Exploring the Utility of Current Polygenic Scores in Capturing Resilience

Running head: Utility of Polygenic Scores in Capturing Resilience

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ABSTRACT

Although resilience has been identified to be moderately heritable, little is known about the genetic variants involved. While there has not yet been a robust genome-wide association study (GWAS) of resilience, existing GWAS of related phenotypes may provide a starting point for developing our understanding of the heritability of resilience. In a sample of older, US adults (N= 9,480), we examined the extent to which proxy polygenic scores (PGS) explained the variance in resilience. Four of the 32 PGS assessed (subjective wellbeing, neuroticism, depressive symptoms, and educational attainment) reached significance among participants with European ancestries, but with relatively small effects ($|\beta| = 0.002 - 0.09$). Notably, PGSs derived from GWAS of PTSD among participants with either European or African ancestries were uncorrelated with resilience. Even aggregated across all available proxy PGSs, existing PGSs are not sufficient to inform our understanding of the genetics underlying the heritability of resilience. A large-scale GWAS of resilience is needed as it would provide greater insight into the genetic mechanisms underlying the heritability of resilience.

Keywords: Behavioral Genetics, Psychological Resilience, Depression, Neuroticism, Stress Disorders, Multifactorial Inheritance

Stress is consistently identified as a risk factor for the onset of psychopathology (Harkness et al., 2015). However, not all people who are exposed to stress respond in the same way. Individual differences in stress response and resilience reflect dynamic interpersonal and intrapersonal factors (Laird et al., 2019). Resilience, often conceptualized as the absence of psychopathology relative to an individual's reported level of exposure to stress, is stable over time (Amstadter et al., 2014) and moderately heritable (Boardman et al., 2008). Still, little is known about the genetic variants that may explain the observed heritability of resilience (Feder et al., 2013, Stein et al., 2019). The reasons for this could be attributed to two important factors: sample size and measurement.

Hurdles To Understanding the Genetics of Resilience

Sample size. Recently, more and more genetic studies have moved toward genome-wide association studies (GWAS) as well as polygenic scoring methods. However, when it comes to research into the genetics of resilience, few studies have used such approaches (Choi et al., 2019). This may partially be explained by the lack of large samples that measure resilience.

Efforts to discover individual genetic variants associated with psychological outcomes require huge samples to overcome the substantial multiple testing burden and incredibly small effect sizes. GWAS (where millions of individual variants are examined for associations with an outcome of interest) typically requires more than 100,000 participants to be adequately powered to detect anticipated effect sizes equivalent to correlations of less than 0.01 (Plomin and von Stumm, 2018, Zhang et al., 2018). As a result, most datasets are unsuitable for conducting a GWAS. These restrictions are further compounded when a trait is not frequently measured in large datasets—as is the case with resilience.

Measurement. Compared to other psychological traits, the study of resilience is relatively recent (Feder et al., 2009). As a result, researchers still have not agreed on the best way to measure or even define psychological resilience (Choi et al., 2019). Moreover, few large-scale datasets include a direct measure of resilience, and those that do, do not have genetic data. Consequently, resilience researchers are frequently

forced to choose between measurement quality and statistical power. This balancing act and its associated consequences are reflected in the only genome-wide association studies (GWAS) of resilience to date^(Stein et al., 2019). While the dataset used in that study did have direct measures of resilience, statistical power was constricted due to the modest sample size ($N = 11,492$).

When a large sample size is imperative to the success of a study (e.g., GWAS), there are generally only two feasible options. One is to obtain a large sample of participants and directly measure the phenotype, which could be both costly and time-consuming; the second is to construct a measure of the trait from variables that are available in large-scale datasets. However, studies that do not require a large sample size (i.e., $N > 100,000$) offer greater flexibility (e.g., selecting a dataset). Considering the hurdles resilience faces when it comes to measurement and sample size, it is worth investigating if there are other approaches that do not require as large of a sample but would still allow us to further our understanding of the genetics of resilience.

Proxy-Phenotype Approach.

In cases where phenotypes, like resilience, do not have data from a large-scale GWAS, is the only option to conduct a GWAS? Or, can the genetics be understood in the absence of a GWAS? To answer this question, we can look to the educational attainment literature where cognitive performance was under constraints similar to resilience.

