vPGS: A better way to do GxE?

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Problem / Question

Typical polygenic GxE relies on PGSs estimated on phenotype levels, extracting signals robust across environments during the meta-analysis phase. This may result in a measure of G that is the least appropriate for capturing response to environmental variation

Hypothesis

- Interaction effects with vPGSs should better reveal significant heterogeneous treatment effects than interaction effects with traditional PGSs

Project Overview

We use extant weights from Yang et al (2011, Nature) from a GWA for variability on BMI and construct a variance PGS (vPGS) and utilize that measure of G to test for GxE in two datasets (Add Health and HRS) and compare that to GxE estimated using the traditional PGS.

(NB: We use measures of E that may be endogenous to G; however, even if proxying GxG, this is interesting with respect to measuring epistasis)

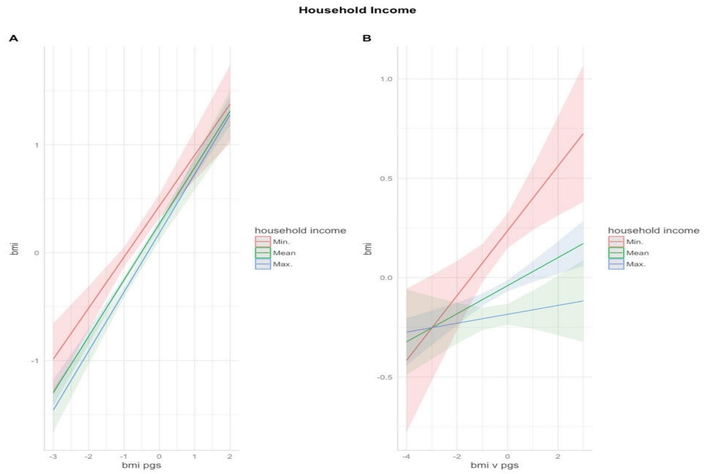
Models Tested

Controlled variables	Independent variable	Dependent variable
• Age • Sex • First 5 PCs • Main effect of E • mPGS or vPGS	• BMI vPGS v. mPGS	• BMI

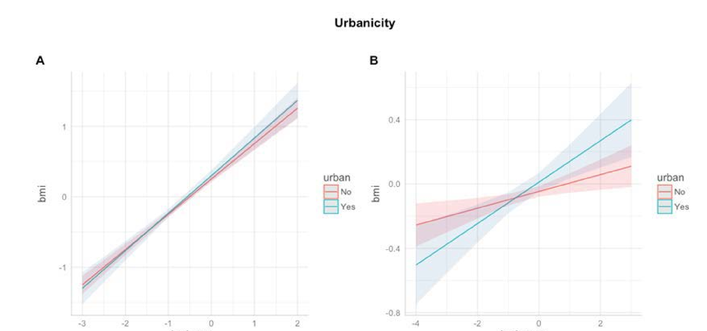
Data & Variables

Test Sample: Add Health	Replication Sample: HRS
Respondent HH Income	Respondent HH Income
Paternal Education (HCG)	Paternal Education (HCG)
Maternal Education (HCG)	Maternal Education (HCG)
Urban/Rural during Childhood	Urban/Rural during Adulthood

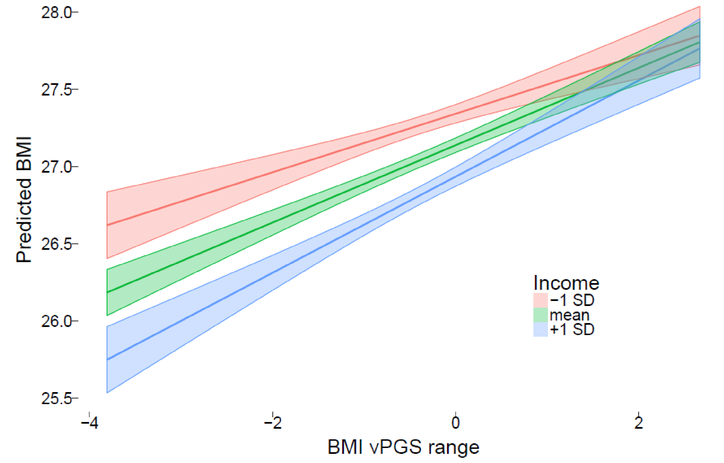
Add Health Results: Income*



Add Health Results: Urbanicity**



HRS Replication Results: Income*



Replication Results from HRS

- HH Income: vPGS significant, sign opposite!
- Urbanicity: NS

Conclusion

- mPGS yields null results for G x E interactions
  - (paternal education is exception in Add Health)
- vPGS inconsistent but potentially promising
- Construction of better vPGS weights with larger samples currently being conducted by Princeton Biosociology Lab
- Use of non-endogenous environmental measures going forward

Works Cited

- **vPGS calculations from weights (N=170,000) of:**
- Yang, J., Loos, R.J., Powell, J.E., Medland, S.E., Speliotes, E.K., Chasman, D.I., Rose, L.M., Thorleifsson, G., Steinthorsdottir, V., Mägi, R. and Waite, L., 2012. FTO genotype is associated with phenotypic variability of body mass index. *Nature*, *490*(7419), p.267.
- **mPGS calculations from weights (N= 339,224) of:**
- Locke, A.E., Kahali, B., Berndt, S.I., Justice, A.E., Pers, T.H., Day, F.R., Powell, C., Vedantam, S., Buchkovich, M.L., Yang, J. and Croteau-Chonka, D.C., 2015. Genetic studies of body mass index yield new insights for obesity biology. *Nature*, *518*(7538), p.197.