Genetics and Subjective Well-being, Depression and/or Cognition: Possible Project Proposals

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# Introduction

This document outlines a proposal for three separate gene/environment studies using the HRS on subjective well-being/Depression. Broadly, this study can include measures of life satisfaction, happiness, cognition, depression, substance abuse, and other psychological or internalized processes. A large GWAS recently analyzed these phenotypes (Okbay et al. 2016), and researchers have cross-applied to the studies in the HRS (Domingue et al. 2016).

Proposed study 1 is a direct extension of the work by Domingue, et al. (2016). Domingue, et al. find that different rates of decay in elevated depressive symptoms after a spouse dies are associated with with polygenic scores (PGS) calculated from the GWAS mentioned above. This proposal anticipates an identical design, but instead of using spousal death as the exogenous environmental treatment, it will use variability in economic conditions (unemployment rate, the great recession, and perhaps exposure to recessive periods in the past).

Proposed study 2 addresses the long-term problem of understanding why there is a gendered difference in depression between men and women. Explanations include biological differences between men and women, differences in the level of exposure to stressful events leading to depression, and gendered responses to stress, which postulates that women are prone to internalizing disorders (like depression) while men are prone to externalizing disorders (like substance abuse). Notably, the social environment regarding gender has changed dramatically over the past several decades (Pampel 2011). This provides an opportunity to examine population heterogeneity in gene-by-environment interactions in a manner like Boardman, *et al.* (2010), and to test larger theories for the sources of population heterogeneity in gene-by-environment interactions as summarized in that work (social control, social trigger, and social push).

Study 3 addresses the relation of depression and subjective well-being with cognition. For many years, studies have linked depression and cognitive processes with depression and well-being. Theories presume that underlying differences in subjective well-being arise from social comparisons and counterfactual thinking or the perception of social support–fundamentally cognitive processes (George 2010). In additioon, there are regularized life-course shapes to subjective well-being and age. These regularized patterns relate to regularized changes in cognitive assessments of life, *i.e.* people become happier and less depressed with age, because they engage in more beneficial cognitive comparisons (George 2010). While large studies of inter genetic correlation show only a weak (and not statistically significant) correlation between major depression and Alzheimer’s disease (Bulik-Sullivan et al. 2015) it is possible (and perhaps likely) that subclinical manifestations of the diseases will be more strongly correlated.

The next section discusses each of the proposed studies in more detail.

# Proposed Studies

## Proposal 1: Heterogeneous Sensitivity to Short Term Economic Conditions

The first study is a simple test of genetic vulnerability or resistance to depressive events. Psychology knows this as the “diathesis-stress” model, but similar theories cross disciplinary boundaries by focusing on vulnerability and resilience to negative stimulus. Studies have found inconsistent results using both candidate gene models and polygenic score models.

A great example of a simple and straightforward study along these lines is Dominigue, et al. (2016), which finds genetic robustness to the death of a spouse. They use a very straightforward approach. (1) They match SNPs in the HRS to SNPS in the GWAS conducted by Okbay et al. (2016) available through the Social Science Genetic Association Consortium. (2) They sum the weighted estimates of well-being associated alleles from the GWAS to calculate a polygenic score. (3) They adjusted the residulized PGS using 10 principal components and PLINK (command: pca), and normalized the PGS residual distribution, which they used as the measure of genetic predisposition to well-being. They then used a discontinuity regression design centered on the loss of a spouse, and find faster decay in depressive symptoms for those with higher PGS for well-being, concluding that the PGS represents a genetic robustness to negative stressors.

In this case, I would propose constructing the polygenic score in an identical manner to Domingue, *et al.* (Dan Belsky tells me that this can occur given a simple request; and it is a request that he is willing to make for us). Alternatives also include testing of candidate genes (table of most-studied candidates under proposal 2), or building our own polygenic score out of the HRS. Instead of the extreme distress of spousal death, I propose modeling the association with short-term fluctuations in the unemployment rate, and/or the experience of a recession in young adulthood. This builds on previous work of mine that does not include biomarkers, which is currently drafted and under review. It is also similar to work that Conley (2009) proposed several years ago regarding larger economic variation as exogenous environmental treatments that can elucidate gene-environment interactions.

