HOME score, SES most common)
- Congeners: varying (47, 99, 100, 153 most common)

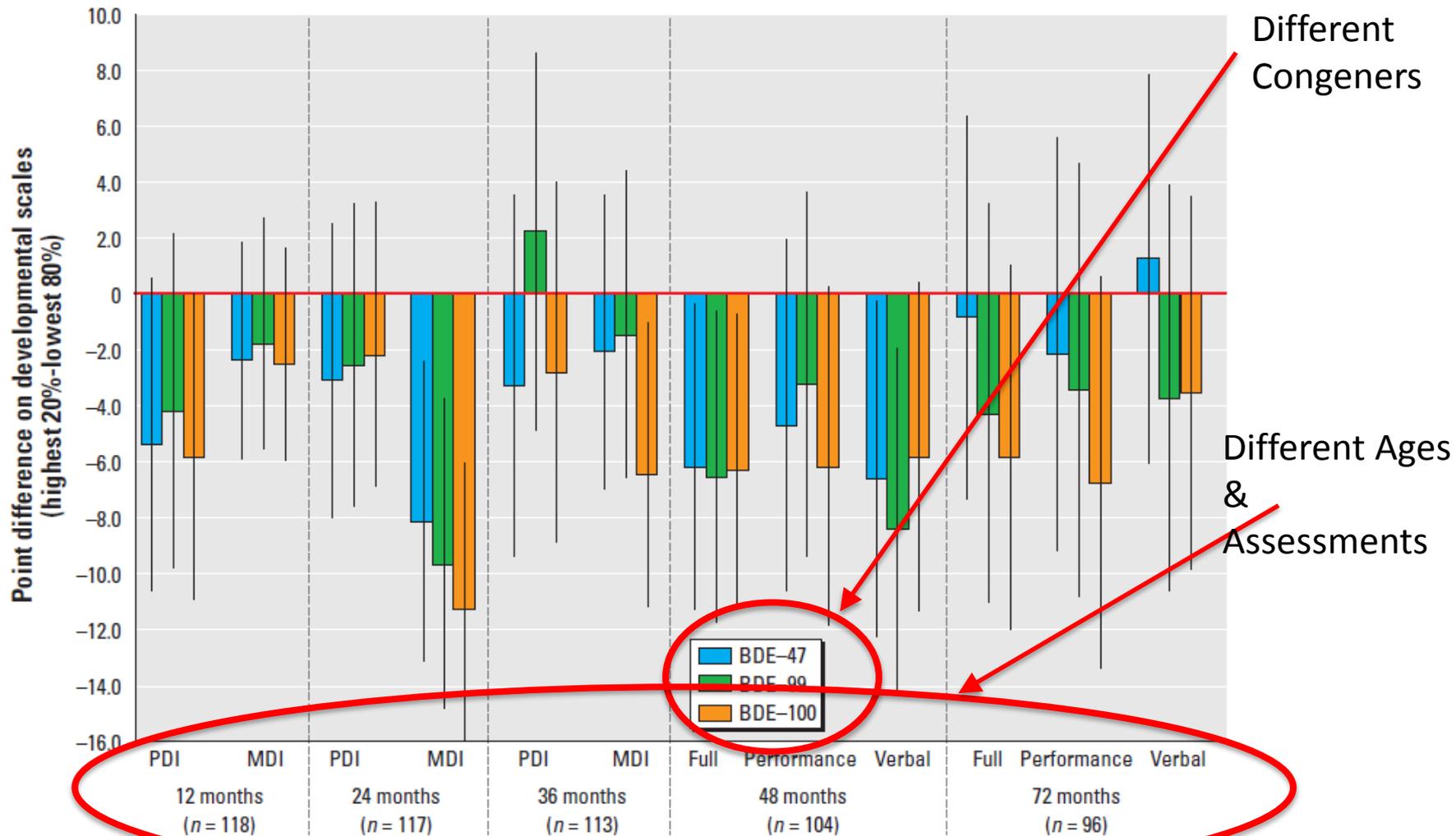
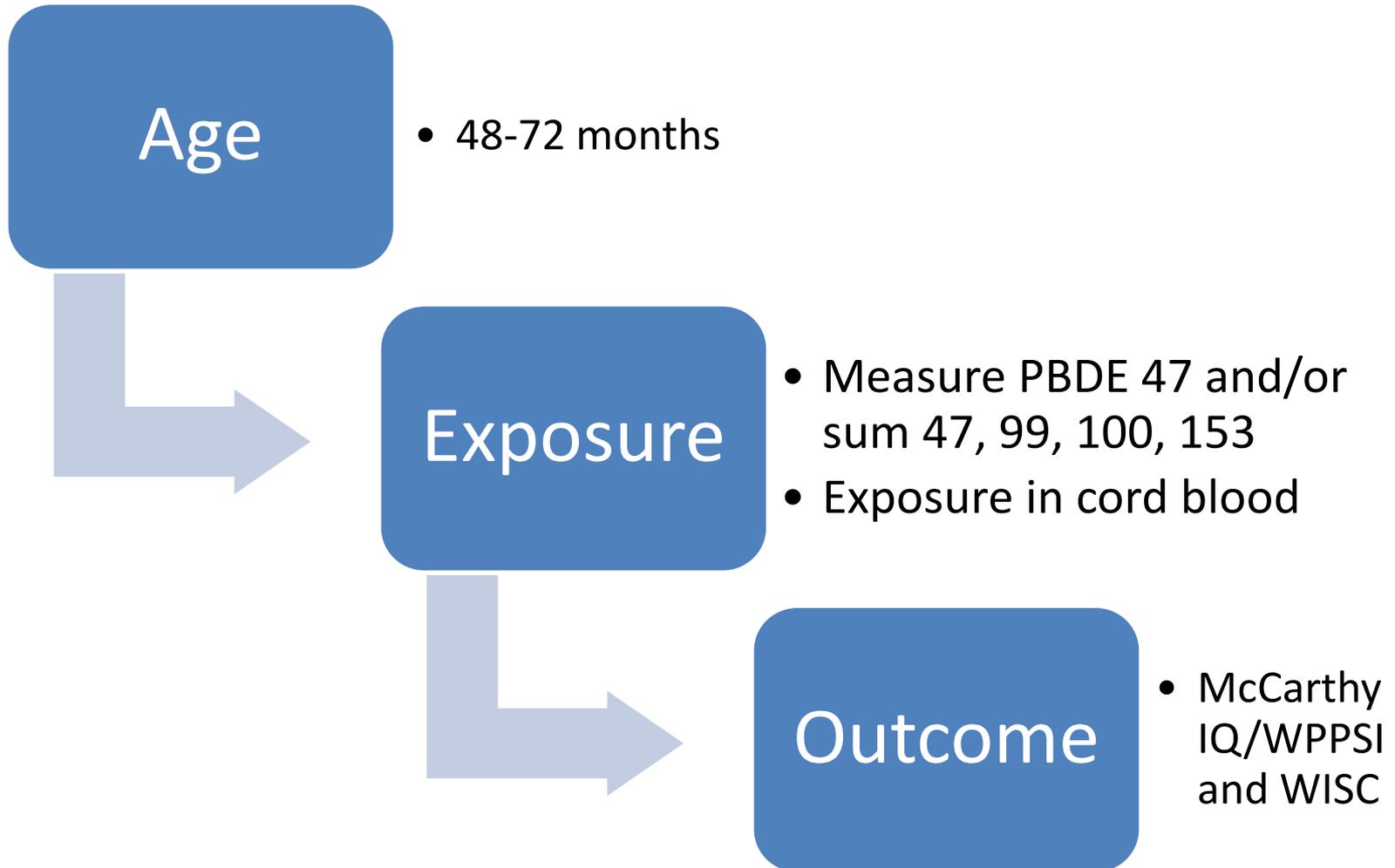