Rietveld et al. (2014) put forth the proxy-phenotype approach in order to identify genetic variants associated with cognitive performance. Even though cognitive performance was identified to be moderately heritable, research into the genetic variants associated with cognitive abilities was largely unsuccessful. GWAS, however, presented a unique opportunity to increase our ability to detect variants associated with a trait. As was previously discussed, sample size is an extremely important factor for the success of a GWAS. Noting that much larger samples were available for educational attainment and that the two traits are highly correlated, Rietveld et al. (2014) conducted a GWAS of educational attainment,

which identified a set of candidate SNPs. This set was then used to estimate the association between the educational attainment candidate SNPs and cognitive performance. This proxy-phenotype approach proved to be successful as several genetic variants associated with cognitive performance were identified, a milestone that had never been reached prior to that study. The results of the Rietveld et al. (2014) study provided concrete evidence for the use of correlated phenotypes as proxies to gain genetic insights in absence of a GWAS.

Here, we aim to do something similar with resilience by using a polygenic proxy score approach. Making use of precomputed PGS derived from GWASs of phenotypes shown to be correlated with resilience in the literature (e.g., subjective wellbeing), we hypothesize that, much like the Rietveld et al. (2014) study, we will be able to identify genetic variants associated with resilience.

Polygenic *Proxy* Score Approach.

A recent review paper on the genomics of psychological resilience put forth recommendations for future studies on the topic (Choi et al., 2019). There were five recommendations outlined, one of which related directly to the proxy score approach. In the review, Choi et al. (2019) address how genomic studies can often be limited in their measures of phenotypes; it is further noted that in the absence of ideal data, researchers should use insights from a large-scale GWAS of related traits and use the PGS from those to validate them in smaller, but better phenotyped, datasets (Choi et al., 2019).

Ensuring that the measure of resilience is as robust as possible becomes increasingly important when using the proxy approach, as inaccuracies in measurement may confound the results. In other words, if the measurement does not capture resilience, then the proxy PGS may not perform as intended—not because they do not work, but rather because the phenotype does not properly represent the correlated trait, which is what the proxy approach hinges on. In this regard, Choi et al. (2019) recommend that to provide for the most robust study design, future studies into psychological resilience include detailed measurements of both adversities and outcomes.

Current study.

In a sample of older, US adults we sought to examine if existing PGS could help explain the variance seen in resilience, even in the absence of a GWAS. More specifically, 32 PGS—that were pre-computed from existing GWAS of phenotypes found to be correlated with resilience—were assessed to ultimately discover if any of the 32 selected PGS were associated with resilience. Data were obtained from the Health and Retirement Study (HRS); however, since HRS does not include a direct measure of resilience, it was constructed from available variables. Considering the importance of including adversities and outcomes, the conceptual definition of resilience, and previous approaches to measuring resilience—we decided to use a residual (i.e., outcome) based approach to measure resilience. Resilience was operationalized as negative affect residualized over trauma and stress, resulting in a continuous outcome measure of resilience (CORE), where higher scores indicate greater resilience. While the residual-based approach to measuring resilience is not novel and has been shown to work well in various studies (Boardman et al., 2008, Amstadter et al., 2014), we still wanted to ensure that our measure of resilience was accurately capturing resilience. To assess this, we compared our measure of resilience to other phenotypes that have previously been found to be correlated with resilience. If the correlations are in line with what has been previously reported in the field, we would be able to conclude that our construct of resilience is performing as expected and thereby lend confidence to the results of the polygenic proxy score analyses.

METHODS

The complete statistical analysis plan was pre-registered at [<https://osf.io/cwzjs/>] prior to the researchers accessing the data. When necessary, deviations from the pre-registered analysis plan are noted and explained below. All data used in this project are publicly available at [<https://hrs.isr.umich.edu/>].

Sample

Participants were sampled from the Health and Retirement Study (HRS). HRS is a nationally representative longitudinal survey of households of older adults living in the USA (Sonnega et al., 2014). Surveying began in 1992, with follow-ups occurring every two years. The initial sample included more than 37,000 individuals from 23,000 households within the USA (Sonnega et al., 2014). Approximately 15,000 participants provided salivary DNA between 2006 and 2012 and met inclusion criteria for HRS' polygenic score construction (Ware et al., 2018). Our analyses were limited to individuals who had available pre-computed polygenic scores and had completed the Self-Administered Psychosocial and Lifestyle Questionnaire, which has been previously described (Smith et al., 2013). The final sample included 9,480 individuals. Among the individuals included in the current study, 58.5% were women, and 41.5% were men. Self-reported race/ethnicity was 84% White/Caucasian, 16% African American. At the time of the assessments used in the current analyses (either 2010 or 2012), the average age was 67.8 (SD = 11.0, range = 27 - 100). To account for technical artifacts in genetic data, HRS provides PGSs estimated in pre-split ancestry groups, labeled African American (AA; N = 1,518) and European American (EA; N = 7,962).

