Assessing the Structure and Specificity of Polygenic Scores for Psychiatric Disorders in a Population-based Cohort of Older Adults

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Abstract

The underlying structure of psychiatric comorbidities has led researchers to investigate whether genetic factors can account for these patterns. Though psychiatric phenotypes are hypothesized to organize into a two-factor structure of internalizing and externalizing domains, few studies have evaluated the structure of psychopathology in older adults, and no studies have evaluated whether genome-wide polygenic scores (PGSs) organize in a similarly hierarchical structure. We used data from 7,157 individuals of European ancestry from the Health and Retirement Study, a large nationally-representative sample of older adults in the United States. Structural equation models utilized validated measures of psychopathology and genome-wide PGSs for multiple psychiatric outcomes. The data were best characterized by a two-factor internalizing-externalizing phenotypic model and a one-factor PGS model. The latent PGS factor (composed of PGSs for neuroticism, Major Depressive Disorder, anxiety disorders, Attention Deficit-Hyperactivity Disorder, and smoking) outperformed every individual PGS in predicting internalizing or externalizing outcomes, suggesting that future studies might construct a single latent PGS factor as a transdiagnostic measure of psychiatric genetic risk. However, neither the individual PGSs, nor the latent PGS factor exhibited specificity in their prediction of phenotypic outcomes, highlighting the tradeoff between polygenic population prediction and the utility of PGSs for clinical use. Several interpretations of the current results are provided: genetic risk for psychiatric disorders is transdiagnostic, GWAS-derived PGSs fail to capture genetic variation associated with disease specificity (e.g., rare variants), and blunt phenotypic measurement in GWAS precludes our ability to evaluate the structure and specificity of genetic contributions to psychiatric disorders.

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Psychiatric disorders impact health, wealth, and wellbeing across the life course (1–3). In the United States, common psychiatric disorders such as Major Depressive Disorder (MDD) are among the top 10 leading causes of disability and injury (4). Among older adults, psychiatric disorders have pronounced effects on physical health and mortality (2,5). Moreover, the 12-month prevalence of having any psychiatric disorder in older adulthood is substantial, with recent estimates of 11.5% (6). As the number of Americans older than 65 years is projected to double in the coming decades (7), more research is needed to understand the presentation and etiology of psychiatric illness in older adults.

Psychiatric disorders show marked comorbidity across developmental stages (8,9). Research suggests that this comorbidity may be explained by an overarching phenotypic meta-structure that includes separate but correlated internalizing (e.g., depression, anxiety) and externalizing (e.g., substance use, ADHD) factors (10). These comorbidity patterns align with phenotypic differences between internalizing disorders, characterized by elevations in negative affect (11), and externalizing disorders, hallmarked by behavioral disinhibition (12). Alternatively, a single factor (or a bifactor) model that explains shared variance across all psychiatric disorders has also been supported (10,13), and may emerge in developmental stages where symptoms are less prominent (e.g., older adulthood) (13). Yet examinations of the meta-structure of psychiatric comorbidity have been limited to child and younger adult samples; the lack of attention to older adults is a striking omission given the still substantial and impairing rates of psychiatric disorders in this population (2,5,6).

Genetic risk for psychiatric disorders may also align in a two-factor meta-structure. Twin and family designs suggest that additive genetic risk accounts for the two-factor internalizing-externalizing meta-structure (14,15), and data from genome-wide association studies (GWAS) has been leveraged to identify single nucleotide polymorphisms (SNPs) that are unique to internalizing or externalizing disorders (16). Yet there is also evidence of shared genetic risk across internalizing and externalizing domains (17–20), including data from psychiatric cross-disorder GWAS showing that genetic risk variants are enriched for biological processes core to many psychiatric conditions (20). Moreover, GWAS summary statistics highlight the ubiquity of genetic correlations across traits (19). Collectively, this research demonstrates that psychiatric disorders are highly polygenic, resulting from both common variants of small effect (likely to impact many psychiatric disorders) and rare variants of larger effect (possibly unique to certain phenotypes) (21,22); polygenic score (PGS) estimation has become an increasingly popular method to capture psychiatric polygenicity.

As with other molecular and behavioral genetic approaches, PGS analyses have revealed widespread cross-phenotype correlations (for a review, see [24]), yet no studies have evaluated whether these associations are indicative of a transdiagnostic genetic risk for psychiatric disorders or are hierarchically organized. A phenome-wide analysis indicated that a PGS of depressive symptoms was associated with several phobias and generalized anxiety disorder but not externalizing phenotypes, while a PGS for smoking initiation was associated with antisocial behavior but not internalizing phenotypes (23); these results suggest that PGS cross-phenotype associations may be hierarchically organized, though no studies have tested this hypothesis. Moreover, although several methodological approaches have been developed to construct better-

performing PGSs by taking advantage of cross-trait correlations (24,25), these methods have not tested the validity of combining such PGSs using factor analytic approaches.

