Evaluating Neurobehavioral Outcomes after Exposures

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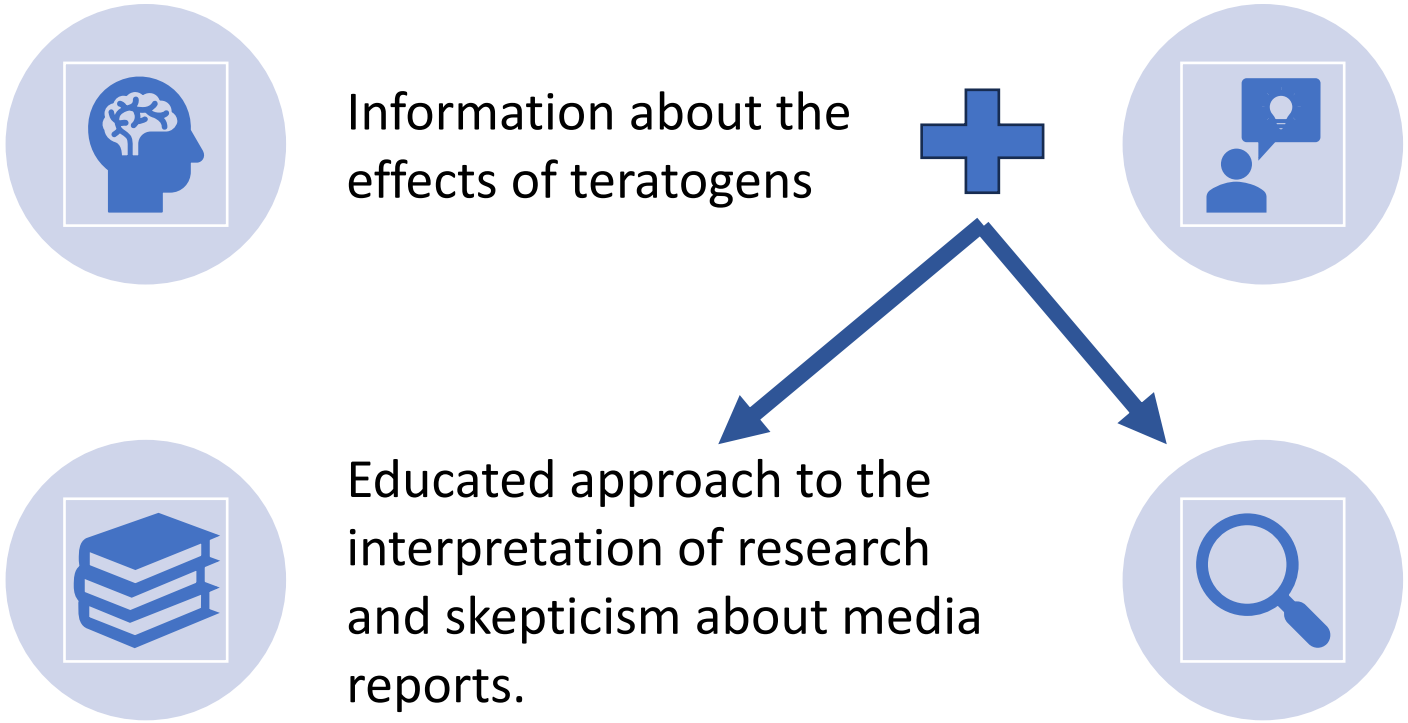
- **The SKK Foundation**

The Speaker has no conflicts of interest to report.

Understanding Effects of Teratogens on Neurobehavior Requires:



Information about the effects of teratogens

Knowledge about development and behavior and factors that influence them over the lifespan.

Educated approach to the interpretation of research and skepticism about media reports.

Employment of Appropriate Methods for Investigation and Analysis

What is a (Neuro)Behavioral Teratogenic Response?

Vorheers stated, (In: Riley & Vorhees, eds,1986, p34)

"Behavioral teratogenesis is expressed as

(1) impaired cognitive, affective, social, arousal, reproductive, and sensorimotor behavior:

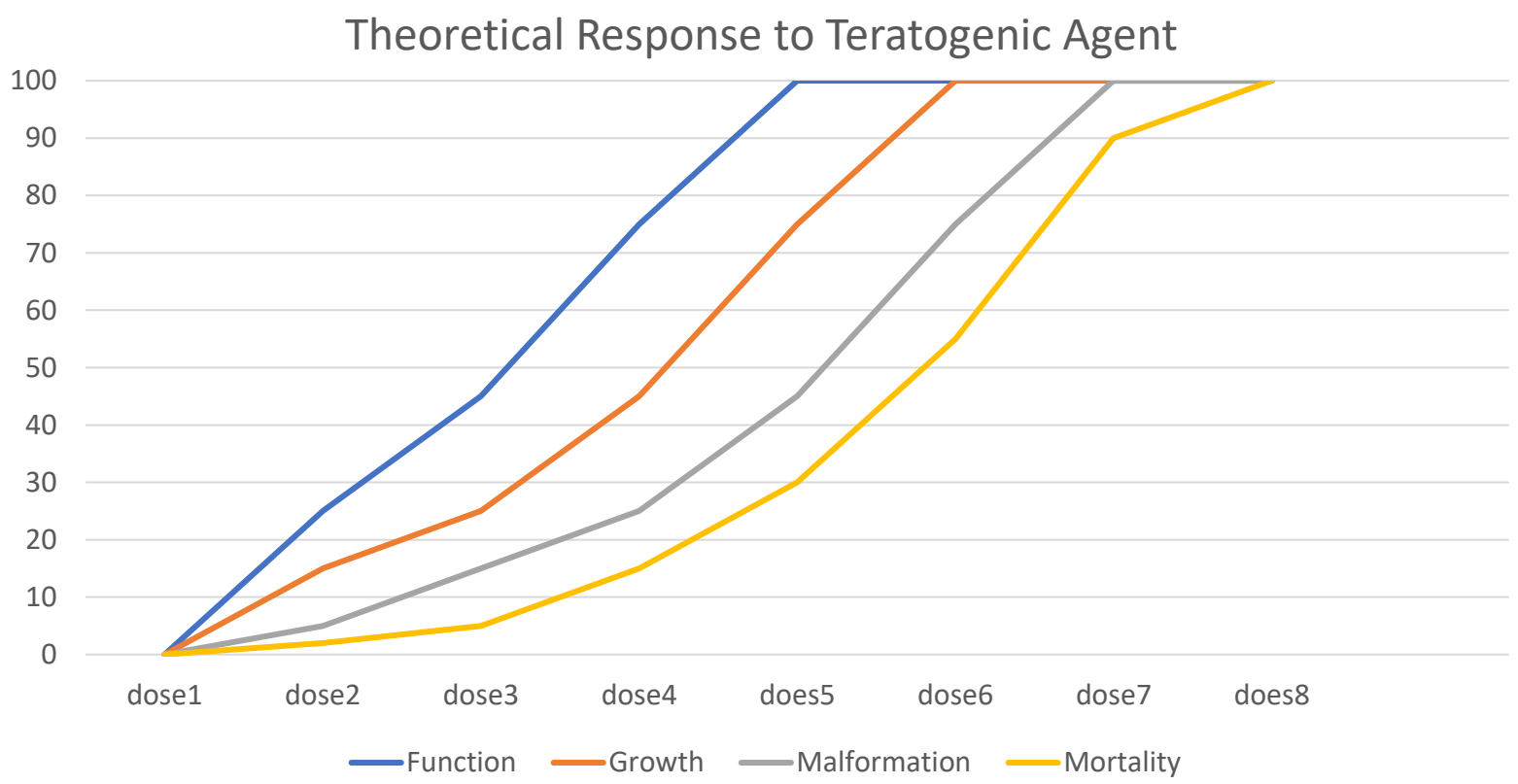
(2) delayed developmental maturation of these capacities; or

(3) other indices of compromised behavioral competence"

