

Genetically-Informed Studies of Psychosocial Risk Factors and Psychiatric Medications

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Research Connection Plus

May 19, 2022



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Funding

Supported by grants from American
Foundation for Suicide Prevention,
NIMH, NIDA, Indiana University,
Swedish Research Council
(Medicine), and Karolinska Institutet.

I have **NO** financial conflicts of
interest.

Outline

- Review of Genetic Studies of Self-Harm Behaviors
- Implications for Studying Risk Factors
- Psychosocial Risk Factors for Self-Harm Behaviors
 - **Bullying Victimization**
 - Overview of other risk factors
- Pharmacoepidemiology Research on Self-Harm Behaviors
 - **ADHD medication**
 - Overview of other medications
- Summary

Review of Genetic Studies of Self-Harm Behaviors

- Genetic factors are important (Emma's presentation)
- These influences are probabilistic
 - There is no gene for suicide
 - **Thousands** of genes likely influence self-harm behaviors
- Genetic factors account for association between childhood psychopathology and adolescent self-harm behaviors (O'Reilly et al., 2020, *J of Abnormal Psychology*)
- Genetic factors do not work according to the DSM/ICD ...or our conceptualizations of mental health vs. physical health!
- Research exploring putative causal risk factors must account for genetic (and environmental) confounding

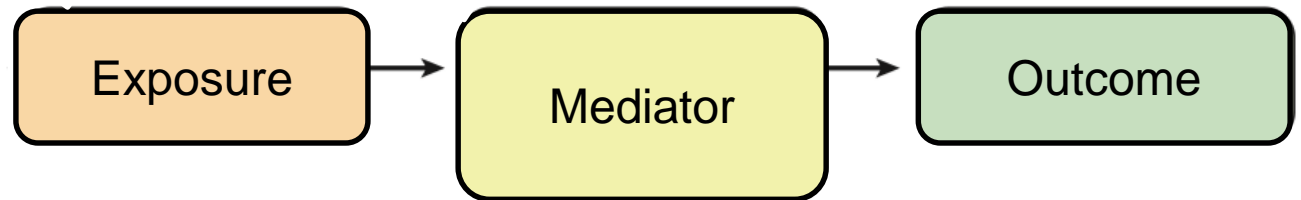
How Do We Study Risk Factors?