Survey Data

Positive and Negative Affect. Twenty-five items from the Positive and Negative Affect Schedule-Expanded Form (PANAS-X; Watson & Clark, 1999) were used to assess positive and negative elements of hedonic wellbeing. Participants were asked to respond on a scale of 1 to 5 (1 = Very much, 5 = Not at all) to each item to determine the degree to which they felt specific emotions (e.g., fear, happiness, boredom, distress) during the last 30 days.

Stressful Life Events. Three questionnaires were available that broadly measured stressful life events, lifetime traumas, and ongoing chronic stressors.

Past five-year stressful events were assessed using a 6-item questionnaire (Turner et al., 1995) where participants indicated whether or not they had experienced each of the events (e.g., robbed or burglarized, victim of fraud, unemployment) within the last five years.

Lifetime trauma was measured using a 7-item questionnaire (Krause et al., 2004) and asked whether or not participants had experienced each of the seven traumas listed (e.g., has a child of yours ever died?, were you the victim of a serious physical attack or assault in your life?).

Ongoing chronic stressors were defined as stressors that have lasted for 12 months or longer. Participants were asked to indicate on a scale of 1 to 4 how upsetting the stressor has been (1 = No, it didn't happen, 2 = Yes, but not upsetting, 3 = Yes, somewhat upsetting, 4 = Yes, very upsetting) for 8 separate potential stressors (e.g., ongoing financial strain, ongoing physical or emotional problems (in spouse or child) (Troxel et al., 2003)).

Construction of the resilience measure. Resilience was operationalized as negative affect (i.e., PANAS score, with negative items reverse coded, such that a higher score indicates higher negative affect and lower positive affect) residualized over sex, age, self-reported race, and item-level responses to the three available measures of stressful life experiences, lifetime trauma, and ongoing chronic stressors. The residual approach to modeling a phenotype is not novel and has been successfully operationalized in twin studies of resilience (Boardman et al., 2008, Amstadter et al., 2014). Although the Positive Affect and Negative Affect dimensions may be scored separately, the factors are correlated (-0.3; Crawford & Henry, 2004), and our pre-registered analytic plan elected to treat them as a single sum score. We entered responses from each of the stress questionnaires (past five-year stressful events, lifetime trauma, and ongoing chronic stressors) at the item level and did not use a sum score as they are relatively independent events and different types of stress might be uniquely impactful with regard to positive and negative affect. From this linear model, we saved standardized residuals such that higher scores on our measure of resilience indicated greater resilience; that is, less negative affect and/or more positive affect than would otherwise be expected given the individual's reported exposure to stress.

Psychosocial variables. Psychosocial variables were pulled from the HRS Self-Administered Psychosocial and Lifestyle Questionnaire (Smith et al., 2013). Variables were selected based on the Connor-Davidson Resilience Scale (CD-RISC), an internally consistent, and well-validated measure of resilience (Connor and Davidson, 2003). The psychosocial questionnaires were compared to the 25-items of the CD-RISC and were chosen for inclusion if they closely matched or addressed the items in the CD-RISC as well as had been previously cited as a predictive factor in the resilience, depression, or stress literature. Exceptions to the criteria were demographic variables that are important to consider when conducting these types of studies: socioeconomic status (SES) and gender. Since HRS does not have a precomputed global SES variable, educational attainment was used as a proxy as it has been shown to be a strong correlate of SES, and is relevant regardless of a person's age or working status—an important consideration in a sample of older and potentially retired individuals (Liberatos, Link, Kelsey, 1988). Gender was not included as a psychosocial correlate as it was used as a covariate in the construction of the measure of resilience. The other included psychosocial variables were social support, loneliness, religiosity/spirituality, personal control, mastery, optimism, pessimism, hopelessness, subjective wellbeing, purpose in life, neuroticism, extraversion, openness, agreeableness, conscientiousness, height, and education (Smith et al., 2013).