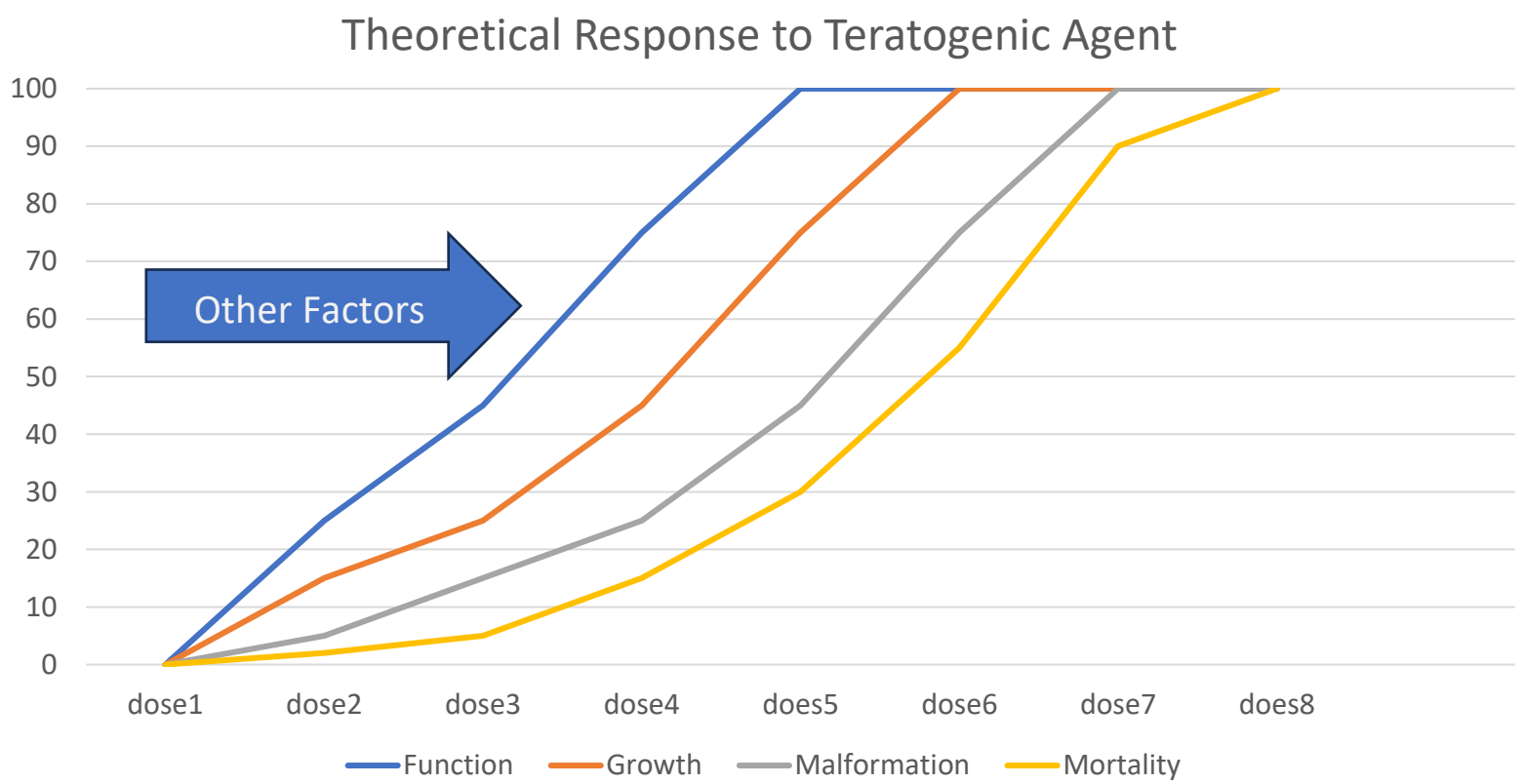
The Developing Embryo (1st Trimester) and Fetus (2nd and 3rd Trimester) Are Vulnerable to Many Agents

- Impact depends on
  - Type of agent
  - Timing of exposure
  - Duration of exposure
  - Amount of exposure
  - Vulnerability of the organism
  - Associated factors that may also affect the organism
    - Other exposures
    - Maternal health
    - Events in pregnancy/delivery
    - Postnatal environment

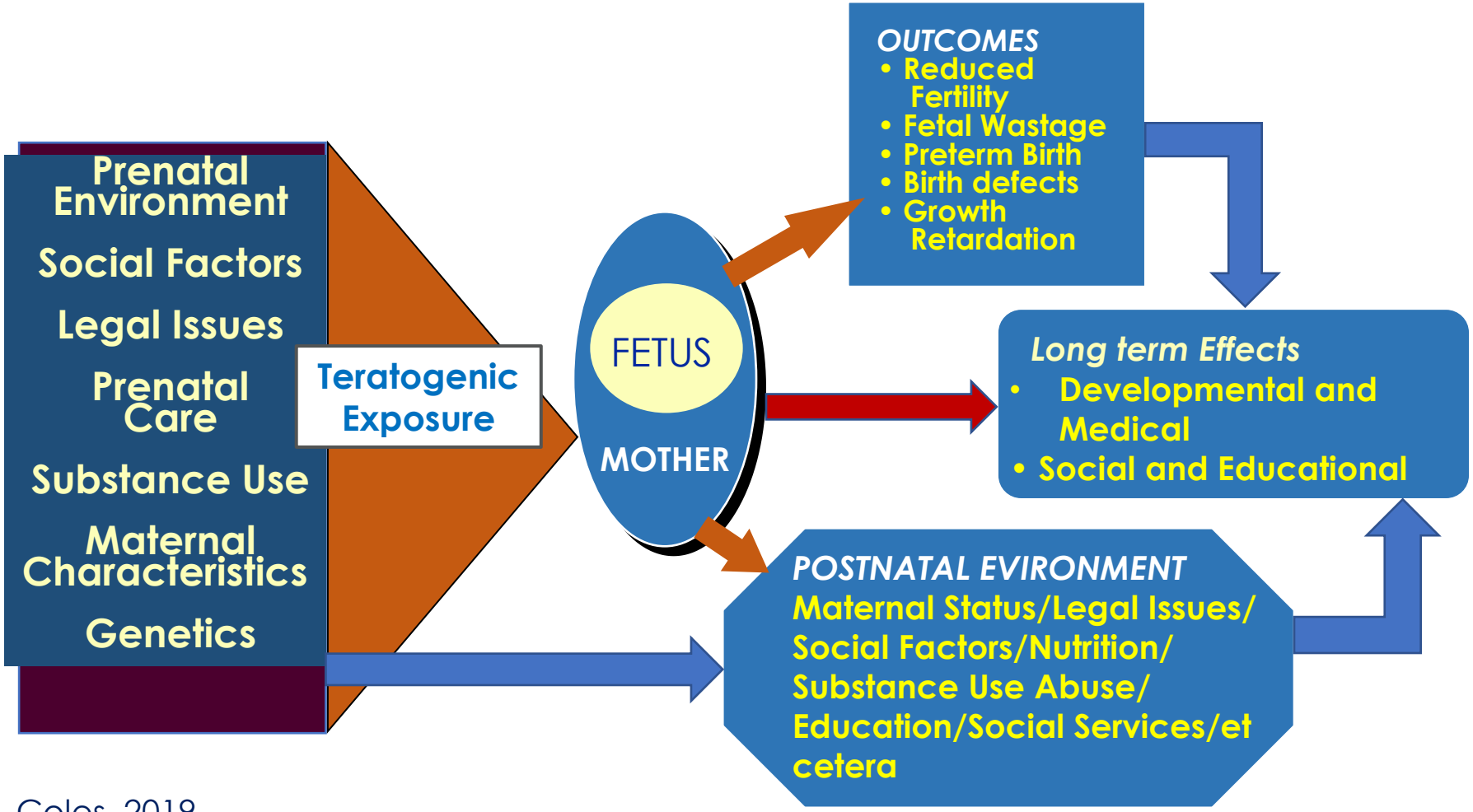
Dose/Response: Function to Mortality



Dose/Response: Function to Mortality



Multi-Factor Model



Coles, 2019

So, how do we know there is a Neurobehavioral effect ?