Based on D'Onofrio et al. 2020, *Annual Review of Clinical Psychology*

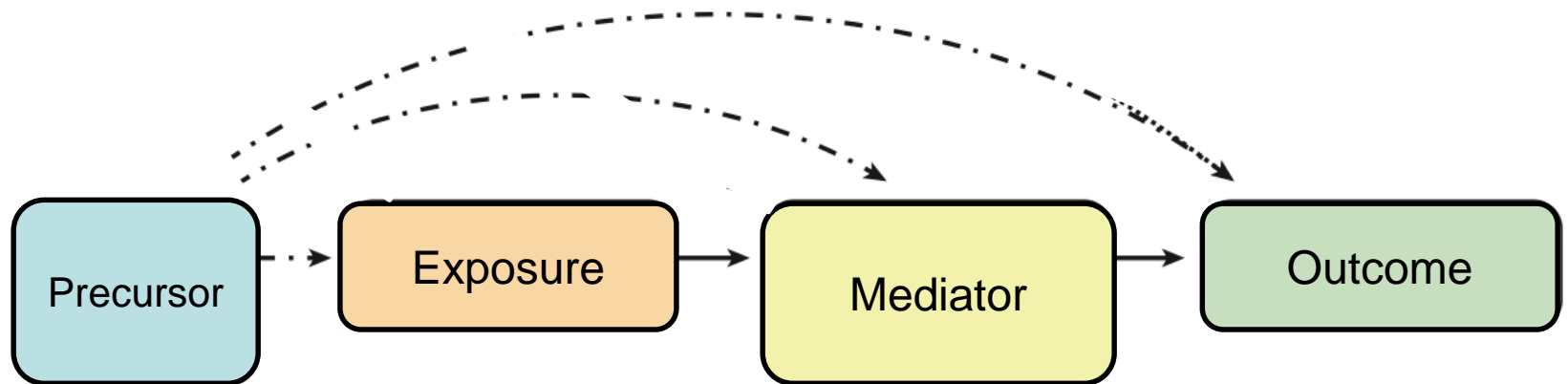
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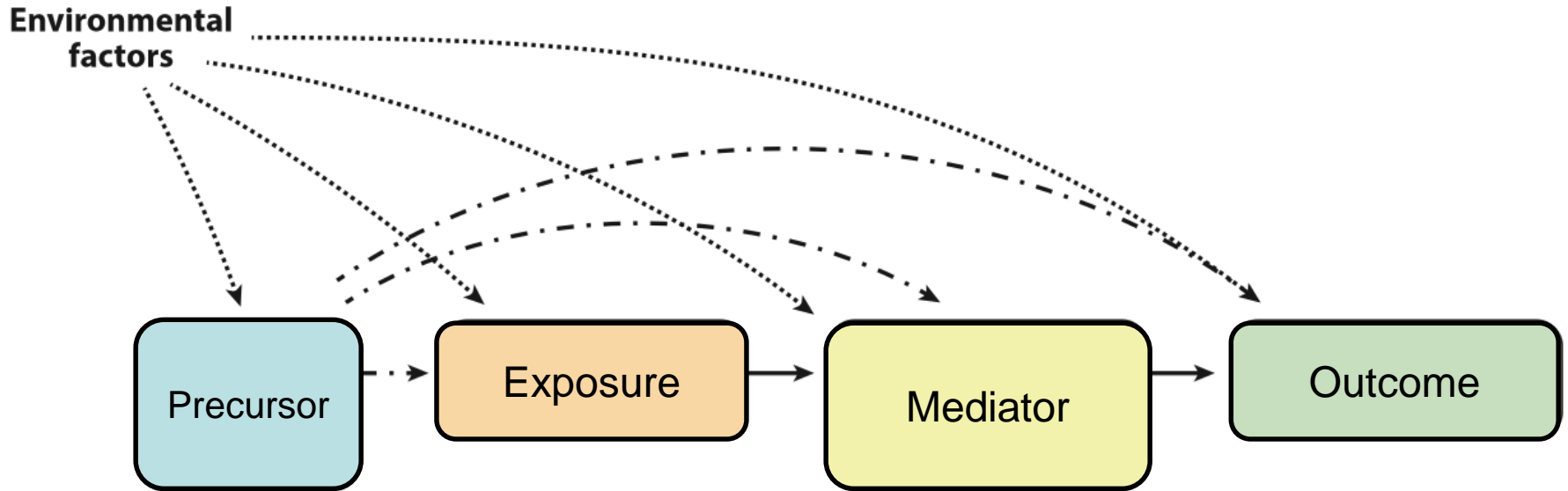


