Evaluating Neurobehavioral Outcomes after Exposures

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- Centers for Disease Control and Prevention (CDC)
- The SKK Foundation

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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.

What is a (Neuro)Behavioral Teratogenic Response?

Vorheers stated,

- *"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"*

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

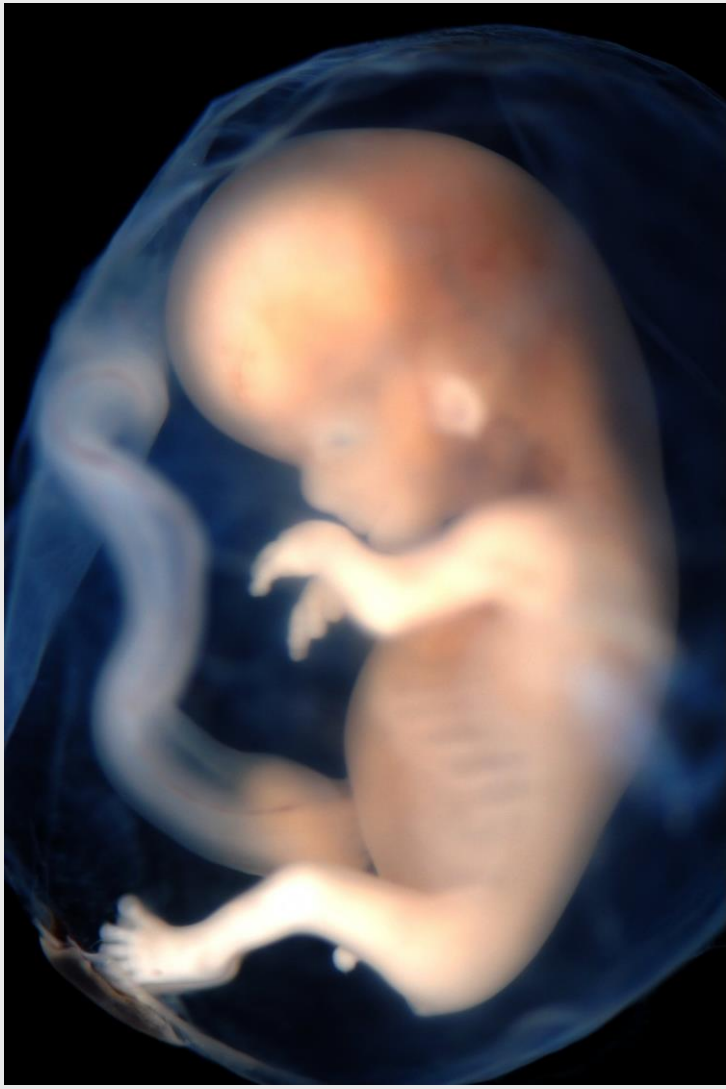
Vorheers' Principles (adapted from Wilson's, 1977)

1. Genetic Determination
2. Critical Periods
3. Specific Mechanism-Phenotypes
4. Behavioral Teratogenic Response (needs more explanation)
5. Target access (Type of agent)
6. Dose-Response
7. Environmental Determinism (pre and post natal)
8. Only CNS/psychoactive agents affect neurobehavior(?)
9. Periods of maximal sensitivity related to brain development
10. Response Relationships (function before structure)
11. (Maybe structural and not functional?)
12. Periconceptional and transgenerational effects

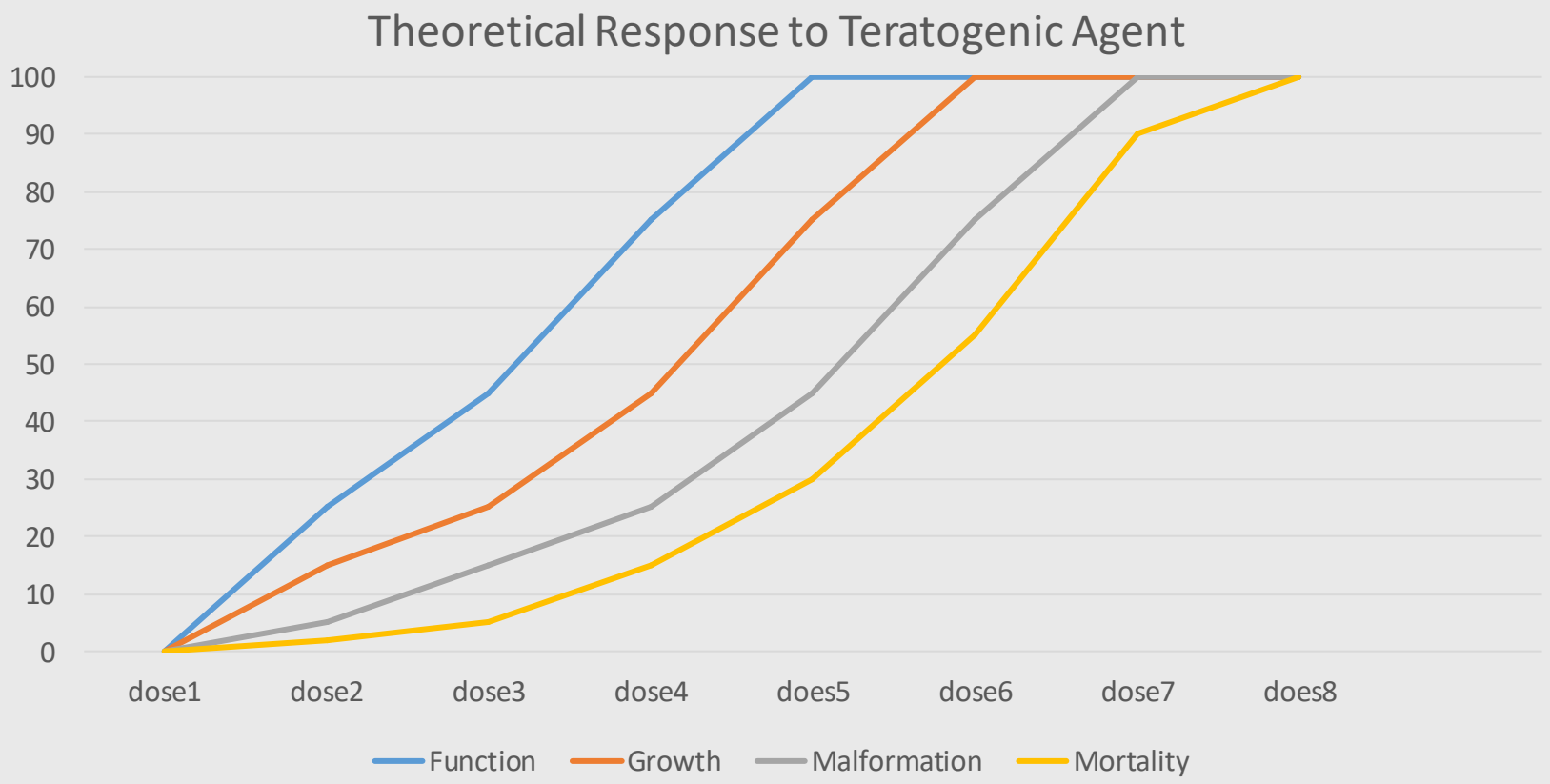
From, Riley & Vorhees, Handbook of Behavioral Teratology, 1986