The current study assessed the meta-structure of psychopathology at the phenotypic- and PGS-level in a large population-based sample of 7,157 older adults from the Health and Retirement Study (HRS). Using novel analytic techniques, validated measures of psychiatric phenotypes, and genome-wide PGSs of psychiatric outcomes, we examined whether two-factor phenotype and PGS models fit the data better than one-factor models. Second, we examined whether the estimated latent PGS factors improved phenotype prediction. Lastly, we evaluated the specificity of the latent PGS factors and the individual PGSs in the prediction of psychiatric phenotypes; that is, whether the shared variance between PGS is a better predictor of psychopathology than each PGS itself.

Method

Sample

Data were drawn from the HRS, a nationally-representative longitudinal panel study of over 43,000 adults over age 50 and their spouses (26). Launched in 1992, the HRS introduces a new cohort of participants every six years and interviews roughly 20,000 participants every two years. Eligible participants for the current study (N = 7,157; 57.2% female; Mean age in years [SD] = 66.28 [8.28]) were of genetically European ancestry (i.e., because PGSs were constructed from European Ancestry GWAS), and participated in the Leave-Behind Psychosocial Questionnaire (LBQ) (27) in 2010 or 2012. Participants younger than 51 years were excluded because they were not part of the original sampling frame, as were participants who completed the LBQ in institutional settings, and participants who were born before 1930 (i.e., to address

concerns for selective mortality, [30]). Within the analytic sample, 51% earned a high school diploma and 28.6% earned a four-year college degree or higher.

Phenotypic Measures

Measures of psychopathology were drawn from the LBQ, a self-reported questionnaire administered to a random 50% of the core HRS participants at each biennial wave during face-to-face interviews (27). We constructed a complete wave of data using the 2010 and 2012 data collections. Depressive symptomatology and smoking were taken from RAND HRS 2010 and 2012 Fat Files (29). All phenotypic data is publicly available through the HRS website (http://hrsonline.isr.umich.edu/).

Measures of internalizing psychopathology included negative affect (30), anxiety symptoms (31), and depressive symptoms (32); externalizing psychopathology was captured by impulsivity (33), trait and state anger (34), and current smoking status (Supplemental Table 1).

Polygenic Scores (PGSs)

PGSs of internalizing and externalizing psychopathology were constructed using well-powered, European ancestry GWAS (35–40) (Table 1; see https://hrs.isr.umich.edu/data-products/genetic-data; [36]). A PGS for height was included as a negative control (42). To construct PGSs, SNPs in the HRS genetic data were matched to SNPs with reported results in each GWAS (see Table 1 for the number of SNPs that contributed to each PGS). Neither trimming for linkage disequilibrium (LD), nor a GWAS p-value threshold/cut-off for included SNPs were used in the creation of the PGSs (43). The PGSs were calculated as weighted sums of the number of phenotype-associated alleles (zero, one, or two) at each SNP, multiplied by the effect size for that SNP estimated from the GWAS meta-analysis. All SNPs were coded to be associated with increasing disease risk (43). To simplify interpretation, the PGSs were

normalized within the European ancestry sample. All analyses in which PGSs were combined with phenotypes included the top 10 ancestry-specific genetic principal components as covariates.

Analytic Strategy

All analyses were conducted in Mplus version 7.2 (44). To increase generalizability and avoid overfitting the data, the analytic sample (N = 7,157) was divided into two random halves. One half was used as a test sample within which to fit confirmatory factor analyses of phenotypic and PGS one-factor and two-factor models; the second half was used to replicate the best-fitting factor structures. Confirmatory factor analysis is a theory-driven form of structural equation modeling that can be used to capture the shared variance among observed (and often correlated) variables to estimate unobserved latent factors (45). This type of analysis has never been used to combine PGSs into latent factors, despite the high genetic correlations across psychiatric phenotypes (19) and shared genetic variance between disorders demonstrated in behavioral genetic analyses (14,18). Linear regression was used within the structural equation modeling framework to examine the effects of the latent PGSs and individual PGSs on latent phenotypic factors (see Supplemental Methods).