Short-term fluctuations in well-being (measured by both satisfaction and depression) follow short-term differences in economic circumstances (as measured by the unemployment rate). Late last week (5/18-5/19), I conducted some basic analyses combining the HRS (using depressive symptoms) and the BLS (for unemployment rates), and there is an effect of short-term unemployment rates on depressive symptoms: when unemployment rates go up or down, depressive symptoms follow. The question is whether vulnerability to these short-term effects vary across genetic endowments. Moreover, do gene effects indicate a buffer or a sensitivity? Do they vary across positive and negative stimuli? Are there thresholds? These are basic questions with little literature to suggest specific directional hypotheses.

## Proposal 2: Heterogeneity in Genetic Correlates of Gendered differences in Depressive Symptoms by Cohort.

Several consistent patterns in psychological well-being relate to gender. First and foremost, women report higher prevalence of affective disorders like Major Depressive Disorder, whether measured continuously or dichotomously (Aneshensel, Rutter, and Lachenbruch 1991; Kessler et al. 2005; Seedat, Scott, and Angermeyer 2009). In contrast, men report higher prevalence of substance abuse disorders such as alcoholism and drug addiction (Simon 2002). Explanations for these differences include (1) fundamental biological differences; (2) differential exposure to stress across genders; (3) differential errors in diagnosis across genders; and (4) differentials in gendered responses to stress across gender, *i.e.* women use internalizing strategies, while men use externalizing strategies.

A recent review in psychology provides a very good overview of this literature, including a summary (and references) to genomic studies in this area (Kuehner 2017). The following table provides a short list of the most studied candidate genes for gendered differences (original studies referenced in the review).

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| **Gene** | **Summary** |
| 5-HTTLPR | Most-studied, including meta-analysis of 78 studies. Shows differences in externalizing & internalizing propensities, and there are different distributions of a “short” allele frequency in a promoter gene across gender |
| FKBP5 | including SNP rs1360780 — involved in the stress system |
| CRHR1 | including SNP rs110402 — protective effect related to childhood trauma |

The review notes that the studies are still sparse and inconsistent, particularly because genetic factors appear to be pleiotropic. The review does not note any studies regarding polygenic risk scores, even though the pleiotropy and the complexity of the trait suggests that this is perhaps a more reasonable approach as explained by Belsky and Israel (2014). In addition to the failure to use a PGS strategy, prior research has also ignored possible heterogeneity in gendered social structures across various cohorts.

An instructive illustration of the potential importance of heterogeneity in social structures across cohorts is Boardman *et al.* (2010). That study presents evidence of differences in gene-environment interactions across cohorts related to the Surgeon General’s warning about smoking in 1964. Before and after this period, there was a great deal of change in the population prevalence of smoking. Similarly, (though perhaps not as dramatic), there were also significant changes in gendered institutions, including a civil rights act outlawing gender discrimination in 1963, and an important law on gender equality in higher education (Title IX) in 1972. These co-occur with large changes in attitudes about gender egalitarianism around the same time (Pampel 2011), although structural changes have still lagged to some degree. In addition, some studies have shown differendes in gender gaps of depressive symptoms over time (as measured by birth cohorts) (Yang 2008; Yang and Lee 2009).