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

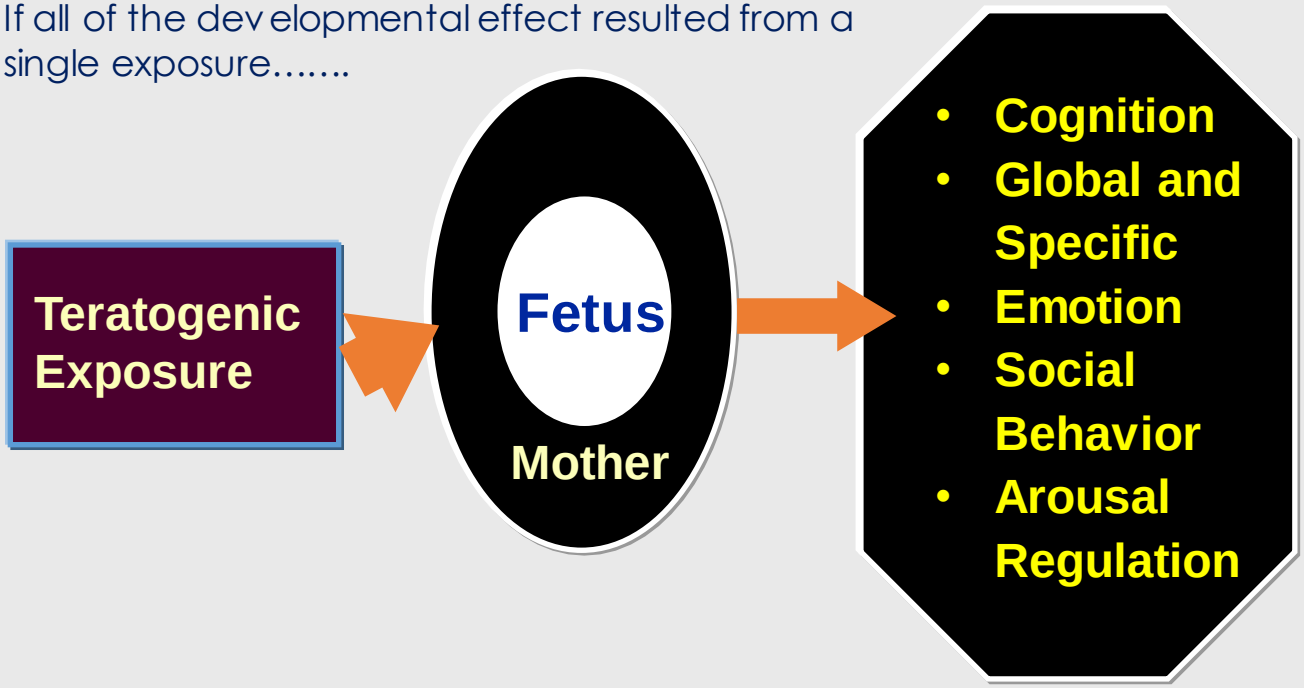


Dose/Response: Function to Mortality



Possible Mechanisms of Teratogenic Exposure (Single Factor) Model on Neurobehavior

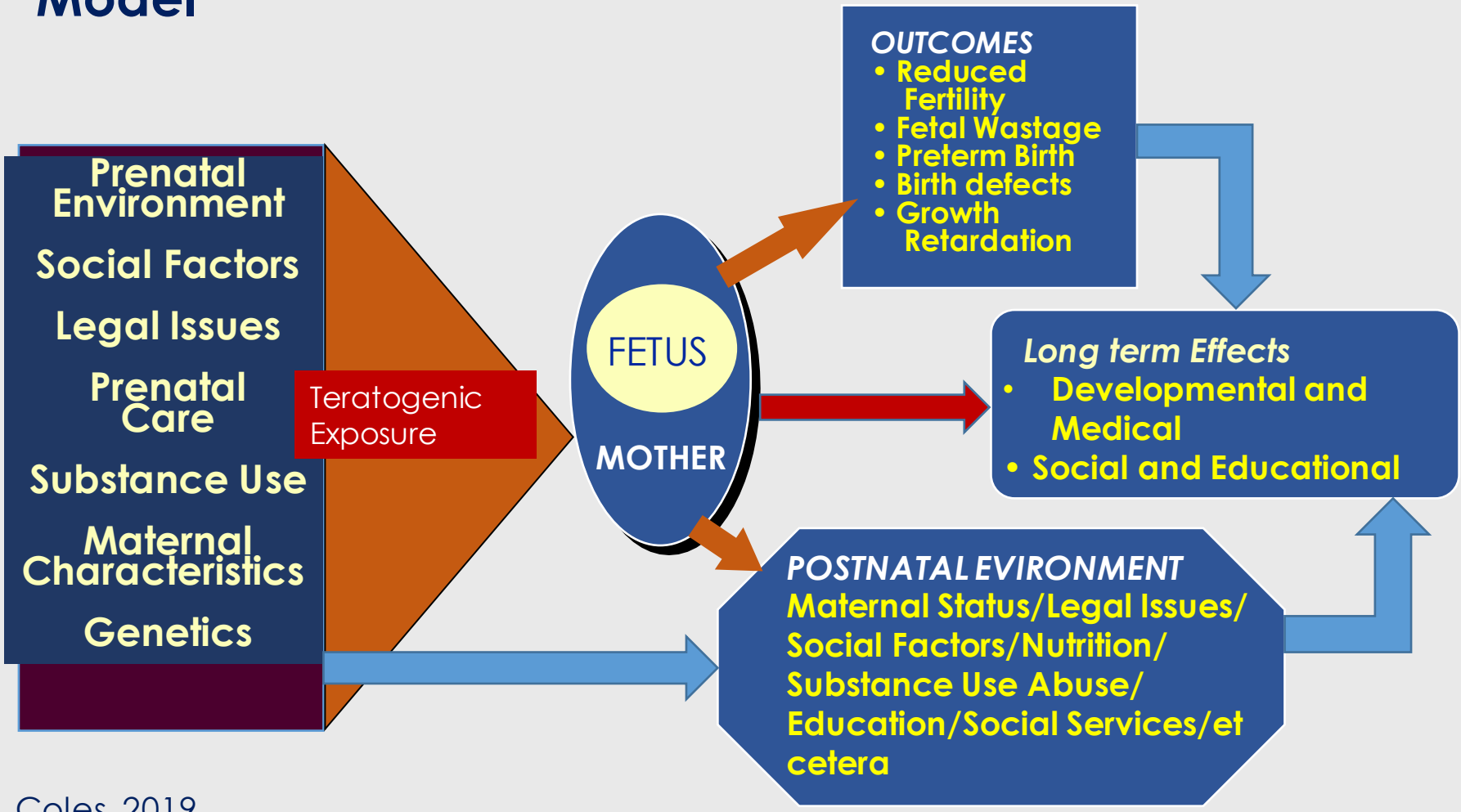
If all of the developmental effect resulted from a single exposure…….



…We would still deal with a lot of outcomes.

