Examining sex differences in pleiotropic effects for depression and smoking using polygenic and gene-region aggregation techniques

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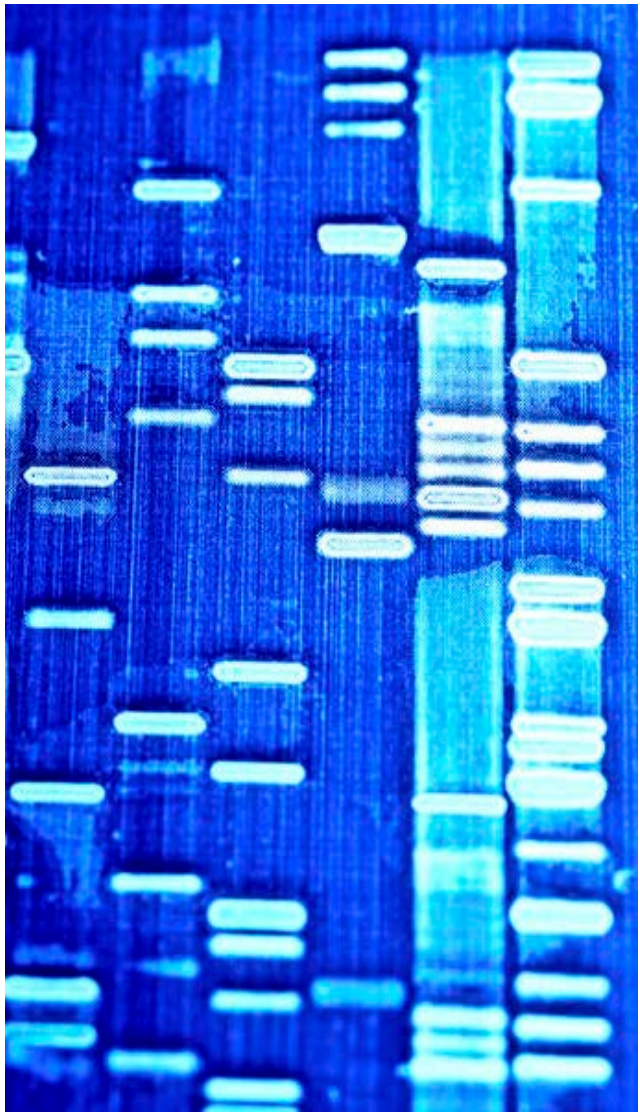


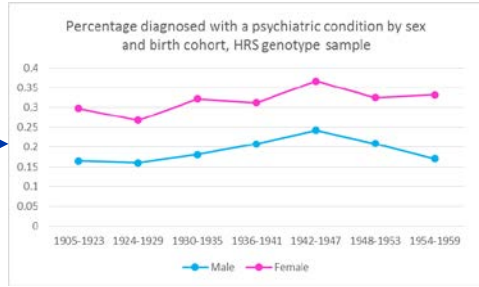
Male-female differences in smoking initiation and persistence

- Men still smoke more than women, the gap is narrowing (CDC, 2016)
- Adolescent girls smoke as much or more than boys and tend to initiate smoking earlier
  - e.g., SAMHSA, 2007
- Women evince more quit attempts and have higher rates of relapse than men
  - Hammond, 2009; Perkins, 2001; Perkins & Scott, 2008; Pogun & Yararbas, 2009; Reynoso, Susabda, & Cepeda-Benito, 2005
- Suggests biological factors, in addition to social norms, may contribute to sex differences in smoking

Smoking linked to depression and HPA-axis functioning in women

Stressful life events

Stronger emotional responses → internalizing symptoms (depression and anxiety)