Results

Zero-order associations between and among phenotypes and PGSs

All PGSs were significantly associated with their target phenotype (e.g., the MDD PGS was positively associated with depressive symptoms) except the PGS for antisocial behavior, which was not associated with any of the externalizing phenotypes (though note that the HRS did not collect a direct measure of antisocial behavior) (Table 2). The degree of cross-domain prediction by each PGS was substantial, particularly for the MDD, neuroticism, and Attention-

Deficit Hyperactivity Disorder (ADHD) PGSs (Table 2). For example, the ADHD PGS was significantly associated with all internalizing phenotypes ($.04 < r < .05$, all ps $< .01$) and all externalizing phenotypes ($.05 < r < .08$, all ps $< .001$). Though there were greater within-domain correlations among internalizing phenotypes ($.49 < r < .64$), than externalizing phenotypes ($.03 < r < .23$), there were also moderate cross-domain positive associations ($.12 < r < .34$) (Figure 1a). Lastly, zero-order correlations between the PGSs revealed no pattern of internalizing-externalizing associations (Figure 1b); for example, the MDD PGS was positively correlated with all other psychiatric PGSs ($.24 < r < .05$).

Next, we evaluated one-factor and two-factor phenotypic and PGS models, separately. In the test dataset, the one-factor and two-factor phenotypic models fit the data well; the latent internalizing and externalizing factors explained a significant proportion of the variance in each of the phenotypic indicators ($.05 < R^2 < .74$, all ps $< .001$) (Supplemental Figure 1). A chi-square difference test and relative fit indices revealed that the two-factor phenotypic model fit the data better than the one-factor model (χ^2 [1] = 23.86, $p < .001$). Moreover, the two-factor phenotypic model was replicated in the hold-out sample (Figure 2a). In the two-factor model, the largest loadings for the internalizing and externalizing factors were negative affect ($\beta = .87$, $p < .001$; $R^2 = .76$, $p < .001$) and state anger ($\beta = .44$, $p < .001$; $R^2 = .18$, $p < .001$), respectively.

In contrast to phenotypic models, only the one-factor PGS model fit the data well in the test dataset ($X^2[2] = 12.14$, $p< .01$, RMSEA = .04, CFI = .99, TLI = .94); model fit of the two-factor PGS model did not meet acceptable standards ($X^2[5] = 187.00$, $p< .001$, RMSEA = .10, CFI = .89, TLI = .87; Supplemental Figure 2). In the one-factor PGS model, we dropped the antisocial behavior PGS because, as previously shown, it did not predict any of the externalizing phenotypes (Table 2). To improve model fit, we used modification indices to add covariances

between select PGSs. The one-factor PGS model was replicated in the hold-out sample, fit the data well ($X^2[2] = 7.34$, $p < .05$, RMSEA = .03, CFI = .99, TLI = .95; Figure 2b), and explained a significant portion of the variance in each the remaining PGSs ($.03 < R^2 < .24$, all ps $< .001$). Moreover, the latent PGS factor explained equal variance in the ADHD PGS and the MDD PGS (both $R^2 = .24$, $p < .001$), indicating that both internalizing and externalizing genetic risk factors were represented in the latent PGS factor.

To test for polygenic specificity, we first demonstrated that the one-factor latent PGS, predicted the internalizing (β[SE] = .20(.03), $p < .001$) and externalizing (β[SE] = .26(.05), $p < .001$) factors in equal magnitude (Figure 3; overlapping 95% confidence intervals around the standardized estimates). Moreover, except for the neuroticism PGS, the one-factor latent PGS outperformed all other PGSs in its prediction of both the internalizing and externalizing factors (Figure 3).

By contrast, although we expected individual PGSs to be more strongly associated with their within-domain than cross-domain phenotypic factors, none of the individual PGSs showed such discriminant validity; the magnitudes of the effects of each PGS on internalizing and externalizing factors were equivalent, indicated by overlapping 95% confidence intervals (Figure 3a). For example, the ADHD PGS was no better at predicting the externalizing factor (β[SE] = .10(.03), 95%CI [.04, .16]) than the internalizing factor (β[SE] = .07(.02), 95%CI [.03, .11]). To confirm that these results were not an artifact of using all SNPs to construct the PGSs (many of which may be common to all complex diseases [25]), we constructed PGSs with more stringent p-value cutoffs (e.g., 'top hits') and examined whether specificity in polygenic prediction of psychopathology could be recovered using PGSs that included SNPs with larger effect sizes from the GWAS. This hypothesis was not supported; the PGSs for ADHD and MDD at multiple

p-value cut-offs showed no discriminant validity for the internalizing and externalizing latent factors (Supplemental Figure 4).