- Cognitive Deficits-How defined?
  - Deficits that impact development and adaptive function in a clinical sense
  - Relative deficits in relation to a non-exposed contrast group (small but significant effect size)

Clinical Significance

Statistical Significance

- Emotional/Behavioral Effects
  - In addition to the above, how to account for potential environmental/social confounds?

How to Measure Neurobehavior

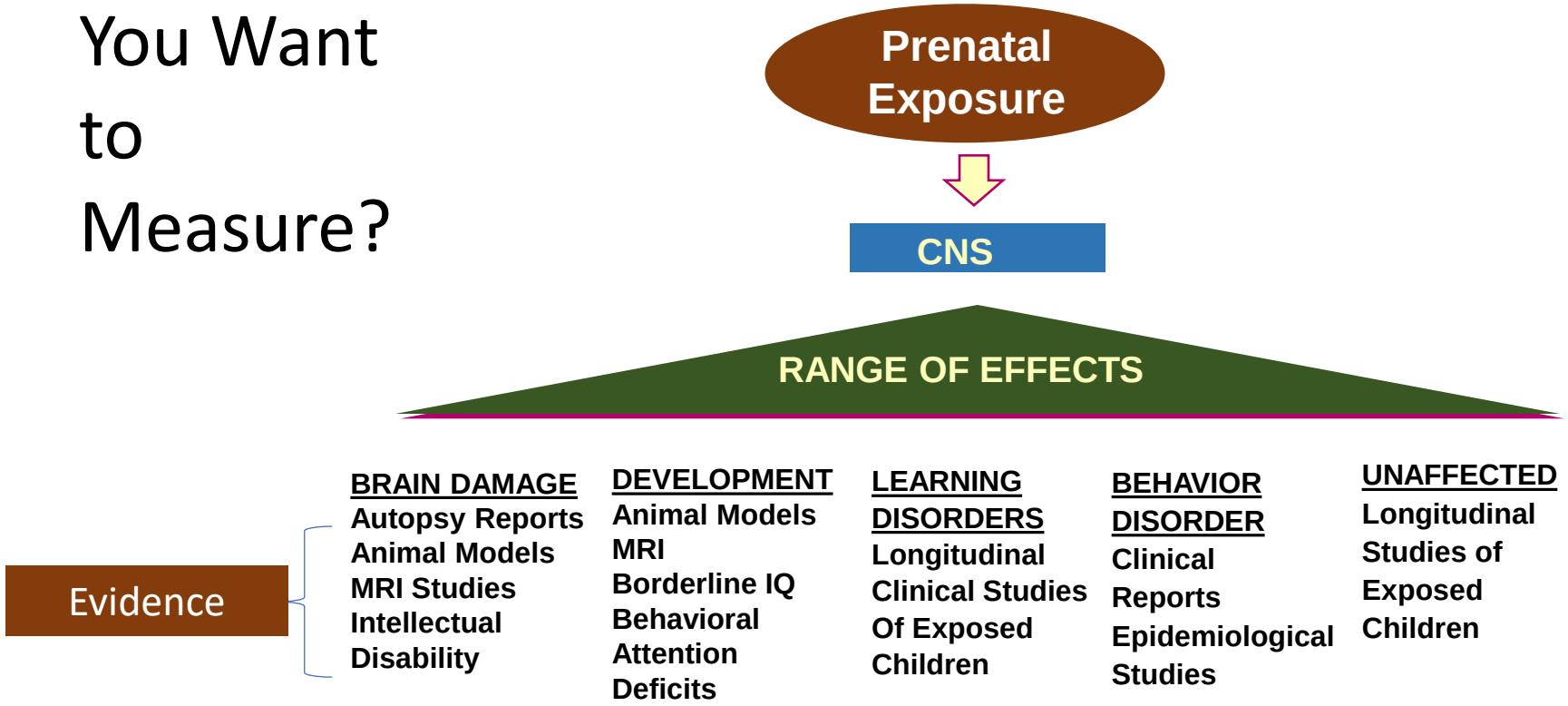
- Assumptions
  - Neurobehavior is based on CNS
  - There is a range of impact of the teratogen on the CNS.
  - There are Normal ranges of all behaviors that we might seek to measure. We have to decide what constitutes an outcome of interest.
  - These outcomes change over development and have a reliable developmental sequence.
  - Because of the developmental sequence, there are limitations on what can be measured, and when.
  - External factors (e.g., SES) affect the outcomes that we are interested in.

Some Initial Questions about Neurobehavioral outcomes

- WHAT do you want to measure (to demonstrate neurobehavioral effects)
  - It can't always be ADHD and Autism!
- WHY have you chosen those outcomes?
  - What constitutes an impact of the potential teratogen?
- WHEN do you want to measure it?
- HOW can you measure it?
- How can you account for other influences?

What Do You Want to Measure?

Effects of Prenatal Exposures On Central Nervous System (CNS)



Ideally, identify the behaviors of interest postnatally rather than waiting until later in life to avoid the effects of confounders and allow early intervention.

- But, you can't do that. You can't give a newborn an IQ test or evaluate their math ability or measure their anxiety.
- If the effects of "prenatal programming" emerge in middle adulthood, you will miss them completely if you stop measuring before that time.
- Longitudinal research is expensive and difficult. If you are going to target a specific outcome, decide when it is likely to be most observable.

WHEN do you want to measure?

- When during development is the appropriate time to measure effects of a teratogen?
- *When the problem occurs, of course!*

- This will depend on the extent of the impact as well as the developmental course of the outcomes of interest.

  - Motor function ⟹ Infancy
  - Language ⟹ Preschool
  - Executive Function ⟹ Early School Age
  - Long term Health ⟹ Middle Age

HOW do you decided what to look for?

- “Standard” Developmental Outcomes used in teratogenic research
- Clinical Reports and Chart Reviews
- Previous Research/Animal Models
- Theory (e.g, DOHaD)
- Latest “fads” in the field-Does everything cause autism and ADHD?
- New “toys” or techniques