Higher rates of internalizing disorders in women

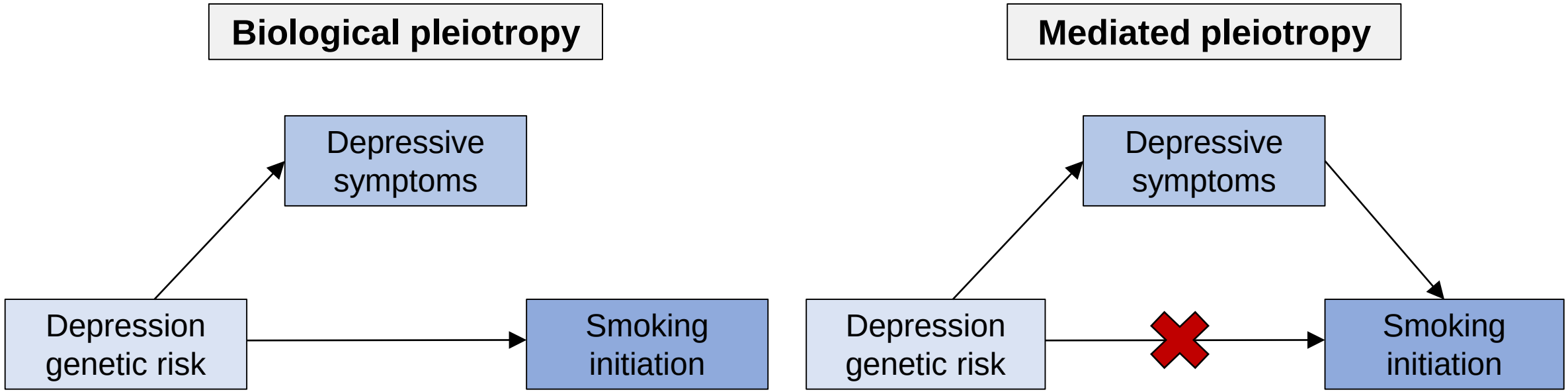
Women smoke more often to cope with anxiety and depression

During nicotine withdrawal women experience higher levels of stress-related HPA-axis hormones (cortisol)→intensifies depressive symptoms

Nicotine replacement therapies less effective

Does genetic risk for depression contribute to sex differences in smoking behavior?

- Tested for sex-specific biological and mediated **pleiotropy:** one genetic variant affects two traits



Data and Measures

- **Data: Heath and Retirement Study (HRS)**
  - 8,086 European ancestry respondents

- **Smoking behavior phenotype**
  - Smoking initiation (SI): smoked more than 100 cigarettes in your lifetime
  - Cigarettes per day (CPD)

- **Depressive symptoms phenotype**
  - Center for Epidemiological Studies-Depression (CES-D) scale (Range: 0-8)
    - Sum of six “negative” indicators (depression, everything is an effort, sleep is restless, felt alone, felt sad, and could not get going) minus two “positive” indicators (felt happy, enjoyed life)

Use two approaches to test for pleiotropy

1. Test for pleiotropy at the *genome-wide level* using **polygenic scores (PGSs)**
    - **Advantages:**
        - Increases power to detect cross-phenotype associations
        - Can easily incorporate into a multiple regression framework
    - **Disadvantages:**
        - Does not implicate a specific region and any related biological processes
        - GWAS does not account for comorbidity between traits

2. Test for pleiotropy at the *gene level* using **sequence kernel association testing (SKAT)**
    - **Advantages:**
        - Maintain biological specificity
        - Level of inference is the gene region instead of a single variant: tests whether beta estimates for set of SNPs in a region has a variance that is different from zero
    - **Disadvantages:**
        - Requires *a priori* knowledge of relevant regions

Overview of the results

- Depression-smoking comorbidity may be partially accounted for by shared genetic factors
  - At genome-wide level, results do not vary by sex (*genome-wide average*)
    - Evidence of mediated pleiotropy
  - At gene level, evidence HPA-axis genes related to cortisol function may contribute to SI in females
    - SKAT → biological pleiotropy for both sexes in *FKBP5*
    - iSKAT → sex-specific biological pleiotropy in *NR3C2*
    - *Results are suggestive—replication in larger cohorts is needed*

What do these results suggest for future research?

- PGSs are a (weighted) genome-wide average of genetic risk → may mask sex-specific environmental effects (hormones, social norms, stress response, etc.)
  - Need for more sex-specific GWAS
- To capture non-mediated pleiotropic effects, may need to look at the gene-region level
  - Variants implicated in GWAS may be working through endophenotypes
- Sex-specific pleiotropy may be a confounding factor in Mendelian Randomization
  - Can we assume one SNP → one pheno if pleiotropic effects vary by sex?
  - Does this assumption hold if pleiotropic effects vary by ancestry or across environments?
- Population-specific pleiotropy may be an important avenue to explore in health disparities research

Thank you!

National Institute on Aging (NIA)

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