Figure 1. Difference in mean developmental score (and 95% confidence interval around the mean) comparing individuals in the highest quintile (20%) of exposure with those in the lower 80% of BDEs 47, 99, and 100. Mean differences were adjusted for age at testing, race/ethnicity, IQ of mother, sex of child, gestational age at birth, maternal age, ETS (yes/no), maternal education, material hardship, breast-feeding, language, and location of interview.

Primary Meta-Analysis



PBDE & ADHD (7 Studies)



- Prospective birth cohorts and 1 cross-sectional
- Two related studies (Adgent and Hoffman)
- Age of children: 24 months-10 years
- Confounders adjusted for: varying (child's sex, age at testing, HOME score, SES most common)
- Congeners: varying (47, 99, 100, 153 most common)

Evaluating the Evidence

Human Evidence

Risk of Bias

each individual study.

Domains

- Recruitment strategy
- Blinding
- Exposure assessment
- Confounding
- Incomplete outcome data
- Selective reporting
- Conflict of interest
- Other bias

Determinations

(for each risk of bias domain)

- Low risk
- Probably low risk
- Probably high risk
- High risk

Quality of Evidence

across all studies.

Downgrade Criteria

Risk of bias across studies

- Indirectness
- Inconsistency
- Imprecision
- Publication bias

Upgrade Criteria

- Large magnitude of effect
- Dose response
- All possible confounding accounted for

Rating

(based on all quality criteria)

- High quality
- Moderate quality
- Low quality

Strength of Evidence

across all studies.