Discussion

We evaluated the phenotypic and polygenic structure of psychiatric outcomes in a large population-based sample of older adults. In models that replicated using a split-half design, psychiatric phenotypes were organized in a two-factor internalizing-externalizing structure, while PGSs loaded onto a single latent factor of polygenic risk. Using factor analytic methods, we constructed a latent PGS factor that outperformed all individual PGSs in predicting internalizing and externalizing factors. Moreover, contrary to our hypothesis, no PGS demonstrated discriminant validity. These results call into question the extent to which any psychiatric disorder-based PGS is specific to one disorder and highlights the potential of creating a latent psychiatric PGS for better prediction of psychiatric phenotypes.

Consistent with research in children and adults (10,13), psychiatric phenotypes in the HRS were organized in a two-factor internalizing-externalizing meta-structure rather than a one-factor model of general psychopathology. Identification of the meta-structure of psychiatric phenotypes in older adults has both etiological and clinical implications. First, the largest loadings on the internalizing and externalizing factors were negative affect and state anger, both of which are dispositional traits central to internalizing (e.g., depression, anxiety) and externalizing disorders (e.g., substance use, antisocial behavior), respectively (46,47). That such dispositional constructs are robustly associated with symptom domains (13) supports a Research Domain Criteria (RDoC) framework in which the biological origins of intermediate phenotypes (e.g., negative affect, poor impulse control) are linked to multiple categorical disorders (48). Clinically, interventions designed for one disorder have widespread effects on multiple disorders

within the same domain (49). For example, pharmacological and psychosocial interventions designed to treat depression are also effective in treating some forms of anxiety (50), which has led to transdiagnostic interventions for emotional disorders (51). Results from the current study can thus inform development of transdiagnostic interventions for older adults.

In contrast to phenotypic models and our hypothesis, the psychiatric PGSs fit a one-factor model better than a two-factor model, highlighting the transdiagnostic nature of psychiatric polygenic risk. Moreover, this single latent PGS factor composed of PGSs for neuroticism, MDD, anxiety, smoking status, and ADHD outperformed every individual PGS, except for the neuroticism PGS, in its prediction of the latent internalizing and externalizing phenotypic factors. One interpretation of these results is that the latent PGS factor is more precise than the individual PGSs; factor analysis isolates the shared variance of multiple observed indicators in a latent factor(s) (52,53). The elimination of measurement error in each PGS that is uncorrelated with the latent factor may explain its greater precision.

Another interpretation of our results is that genetic risk for psychiatric phenotypes is transdiagnostic. Psychiatric GWAS repeatedly show that associated SNPs tend to cluster in genes underlying neurodevelopmental processes, signal transduction, and synaptic plasticity (35–37), all processes common to complex diseases. Moreover, biometric analyses in behavioral genetic designs demonstrate that a general genetic factor influences multiple psychiatric disorders (and their overlap) and explains more of the variation in psychiatric outcomes than the unique internalizing and externalizing genetic effects (17,54). In the behavioral literature, the latent general psychopathology factor is most often conceptualized as neuroticism or negative emotionality (13,55), which robustly predicts both internalizing and externalizing disorders (56). That the neuroticism PGS predicted internalizing and externalizing phenotypic factors as well as

the latent PGS factor in the current study suggests that polygenic risk for psychiatric phenotypes may also index neuroticism or general distress. More research is needed to understand whether psychiatric polygenic risk is pleiotropic and if so, what kind of pleiotropic processes are at play. For example, biological pleiotropy would suggest that a genetic risk variant for neuroticism (or another intermediate transdiagnostic phenotype) predicts multiple disorders (57,58). By contrast, mediated pleiotropy would suggest that a genetic risk variant predicts one phenotype (e.g., neuroticism), which subsequently predicts the onset of other phenotypes. Longitudinal phenotypic data and causal inferences techniques (59) are needed to evaluate these hypotheses.

Another contribution of our results is the lack of specificity in PGS prediction of psychiatric phenotypes. It is surprising that a PGS designed to capture genome-wide genetic risk for a single disorder (e.g., MDD) was no better at predicting its' within domain (i.e., internalizing) than cross-domain (i.e., externalizing) phenotypic factor. One explanation for these results is that psychiatric GWAS rarely account for comorbidity (e.g., MDD cases without comorbid Substance Use Disorder). By ignoring psychiatric comorbidity, GWAS may be identifying genetic risk factors for multiple phenotypes or clinical severity instead of a single phenotype. Examples of this approach include a study of bipolar disorder and schizophrenia (60) and a GWAS of comorbid depression and alcohol dependence (61). Precision phenotyping of homogenous subgroups (e.g., stratification by age of disorder onset) is also likely to improve to GWAS and resultant PGSs (62,63).