4. When specific effects are described, mechanisms may be identified.

3. Longitudinal research can identify confounding factors and stability of effects as well as later emerging problems.

2. The next steps will be more focused and refined based on earlier research.

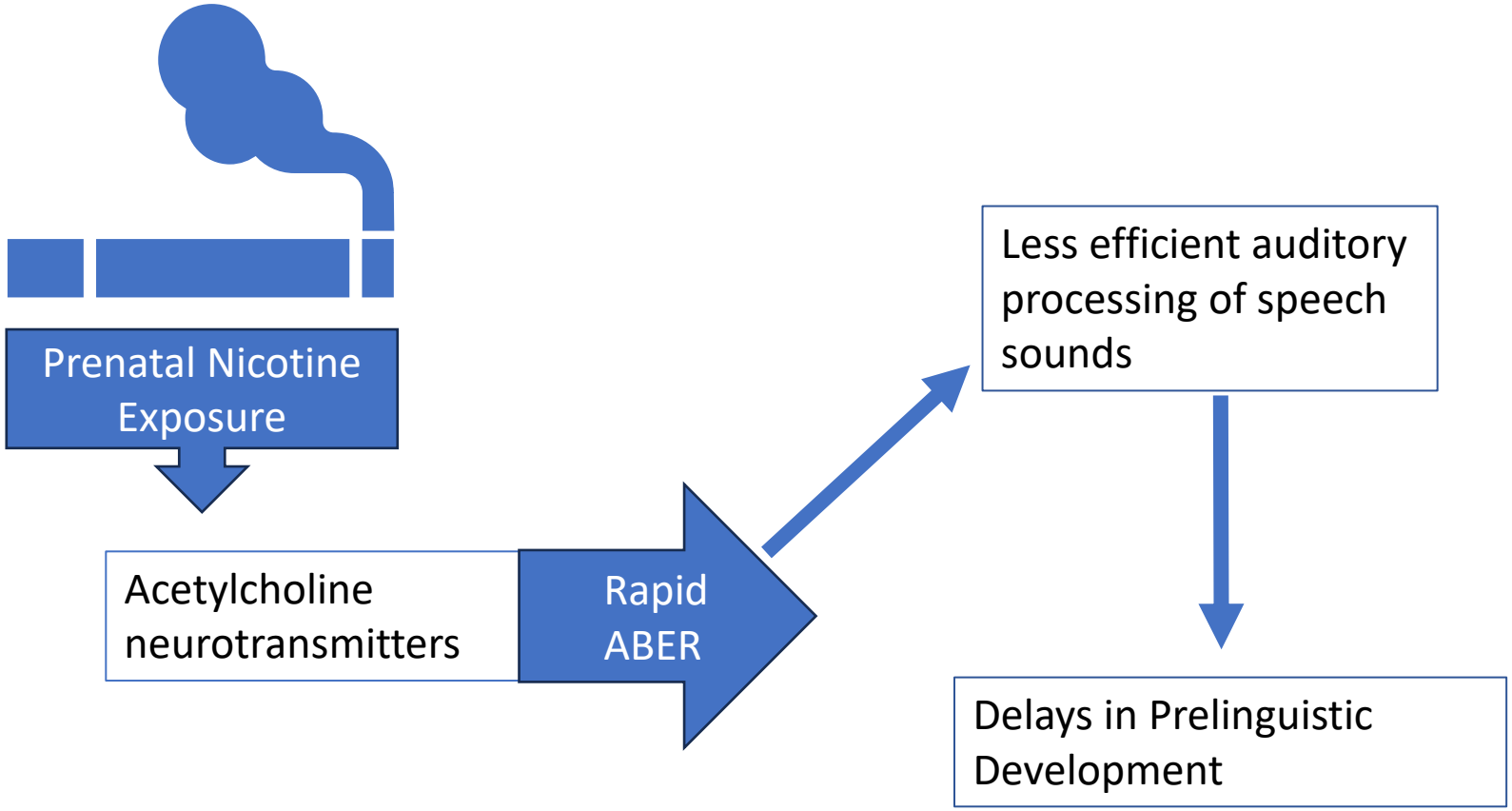
1. First steps are a general descriptive “scan” of outcomes

Should you do a Global or Targeted Assessment?

- A teratogen (alcohol, lead) may have a global impact
  - e.g., leading to lower IQ scores in exposed individuals
- The same agent may produce more specific deficit due to difference in dose, critical period or individual characteristics.
  - e.g., specific deficits in memory and attention
- Different agents (i.e., nicotine vs alcohol) might be associated with specific and different deficits.

When there is not a global effect, understanding the neurobehavioral effect may require a targeted focus

- Tobacco exposure affects birthweight but does not produce dysmorphology. Similarly, its neurobehavioral effects are specific rather that global.
- Alcohol which, at high doses, can lead to birth defects and growth retardation as well as global cognitive deficits, at lower doses may have specific effects in limited domains.



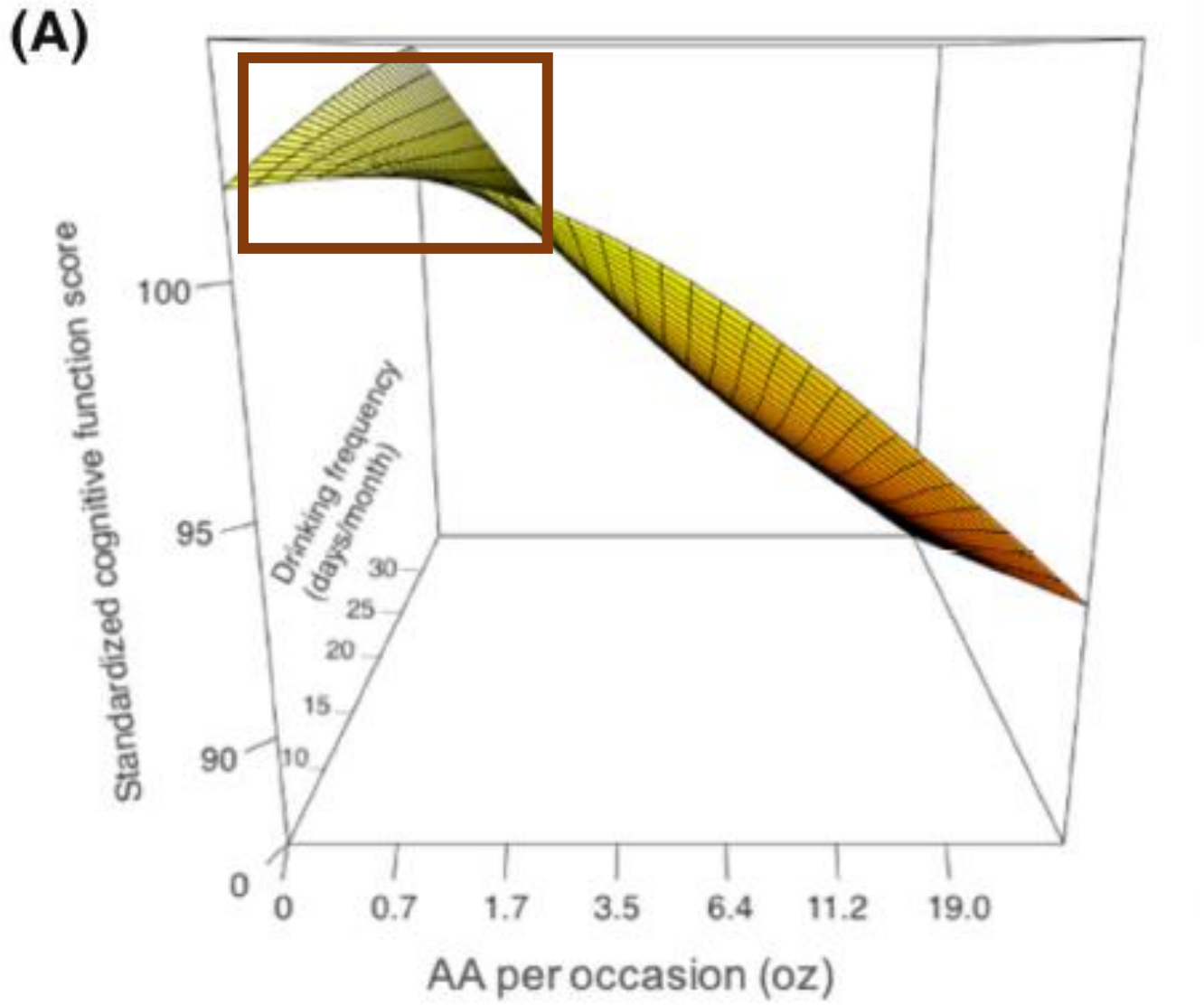
With:
No effect on DQ or IQ
No effect on global motor
Probably effects on Behavior

(Specific) Nicotine Effects on Early Language Development

Kable, JA, Coles, CD, Lynch, MA, & Carroll, J (2009). The Impact of Maternal Smoking on Fast Auditory Brainstem Responses, Neurotoxicology and Teratology. 31 (4) 216-224. PMID 19224709

Surface plot showing the joint effects of maternal alcohol dose/occasion and drinking frequency (Adjusted for propensity scores) on offspring cognitive function.

As drinking frequency (days per month) increases, scores decrease. Similarly, as AA per occasion increases, scores decrease. There is a “threshold” after 1 to 2 drinks per occasion where cognitive function falls off.