Considerations

Quality of body of evidence

- Direction of effect
- Confidence in effect
- Other compelling attributes of the data that may influence certainty

Rating

(based on all strength considerations)

- Sufficient evidence
- Limited evidence
- Inadequate evidence
- Evidence of lack of toxicity

Risk of bias

- 1. Are the study groups at risk of not representing their source populations in a manner that might introduce selection bias?**
- 2. Was knowledge of the group assignments inadequately prevented (i.e., blinded or masked) during the study, potentially leading to subjective measurement of either exposure or outcome?**
- 3. Were exposure assessment methods lacking accuracy?**
- 4. Were outcome assessment methods lacking accuracy?**
- 5. Was potential confounding inadequately incorporated?**

Maternal age, Maternal education, Marital status, Maternal use of alcohol during pregnancy, Maternal depression, Household income/poverty (measure of socioeconomic status (SES)), Gestational exposure to environmental tobacco smoke (active), Child sex, Exposure to other neurotoxic agents (i.e., lead), Home Inventory

Risk of bias

6. Were incomplete outcome data inadequately addressed?

7. Does the study report appear to have selective outcome reporting?

8. Did the study receive any support from a company, study author, or other entity having a financial interest in any of the exposures studied?

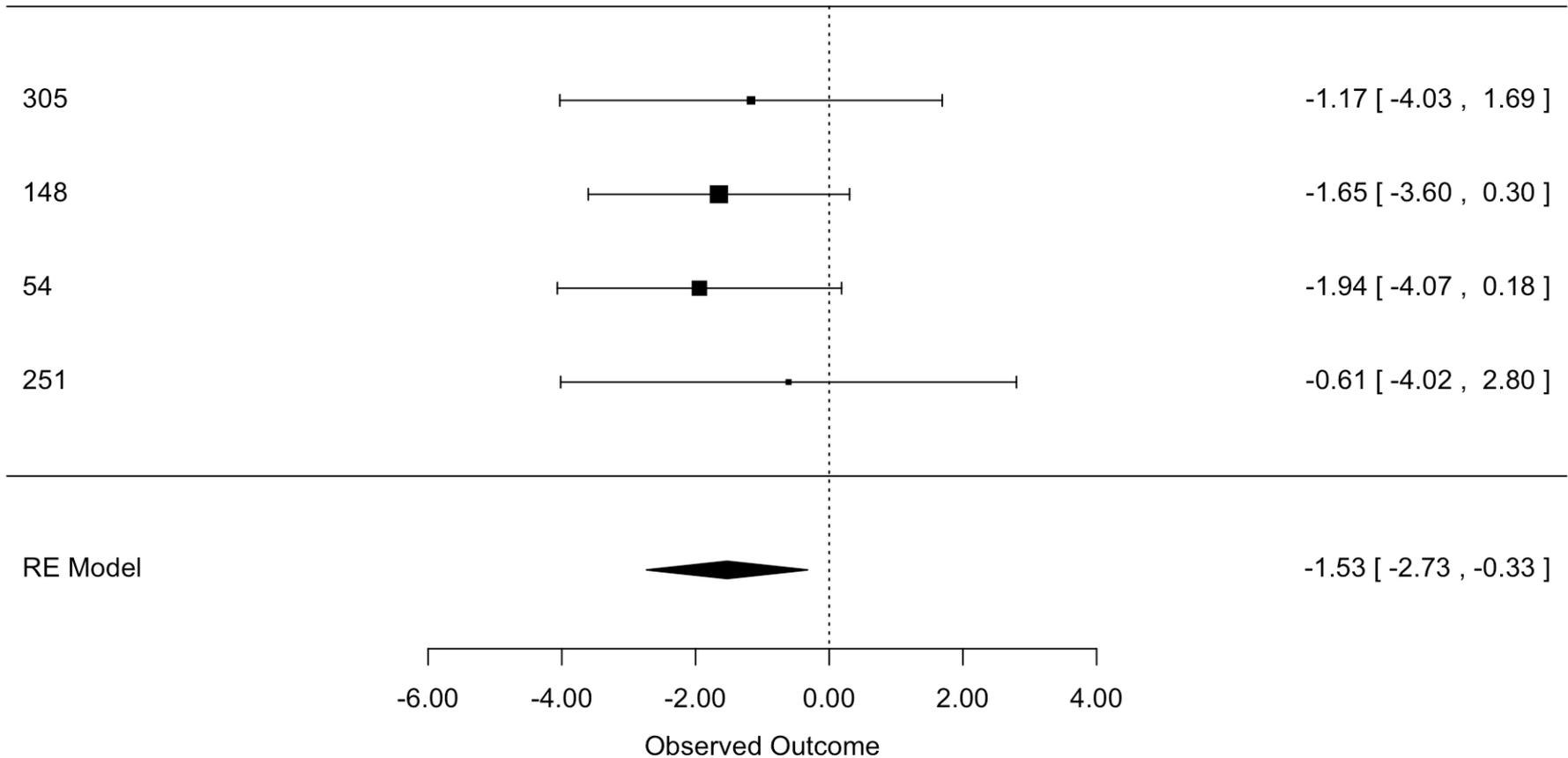
9. Did the study appear to have other problems that could put it at a risk of bias?