A second explanation for low polygenic specificity in the current study is that PGSs are derived from GWAS of common genetic variation – most often SNPs with minor allele frequencies greater than 1% (64). An 'omnigenic model of complex traits' suggests that SNPs that contribute to the bulk of heritability in complex disorders are spread across the genome as

common variants of small effect that contribute to cellular processes (e.g., protein binding, sequence-specific DNA binding) common to many complex disorders (21). Disease-specific genetic risk variants, by contrast, are likely to be rare variants of large effect that are often not captured in GWAS of common genetic variation (21,22). Moreover, GWAS do not capture copy number variants (CNVs), which are also linked to psychiatric disorders and may function in a disease-specific manner (65). Thus, it may be that PGSs derived from GWAS are not appropriate for examinations of disorder-specific etiology.

Results from the current study do not discount the possibility that genetic risk for psychiatric disorders is hierarchically structured; these results suggest that PGSs, as they are currently constructed, are not appropriate for examinations of the genetic architecture of psychiatric disorders and cannot be used to index polygenic risk for a single disorder. New methods, including Genomic SEM (66), can be used to analyze the joint genetic architecture of comorbid traits by modeling the covariance structure of GWAS summary statistics. In fact, a recent paper that applied Genomic SEM to psychiatric GWAS summary statistics found that a correlated three-factor model composed of internalizing, externalizing, and thought problem factors, fit the data well (67).

Limitations

Though the current study is the first to evaluate the phenotypic and polygenic structure of psychiatric outcomes in older adults and uses a large, representative sample, several limitations are worth noting. First, the estimation of latent factors in confirmatory factor analysis is dependent upon the quality of the indicators. Based on previous recommendations (43,68), we only constructed PGSs based on large GWAS meta-analyses with independent replication samples. As a result, we did not include PGSs derived from smaller GWAS of relevant

phenotypes, including several studies of externalizing disorders (69,70). Relatedly, the phenotypic measures available in the HRS were abbreviated scales, as is common in large population-based surveys. Thus, one alternative phenotypic model that we were unable to fit is a bifactor model of psychiatric outcomes (our models didn't converge, likely due to the sparse measurement of symptoms), which posits that there are internalizing and externalizing factors as well as a higher-order bifactor that captures shared variance between the lower-order factors (10,13,65). Indeed, we observed a high correlation between the internalizing and externalizing factors in our sample, which is thought to indicate the presence of a higher-order bifactor (10,13,46).

Second, our analyses only focused on a subset of the population: older U.S. adults of European ancestry. Though the focus on older adults is a critical addition to research on the meta-structure of psychiatric disorders in adulthood, psychiatric genetics and human genetics studies overall are overwhelmingly Eurocentric (72) – a trend that reduces generalizability of all genetic work and is likely to exacerbate health disparities (73). We did not include participants of African ancestry in the current study because the available GWAS were conducted in European samples and, thus, would not be comparable for methodological rather than substantive reasons. In addition, the results need to be replicated in samples across the life course. Though several behavioral genetic studies in child and adolescent samples have identified the structure of additive genetic risk for psychiatric disorders (18,54), the structure and specificity of genome-wide PGSs in younger cohorts has not been evaluated.

Conclusion

Using multiple genome-wide PGSs of psychiatric outcomes, well-validated phenotypic measures, and novel analytic techniques in a relatively large, representative sample, we showed

that although the phenotypic meta-structure of psychopathology in older adults fit a two-factor internalizing-externalizing model, polygenic risk for psychiatric outcomes was better captured by one latent PGS risk factor. That this latent PGS factor outperformed most individual psychiatric PGSs, which themselves showed no specificity in predicting internalizing and externalizing outcomes, offers researchers a relatively easy method to construct a high-performing PGS that captures genome-wide polygenic risk for psychiatric disorders. Moreover, our results highlight several avenues of research including well-powered GWAS of both transdiagnostic factors and precision phenotypes, as well as the integration of methods that can be used to examine the genetic structure of pleiotropic effects in psychiatric disorders.

