Genetically-Informed Studies of Psychosocial Risk Factors and Psychiatric Medications

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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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Environmental factors

Precursor → Exposure → Mediator → Outcome

Based on D’Onofrio et al. 2020, Annual Review of Clinical Psychology
How Do We Study Risk Factors?

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

Kraemer et al., 1997; Rutter et al., 2001; Shadish, Cook, & Campbell, 2002
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

e.g., D’Onofrio et al., 2014; McGue et al., 2010; Rutter, 2007
# Bullying Victimization & Self-Harm Behavior

<table>
<thead>
<tr>
<th>Sample</th>
<th>Large-scale, longitudinal twin study in Sweden (CATSS)</th>
<th>13,852 twins born 1994-1999, followed from age 9 to 18 years old</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure</td>
<td>Bullying Victimization</td>
<td>Revised Olweus Bully/Victim Questionnaire at age 15</td>
</tr>
<tr>
<td>Outcome</td>
<td>Self-harm and suicide attempt</td>
<td>Questions from Lifetime History of Aggression questionnaire at age 18</td>
</tr>
<tr>
<td>Methods</td>
<td>Co-twin control design while accounting for covariates</td>
<td>Fixed-effects logistic regression models that accounted for previous psychopathology</td>
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O’Reilly et al. 2020, *J. of Adolescent Health*
Bullying Victimization and Self-Harm

- Environmental factors
- Genetic factors

Childhood Psychopathology → Bullying Victimization → Self-Harm and Suicide Attempt

?
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

e.g., Lichtenstein et al., 2012; Whitacker et al., 2019
# 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

*Emergency department, ambulance ride, or inpatient hospitalization w/ ICD diagnosis for suicide attempt*

## Methods
Concurrent associations

Within-individual comparisons (i.e., monthly) while accounting for covariates (e.g., antidepressant use, & psychological treatment)
ADHD Medication and Suicide Attempt

- ADHD and severity of problems
- ADHD Medication
- ?
- Suicide Attempt

Genetic factors

Environmental factors
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

Odds Ratio (95% CI)
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/