Risk of bias ratings

	CHEN Ref ID 54	GUMP RefID 56	ADGENT RefID 84	ESKENAZI RefID 148	GASCON RefID 154	HOFFMAN RefID 169	SHY RefID 209	CHAO RefID 214	GASCON Refid 251	HERBSTMAN RefID 305	ROZE RefID 306	DING-YAN RefID 3539
1. Study groups representation	Probably No	Probably No	Probably No	Probably No	Probably No	Probably No	Probably Yes	Probably Yes	Probably No	Probably No	Probably No	Probably Yes
2. Knowledge of the group assignments	Probably No	Probably No	Probably No	Probably No	Probably No	Probably No	Probably Yes	Probably Yes	Probably No	Probably No	Probably Yes	Probably Yes
3. Exposure assessment methods	Probably No	Probably No	Probably No	Probably No	Probably No	Probably No	Probably No	Probably No	Probably No	Probably No	Probably No	Probably No
4. Outcome assessment methods	Probably No	Probably No	Probably No	Probably No	Probably No	Probably No	Probably Yes	Probably No	Probably No	Probably No	Probably No	Probably Yes
5. Potential confounding	Probably No	Yes	Probably Yes	Probably No	Probably No	Probably No	Probably Yes	Probably Yes	Probably No	Probably No	Probably Yes	Probably Yes
6. Incomplete outcome data	Probably No	Probably No	Probably No	Probably No	Probably No	Probably No	Probably No	Probably No	Probably No	Probably Yes	Probably No	Probably No
7. Selective outcome reporting	Probably No	Probably No	Probably No	Probably No	Probably No	Probably No	Probably No	Probably No	Probably No	Probably No	Yes	Yes
8. Financial conflict of interest	Probably No	Probably No	Probably No	Probably No	Probably No	Probably No	Probably No	Probably No	Probably No	Probably No	Probably No	Probably No
9. Other	Probably No	Probably No	Probably No	Probably No	Probably No	Probably No	Probably No	Probably No	Probably No	Probably No	Probably No	Probably No