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RESEARCH ARTICLE

ALCOHOL CLINICAL & EXPERIMENTAL RESEARCH

A dose–response analysis of the effects of prenatal alcohol exposure on cognitive development

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ALCOHOLISM: CLINICAL AND EXPERIMENTAL RESEARCH

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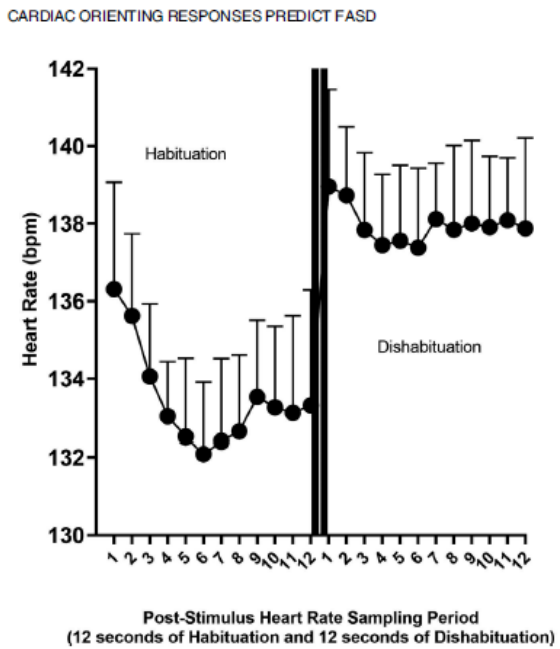
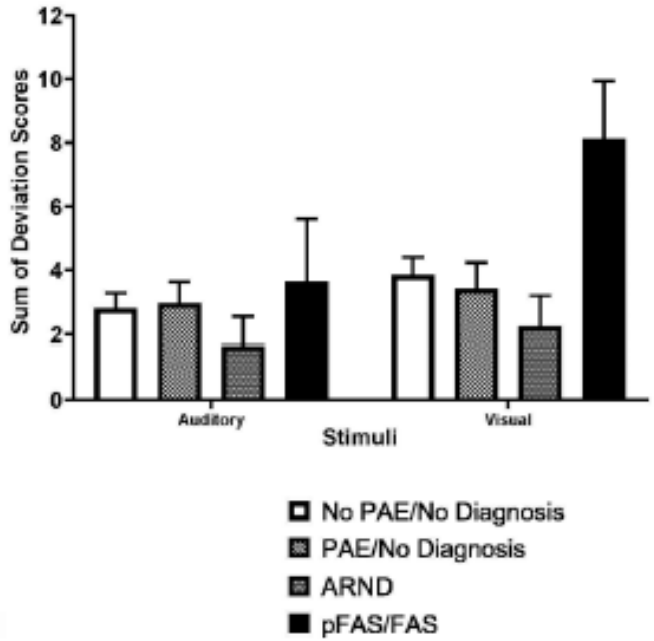
Infant Cardiac Orienting Responses Predict Later FASD in the Preschool Period

Julie A. Kable, Claire D. Coles, Kenneth L. Jones, Lyubov Yevtushok, Yaroslav Kulikovsky, Natalya Zymak-Zakutnya, Iryna Dubchak, Diana Akhmedzhanova, Wladimir Wertelecki, Christina D Chambers, and CIFASD

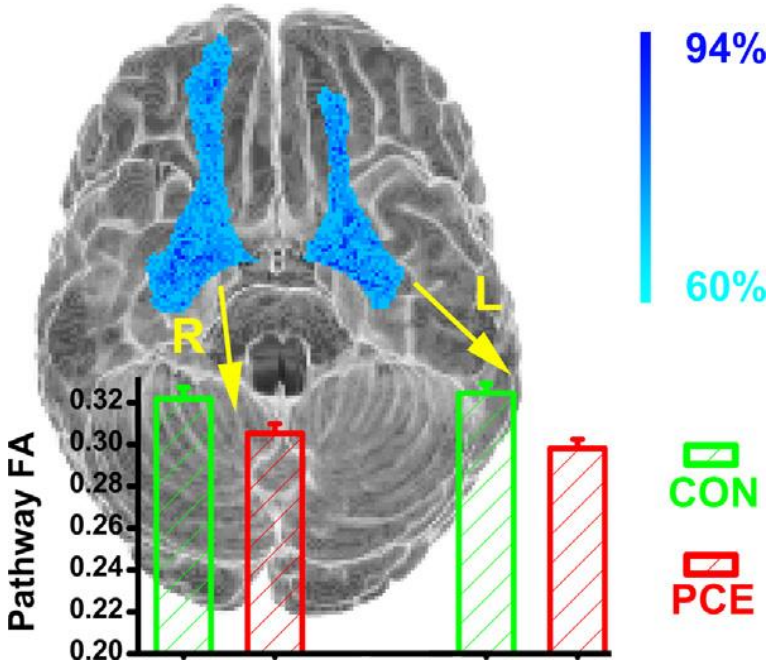




Long term effect of stimulants on development

In the absence of effects on Growth or Ability, stimulant exposure appears to affect Arousal Regulation and Externalizing Behavior.

- Based on neuroimaging studies with our samples, the amygdala seems to be more sensitive to stimuli than in controls and the regulatory function of the prefrontal cortex in moderating arousal is attenuated.
- This was suggested by behavior in the sample as young as 8 weeks and observed via neuroimaging during adolescence in the same individuals.



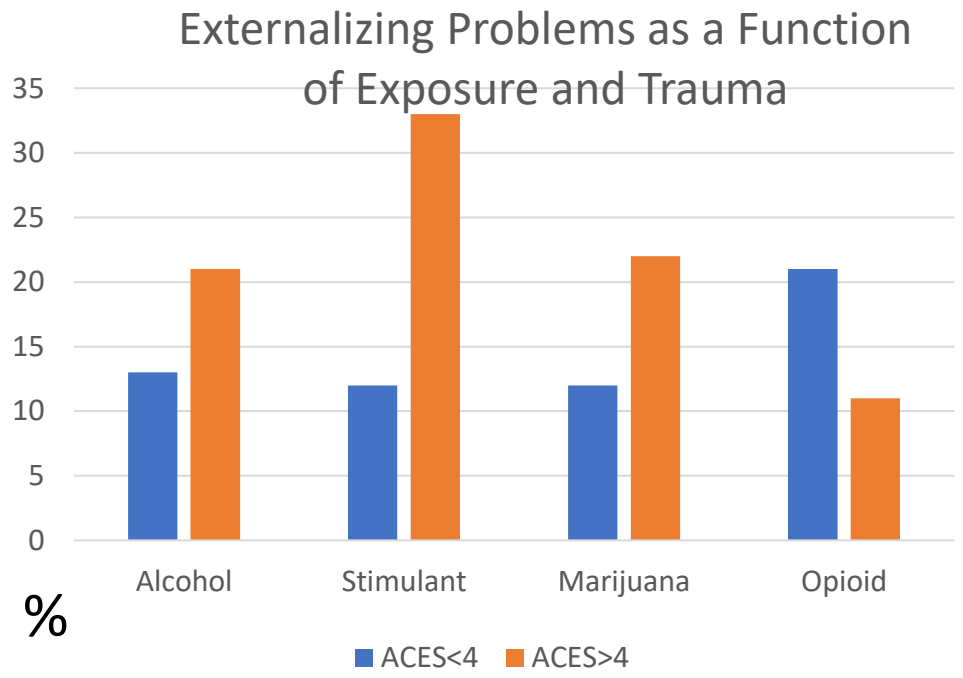
From, Li, et al, Psychiatry Research: Neuroimaging 213 (2013) 47–55

And understanding effects may have to take into account the effects of other environmental events.