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Table 1. GWAS summary statistic files used to construct polygenic scores

Construct	**GWAS Discovery N/ Replication N**	**$N_{overlapping\ SNPs}$ with HRS genetic data**	**Citation**	**Location of GWAS Summary Statistics**
Neuroticism	Meta-analysis: 170,911	1,134,281	Okbay, A., et al. (2016). [22]	https://www.thessgac.org/data
Anxiety Case-Control	Meta-analysis: 17,310	1,079,599	Otowa, T., et al. (2016). [33]	https://www.med.unc.edu/pgc/results-and-downloads
MDD Case-Control*	59,851/ 113,154	1,340,536	Wray, N. R., et al. (2018). [21]	https://www.med.unc.edu/pgc/results-and-downloads
ADHD Case-Control‡	55,374/ 93,916	1,043,408	Demontis, D., et al. (2017). [35]	http://www.med.unc.edu/pgc/results-and-downloads
Ever Smoker	74,053/ 143,023	710,288	Tobacco and Genetics Consortium. (2010). [23]	https://www.med.unc.edu/pgc/results-and-downloads
Antisocial Behavior	16,400/ 9,381	1,289,915	Tielbeek, J. J., et al. (2017). [34]	http://broadabc.ctglab.nl/summary_statistics

*The MDD GWAS weights used to construct polygenic scores were based on publicly-available data only and thus, did not include 23anMe data due to data use agreements. ‡The replication sample in the ADHD GWAS included one cohort that utilized a case/control design and another cohort that measured ADHD continuously.

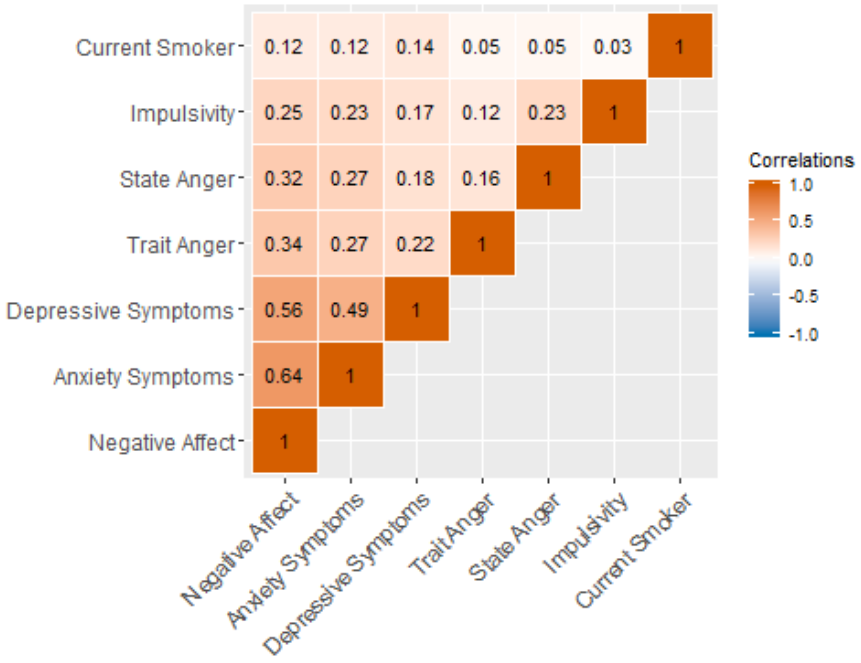
Table 2. Psychiatric polygenic scores correlate with multiple psychiatric phenotypes in the Health and Retirement Study

		Phenotypic Measures						
		Negative Affect	Anxiety	Trait Anger	State Anger	Impulsivity	Depression	Current Smoker
Polygenic Scores	Neuroticism	.10***	.11***	.05***	.07***	.04**	.07***	.01
	Anxiety	.03**	.05***	.02	.02	.001	.03**	.01
	MDD	.07***	.09***	.04**	.04***	.01	.08***	.03*
	Ever Smoke	.02	.01	.01	.03*	.02	.04***	.03**
	Antisocial Behavior	.001	.02	.001	.01	.001	.04**	.01
	ADHD	.04**	.05***	.001	.05***	.04**	.05***	.08***

