Polygenic and Prenatal Maternal Smoke Exposure Risk for Adolescent Substance Use

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Smoking During Pregnancy

SDP prevalence

- A substantial proportion of women still smoke during pregnancy

  - **Decline from 15% (2006) to 11% (2016) in the UK**
    - Some areas still above 25%

  - **Decline from 13% (2000) to 12% (2010) in the US**
    - Some areas still above 25%, Some areas increased (LA, ME, MI, WV)

Tong et al, 2013

SDP correlates

- Highly associated with lower birth weight (dose-response)
  Kraemer et al. 1987; 2001; Knopik, Marceau, Palmer et al., 2016; Marceau et al., 2016

- Associations with increased externalizing and substance use problems most often likely due to familial confounding
  Bidwell et al., in press; D’Onofrio et al., 2008, 2012; Estabrook et al., 2015; Knopik et al., 2005, 2006; Knopik, Marceau, Bidwell et al., 2016; Lindblad & Hjern, 2010; Thapar et al., 2009

  - Some potentially causal associations
    Gaysina et al., 2013; Knopik et al., 2016; Marceau et al., under review
**Shared Genes**

- **Xenobiotic metabolism genes regulate metabolism of nicotine**
  - *In Mothers, likely to have an effect on:*
    - Amount of nicotine available to affect fetal development
    - Extent of SDP, ability or desire to quit or continue during pregnancy
  - *Inherited by children*
    - 3rd line of defense for action of nicotine in prenatal development
    - Same genes may lead to child substance use problems later
  - *Moderation of SDP effects?*  

**Confounding Environmental Influences**

- **Maternal characteristics**
  - Age at childbirth, psychopathology/substance use, SES, education
Developmental Influences on SU

#1 Predictor: Externalizing Problems in Childhood

Colder et al., 2013; Disney et al., 1999; Helstrom et al., 2004; Molina & Pelham, 2003; Wilens et al., 2011

- Shared Genetic Influences

Hicks et al., 2011; Iacono et al., 1999

- Also linked with SDP, potentially causally

Gaysina et al., 2013; Knopik et al., 2016; Marceau et al., under review
Can we identify shared genes that account for SDP-SU associations?

- **Candidate system = Xenobiotic Metabolism Pathway**
  - *Polygenic scores*

- **Control for potential “environmental” familial confounds**
  - *Age at childbirth, psychopathology/substance use, SES, education*

**Hypotheses:**

1. *There will be a polygenic effect on adolescent substance use from the Xenobiotic metabolism pathway*

2. *The SDP effect on substance use will attenuate after controlling for xenobiotic metabolism genes*

3. *The SDP effect will further attenuate after controlling for other potential familial confounds*

4. *Earlier conduct problems will mediate SDP-SU and PRS-SU associations*
Avon Longitudinal Study of Parents and Children

- 14,701 pregnant women
- Live births, alive at 1 year \((N = 14,541)\)
- Valid data on relevant variables
  - SDP \((N = 11,889)\)
  - child SNPs \((N = 6,754)\)
  - Substance use \((N = 4,935)\)
- 1 child per family if multiple birth \((N = 406)\)
- Analytic N: 2,528
Measures

■ SDP
  - # of cigs per day (average) across 1st trimester assessed at 18 weeks pregnant
  - Current # of cigs per day assessed at 32 weeks pregnant

0 = no SDP in either the 1st trimester or later in pregnancy (N = 8036)
1 = 1-10 cig/day in the 1st trimester, no SDP later in pregnancy (N = 473)
2 = 11-20 cig/day in the first trimester, no SDP later in pregnancy (N = 45)
3 = 21+ cig/day in the 1st trimester, no SDP later in pregnancy (N = 33)
4 = any SDP later in pregnancy but not during the 1st trimester (N = 169)
5 = 1-10 cigs/day later in pregnancy and any SDP in the 1st trimester (N = 1289)
6 = 11-20 cig/day later in pregnancy and any SDP in the 1st trimester (N = 457)
7 = 21+ cig/day later in pregnancy and any SDP in the 1st trimester (N = 343)

Analytic Sample: Marceau et al., 2016
Measures

- **Child xenobiotic metabolism genes**
  - 18 SNPs from 10 genes

- **Conduct Problems**
  - Age 11.6 years
  - Maternal report
  - *Strengths and Difficulties Questionnaire*: conduct problems
    - 5 items, 0-2 scale, summed, prorated

- **Substance Use Frequency (current use)**
  - Age 16 years
  - Child Report
    - “How often do you have a drink containing alcohol”
    - “Mark the box next to the statement that describes you best”
ALSPAC Conduct Problems & SU

Conduct Problems: $M = 1.08$, $SD = 1.30$, $Range = 0-10$, 0 problems: 40%

<table>
<thead>
<tr>
<th>Ever (% yes)</th>
<th>Alcohol</th>
<th>Tobacco</th>
<th>Marijuana</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>94%</td>
<td>46%</td>
<td>30%</td>
</tr>
</tbody>
</table>