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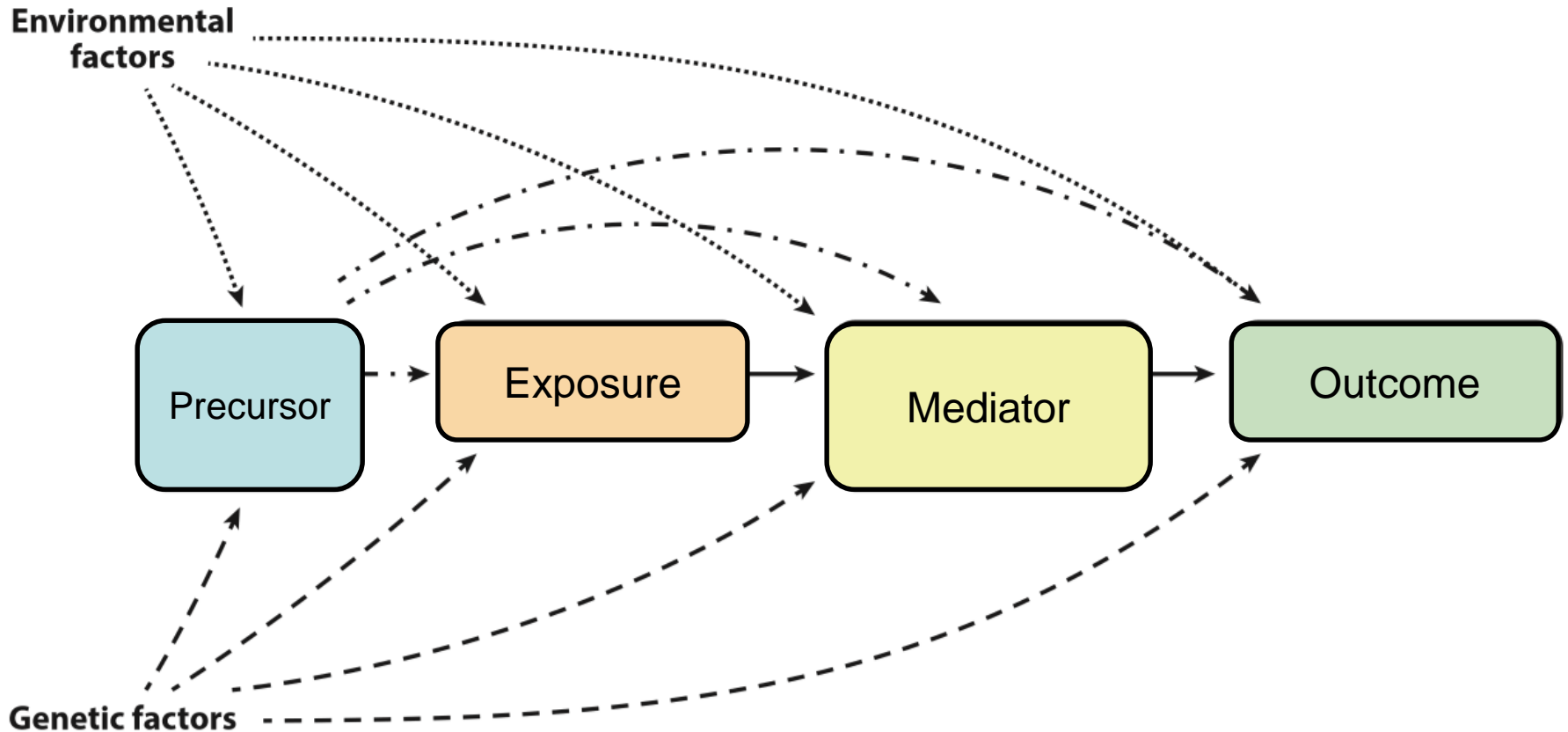


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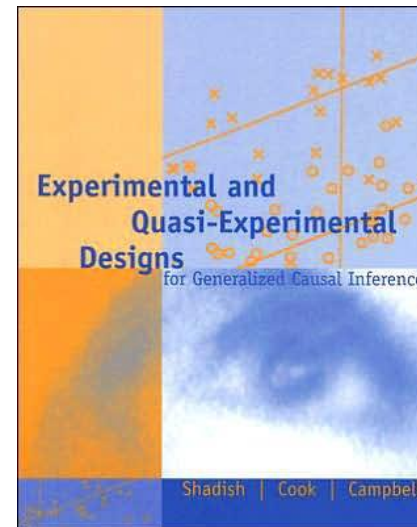
How Do We Make Causal Inferences?

- Most research relies on statistical covariates to rule out plausible alternative hypotheses
- Importance of using [design features](#)
- Need converging evidence from multiple methods

Statistically Controlling for Confounding Constructs Is Harder than You Think

Jacob Westfall*, Tal Yarkoni

PLOS ONE | DOI:10.1371/journal.pone.0152719 March 31, 2016



Bullying Victimization & Self-Harm Behavior

- Bullying victimization is a well-established predictor of suicidal ideation and attempt (Holt et al., 2015)
- Research is limited by several factors (Moore et al., 2017):
 - Reliance on cross-sectional designs
 - Minimal adjustment for prior psychopathology
 - Inability to account for unmeasured confounding (genetic and environmental) factors