Polygenic Scores

Polygenic scores (PGS) were constructed by HRS and available for public access on the Health and Retirement Study website (<https://hrs.isr.umich.edu/>). PGS for each of the phenotypes were each calculated from a single large-scale genome-wide association study (GWAS), excluding HRS data where present in order to produce scores independent of HRS. PGSs were released for HRS's pre-defined European American (EA) and African American (AA) ancestry groups, along with five ancestry principal components suitable for inclusion as covariates. Because the ancestry principal components had been estimated within the EA and AA groups separately, genetic data analyses could not be combined across the two groups. Information regarding PGS construction and ancestry estimation can be found in the HRS Polygenic Scores documentation report (Ware et al., 2018).

PGSs were selected for inclusion in the statistical analyses based on whether the phenotype of interest had previously been investigated for association with psychological resilience, stress, or depression in the existing literature (see Table S5). Phenotypes were automatically excluded if the GWAS used to construct the PGS included HRS and was not re-run without HRS to avoid overfitting (Wray et al., 2013). The full list of selected PGSs was included in the pre-registered statistical analysis plan available at [https://osf.io/cwzjs/].

Data analytic plan

For this study, we examined the extent to which polygenic scores derived from GWAS of 32 phenotypes (Supplementary Table S5), explained the variance in resilience. In order to assess the extent to which polygenic scores correlated with resilience, separate regressions were performed for each of the 31 polygenic scores of interest and analyzed separately within the African ancestry and European ancestry groups. Specifically, the linear model was

$$Y = b_0 + b_1X_1 + b_2(PC1) + b_3(PC2) + b_4(PC3) + b_5(PC4) + b_3(PC5)$$

Where Y is the residuals collected from our model of resilience, and X_1 represents each polygenic score that will be substituted into the equation. Importantly, pre-existing HRS genomic principal components will be included in the equations (PC1-PC5) in order to control for ancestry (Ware et al., 2018). The same process was applied to the psychosocial variables, where X_1 represents each of the 26 psychosocial (and height) variables of interest.

Power analyses. Power analyses were conducted using the “*pwr*” package in R (Champely et al., 2018). The *pwr* package provides various functions for power analyses following Cohen (1988) guidelines. As aforementioned, $r = 0.1$ to 0.2 are the commonly observed outcomes for psychological variables; per Cohen (1988), such effects would fall under the small effects category. A simple correlation power analysis using *pwr.r.test* reveals that a sample size between 364 and 1,480 is needed in order to be 90% powered to detect effect sizes between 0.1 to 0.2 ($\alpha = 0.01$).

Since most of the analyses for this study were regressions, we used the *pwr* package function for linear models: *pwr.f2.test*(*u* = , *v* = , *f2* = , *sig.level* = , *power* =). Where,

$$\begin{aligned} u &= \text{number of predictors} \\ v &= n - u - 1 \\ f2 &= \frac{R^2}{(1-R^2)} \end{aligned}$$

Cohen (1988) guidelines suggest interpreting 0.35 as large *f2* values, 0.15 as medium, and 0.02 as small. Considering the relationship between correlation coefficients and regression coefficients, we could extrapolate that our study would be well powered to detect *f2* values in the small effects range as well. In which case, we would need an *n* = 1,170 to be 90% powered to detect an *f2* of 0.02 at $\alpha = 0.01$.

Alternatively, if we go away from this assumption and enter the present study's sample size of ~15,000 to determine the *f2*, we would be 90% powered to detect at $\alpha = 0.01$, we get an *f2* = 0.002 ($R^2 = 0.002$; $r = 0.04$).

Multiple test corrections. In order to account for multiple testing, we corrected the overall significance threshold of $p < 0.05$ for the effective number of tests (M_{eff}) correction (Nyholt, 2004; Derringer, 2018). M_{eff} allows for the correction of multiple tests without the assumption of independence of tests (i.e., compared to Bonferroni correction, which would be overly conservative if the PGS are not independent of one another). As the PGSs become less strongly correlated with one another, M_{eff} correction approaches Bonferroni correction. Among the 32 PGSs explored for association with resilience, the effective number of tests was estimated as 30.5 and 31.5 in AA and EA, respectively. Therefore, our adjusted threshold for the statistical significance of any one PGS associated with resilience in the AA sample was $p 0.05 / [30.5] = 0.0016$ and the EA sample $p 0.05 / [31.5] = 0.0016$. At this level, we had 90% power to detect PGS effects of $r = 0.05$ in the EA sample ($N = 7,962$) and 90% power to detect PGS effects of $r = 0.11$ in the AA sample ($N = 1,518$).