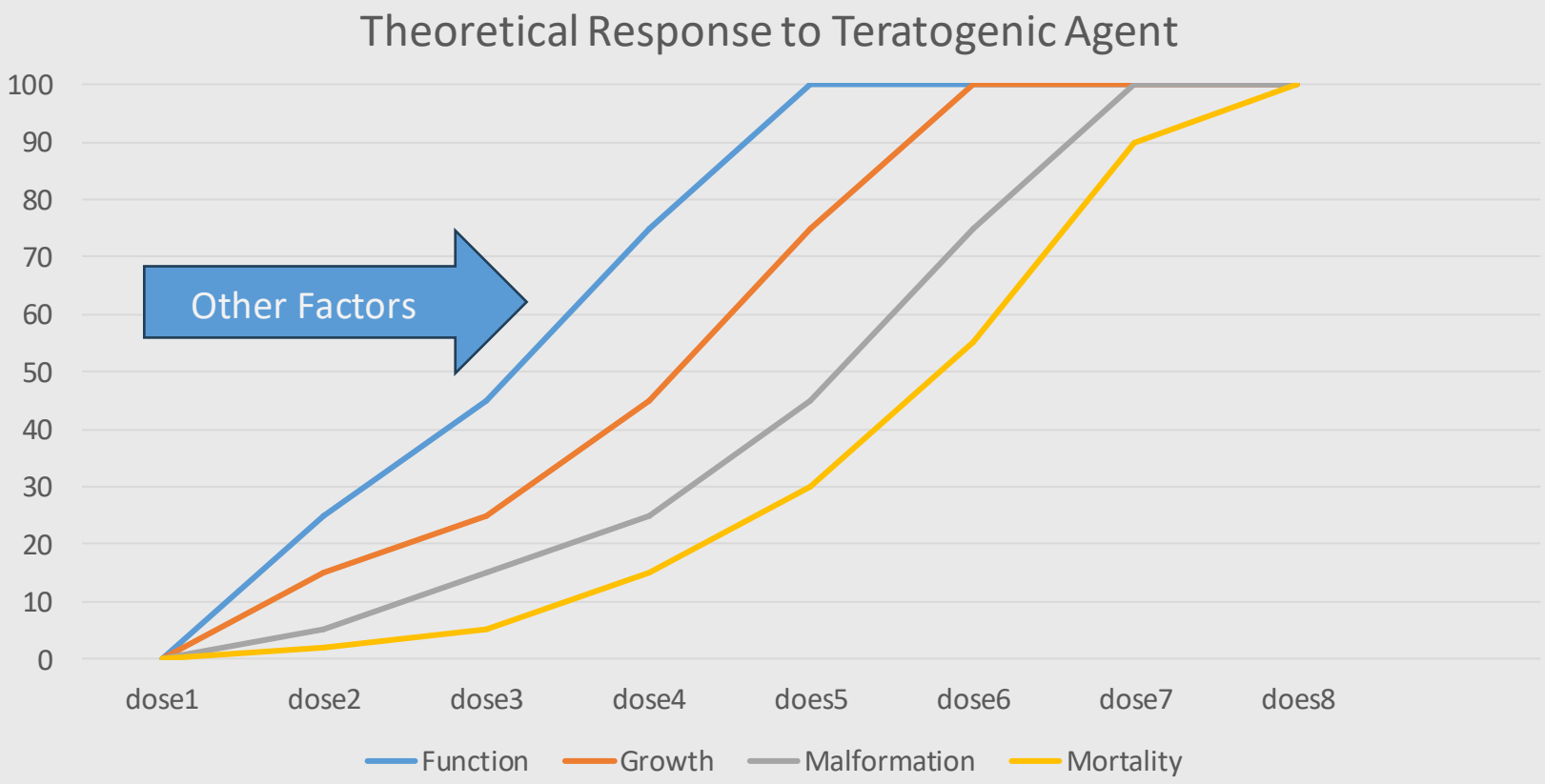
Coles, 2019

Multi-Factor (Closer to Reality) Model



Coles, 2019

Dose/Response: Function to Mortality



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

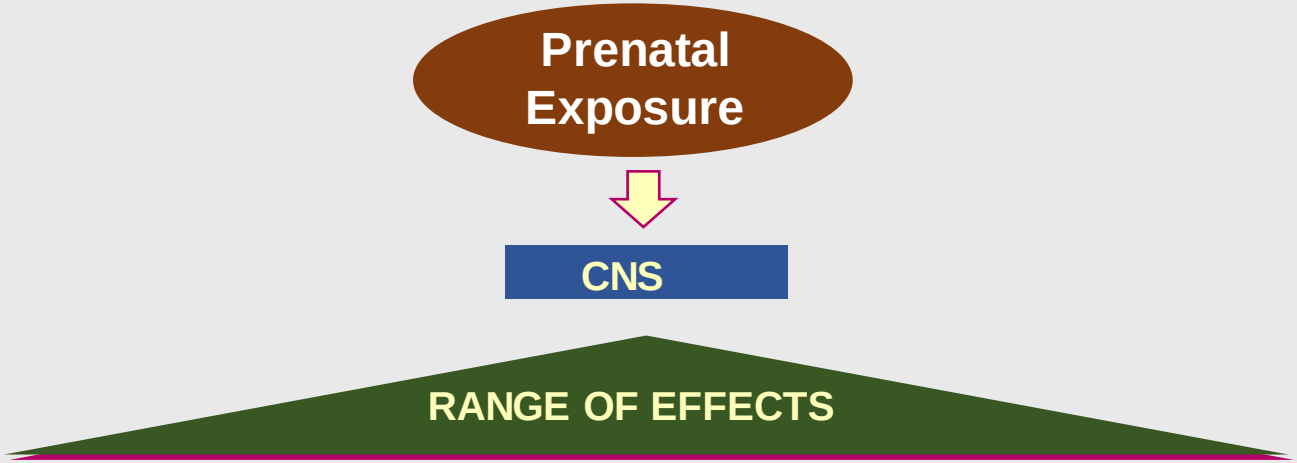
- Cognitive Deficits-How defined?
  - Deficits that impact development and adaptive function in a clinical sense
  - Relative deficits in relation to a non-exposed contrast group (small but significant effect size)
- Emotional/Behavioral Effects
  - In addition to the above, how to account for potential environmental/social confounds?

Some Initial Questions about Neurobehavioral outcomes

- WHAT do you want to measure (to demonstrate neurobehavioral effects)?
- 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)



Evidence

BRAIN DAMAGE
Autopsy Reports
Animal Models
MRI Studies
Intellectual Disability

DEVELOPMENT
Animal Models
MRI
Borderline IQ
Behavioral Attention Deficits

LEARNING DISORDERS
Longitudinal Clinical Studies Of Exposed Children

BEHAVIOR DISORDER
Clinical Reports
Epidemiological Studies

UNAFFECTED
Longitudinal Studies of Exposed Children

WHAT to Measure? Where to look for effects of specific agents?

- Sometimes, effects are very easy to observe. There are global development problems early in life.
- Other times, effects are more subtle or may be delayed (sleeper effects).
- In some situations, effects are observed only when other factors (stressors) are present.
- Certain agents may target only some systems while others are comprehensive.
- Extent of Exposure may affect these outcomes.

There is usually a pattern of deficit, with some functions more vulnerable than others.

- *Arousal Regulation*
- *Attention*
- *Behavior*
- *Memory*
- *Motor problems (Visual/Motor)*
- *Language*

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

When specific effects are described, mechanisms may be identified.

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

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

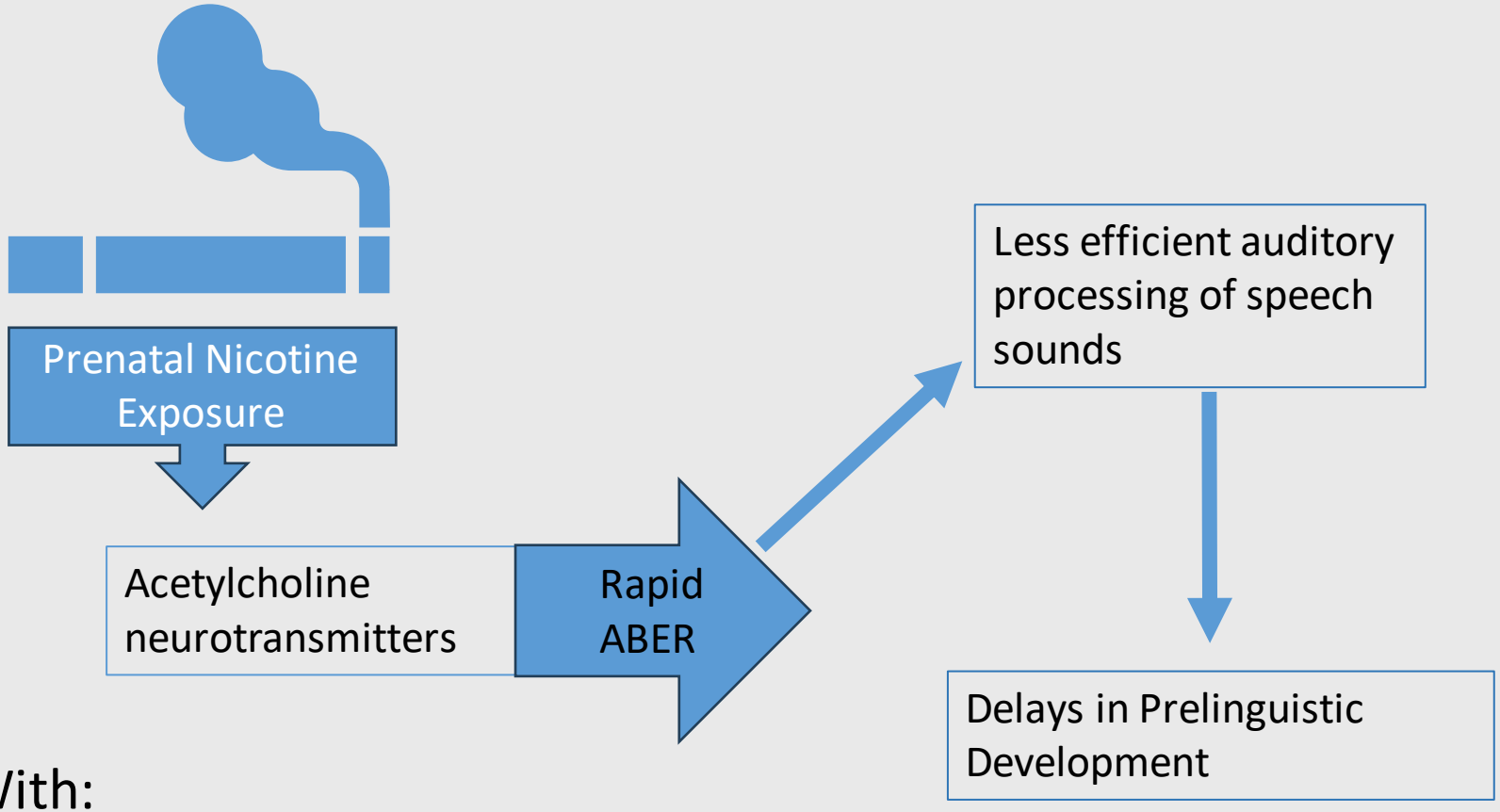
First steps are a general descriptive "scan" of outcomes

