Methods of measurement: Implications of polygenic scores’ estimation methods

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Polygenic Scores (PGS)s

• Represent a **cumulative genetic susceptibility**
  • Could be useful for traits that may not even be measured in a particular study
• Knowledge about the biological processes involved is not needed
• Reduces multiple testing burden

\[ PGS_i = \sum_{j=1}^{J} W_j G_{ij} \]

where \( i \) is individual \( i \) (\( i=1 \) to \( N \)), \( j \) is SNP \( j \) (\( j=1 \) to \( J \)), \( W \) is the meta-analysis effect size for SNP \( j \) and \( G \) is the genotype for individual \( i \) for SNP \( j \).
Why look at estimation methods?

- Vast heterogeneity in the literature
- Replication crisis
  - The Health and Retirement Study
    - Make available polygenic scores for multitude of traits
    - Public (non-restricted) data
- Which score to post? Does it make a difference?

Genotyped or Imputed SNPs?

Include all GWAS SNPs or significant SNPs?

Remove highly redundant SNPs?

Prune out based on genetic correlation (LD)?

Clump regional low LD SNPs by lowest p-values?
Previous work

**Heterogeneity in polygenic scores for common human traits**

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These analyses use data from non-Hispanic white (n=9,991) and non-Hispanic Black (n=2,279) HRS participants from the genetic collection years of 2006, 2008, and 2010. All measures were taken from the same exam at which the genetic data were collected.
Summary of previous work

• Many PGSs are not significant predictors of their phenotype of interest
• Correlations between scores range from [-0.03, 1]
• PGSs from genotyped data higher $R^2$ and lower p-values
• PGSs Generally do not perform as well in individuals of African Ancestry
• Different decisions explain (significantly) different percentages of variation in the phenotype of interest
• Clusters of PGSs that are significantly different from one another

(Ware et al., BioRxiv 2017)
Suggestions for using PGSs

FOR RESEARCHERS ESTIMATING POLYGENIC SCORES

• Use effect estimates from large, replicated genome-wide association meta-analyses that do not include the study of interest

(Ware et al., BioRxiv 2017)
What implications does this have for gene x environment interactions?

<table>
<thead>
<tr>
<th>Outcome</th>
<th><strong>Outcome</strong> = PGS + Environment + PGS*Environment</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Cognition</td>
<td></td>
</tr>
<tr>
<td>Body Mass Index</td>
<td></td>
</tr>
<tr>
<td>Educational Attainment</td>
<td></td>
</tr>
</tbody>
</table>

† *General cognition*: adjusted for age, sex, PC1 – PC4, and education*
† *Body Mass Index*: adjusted for age, sex, PC1 – PC4, and physical activity*
† *Educational attainment*: adjusted for age, sex, PC1 – PC4

*unless this was the environment of interest*
# Environment bivariate effects

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Environment</th>
<th>Unadjusted</th>
<th>Adjusted†</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Cognition</td>
<td>Educational Attainment</td>
<td>0.18***</td>
<td>0.16***</td>
</tr>
<tr>
<td></td>
<td>Childhood Adversity</td>
<td>-0.09***</td>
<td>-0.02</td>
</tr>
<tr>
<td></td>
<td>Stressful Life Events</td>
<td>0.11***</td>
<td>0.06**</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>Educational Attainment</td>
<td>-0.12***</td>
<td>-0.2***</td>
</tr>
<tr>
<td></td>
<td>Childhood Adversity</td>
<td>0.14*</td>
<td>0.6***</td>
</tr>
<tr>
<td></td>
<td>Stressful life events</td>
<td>0.8***</td>
<td>0.13*</td>
</tr>
<tr>
<td></td>
<td>Physical activity</td>
<td>-1.66***</td>
<td>-3.12***</td>
</tr>
<tr>
<td>Educational Attainment</td>
<td>Stressful life events</td>
<td>0.19**</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>Childhood Adversity</td>
<td>-0.35***</td>
<td>-0.29***</td>
</tr>
</tbody>
</table>

***p<0.001; **p<0.01, *p<0.05

† **General cognition**: adjusted for age, sex, PC1 – PC4, and education*
† **Body Mass Index**: adjusted for age, sex, PC1 – PC4, and physical activity*
† **Educational attainment**: adjusted for age, sex, PC1 – PC4
*unless this was the environment of interest
## Gene by environment interactions

<table>
<thead>
<tr>
<th></th>
<th>Outcome/PGS phenotype</th>
<th>PGS</th>
<th>Childhood Adversity</th>
<th>Educational Attainment</th>
<th>Stressful Life Events</th>
<th>Physical Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-Hispanic White</strong></td>
<td>General Cognition</td>
<td>216</td>
<td>0</td>
<td>0</td>
<td>36</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Body Mass Index</td>
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<td>131</td>
<td>38</td>
<td>0</td>
<td>9</td>
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<tr>
<td></td>
<td>Educational Attainment</td>
<td>217</td>
<td>3</td>
<td>-</td>
<td>23</td>
<td>-</td>
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<tr>
<td><strong>Non-Hispanic Black</strong></td>
<td>General Cognition</td>
<td>216</td>
<td>47</td>
<td>0</td>
<td>7</td>
<td>-</td>
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<tr>
<td></td>
<td>Body Mass Index</td>
<td>217</td>
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<td>77</td>
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<td>1</td>
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<tr>
<td></td>
<td>Educational Attainment</td>
<td>217</td>
<td>2</td>
<td>-</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>

*217 = (2 genotype/imputed x 6 p-value thresholds) x (8 pruning methods + 9 clumping methods + 1 no LD trimming method) + 1 top SNPs score
*216 = same as above, no top SNPs score
Preliminary results: $\text{PGS}_{\text{BMI}}$ and Childhood adversity

Outcome = Body Mass index, non-Hispanic Whites
Genotyped SNPs only

One LD trimming method, done at six different p-value thresholds

$pT$: GWAS meta-analysis p-value threshold; $\text{GWS}$: genome-wide significant; LD: Linkage Disequilibrium. None: no LD trimming; LD Pruning [LD R^2, window size (kb), sliding increment (number of SNPs)], LD Clumping [LD R^2, region size (kb)]
Preliminary results: $\text{PGS}_{\text{BMI}}$ and Childhood adversity

Outcome = Body Mass index, non-Hispanic Whites, Genotyped SNPs only

$\text{PGS}_{\text{BMI}}$: $t = 1.96$

$\text{pT}$: GWAS meta-analysis p-value threshold

$\text{GWS}$: genome-wide significant
What can we say, so far?

- This is a complicated landscape
- PGS method has an effect on the gene by environment interaction (p-value threshold of 1)
- Urge researchers to run their data with multiple PGSs as a sensitivity test to assure the robustness of their results
- Suggest that a p-value threshold equal to 1 with no LD trimming be included