There are three potential effects of these sorts of social environments on the ability to identify genetic correlates of complex behavior (Boardman et al. 2010). First, is the idea of a *Social Trigger.* In this case, genetic differences occur only in the presence of norms. With respect to gender differences in subjective well-being, Sex Role Theory predicts a genetic social trigger. More than forty years ago Gove and Tudor (1973) proposed sex role theory as an explanation for the gender discrepancy in mental health. Gove and Tudor hypothesized that gendered differences in psychological well-being arose out of women’s restriction to a very narrow set roles: primarily wife and mother. This was truer for the oldest cohorts, and less true for younger cohorts. To the extent sex role theory is correct, we should find evidence of social trigger (*i.e.* gendered effects in the gene-by-environment interaction) for older cohorts, but not for younger cohorts. This seems to be the strongest theoretical hook, and may vary by occupational status, education, work history, and number of children for women. In addition, there is a variable in the HRS often used to measure gender egalitarian attitudes (centered on how much household decision-making control each spouse has), which may be of use in estimating inter-cohort heterogeneity. A null result would also be interesting in this regard (assuming the HRS analyses are sufficiently powered).

Second, is the phenomenon of *Social Control.* In this case, norms eliminate genetic differences by requiring homogeneity or heterogeneity in individuals regardless of biological impulse. Unlike smoking, which is a behavior, there is little to suggest a social control phenomenon, because subjective well-being is a reported feeling. To the extent social control eliminates genetic correlates, it’s likely cause is the gendered reporting or recognition of symptoms. This is something that would be difficult to measure, and has weak evidence as outlined in the review mentioned above.

Finally, is the concept of *Social Push.* This theory is non-causal, and suggests that social norms can either minimize or generate noise to make detection of genetic effects easeir or harder at different time-periods. For example, if there is a genetic impulse to smoke, but everyone smokes, then there is no statistical leverage to find a genetic effect, because there is no variance in the behavior. This difference between this and social control is the concept of cause. Accordingly, similar evidence and analysis are potentially applicable for social push versus social trigger. Assuming we find interesting results, we must create an analytic plan to distinguish between these effects.

Boardman, et al. use a twin study in the MIDUS data to calculate cohort heterogeneity in the heritability of smoking, so their study design does not apply to the HRS. However, alternative designs may also work. The first design would analyze the effect (if any) of the candidate genes listed above across birth cohorts. Similarly, we could calculate polygenic scores and identify whether they are stronger or weaker over various birth cohorts. The problem with the PGS approach, however, is how to account for heterogeneity across cohorts in the risk score (which are likely to include biases related to the gene-by-environment interaction, depending on the cohorts used to generate the PGS). To pursue this study, I suggest a thorough review of the manner polygenic scores are (and could be) calculated. This may represent an opportunity for a methodological advancement, depending on the state of the literature regarding the development of polygenic risk scores.

## Proposal 3: Cross-Association of Cognition, Subjective Well-Being, and/or Other Illnesses

The final proposal is more exploratory, and relates to fundamental assumptions on the relationship between subjective well-being and cognition in social psychology. Simply put, models of subjective well-being presuppose that it rests on a cognitive framework. In other words, people feel good or poor *after* evaluating their situation, and the meaning of their situation (McLeod 2012). In a stress process model, this is fundamentally a cognitive process which precedes and underlies differences in subjective well-being. Under this model, there should be a close association between the biological bases of subjective well-being (for example, depressive symptoms) and cognitive function.

In contradiction to these presumptions, some studies identify little genetic association between some measures of poor subjective well-being (depression) and some measures of cognitive decline (Alzheimer’s) (Bulik-Sullivan et al. 2015). However, this study does not include gene-by-gene or gene-by-environment interactions. Applying these extensions are straightforward, and would require comparing multiple measures of subjective well-being and cognitive decline. In addition, we can also extend the proposals above to include a parallel analysis of cognition, with some mediation, moderation, and interaction designs. Similarly, we can test whether resilience to depression also predicts resilience to cognitive decline, and/or resilience to the development of disabilities or mortality (ADL/IADL).

Pursuing these lines would require replicaiton of genetic analysis for cognition in parallel fashion to that spelled out for depression, or may require gene-by-gene interactions in additon to gene-by-environment interactions.

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