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

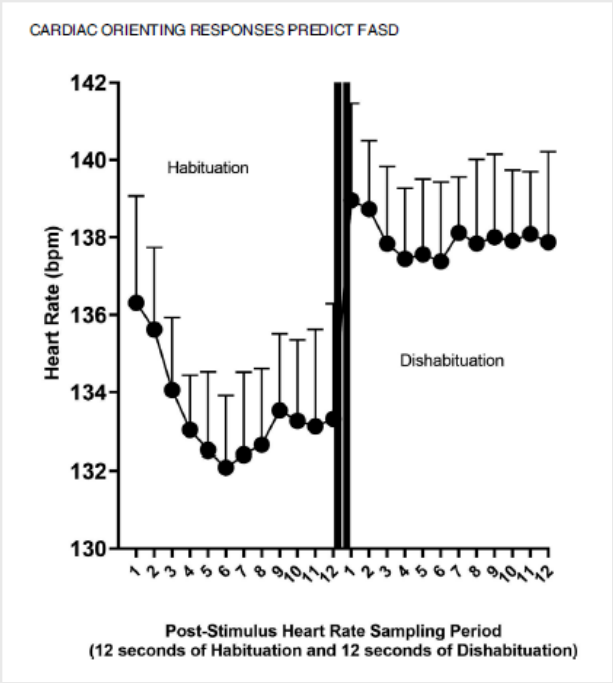
Kable, JA, Coles, CD, Lynch, MA, & Carroll, J (2009). The Impact of Maternal Smoking on Fast Auditory Brainstem Responses, Neurotoxicology and Teratology. 31 (4) 216-224. PMID 19224709

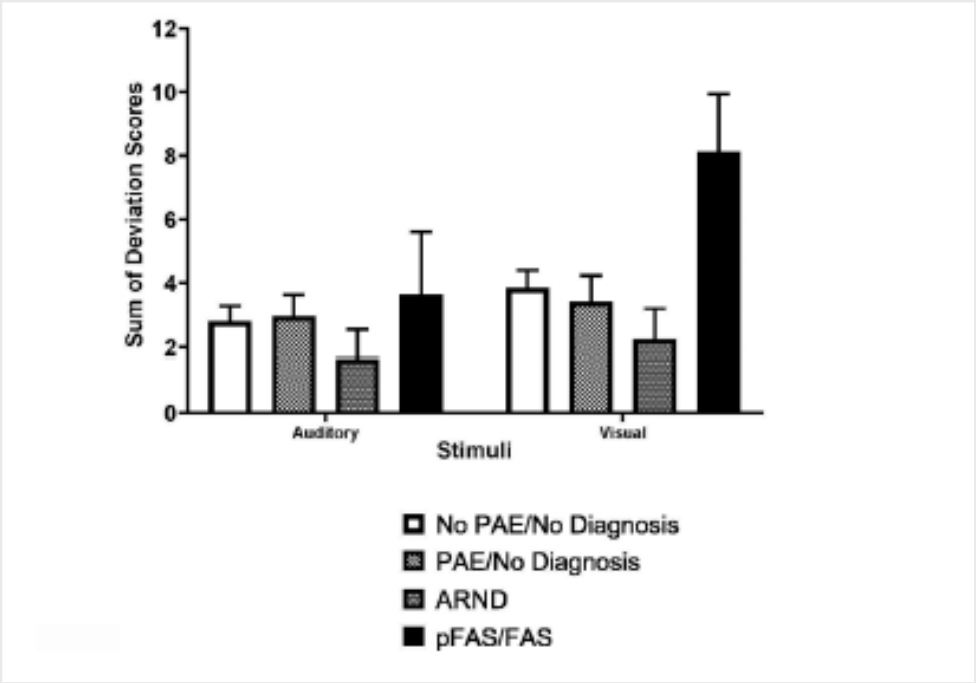
Alcoholism: Clinical and Experimental Research

Vol. 45, No. 2
February 2021

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





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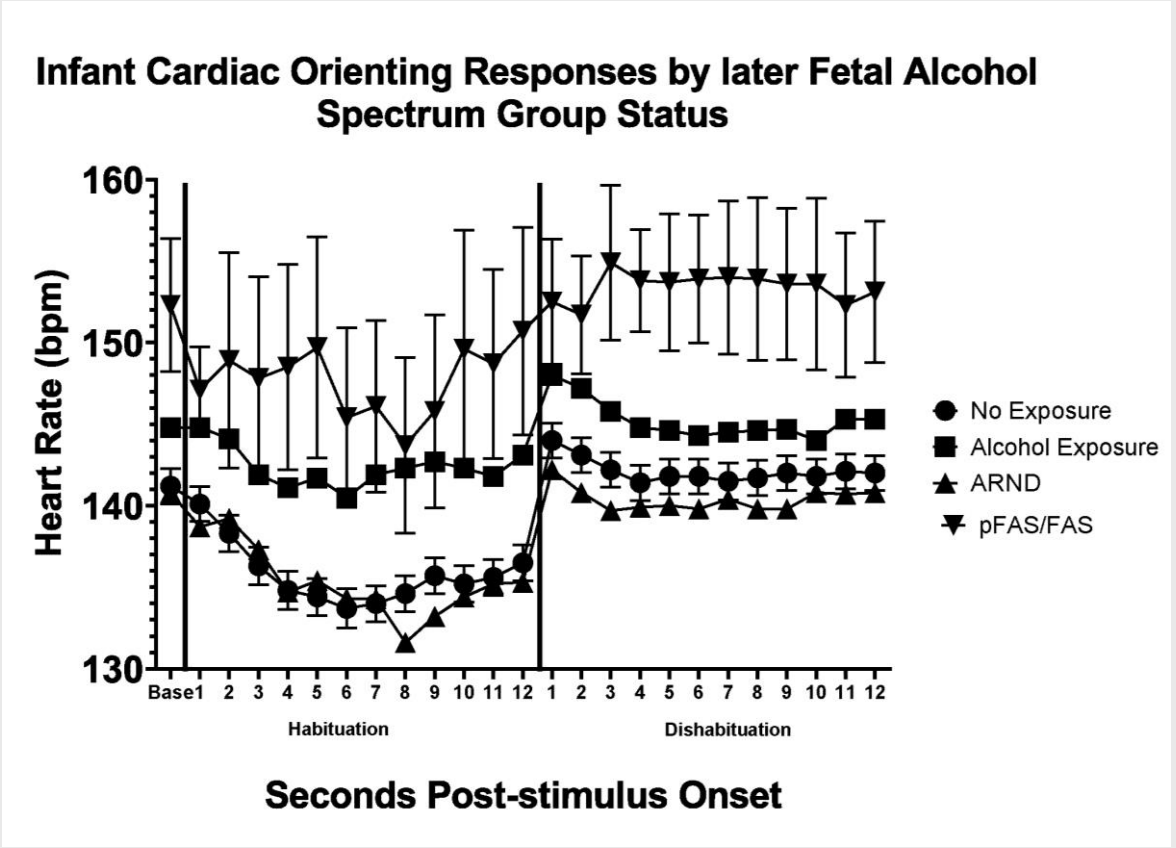
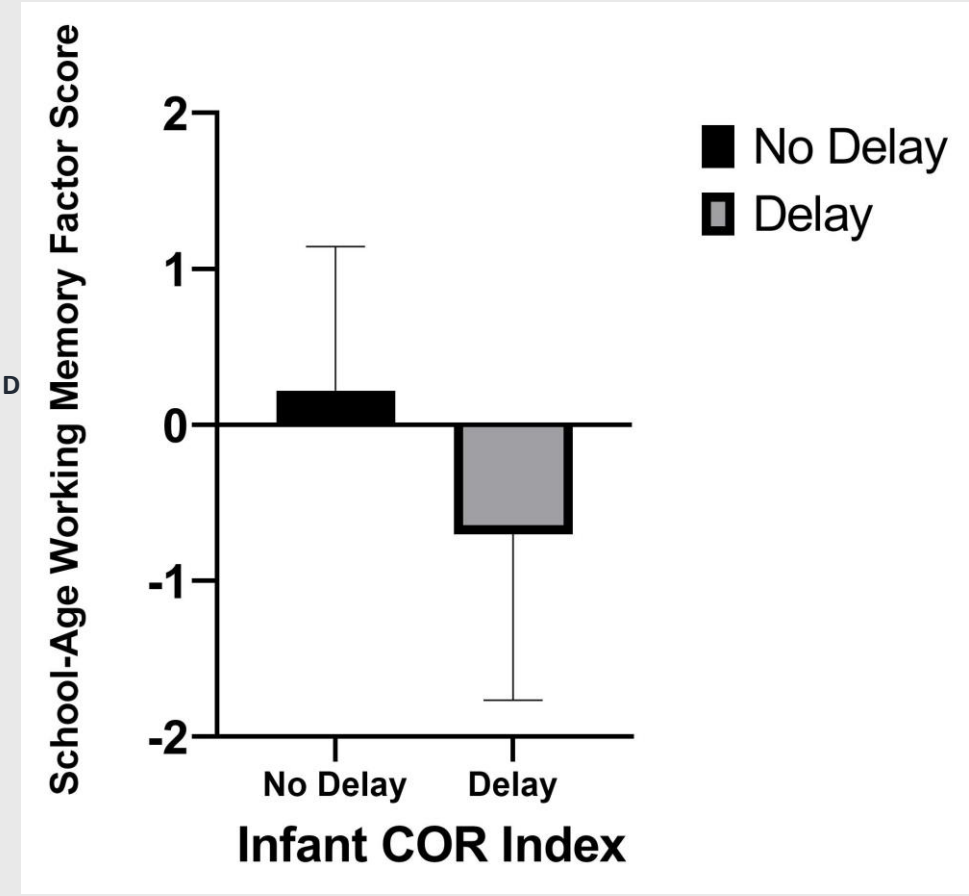
Cardiac Orienting Responses by Preschool Diagnostic Group in Ukraine Cohort