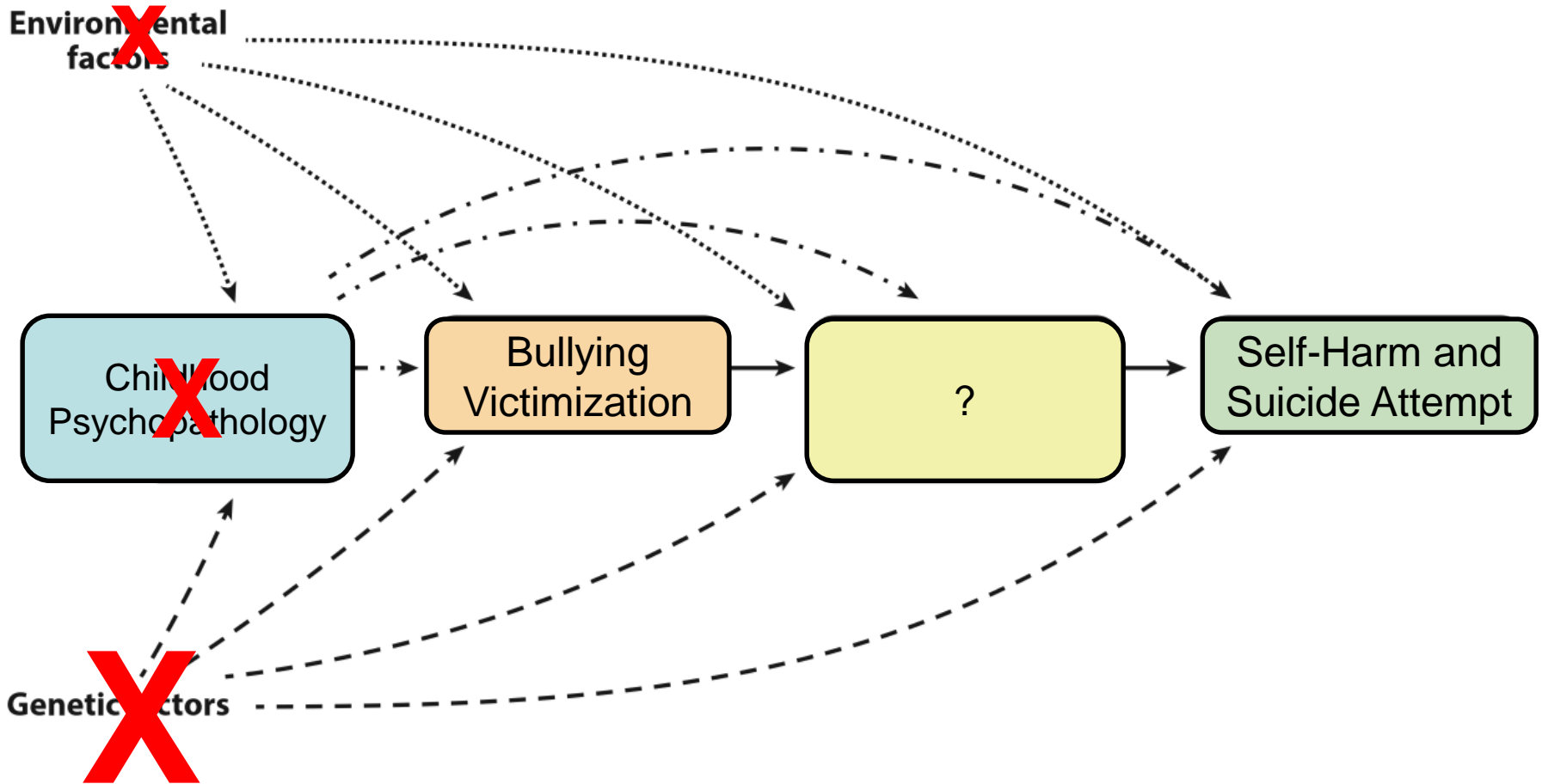
Co-Twin Control Studies

- The counterfactual for bullying victimization
- Uses unexposed twin as comparison
 - Rules out **environmental factors shared by twins**
 - Controls for **genetic factors** (identical twins)
- Does not account for environmental factors that vary within twin pairs
 - Can statistically adjust for within-pair covariates to help account for these factors

Bullying Victimization & Self-Harm Behavior

Sample	Large-scale, longitudinal twin study in Sweden (CATSS)	13,852 twins born 1994-1999, followed from age 9 to 18 years old
Exposure	Bullying Victimization	Revised Olweus Bully/Victim Questionnaire at age 15
Outcome	Self-harm and suicide attempt	Questions from Lifetime History of Aggression questionnaire at age 18
Methods	Co-twin control design while accounting for covariates	Fixed-effects logistic regression models that accounted for previous psychopathology