Effects of Prenatal Exposure and Adverse Childhood Experiences (ACES) on Behavior Problems

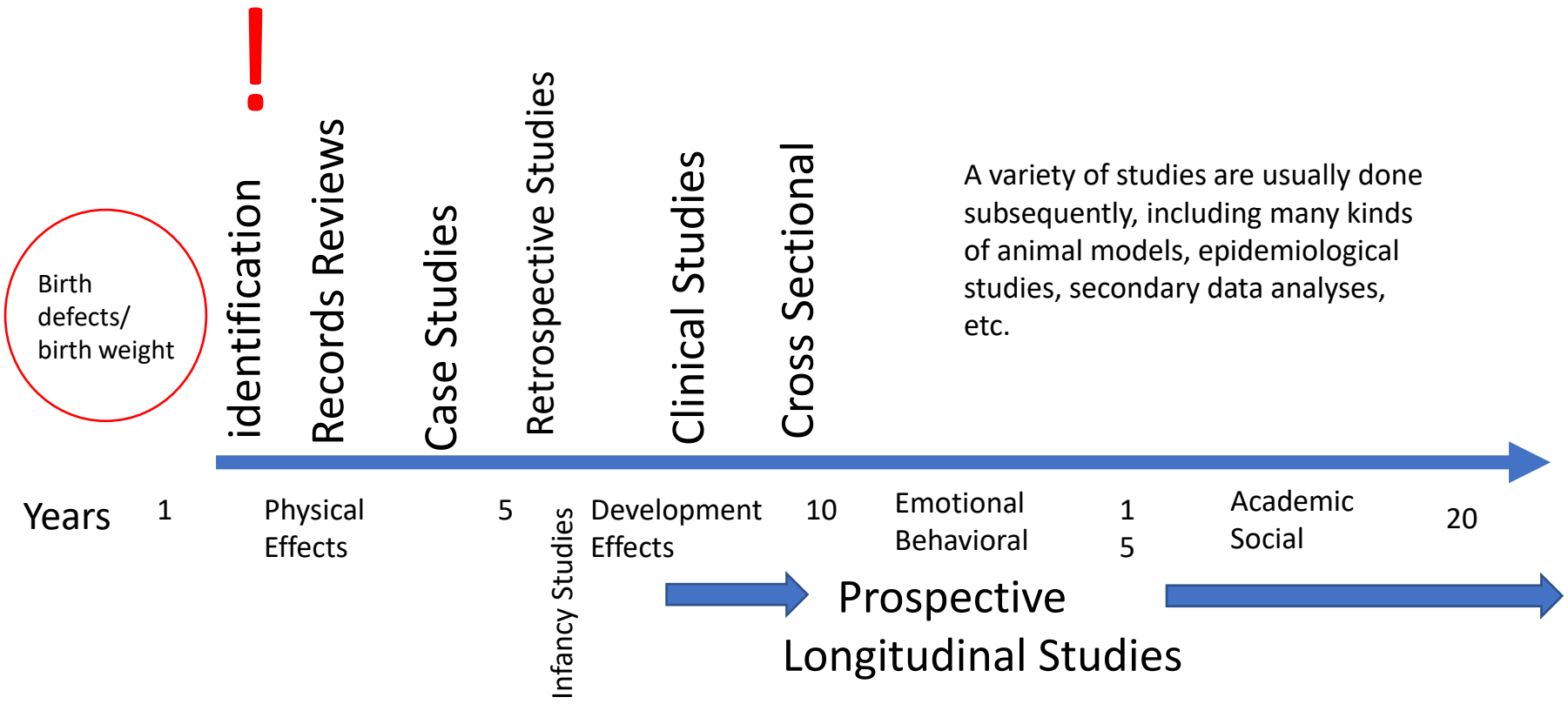
In 308 children, males (56.5%) and females (43.5%), we compared the effects of ACEs on those exposed to Alcohol, Tobacco, Stimulants (Cocaine/Methamphetamines), Marijuana and Opiates.

- Ages were 1 to 18 years with 60%, 5 years or less.
- Mean ACES= 3.90 (SD=2.39)
- On the Child Behavior Checklist (CBCL), more problems reported in males; but females' behavior was more affected by trauma (ACES) showing a greater increase in negative behaviors as a ACEs increased.
- Stimulant exposure showed an interactive effect with ACES on Externalizing problems .
- Effect of other drugs and ACEs were additive vs. interactive.



Bowers, PT, Kable, JA, Millians, M, & Coles, CD. Behavioral impact of childhood traumatic stress in children with prenatal substance exposure. Child Welfare, 2023.

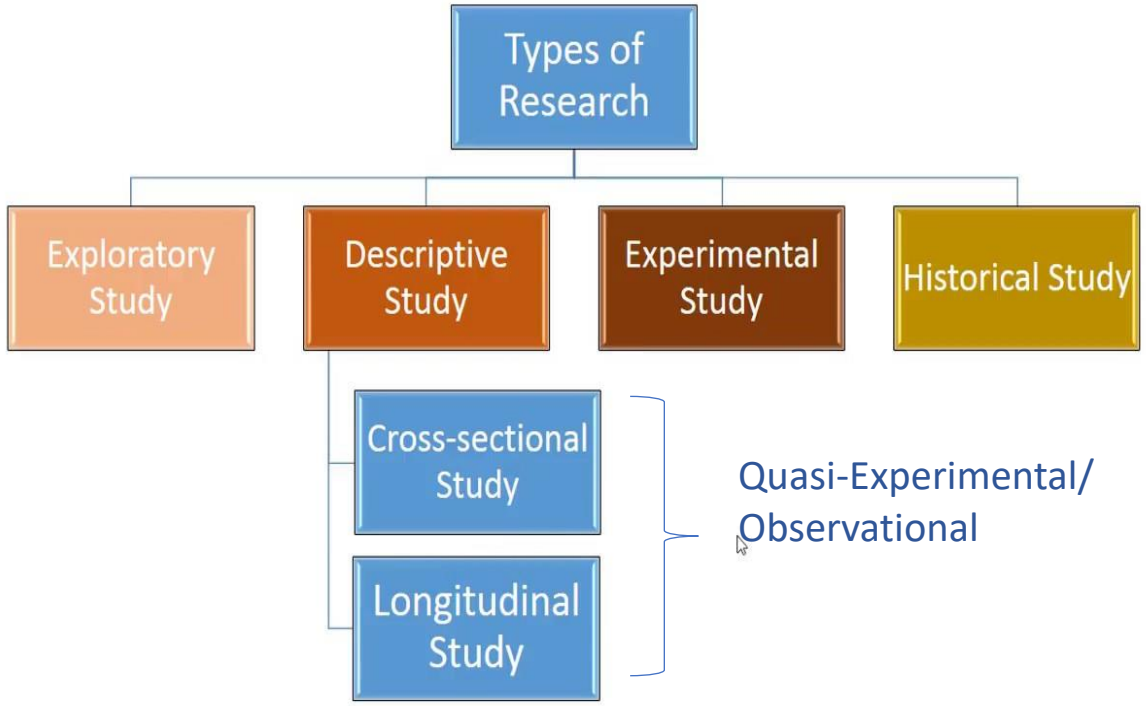
Teratogens:
From Discovery to Prevention



Research Design Considerations:

Did the design maximize effects and reduce error while yielding an accurate result?

- Did it answer the research question?
- Avoid various sources of error (bias)?
- Appropriate sample size?