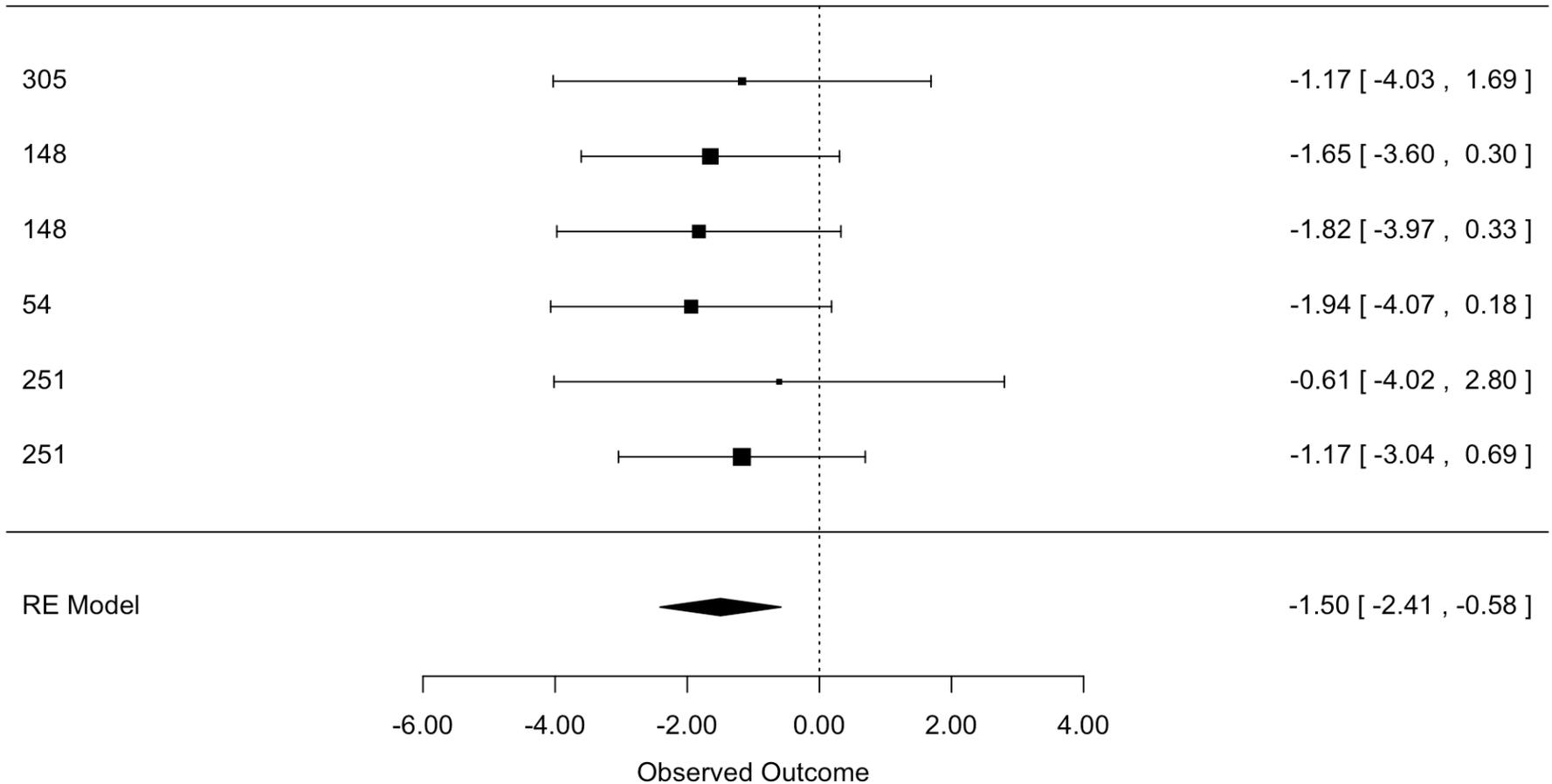
YES
Probably Yes
Probably No
NO

Data analysis--preliminary



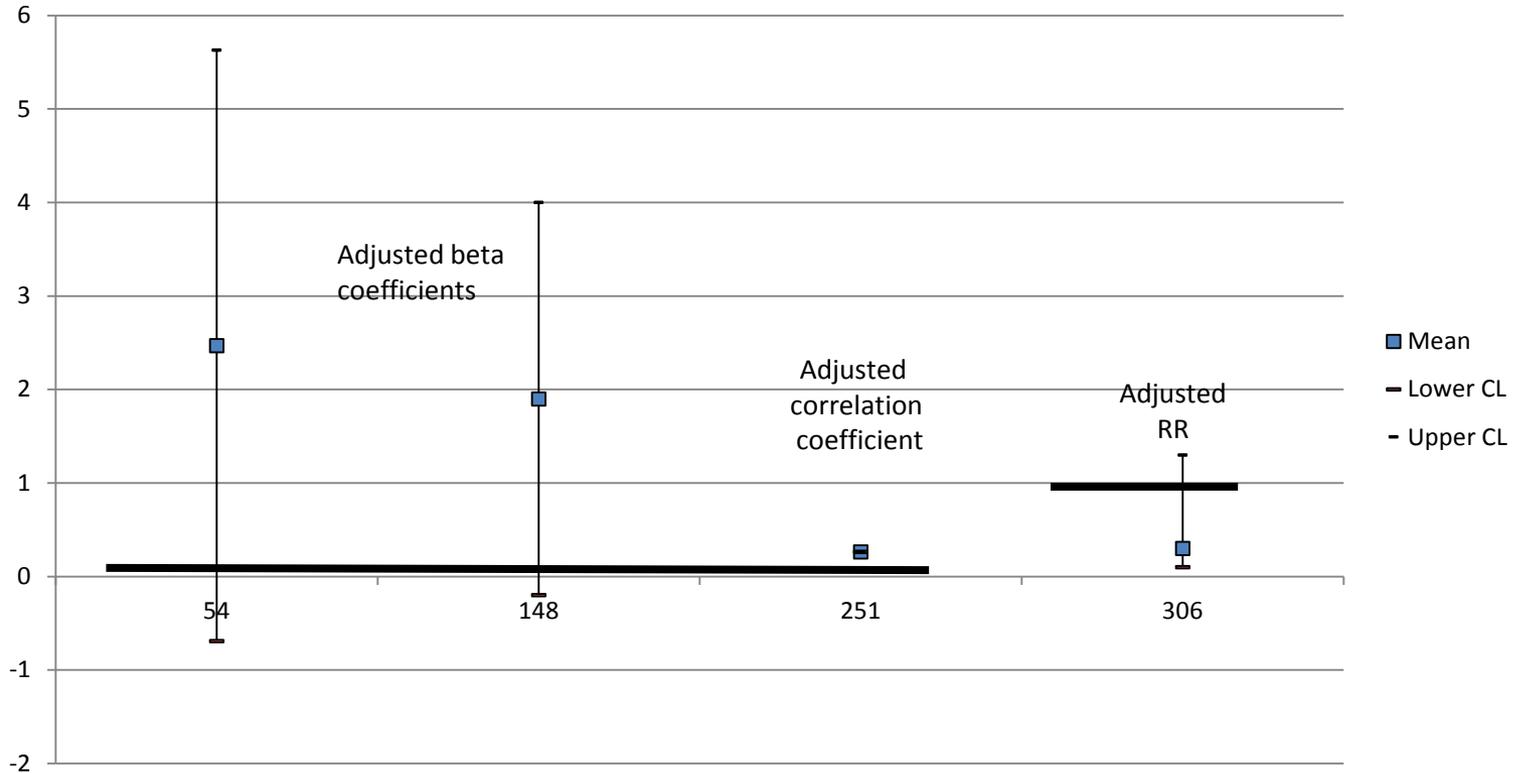
Main Meta-Analysis:
Fetal exposure to BDE-47 → Full Scale IQ