Attenuation analysis. We assessed whether PGS performance was attenuated using the equation:

$$r_{\text{proxy-PGS}}^2 = r_{\text{target-PGS}}^2 \times r_{\text{proxy-phenotype}}$$

Where, $r^2_{\text{target-PGS}}$ is the reported relationship between our proxy PGS and its target variable (e.g., neuroticism PGS x measured neuroticism). Proxy manifest correlations were obtained from the PGS reference papers. $r_{\text{proxy-phenotype}}$ is the correlation between our measure of resilience and the psychosocial trait (Table S1). The resulting solution was our expected $r^2_{\text{proxy-PGS}}$, or what we could reasonably expect our effect size to be. As aforementioned, we would expect the EA sample to perform the best due to the demographics of the GWAS from which the PGS were derived. Due to this, we chose to perform attenuation analyses within the EA ancestry group as it would represent the closest available comparison sample to the original PGS derivation GWASs.

RESULTS

We hypothesized that existing PGSs of resilience-related phenotypes (such as post-traumatic stress disorder) might provide a starting point for developing our understanding of the molecular genetic underpinnings of the observed heritability of resilience. In a population sample of older US adults (the Health and Retirement Study, HRS, <http://hrsonline.isr.umich.edu/>), we estimated resilience as the residual of positive and negative affect scores over self-reported experiences of a variety of stressors, both chronic and acute (see complete Methods below). Analyses were conducted separately within HRSs pre-defined subsamples of African American (AA; N = 1,518) and European American (EA; N = 7,962) participants; defined both by self-identified race and genomic ancestry. To demonstrate the validity of our operationalization of resilience, we first estimated correlations between our measure of resilience and other psychosocial variables. Correlations between the psychosocial variables and our operationalization of resilience were substantial ($|\beta| = 0.08 - 0.5$), with little observed correlation between resilience and height, as a negative control (EA $\beta = 0.005$; AA $\beta = 0.03$; Figure 1; full results in Supplemental Tables S1 & S2). These results demonstrate the validity of the current operationalization of resilience.

We examined the extent to which PGSs derived from GWAS of proxy phenotypes were associated with resilience. We selected 32 pre-computed PGSs available in HRS for testing for association with resilience. In addition to PGSs selected due to prior suggestion that they may be related

to resilience, we again included height as a negative control. Of the 32 PGSs tested, only subjective wellbeing, neuroticism, depressive symptoms, and educational attainment were significantly associated with resilience in the EA group after correcting for multiple testing ($|\beta| = 0.04 - 0.09$; $p < 4.3E-12$; see Figure 2 and Supplemental Tables S3 & S4 for full results). Effect sizes were generally small across both EA and AA groups ($|\beta| = 0.002 - 0.03$ for physical PGSs, $0.001 - 0.1$ for psychological PGSs). For comparison, the intended negative control of the height PGS (EA $\beta = 0.003$; AA $\beta = 0.1$) was not consistently more weakly associated with resilience than either the physical or psychological PGSs analyzed. The inclusion of age, gender, and self-reported race as covariates did not change the pattern of results (Figures S2 & S3; Tables S6- S9).

In aggregate, the multiple regression for resilience on all PGSs had an adjusted R^2 of 1.2% and 0.2% in the EA ($|\beta| = 0.005 - 0.011$) and AA ($|\beta| = 0.003 - 0.249$) groups, respectively (Tables S10 & S11). We further explored whether the observed PGS performance could be explained by attenuation due to imperfect correlations between the PGSs' trait and resilience. We analyzed the four measures that were included in both our psychosocial and PGS analyses (extraversion, subjective wellbeing, educational attainment, neuroticism). To do this, we took into consideration the original performance of each PGS with its intended trait (5% for extraversion, 0.91% for subjective wellbeing, 11.4% for educational attainment, and 0.7% for neuroticism) (Okbay et al., 2016, van den Berg et al., 2016, Lee et al., 2018) as well as the observed correlation between the trait and resilience to estimate the expected performance of each proxy PGS for resilience. We restricted the analyses to extraversion, subjective wellbeing, educational attainment, and neuroticism measures obtained from HRS's European ancestry sample, as all of the PGSs for available psychosocial measures were derived from samples of European ancestry ($r = 0.03, 0.08, 0.04$, and 0.09 , respectively). The observed association between the subjective wellbeing and neuroticism PGSs and resilience were slightly stronger than would be expected; however, the PGSs for extraversion and educational attainment were less strongly associated with resilience than might be expected (Figure 3). We therefore conclude that our results are generally in agreement with the expected performance of a

proxy PGS. Nonetheless, the overall weakness of the observed associations between existing PGSs and resilience, even aggregated across multiple phenotypes, suggests that a large-scale GWAS of resilience will be necessary to identify the genetics underlying the observed heritability of resilience.