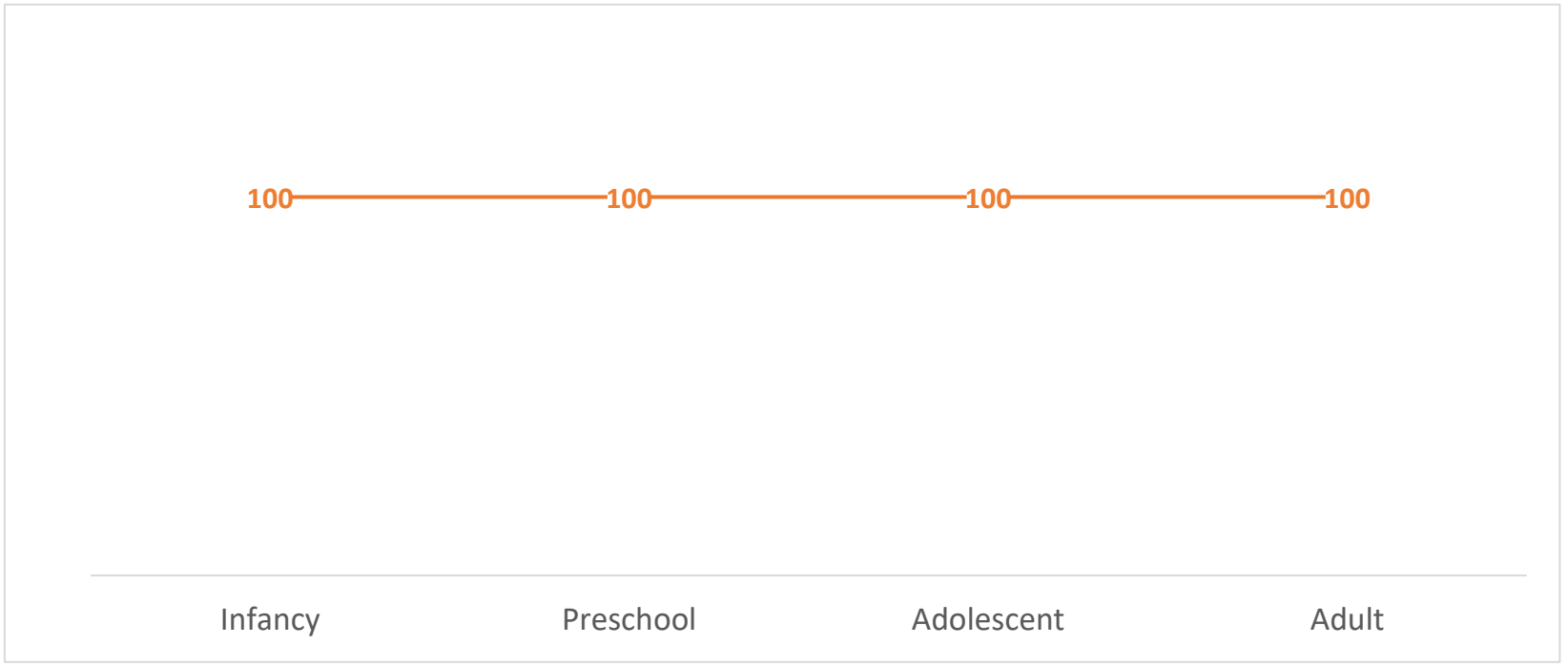


Experimental Studies, that best control Confounding factors and can infer causation, cannot be done in human samples.
Cross-Sectional Studies are faster and typically employ clinical samples and therefore exaggerate effects.
Longitudinal Studies better describe the range of outcomes but take time and money.

The Challenge in understanding observed effects

- We observe that clinically-referred individuals who have prenatal exposure to alcohol (for instance) have cognitive challenges, “hyperactive” behavior, emotional dysregulation, social problems, difficulties with academics, poor judgement and may have trouble with the law.
- Many of the observed behaviors might be attributable to environmental factors. Which of these outcomes can we attribute to the prenatal exposure?
- Have we controlled for:
  - Socioeconomic status (Appropriate Contrast Groups)
  - Early Adversity (ACEs)
  - Other pre and postnatal exposures
  - Internal and External Validity Threats

Effects of prenatal Alcohol exposure in relation to various contrast groups



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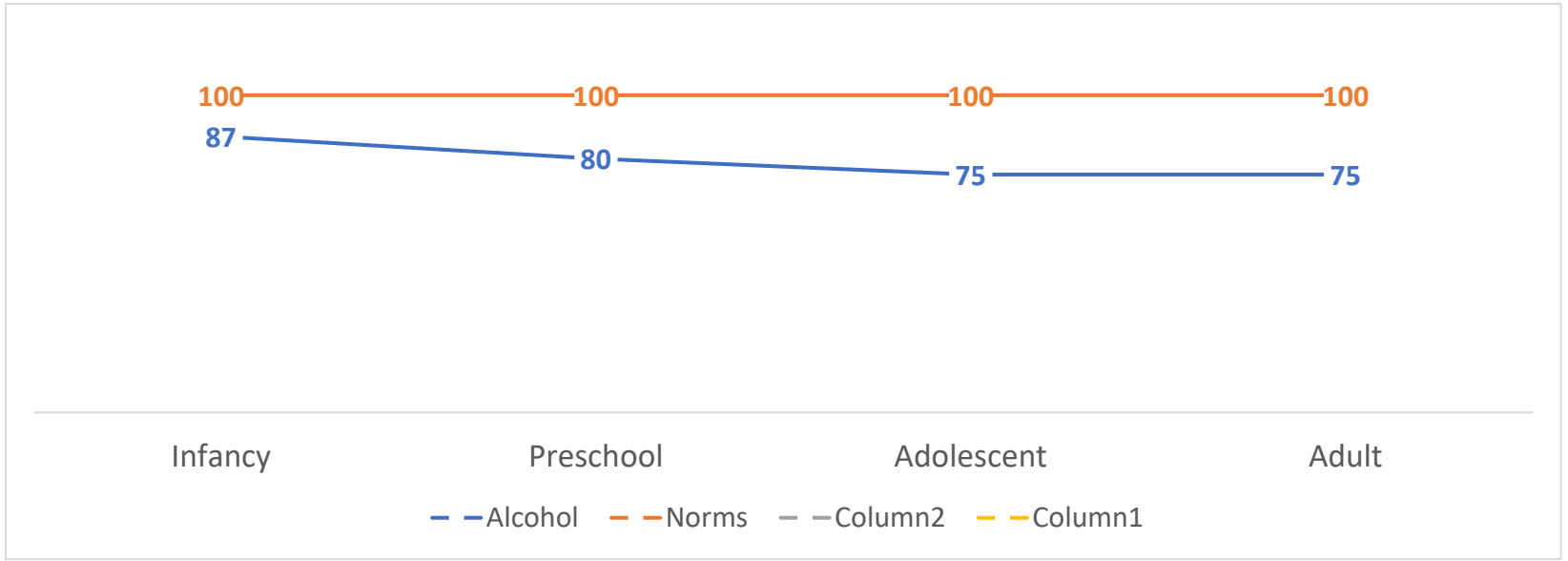

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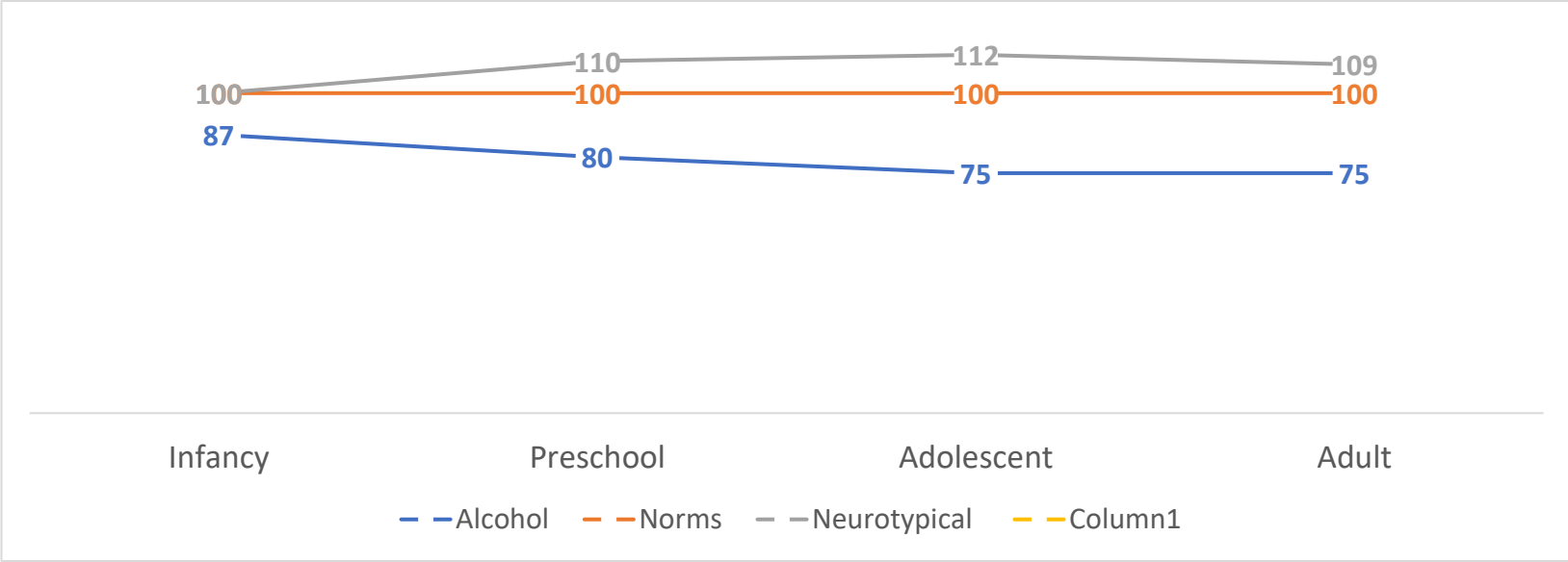