Data analysis--preliminary



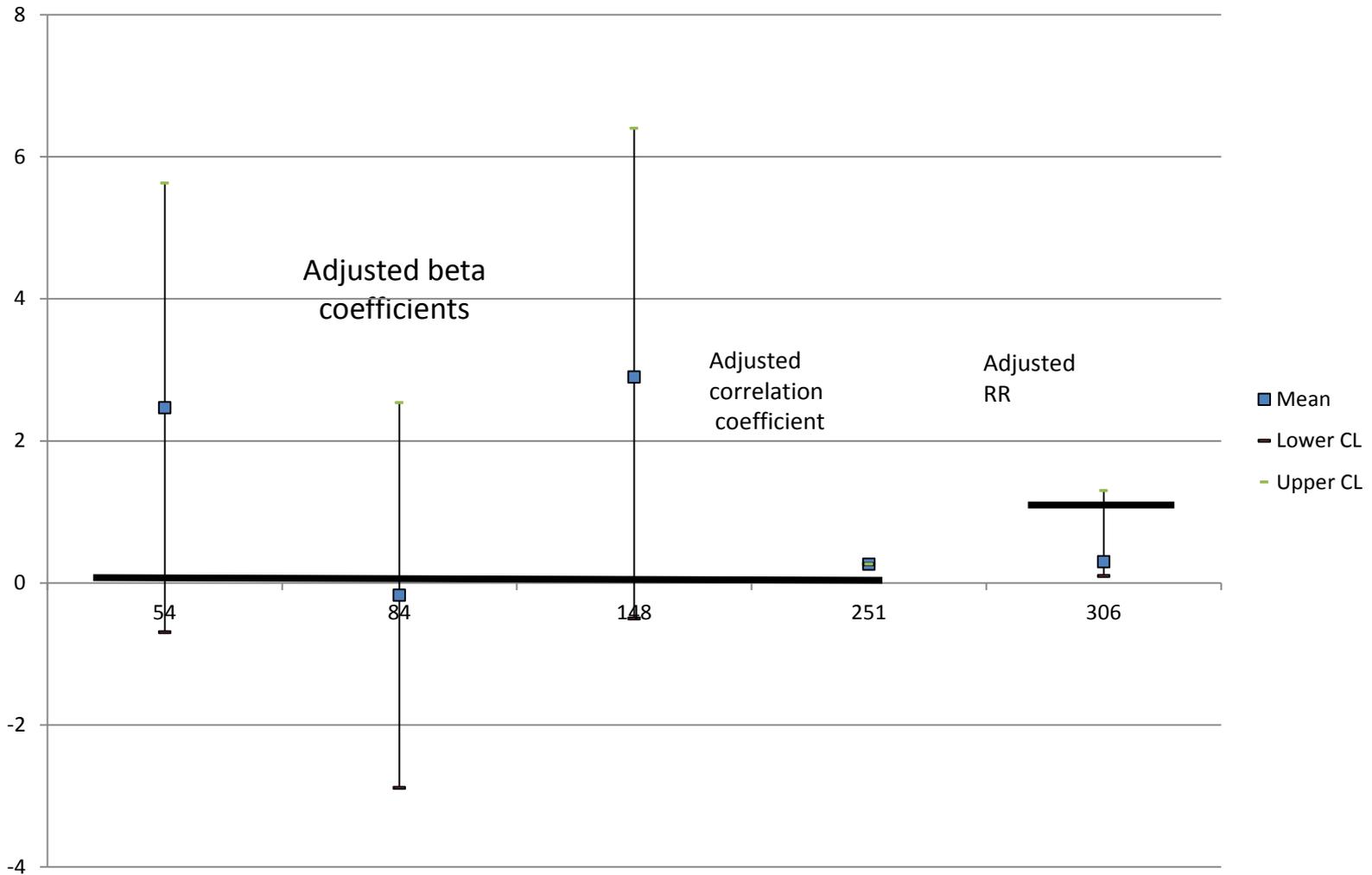
Secondary Meta-Analysis:
Fetal/childhood exposure to BDE-47 → Full Scale IQ