Bullying Victimization and Self-Harm



Bullying Victimization and Self-Harm

- A one standard deviation increase in bullying victimization was associated with increased odds of either self-harm or suicide attempt.
 - Unrelated individuals: 1.35 (1.28-1.42)
 - Co-twin control: 1.21 (1.11-1.33)
 - Co-twin control & covariates: 1.14 (1.05-1.24)
- Comparable associations when examining different forms of victimization (e.g., physical, verbal, relational, cyber bullying)

Other Psychosocial Risk Factors for Self-Harm Behaviors

- Co-Twin Control Studies
 - Sexual orientation (O'Reilly et al., 2020, *JCPP*)
 - Protective factors (e.g., friendship quality and physical activity, O'Reilly et al., submitted)
- Sibling Comparisons
 - Pregnancy-related risk factors (e.g., preterm birth, D'Onofrio et al., 2013, *JAMA Psychiatry*)
 - Maternal age at childbearing (Sujan et al., 2022, *Behavior Genetics*)
 - Childhood relocations (Bramson et al., 2016, *Psychological Medicine*)
 - Traumatic brain injury (Sariaslan et al., 2016, *PLOS Medicine*)
- Children of Twins/Siblings
 - Intergenerational transmission of suicidal behavior (O'Reilly et al., 2020, *Translational Psychiatry*)

Review of Family-Based Studies

- Can provide greater support for a causal interpretation
- Have shown that several putative causal risk factors likely have no causal effect
- Each design has limitations. Thus, researchers must try to triangulate findings from multiple designs
- Requires greater collaboration among researchers to facilitate stronger measurement, developmental considerations, and implementation of multiple designs/approaches

ADHD Medication

- Randomized Controlled Trials (RCTs) have shown short-term effects (Cortese et al., 2018)
- Serious concerns about concomitant and long-term problems (e.g., substance use problems and suicidal behavior)
- Serious limitations of RCTs
 - Cannot study rare outcomes (Chan et al., 2016)
 - Generalizability of findings (Surman et al., 2010)
- Observation studies – Confounding by Indication
 - Patients who receive medication are different than patients who do not