Infant Cardiac Orienting Responses (COR) during Information Processing Predict Working Memory Impairment in School-Age Children

JA Kable, CD Coles, KL Jones, L Yevtushok, Y Kulikovsky, N. Zymak-Zakutnya, D Akhmedzhanova, W Wertelecki, CD Chambers, & and the CIFASD

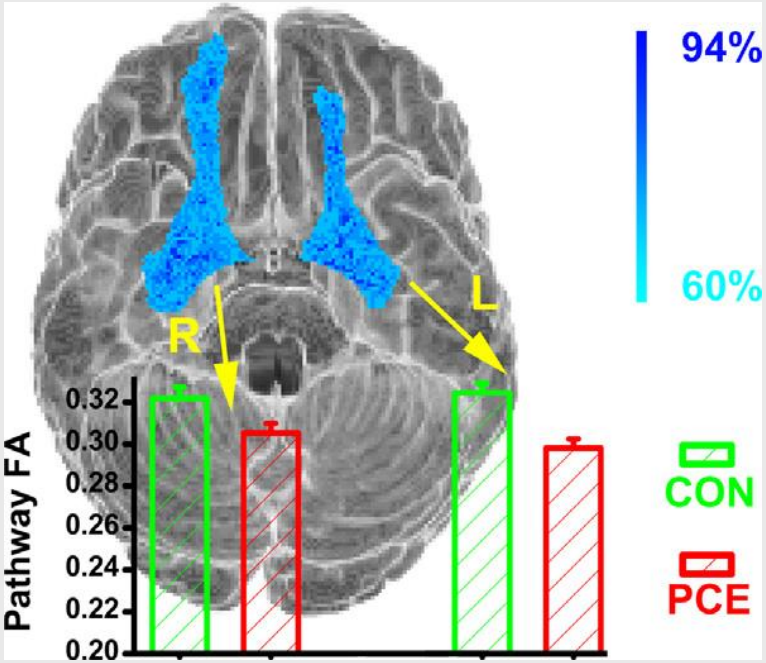
- Greater deviance in the COR response was associated with poorer working memory skills (Auditory CoDI: $r = -.383$, $p < .010$; Visual CoDI: $r = -.363$, $p < .021$; Combined CoDI: $r = -.372$, $p < .013$).
- Individuals with delay in any of the CORs performed in infancy had significantly lower scores on the working memory factor score than did those who had no evidence of an impaired COR in the infancy ($F(1,42) = 7.092$, $p < .011$). This was also true of those having a delay on auditory ($F(1,41) = 7.270$, $p < .010$) and visual ($F(1,37) = 5.995$, $p < .019$) stimuli when analyzed separately.



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.



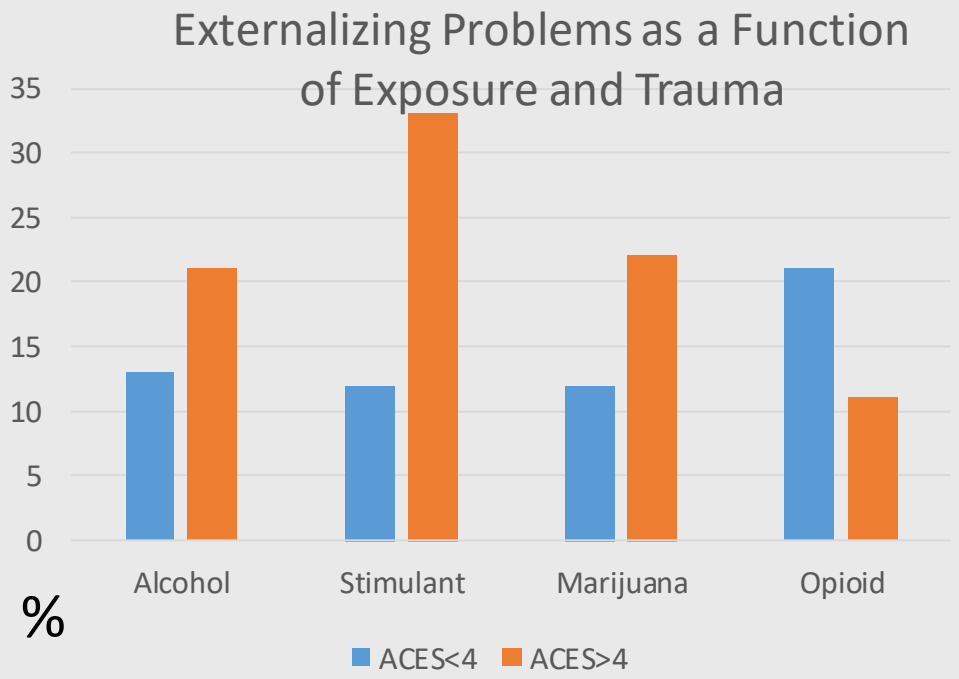
From, Li, et al, Psychiatry Research: Neuroimaging 213 (2013) 47–55

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.

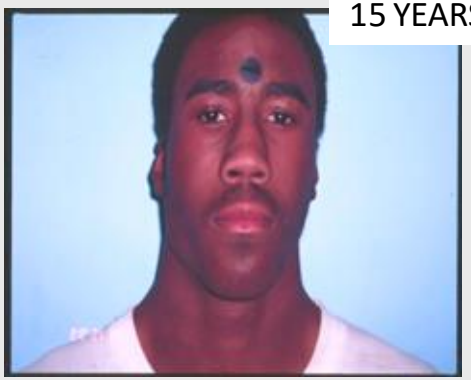
WHEN do you want to measure?

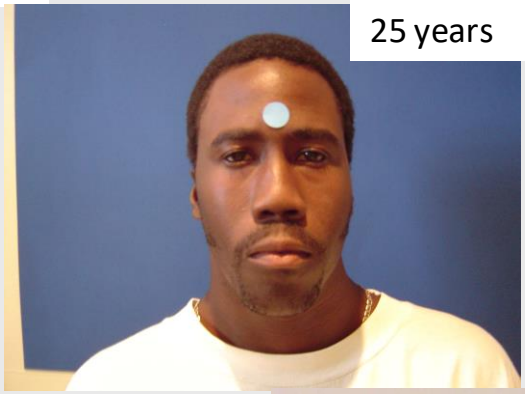
- When during development is the appropriate time to measure effects of a teratogen?
- This will depend on the extent of the impact as well as the developmental course of the outcomes of interest.
  - Motor function ⟹ Infancy
  - Language ⟹ Preschool
  - Executive Function ⟹ Early School Age
  - Long term Health ⟹ Middle Age

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.