DISCUSSION

Existing PGSs for proxy phenotypes do not correlate substantially with resilience. In aggregate, the available PGSs fall far short of explaining the 30-50% heritability observed from twin studies, explaining 1.2% and 0.2% of the variance in resilience in the EA and AA groups, respectively. The observed statistically significant individual PGS effects were small, appeared only in the EA group, and were moderately weaker in the AA group. Attenuation analyses for the four traits for which both PGSs and direct measures were available suggested that observed effects were neither consistently larger nor consistently smaller than would be expected on the basis of overall PGS performance—taking into account the imperfect correlations between the proxy PGS traits and resilience. The small overall multiple R^2 compared to the moderate heritability of resilience and the typical performance of a PGS with its own trait, suggest that a GWAS of resilience would be able to improve upon these results.

When considering these results, it is also important to consider potential limitations. While secondary data provides an efficient and effective opportunity to address novel research questions, one caveat is that you are at the discretion of those that collected the data. As a result, decisions that have been made may be in contrast to the ones you would have made had you collected the data. Largely, the benefits of secondary data outweigh the potential pitfalls; however, in using that data, your study takes on the limitations related to the dataset—even if you didn't have a role in the decisions that might have led to the introduction of such limitations. Such is the case here when discussing the construction of the PGS.

Generally, when constructing PGS, the main approach employed is known as clumping and thresholding (C+T)(^{Privé et al., 2019}). The benefit to this method is that the clumping allows for the removal of

redundant correlated effects that can be attributed to linkage disequilibrium (LD). Similarly, thresholding helps to separate truly predictive variants out from noise (Privé et al., 2019). When constructing PGS, HRS weighed employing such an approach but ultimately decided to not account for LD or p-thresholding and retain all available SNPs (Ware et al., 2017). This introduces potential limitations as it can result in inflated scores being generated as well as violating the assumption of independence (Choi et al., 2020). Though such limitations are worth discussing, we do not feel they would substantially change the conclusions of this study (i.e., polygenic proxy scores are not sufficient for furthering our understanding of the genetic mechanisms underlying resilience).

The decision HRS made to include all available SNPs resulted in a PGS with the greatest predictive power (Ware et al., 2017). This suggests that even when using a PGS that would allow for the greatest predictive power, our results for the genetic analyses were still virtually null across all 32 PGS, save for 4 of them. This presents one reason why we feel that had they accounted for LD, and generated a PGS with a lower predictive power, one could theorize that it would probably increase our null findings and therefore still result in us drawing the same conclusions—in regard to our current understanding of the genetics of resilience. Additionally, it should be stated that the decision HRS made to not account for linkage disequilibrium or p-thresholding wasn't without reason or the result of an oversight. As aforementioned, HRS did consider the approach; they ran through various scenarios related to clumping and thresholding, but their findings showed that there was not a significant difference between the incremental R^2 when all the SNPs were included in the PGS calculation versus when there was some degree of LD correction applied (Ware et al., 2017). Even with that, concern over the conclusions drawn and the decision to include all SNPs in the calculation can, and should, still be raised. However, in regard to this study in particular, we do not feel it has substantially impacted our findings.

Another limitation that is worth noting is that most of the GWAS used to compute SNP weights came from GWAS of individuals of European ancestry. This is because it poses a limitation to generality and would be expected to show weaker associations in other ancestry groups (Martin et al., 2019). However,

since the data for the AA sample was available, we still chose to include it. However, in line with the advice given by HRS, we analyzed each ancestral group separately and adjusted for PCs 1-5. Notably, the PGS for PTSD—probably the most likely candidate of the available PGSs—was derived from both a GWAS of EA and a GWAS of AA individuals and would provide another point of comparison for PGS performance. Surprisingly, PTSD was among the PGSs not significantly associated with resilience, regardless of an EA-sampled GWAS (EA β = -0.005, AA β = 0.1) or an AA-sampled GWAS (EA β = 0.01, AA β = -0.03).