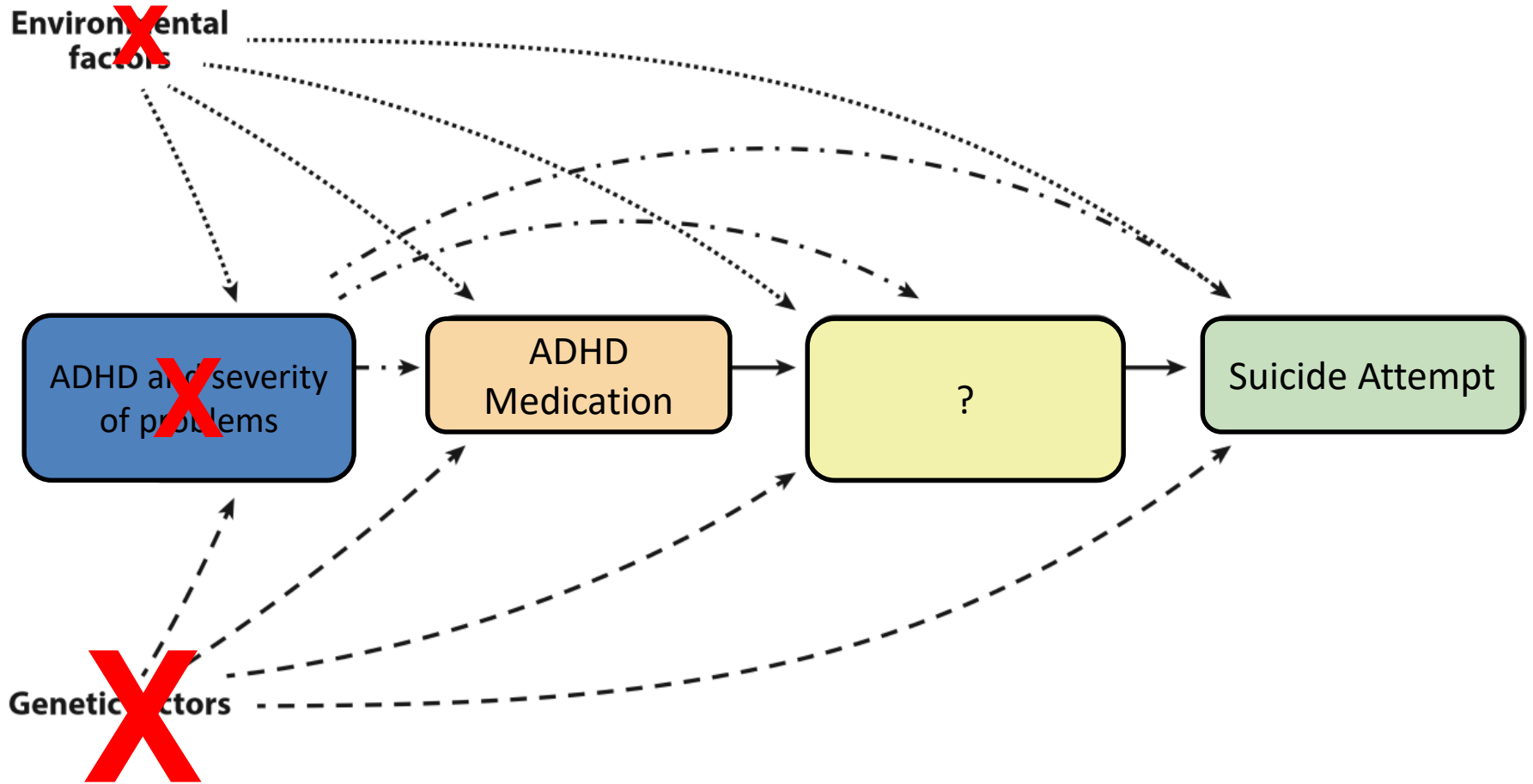
Within-Individual Comparison

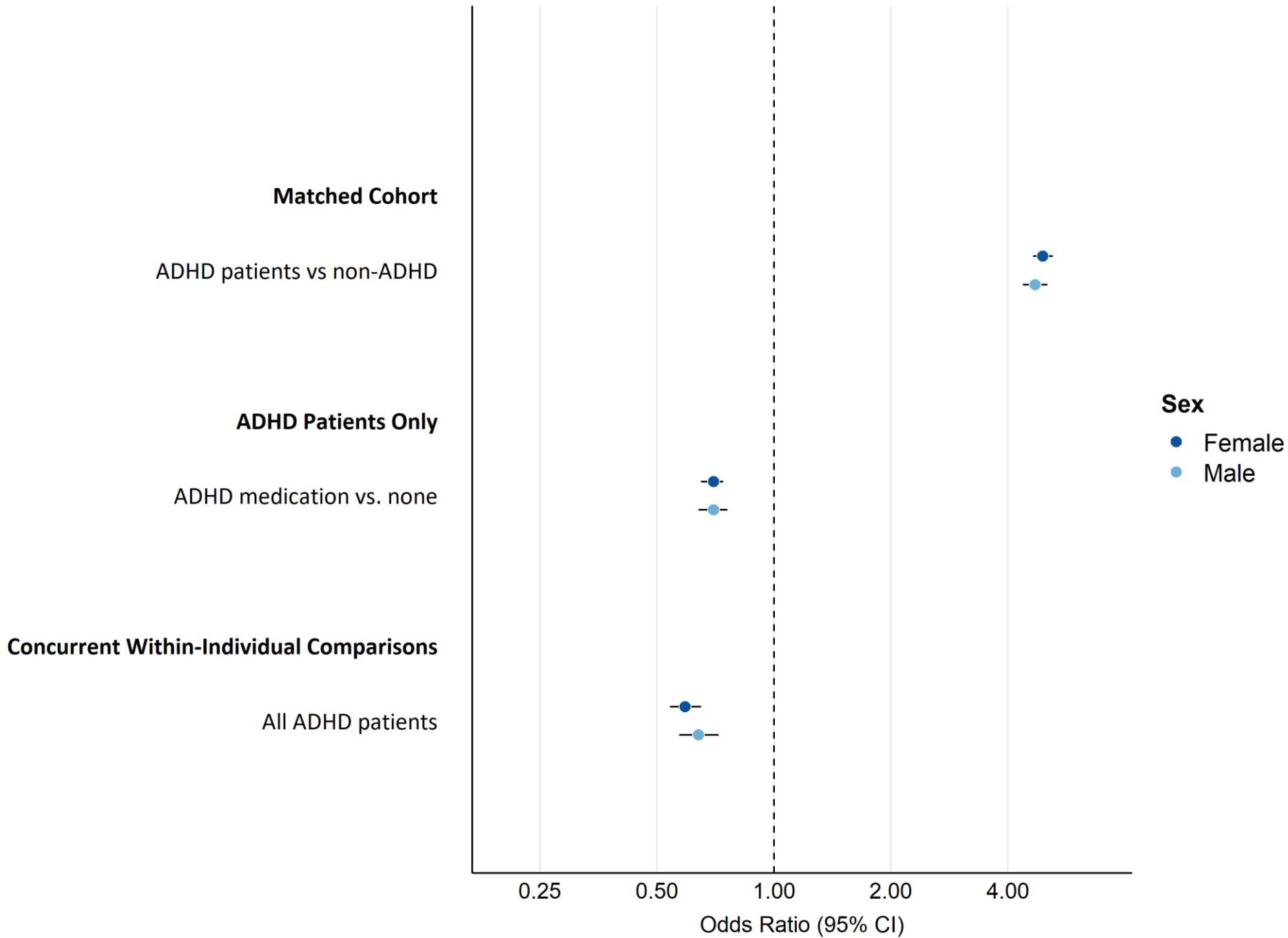
- The counterfactual for ADHD medication
- Each person as their own control
 - Compare risks when same individual is on versus off their medication
 - Accounts for all **stable environmental and genetic** factors
- Does not account for dynamic confounding
 - Can statistically adjust for time-varying covariates to help account for these factors