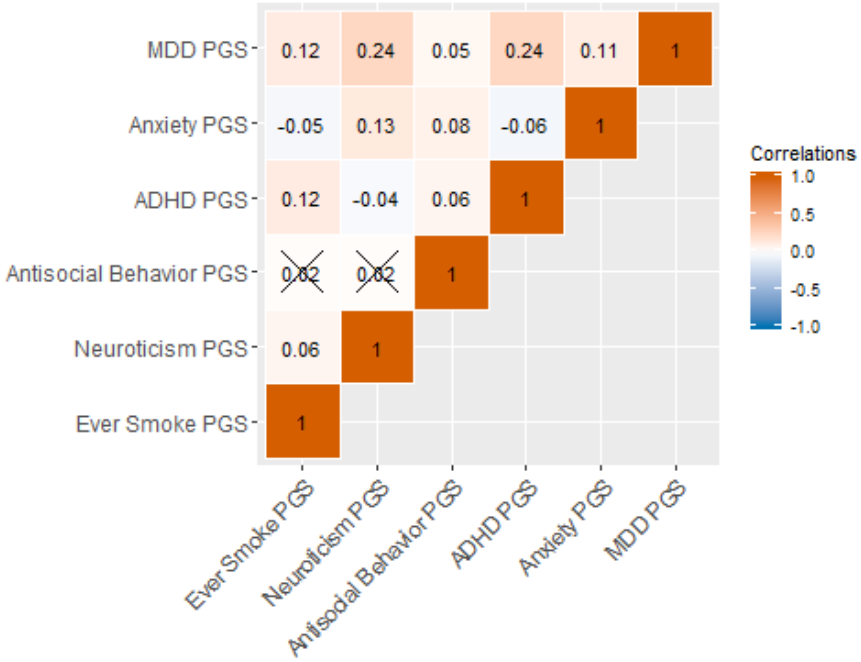
Note. 7,052 < *N* < 7,123. * $p < .05$, ** $p < .01$, *** $p < .001$; MDD, Major Depressive Disorder; ADHD, Attention Deficit-Hyperactivity Disorder. All estimates are partial correlations, controlling for the top 10 ancestry-specific genetic principal components. Associations with current smoker, which is dichotomous, utilize Spearman's rank correlations. Except for smoking status, phenotypic measures were constructed as mean scores for negative affect (Positive and Negative Affect Schedule - Expanded Form [33]), anxiety symptoms (Beck Anxiety Inventory, 34), trait and state anger (State-Trait Anger Expression Inventory, 37), impulsivity (Multidimensional Personality Inventory, 36), and depressive symptoms (Center for Epidemiologic Studies Depression Scale, 35).

Figure 1. Widespread within- and across-domain correlations among phenotypes and polygenic scores in the Health and Retirement Study

(A)

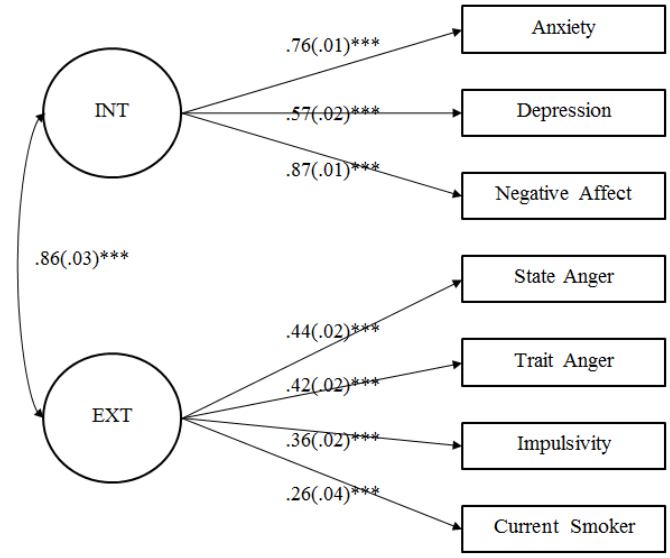


(B)

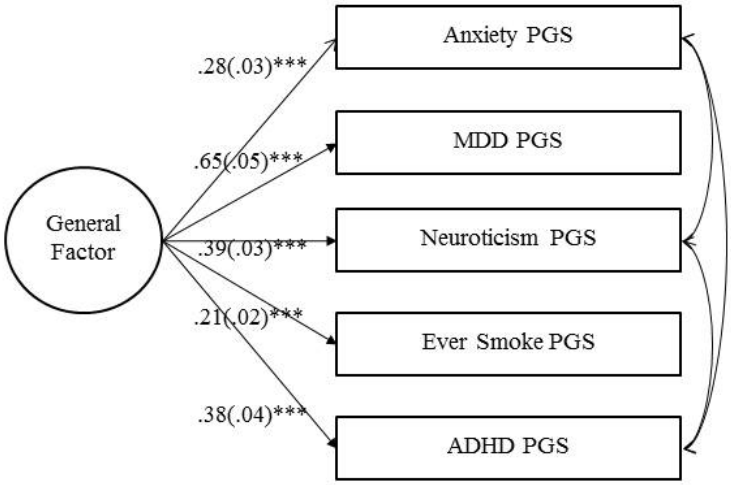


Note. 7,052 < *N* < 7,123. All estimates are partial correlations, controlling for the top 10 ancestry-specific genetic principal components. Associations with current smoker, which is dichotomous, source from Spearman's rank correlations, also controlling for the top 10 ancestry-specific genetic principal components. Associations that were not significant at $p < .05$ are marked with an 'X'.