**Alcohol Use Frequency**

**Tobacco and Marijuana Frequency**

- Tobacco and Marijuana Usage Frequency
- Smoking
- Marijuana
Zero-order correlations with SDP

SDP – SU association attenuated after accounting for Conduct Problems. $F(2) = 11.71, p < .0001; R^2 = .01$

Conduct Problems: $\beta = .198 (.044), p < .0001$
SDP: $\beta = -.016 (.011), p = .15$

<table>
<thead>
<tr>
<th></th>
<th>Prenatal</th>
<th>Age 11.6 years</th>
<th>Age 16 years</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Conduct Problems</td>
<td>Alcohol Frequency</td>
</tr>
<tr>
<td>SDP</td>
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<tr>
<td>Conduct Problems</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol Frequency</td>
<td>-.02</td>
<td>.05*</td>
<td></td>
</tr>
<tr>
<td>Smoking Frequency</td>
<td>-.02</td>
<td>.14*</td>
<td>.37*</td>
</tr>
<tr>
<td>Marijuana Frequency</td>
<td>-.04*</td>
<td>.12*</td>
<td>.35*</td>
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</table>
Analytic Strategy

Split-half replication approach

- Single-SNP associations
- Regressions and SEM
  1. Main effects of PRS and SDP on SU
  2. Interaction of PRS and SDP on SU
  3. Full SEM:

Covariates
- Child sex
- Mother education
- Mother social class
- Mother psychopathology
- Mother age at child birth

![Diagram showing MSDP Severity, Xenobiotic PRS, Child Conduct Problems, Age 16 Substance Use, and their relationships.](image-url)
## Analytic Strategy

### 1. Select discovery (1\textsuperscript{st} half) and test (2\textsuperscript{nd} half) sets
- Mean center each SNP
- Identify monomorphic SNPs
- Run baseline, individual SNP regressions

**Child SNPs → Marijuana use (Zero-inflated Poisson regression)**

### Variations

- P-value for SNP inclusion in score
- Child vs. Maternal genes

### Loop repeated 18 times

<table>
<thead>
<tr>
<th>SNP</th>
<th>$\beta$ from discovery set</th>
<th>Person 1 # minor alleles</th>
<th>Person 1 SNP score</th>
<th>Person 2 # minor alleles</th>
<th>Person 2 SNP score</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNP1</td>
<td>.5</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>.5</td>
</tr>
<tr>
<td>SNP2</td>
<td>.1</td>
<td>2</td>
<td>.2</td>
<td>1</td>
<td>.1</td>
</tr>
<tr>
<td>Polygenic score</td>
<td></td>
<td>0.2</td>
<td></td>
<td></td>
<td>0.6</td>
</tr>
</tbody>
</table>

### 4. Multiply test matrix by SNP coefficients → polygenic scores
### 5. Run hypothesis testing regressions (same as above) and SEM (using bootstrapped standard errors)
Single-SNP associations

- Assumed additive effects
- Only 3 (of 90) nominally significant associations
  - none survive multiple testing

Split-half replication

- Polygenic Score (at $p < .25$, $p < .50$, $p < 1$)
  - No main effects
- SDP
  - No main effects
- Polygenic X SDP interaction
  - No interaction effects
Results

- **p inclusion = 1** (same pattern for all p thresholds)

- **Bootstrapped SE’s** (to account for skewed outcome)

- **Covariates**
  - Child sex
  - **Mother education**
  - Mother social class (in one replicate)
  - **Mother psychopathology**
  - Mother age at child birth

- **SDP Severity**
  - only in 1 replicate: (-)

- **Xenobiotic PRS**

- **FIML** (to accommodate missing data)

- **Age 16 Marijuana Use**

Gray lines = paths that were included but not significant
**Bold lines** = significant
Discussion & Implications

- Odd, small effect in ALSPAC in opposite direction
  - Other ALSPAC studies
    - Latent classes of offspring smoking initiation at 14-16 years
      - SDP associated with greater odds of being an experimenter, late onset, and early onset smoker compared to non-smoker
    - Higher ADHD multiple ages, higher conduct problems at age 4,
- Negative effects did not survive any sort of control
  - Small, unlikely to be real or meaningful
- Suggests that there is not a link between SDP and adolescent SU or child conduct problems
Limitations & Future Directions

- Limited coverage of xenobiotic metabolism system
  - Difficult to find polygenic effects
- Not a biologically relevant way to aggregate SNPs
  - Theory-based scores may help
  - Advanced methods being developed
- Models built on very weak links
  - Other phenotypes may yield more interesting results
    - Trajectories of change
    - ADHD/attention specific?
  - Other systems or exposures more important for adolescent SU?
    - Cumulative stress exposure mechanism
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