Longitudinal Exposure Research Design: Effects of Prenatal Alcohol Exposure





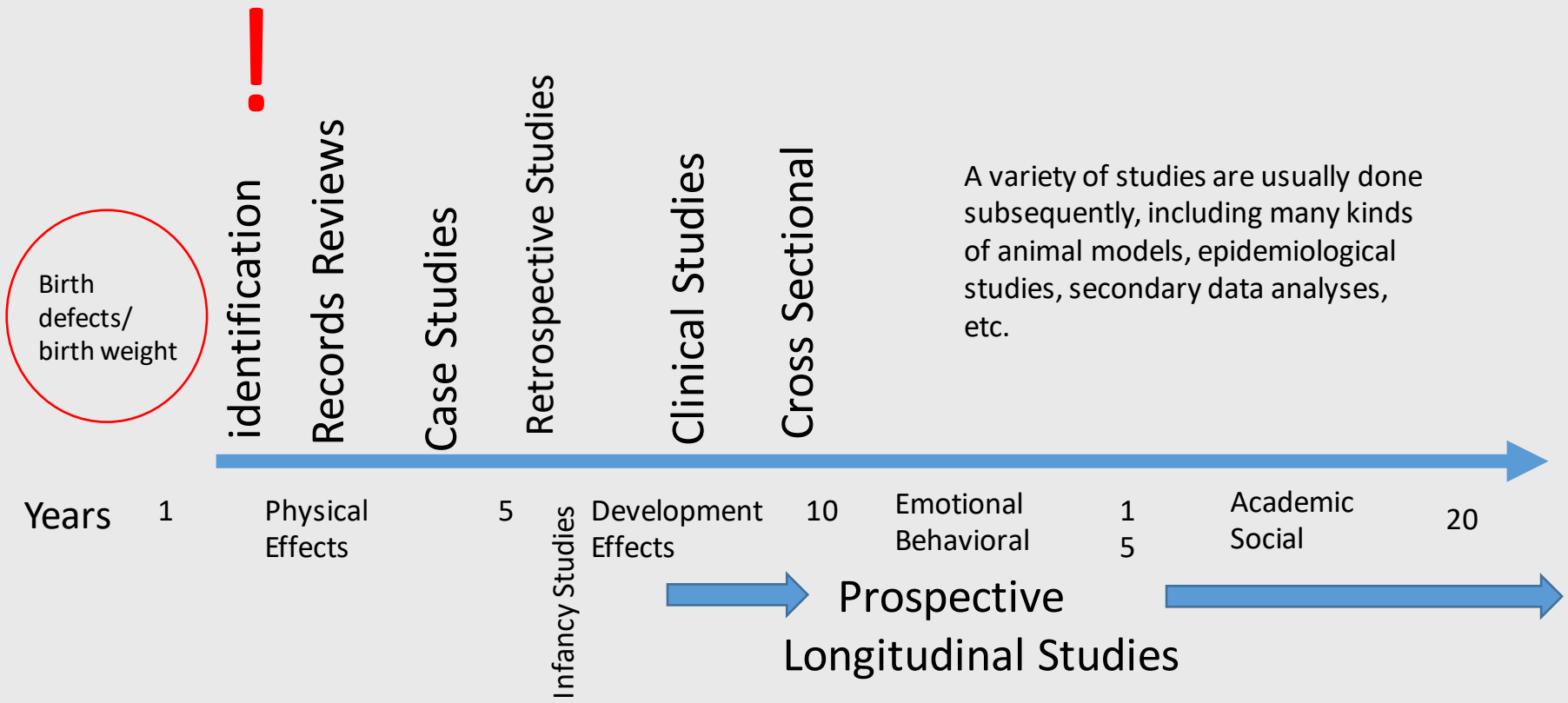
PRIMARY DISABILITIES: Intellectual Deficiency - Developmental and Learning Disabilities - Cardiac Problems - Vision/Hearing Loss - Facial Dysmorphia - Motor Dysfunctions-Microcephaly

SECONDARY DISABILITIES: School Failure-Depression- Vocational Failure-Legal Problems-Psychiatric Diagnosis-Substance Abuse-Long Term Health Issues

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.
  - 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.

Teratogens:
From Discovery to Prevention



Identification?

Genetics in Medicine Open (2023) 1, 100834

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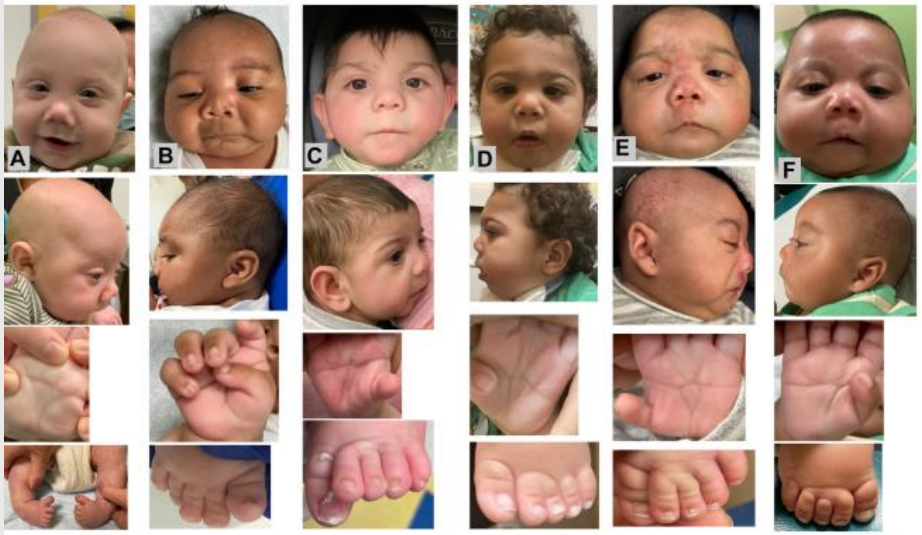
Genetics in Medicine OPEN
An Official Journal of the ACMG

www.journals.elsevier.com/genetics-in-medicine-open

BRIEF REPORT

A novel syndrome associated with prenatal fentanyl exposure

Erin Wadman[1], Erica Fernandes[1], Candace Muss[1], Nina Powell-Hamilton[1], Monica H. Wojcik[2,3], Jill A. Madden[3], Chrystalle Katte Carreon[4], Robin D. Clark[5], Annie Stenftenagel[6], Kamal Chikalard[6], Virginia Kimonis[6], William Brucker[7], Carolina Alves[8], Karen W. Gripp[1,*]



gure 1 Facial photographs of Individuals 1-6 (A-F) as used in the GestaltMatcher analysis. Below each image are a lateral facial ew, a hand, and a foot photo of the respective individual.

Is Prenatal Fentanyl Exposure Associated with impaired cholesterol metabolism?

Mixed findings of the relationship of opioids and birth defects. To date clear relationships not yet established.

In this recent paper 10 individuals were identified based on distinctive facial features, physical findings, no genetic etiology identifiable, and shared history of fentanyl exposure. Features included microcephaly, short nasal tip, thin upper lip, clecft palate, micrognathia, single palmer crease, syndactyly, talipes/rocker bottom.

All cases showed effects on cholesterol metabolism in early screening tests that resolved subsequently.

These cases may represent the extreme end of a possible syndrome that could have a range of effects.

Records review/Case Study

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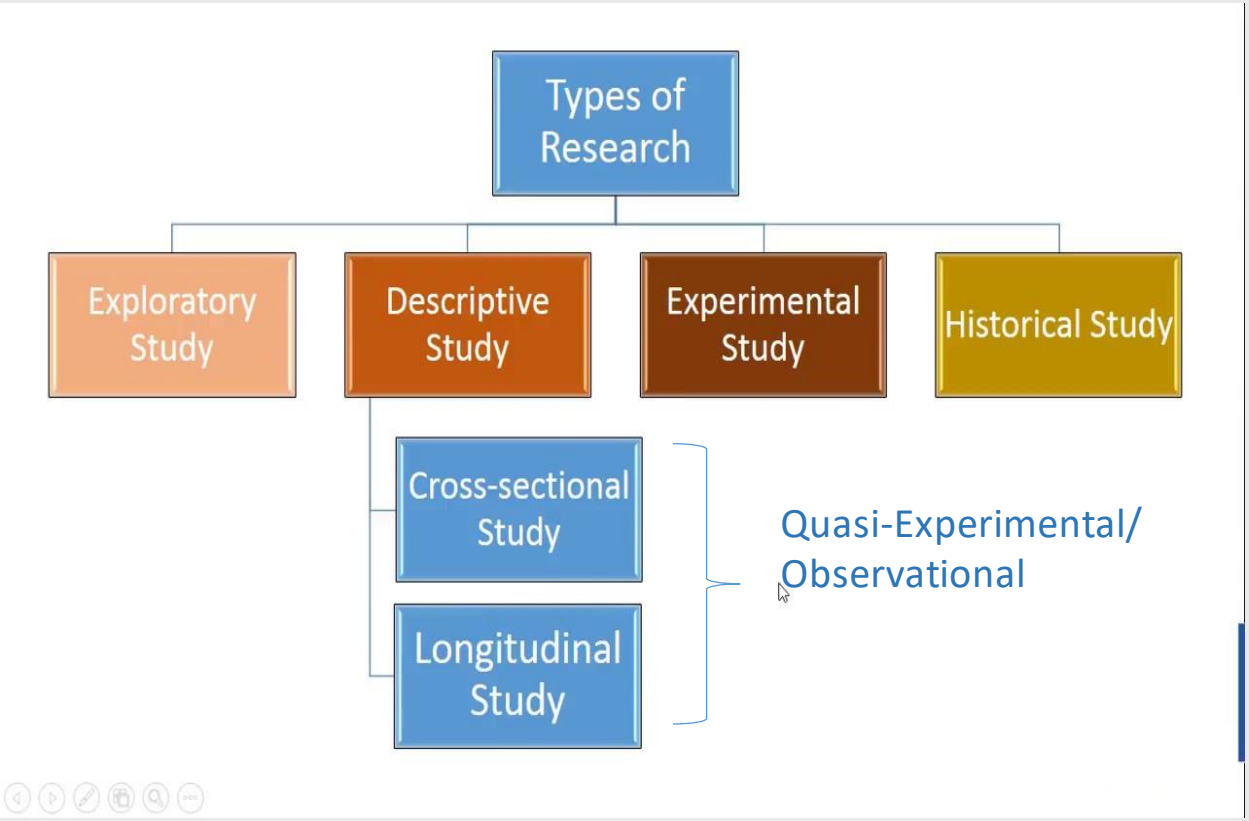
Research Design Considerations:

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.