Data analysis--preliminary



Summary estimate plots
Fetal exposure to BDE-47 → ADHD

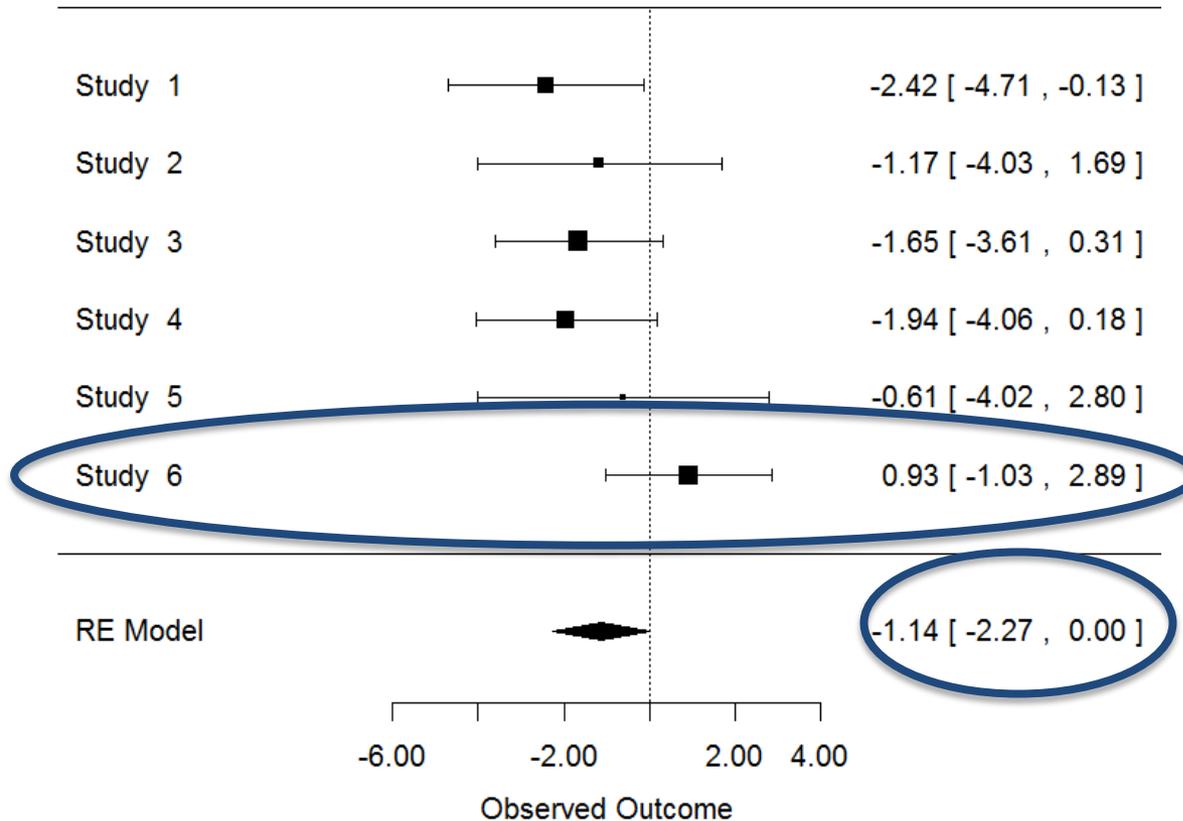
Data analysis--preliminary



Summary estimate plots

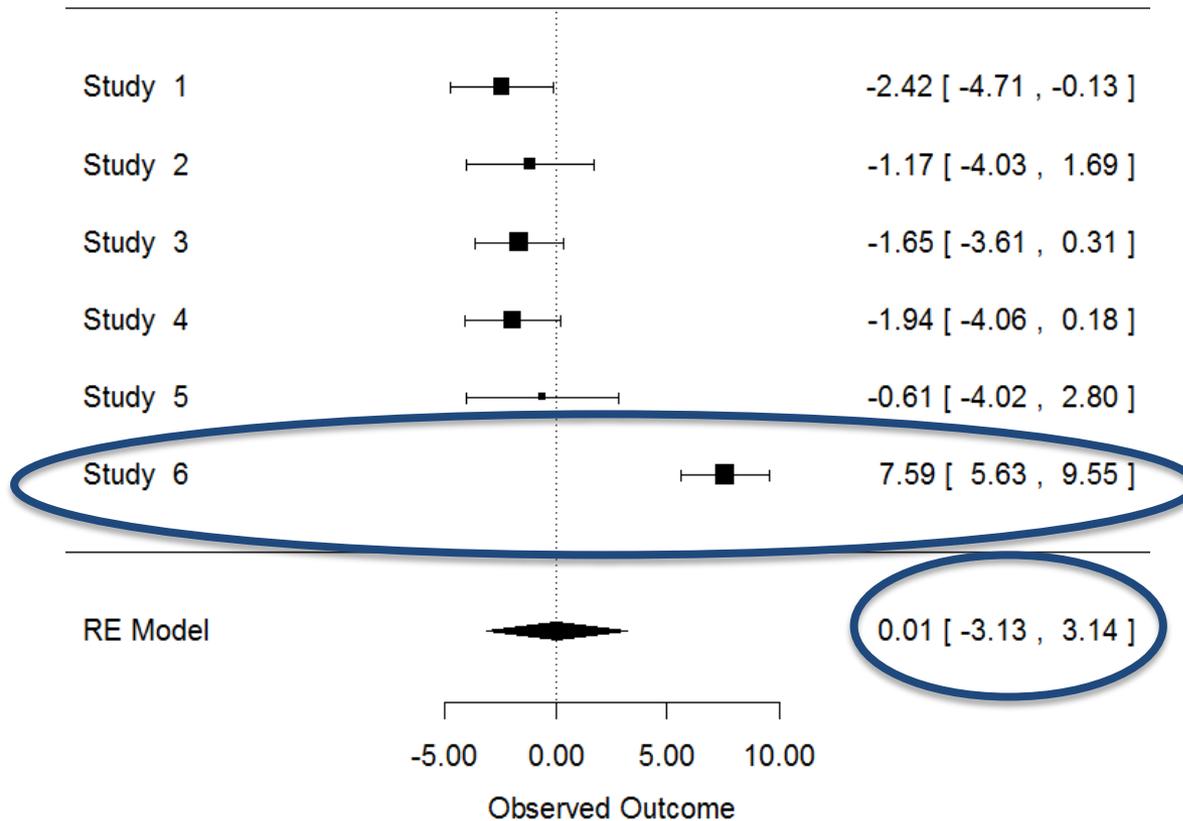
Fetal/childhood exposure to BDE-47 → ADHD