Figure 2. Two-factor phenotypic model and one-factor polygenic score model demonstrate good model fit in the hold out sample, in the Health and Retirement Study



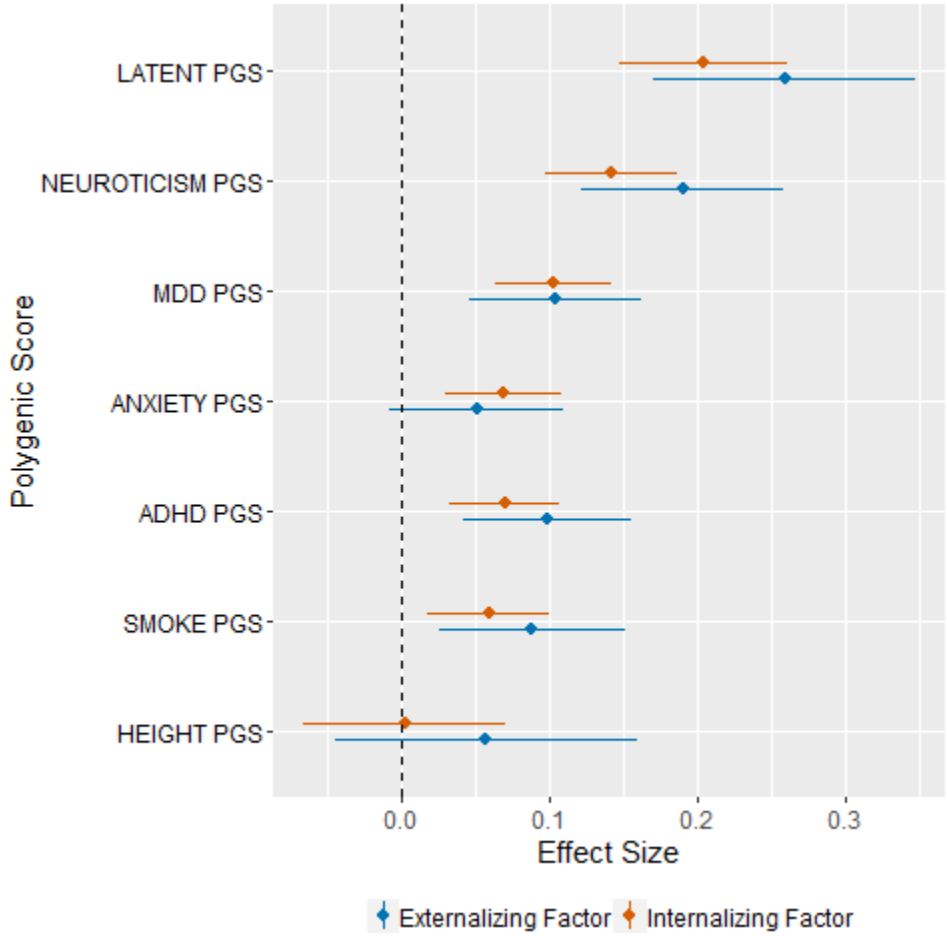
(A)



(B)

Note. N = 3,510. Standardized estimates are shown. Confirmatory factor models were tested in a random 50% of the total sample; the initial models were fit in the first half of the data. Phenotypic models used the weighted-least squares means- and variances-adjusted estimator to account for the dichotomous smoking indicator. Genotypic models used the maximum likelihood estimator. Model fit for the two-factor phenotypic model: $X^2(13) = 138.23$, $p < .001$, RMSEA = .05, CFI = .96, TLI = .94. The internalizing and externalizing factors explained a significant proportion of the variance in the indicators ($.07 < R^2 < .76$, $p < .001$). Model fit for the one-factor genotypic model: $X^2(2) = 7.34$, $p < .05$, RMSEA = .03, CFI = .99, TLI = .95.

Figure 3. One factor latent polygenic score factor and neuroticism polygenic score outperform all other psychiatric polygenic scores within respect to internalizing and externalizing outcomes, with no specificity in the Health and Retirement Study



Note. N = 3,510 (hold-out sample); PGS, polygenic score; Estimates were derived from seven structural equation models, one for each polygenic score as the predictor, and accounted for the covariance between the internalizing and externalizing latent factors. Standardized regression estimates and 95% confidence intervals are plotted.

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