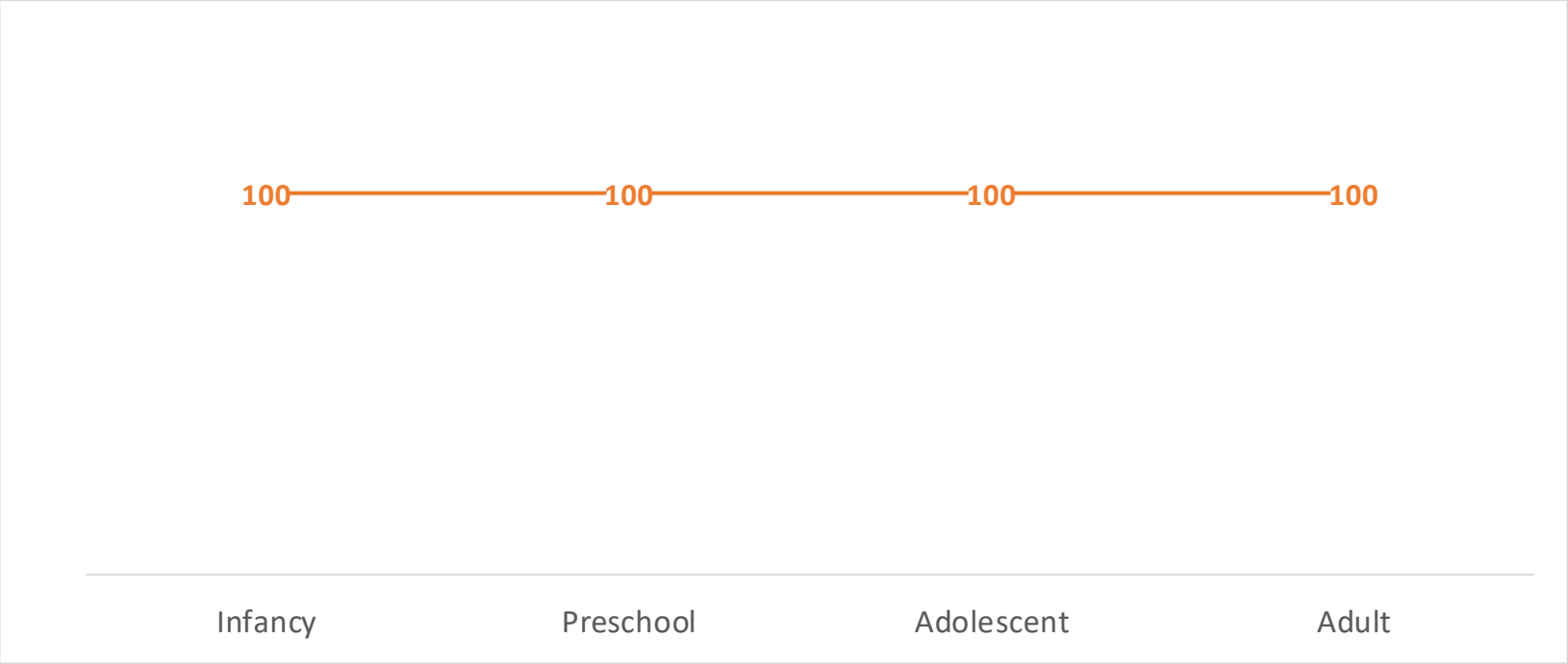
Cross-Sectional Studies are faster and typically employ clinical samples and therefore exaggerate effects.

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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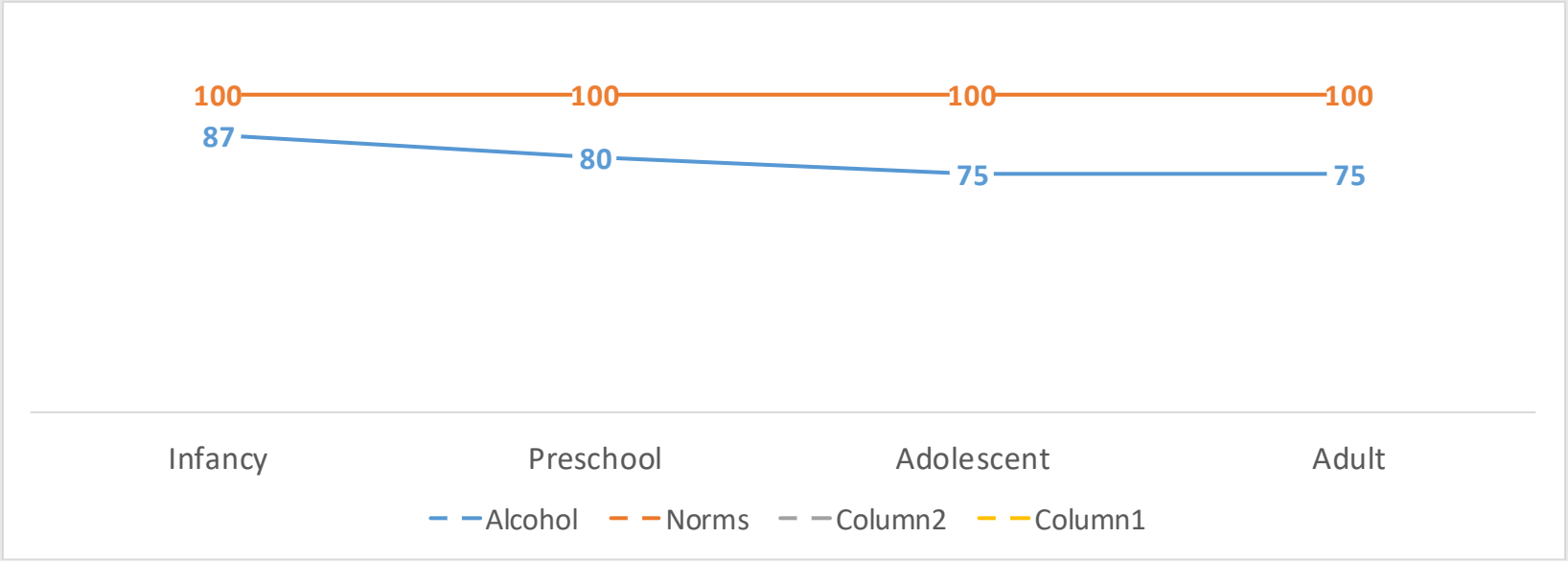