The Counterfactual



A new study would have to have effect size of about 0.93 IQ points to change the overall effect so that the **95% CI overlaps zero**—i.e., no longer statistically significant

The Counterfactual



A new study would have to have effect size of about 7.59 IQ points to change the overall effect size to the **opposite direction**, with 95% CI overlapping zero

Improving the process: registering protocol

- Ongoing debate for epidemiologic study protocols
- PROSPERO: University of York's Center for Reviews and Dissemination.
 - International database of prospectively registered systematic reviews in health and social care
 - Creates permanent online record of protocols, and allows tracking of changes in the process

UNIVERSITY *of York*
Centre for Reviews and Dissemination

PROSPERO International prospective register of systematic reviews

Applying the navigation guide systematic review methodology. Case Study #4: association between developmental exposures to ambient air pollution and autism

Juleen Lam, Patrice Sutton, Alycia Halladay, Lisette Davidson, Cindy Lawler, Craig Newschaffer, Amy Kalkbrenner, Gayle Windham, Natalyn Daniels, Saunak Sen, Tracey Woodruff

Citation

Juleen Lam, Patrice Sutton, Alycia Halladay, Lisette Davidson, Cindy Lawler, Craig Newschaffer, Amy Kalkbrenner, Gayle Windham, Natalyn Daniels, Saunak Sen, Tracey Woodruff. Applying the navigation guide systematic review methodology. Case Study #4: association between developmental exposures to ambient air pollution and autism. PROSPERO 2015:CRD42015017890 Available from http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015017890

Review question(s)

Does developmental exposure to air pollution affect diagnosis of Autism Spectrum Disorder (ASD)?

Searches

We will collaborate with an Information Specialist who has training, expertise, and familiarity with developing and performing systematic review literature searches. We will employ a variety of methods to identify relevant data, as described in the protocol. Our search will not be limited by language or publication date.

We will perform electronic searches of online databases (PubMed, ISI Web of Science, Biosis Previews, EMBASE, Google Scholar, and Toxline) using the search terms developed by a Cochrane-trained librarian (LS) who will implement the search for relevant studies.


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Revision Notes

Revision History

There are no previous versions

<http://www.crd.york.ac.uk/PROSPERO/>

Record ID: CRD42015017890

Improving the process:

: Conflict of Interest Statements

- Conflict of interest is evaluated as risk of bias for each study
- Conflict of interest statements collected from each author
 - Reviewed COI disclosures (OSHA, IRIS, EHP, ES&T, Toxicol Sci, Nature, Science)
- Adapted Science/AAAS
 - List all academic/corporate/industrial affiliations
 - Financial contributions relevant to the case study
 - Financial holdings, professional affiliations, advisory positions, board memberships, patent holdings, etc.

Navigation Guide Authorship Form and Statement of

Conflicts of Interest

Author Name: Tracey Woodruff

Case Study Title: Autism Spectrum Disorder and Air Pollution

Each author must complete the following form.

Conflict of Interest

1. Complete listing of the current institutional affiliations of the authors.

This list must include academic as well as corporate and other industrial affiliations. Please indicate below:

All my affiliations are listed in the case study protocol.

Additional affiliations not on the title page are:

Declaration: I declare that I have read the Navigation Guide's Conflict of Interest form and have disclosed all declarable relationships as defined therein, if any.

This form was submitted on February 13, 2015



Signature _____

Name Tracey Woodruff

Lessons/Issues

- Multiple methods for measuring IQ, ADHD, Neurodevelopment
 - Need more standard approaches for measuring and reporting
- Can sort into more similar outcomes/exposures, but could influence power
 - Focus on most ‘same’, but can also use statistical approaches to integrating ‘diverse’ measurements
- Only evaluated human literature.



Conclusions

- Clarifies and standardizes relationships
- Identifies research needs
- Can be used to say when enough studies are done
- Systematic review approaches to evidence-based decision making can improve capacity to better protect public health



Thank you!

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San Francisco

Program on Reproductive
Health and the Environment

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Case Study Authors

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