ADHD Medication and Suicide Attempt

Sample	Dataset with inpatient, outpatient, and filled prescription claims	3,874,728 ADHD patients from MarketScan Commercial Claims Dataset
Exposure	Filled Prescription Claims	ADHD Medication (Mostly amphetamine & methylphenidate; monthly)
Outcome	Acute suicide attempt event	<u>Emergency department, ambulance ride, or inpatient hospitalization w/ ICD diagnosis for suicide attempt</u>
Methods	Concurrent associations	Within-individual comparisons (i.e., monthly) while accounting for covariates (e.g., antidepressant use, & psychological treatment)

ADHD Medication and Suicide Attempt





Concurrent Within-Individual Comparisons

With Prior Diagnosis of Depression

With Prior Diagnosis of SUD

Incident Diagnosis Cohort and First Event

Age Categories

5-12 years of age

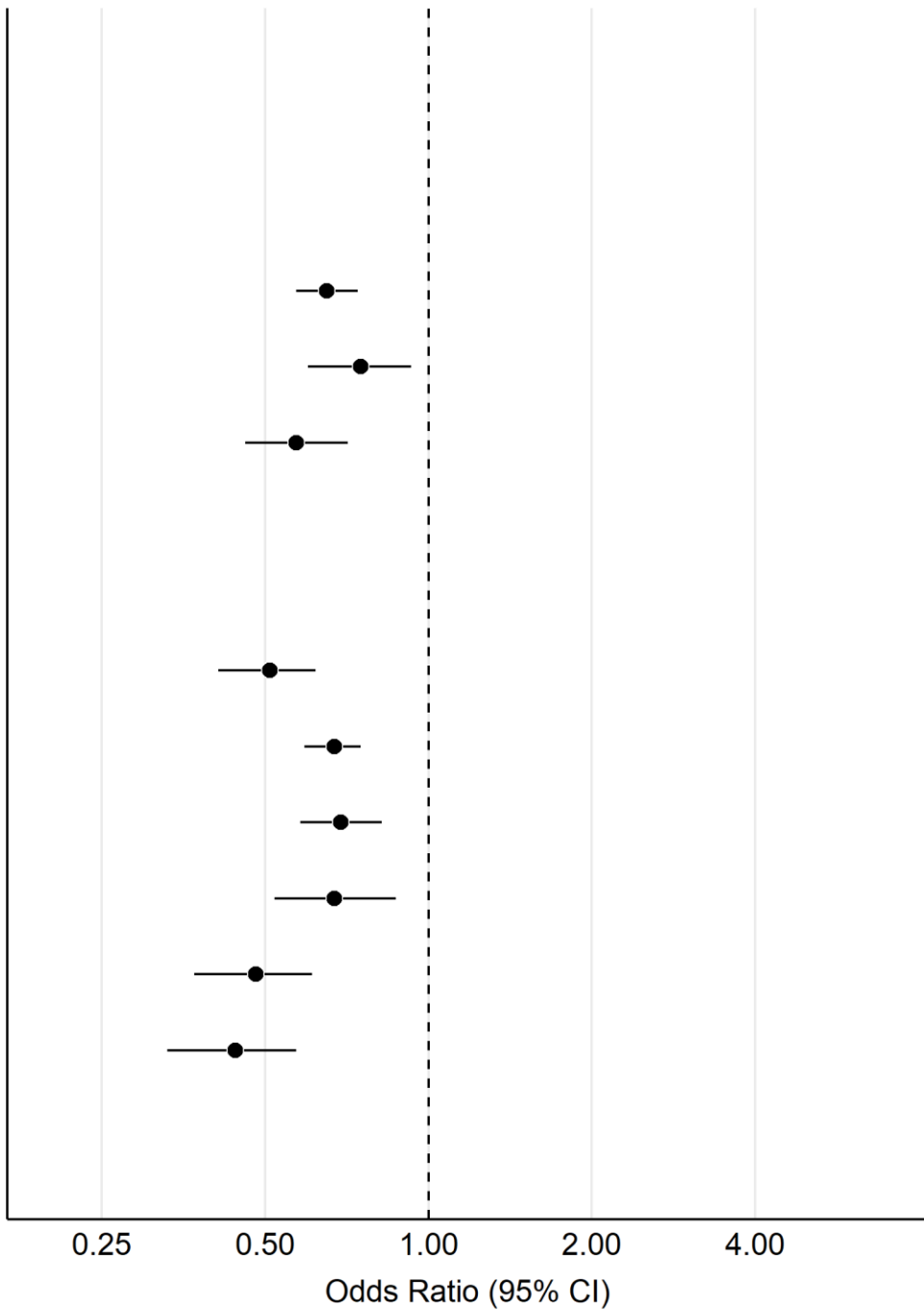
13-17 years of age

18-25 years of age

26-35 years of age

36-45 years of age

46+ years of age



Other Pharmacoepidemiology Studies of Self-Harm Behaviors

- ADHD Medications (Chang et al., 2020, *Biological Psychiatry*)
 - Consistent with studies of [suicidal behavior in other countries](#) (Chen et al., 2014, *JCPP*)
 - Consistent with related outcome (e.g., [substance problems](#); Quinn et al., 2017, *Am. J of Psychiatry*)
 - Consistent with [RCTs](#) of ADHD (Faraone, 2020, *Biological Psychiatry*)
- Other Medications
 - Opioid analgesics (Fine et al. 2022, *Pediatrics*)
 - Gabapentinoids (Molero et al. 2019, *BMJ*)
 - Statins (Molero et al., 2020, *Lancet Psychiatry*)

Review of Within-Individual Studies

- Results can help mitigate concerns about medication effects on rare-but-serious consequences, such as suicide attempts
- Findings can highlight possible protective effects, as well as possible iatrogenic effects
- Studies can explore at-risk subgroups that aren't included in previous research
- Need to include the most vulnerable and marginalized patients
- Similarly, will require research collaborations across multiple disciplines

Meta Messages

- Using large-scale observational studies can inform basic and applied research (i.e, **Translational Epidemiology**)
 - Can help guide research on mediating factors
 - Can help inform prevention/intervention studies
 - Can help patients and their physicians better weigh the risks and benefits of medications
- Without the ability to randomize exposure researchers need to rely on advanced design features to help rule out alternative explanations, including **genetic factors**

Thank you

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<http://www.iub.edu/~devpsych/>