Although recent work in twins found that genetic factors contribute to a continuous measure of traumatic stress, with resilience at one end and high PTSD symptom severity at the other (Wolf et al., 2018), our findings lend support to the argument that resilience is more than just the opposite side of the proverbial coin of PTSD (Almedom and Glandon, 2007; Rutten et al., 2013; Kalisch et al., 2017). As analogized by Almedom & Glandon (2007), the absence of fever (i.e., PTSD) is not evidence of good health (i.e., resilience). This argument posits that resilience should not be considered as the absence of psychopathology but rather a dynamic process that can be influenced by many factors, including biological, psychological, and sociological (Kalisch et al., 2019). To date, only one small GWAS of resilience among fewer than 12,000 participants has been conducted (Stein et al., 2019)¹. Our current results suggest that increasing sample sizes available for genetically-informed PTSD research would not be sufficient to advance our knowledge of the genetic underpinnings of resilience. However, while our results do lend credence to this argument, it is important to note that other factors might contribute to the null association (e.g., low power), and make any definitive claims about resilience and its association with PTSD require further study.

One paramount concern when considering the use of polygenic scores in applied settings has been the inability to separate observed “genetic” associations from structural, social mechanisms influencing a myriad of factors—including individual exposures to stress. The influence of an individual’s environment

¹ The full results are not posted publicly and so were not available as a pre-computed PGS within HRS.

is also important to consider when examining resilience. There is increasing evidence supporting the idea that resilience may be explained as a form of gene-environment interaction (G x E; Elbau, Cruceanu, & Binder, 2019). One of the most common G x E interactions theorized in the psychological literature is that of diathesis-stress. Diathesis-stress refers to an interaction between biological vulnerability (diathesis) and exposure to stress, where the development of psychopathology may be a result of stress activating this biological risk (Monroe and Simons, 1991, Colodro-Conde et al., 2018). When viewing resilience through the lens of the diathesis-stress model, it suggests that resilience may be more than just the sum of its parts. Rather, any genetic correlates of resilience must be identified in conjunction with exposure to stress. Rather than conceptualizing outcomes in terms of the absence or presence of psychopathology without consideration of environmental contexts, a focus on resilience (where stress exposure—however defined—may be partly taken into account in the operationalization of the construct) may serve as a formalization of the diathesis-stress approach to understanding the observed heritability of psychological outcomes, and resilience among individuals.

The limitations of existing PGSs derived from GWASs of plausible proxy phenotypes highlight the need for a large-scale GWAS specifically targeted at resilience to unravel the observed heritability of individual differences in risk and resilience. The observed heritability in twin studies indicates there is a genetic mechanism underlying resilience. However, the results of this study did not support that. Since, theoretically, the proxy score approach should have worked—it indicates that further study is needed, and the logical step forward would be to move away from the proxy approach and investigate the genetic mechanism directly through a GWAS.

Importantly, our main purpose for this study was to further understand the genetics of resilience—not to identify predictors of resilience. Rather this study serves as a steppingstone on a long path to growing our understanding of the genetic mechanisms underlying resilience. Based on the findings of this study, we feel that the next step on that path is to conduct a robust GWAS of resilience. We feel that this is the most productive path forward as having GWAS summary statistics opens up

pathways to many bioinformatic analyses that can provide more information on not only the candidate SNPs identified in the GWAS but also more mechanistic insight. For example, SNP-based enrichment analyses which would identify SNPs that implicate biological pathways. Another example might be expression quantitative trait loci (eQTL) analyses. eQTL analyses identify functional SNPs that affect gene expression. These post-GWAS analyses will provide greater insight into resilience and may even provide some context for why the proxy score approach was ineffective. However, such analyses require GWAS summary statistics, and as such, a GWAS would need to be conducted.

In summary, with a GWAS of resilience, pathways for greater understanding of protective genetic factors that mediate stress adaptation would be opened and, with more study, could eventually lead to the development of prevention and early intervention measures for those at risk.

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OPEN PRACTICES

The experiment in this article was eligible for both an Open Materials and Open Data badge for transparent practices. Materials for the experiment are available at <https://osf.io/cwzjs/> and data from HRS is publicly available at <https://hrs.isr.umich.edu>.

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Figure 1. Psychosocial Correlates of Resilience

Figure 2. Genetic Correlates of Resilience

Figure 3. PGS x Resilience Attenuation