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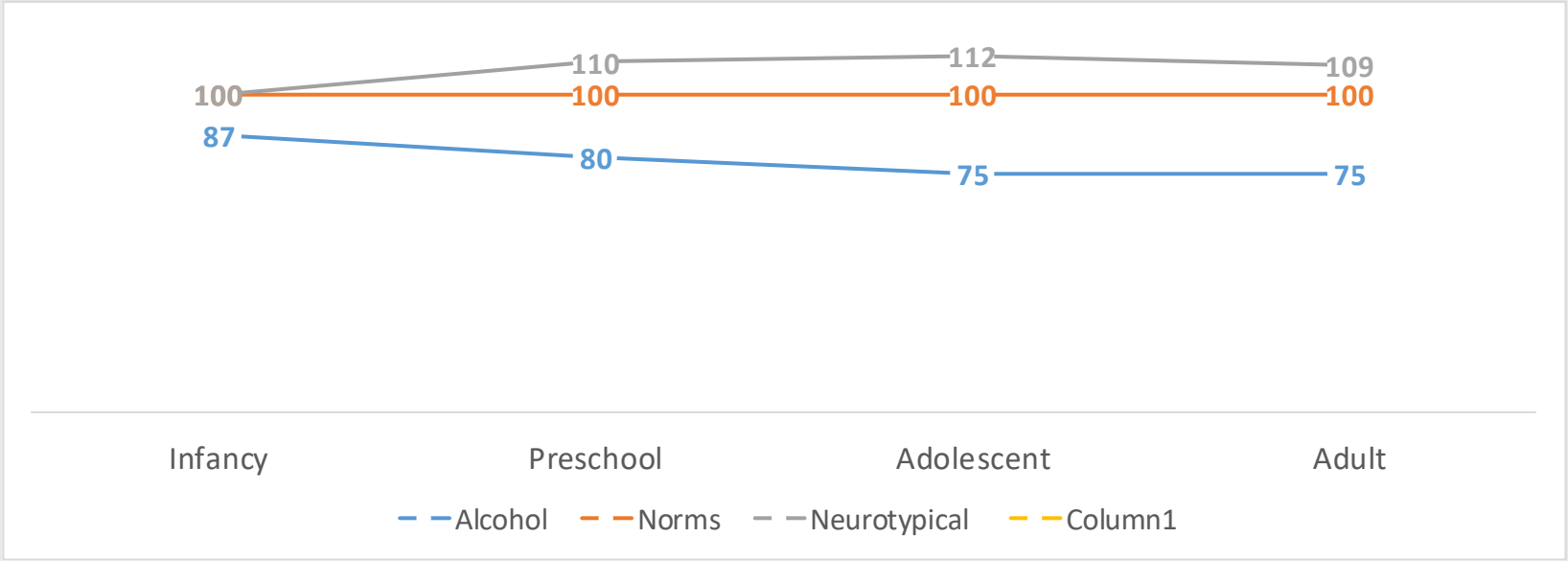

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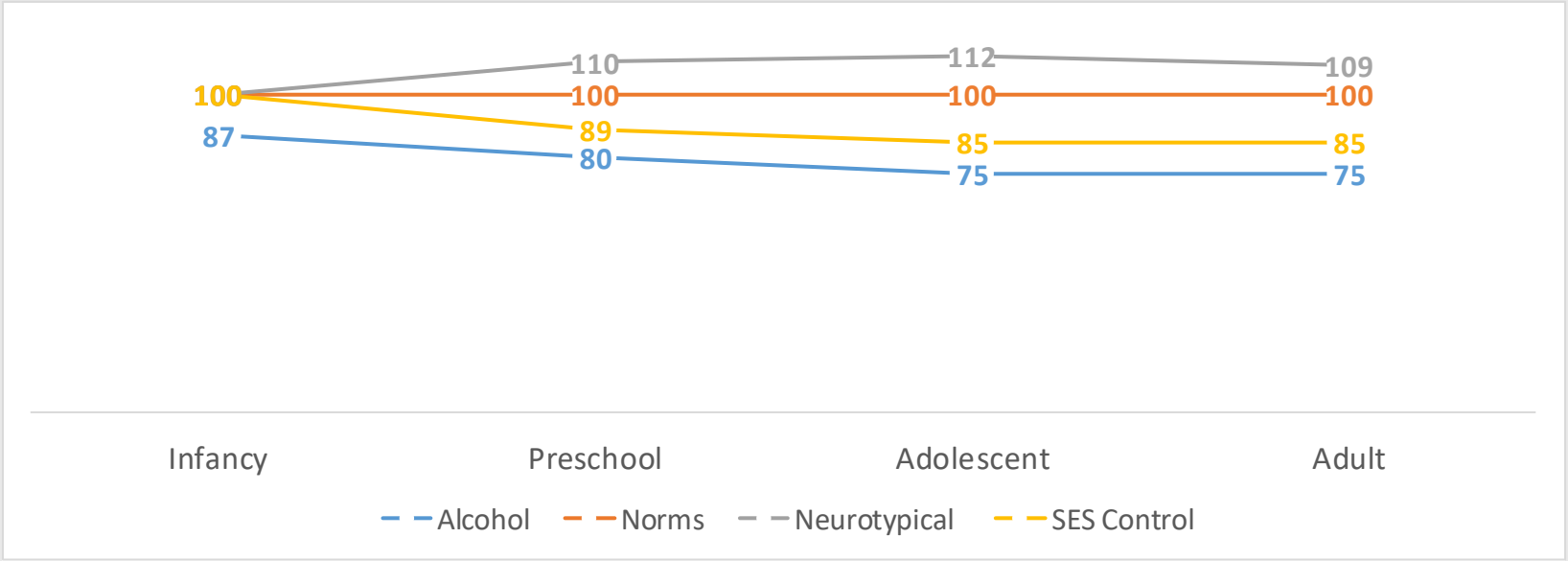
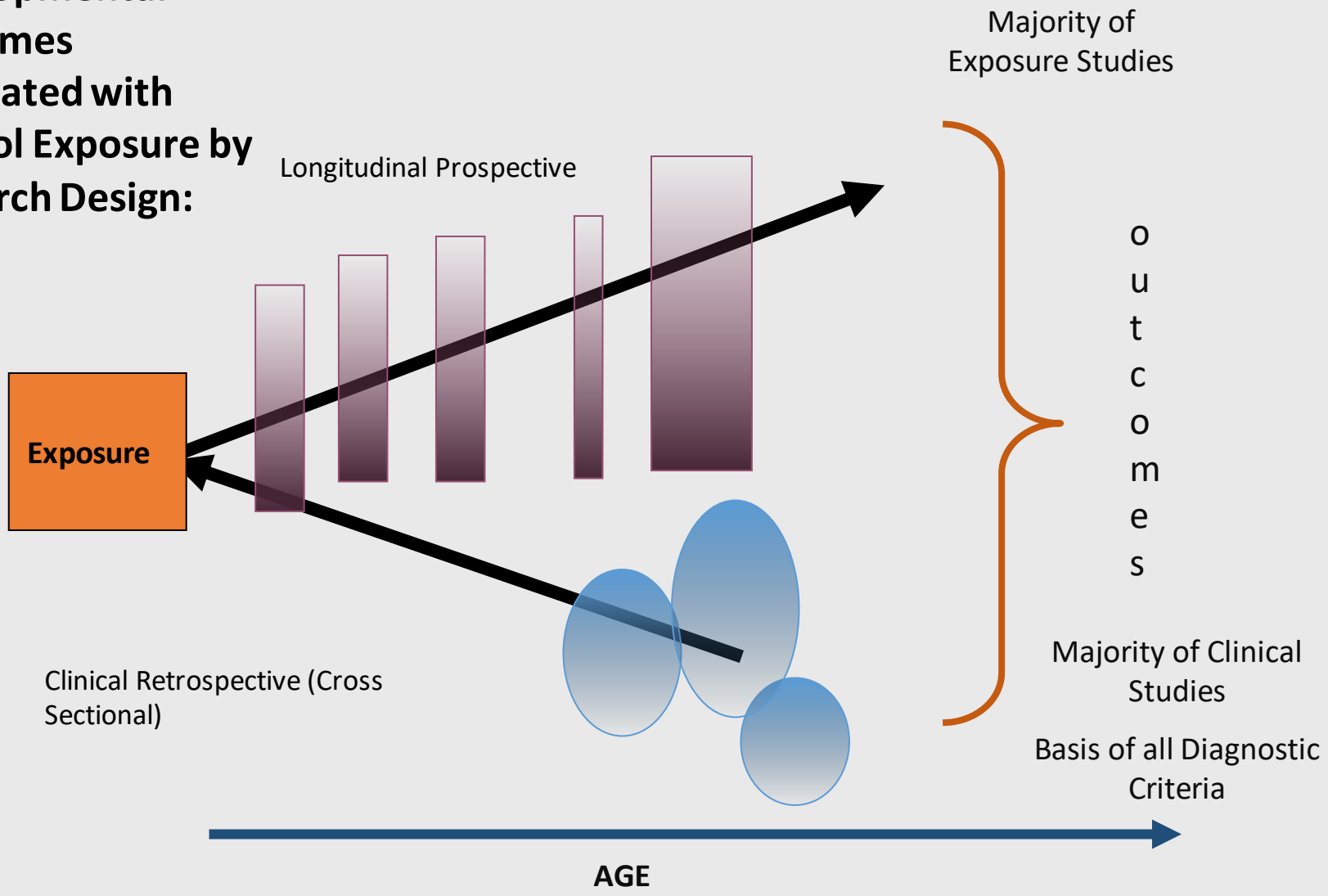


Discrepancy in Developmental Outcomes Associated with Alcohol Exposure by Research Design: FASD



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.

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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?