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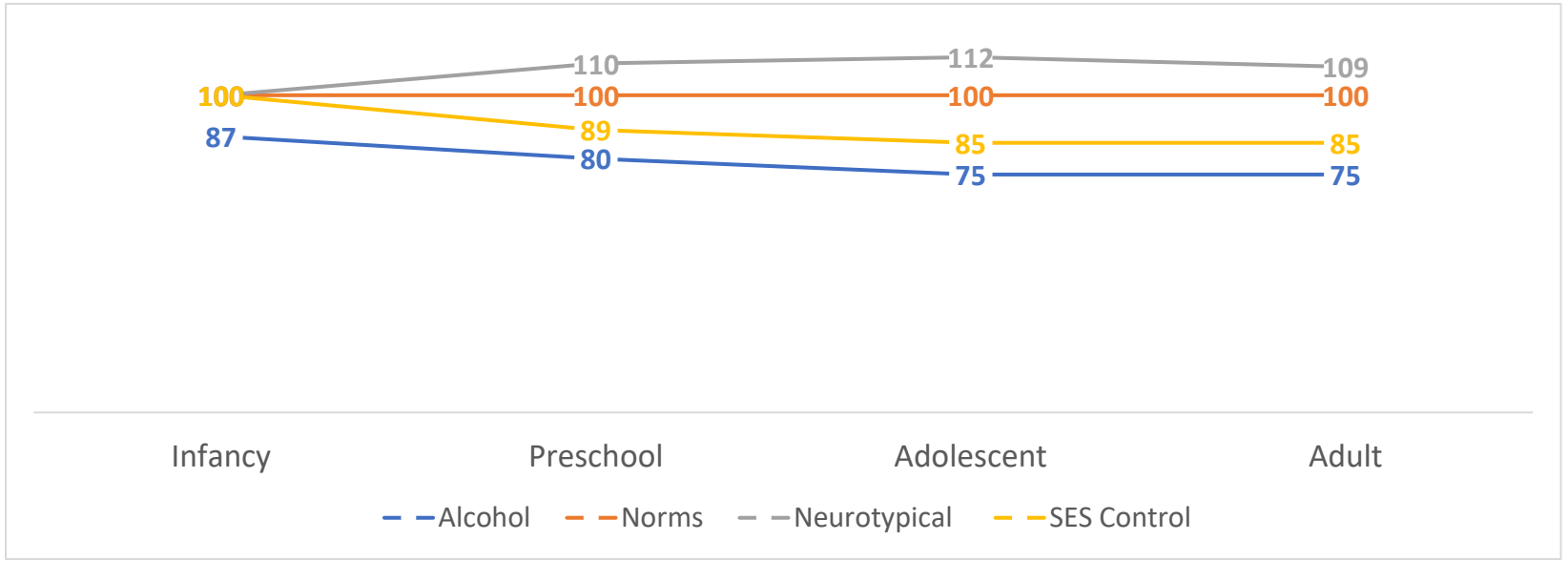
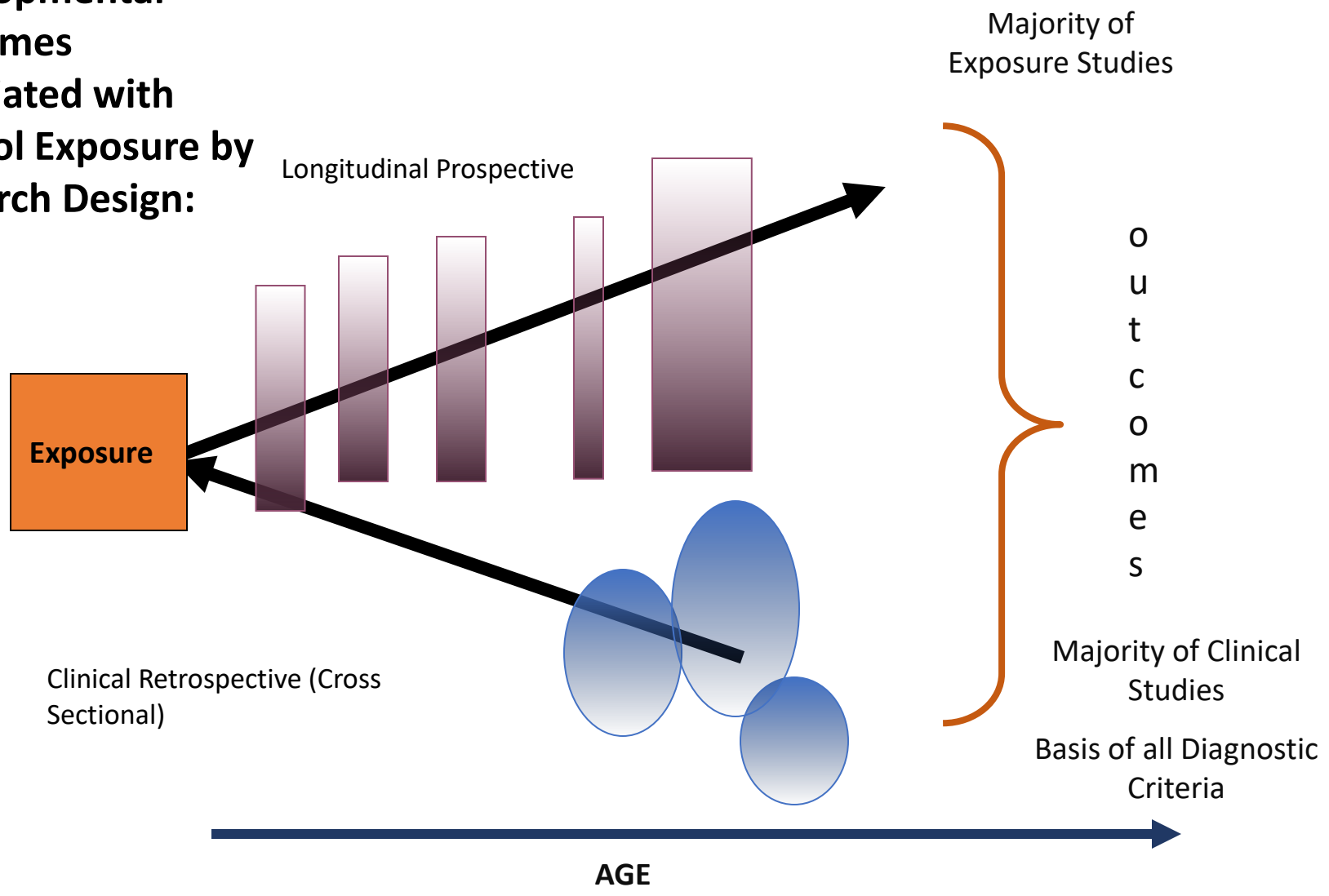


Discrepancy in Developmental Outcomes Associated with Alcohol Exposure by Research Design: FASD



Bandoli, G, Hayes, S, & Delker, E (2023). Low to moderate prenatal alcohol exposure and neurodevelopmental outcome: A narrative review and methodological considerations. Alcohol Research: Current Reviews, 43.

To Summarize

Understanding neurodevelopmental effects of exposure requires:

- Systematic observation of outcomes among exposed individuals and appropriate contrast groups using appropriate research designs.
- Developmentally informed assessment that takes into account the exposure, typical patterns of development and other factors that can impact development.
- Multiple studies that converge on the same results, typically involving different types of research designs.

Questions and Comments?

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- Center for Maternal Substance Abuse and Child Development (MSACD)

  MotherToBaby.GA-A Teratology Information Service (M2B.GA)

  Emory Neurodevelopment and Exposure Clinic (ENEC)