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Marital Satisfaction as a Moderator of Molecular Genetic Influences on Mental Health

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Abstract
The quality of one's romantic relationship is associated with mental health. Low levels of relationship quality may be a stressor that triggers a predisposition or *diathesis* to mental illness. Analyses were conducted to examine whether relationship quality moderated the association between polygenic risk scores (PRSs) for several mental health syndromes on phenotypic measures of those syndromes. Data were drawn from the Midlife in the United States (MIDUS) study of health and well-being. A subsample was genotyped, and PRSs were calculated. The PRS for anxiety was more strongly related to the anxiety phenotype when satisfaction was low than when satisfaction was high, providing evidence of a genetic susceptibility process between marital distress and anxiety. The expression of genetic influences on a phenotype in the presence of certain environmental stressors is complex and may depend on the specific phenotype and the methodology by which genetic influences are estimated.

Keywords
marital satisfaction, psychopathology, polygenic risk score, G×E

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Intimate romantic relationships are ubiquitous and an important context for the expression of mental health. A marital or marriage-like relationship is a significant correlate of both overall psychopathology and specific mental health syndromes (for a recent review, see South, 2021). Previous work demonstrated that the quality of one's marital relationship has a moderating effect on the quantitatively estimated genetic influences on internalizing psychopathology such that genetic influences (i.e., heritability) were greatest in very unsatisfying relationships but environmental influences were highest in satisfying relationships (South & Krueger, 2008). In the current study, we extend this work to examining moderation of *measured* genetic influences on psychopathology, as indexed by a polygenic risk score (PRS) for different mental health phenotypes. If found, it would lend support to the premise that a committed romantic relationship is an environmental context that has an impact on the expression of genetic influences on psychopathology.

Marital Quality and Mental Health

Marital quality has been consistently associated with various forms of psychopathology, from major clinical syndromes (Whisman, 1999, 2007) to substance use disorders (Leonard & Eiden, 2007) and personality disorders (South et al., 2008). Marital quality is related to general forms of psychopathology as well as more specific manifestations. Whisman (2007) found that marital distress was associated with specific phobia, social phobia, generalized anxiety disorder, posttraumatic stress disorder, major depressive disorder, bipolar disorder, and alcohol use disorder. In a later study, South, Krueger, and Iacono (2011) found negative, moderate associations between internalizing (−.28) and externalizing (−.26) latent factors and marital satisfaction.

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Much of this work has been cross-sectional, thus it is difficult to conclude whether relationship quality leads to psychopathology or whether psychopathology has a negative impact on relationship functioning. Certainly, it is possible that one of the negative side effects of psychopathology may be interpersonally antagonistic behavior that drives away others (e.g., Coyne, 1976). The longitudinal research that does exist, however, provides evidence that for some disorders (e.g., depression, alcohol use disorder), lower satisfaction predicts greater likelihood of subsequent disorder (Whisman et al., 2006; Whisman & Uebelacker, 2009). This fits well in a Diathesis × Stress interaction model of psychopathology in that the stressful context of an unsatisfying and conflict-laden marriage may trigger psychopathology in an individual with enough loading on a *diathesis* for that form of pathology. A diathesis may encompass many things (from biology to physiology to cognitive factors), but one that has received much attention of late has been genetic influences, a topic we turn to next.

Gene × Environment Interaction in Psychopathology Research

A wealth of twin, family, and adoption studies have conclusively demonstrated that almost every form of psychopathology has a nontrivial amount of genetic influence on variation in that syndrome within the population (Kendler, 2001; Plomin et al., 2013). It is well established at this point that almost any form of mental illness will most likely be explained by many genes of small effect size. The history of molecular genetic underpinnings of common forms of mental illness, however, is generally one of small effects, nonreplicated findings, or unknown mechanisms for the effects that are found (see McCarthy et al., 2014). Most recently, researchers have used sophisticated analytic techniques applied to whole genome sequencing. From this work, we know that the percentage of phenotypic variance explained by many genetic variants (i.e., single nucleotide polymorphisms [SNPs]) are small, particularly compared with heritability estimates (see Wray et al., 2014). One reasonable possibility is that genetic influences on a phenotype are contingent on an environmental stressor or trigger.

Beginning with advances in twin modeling almost two decades ago (Purcell, 2002), researchers were able to estimate genetic (and environmental) influences on a phenotype at different levels of a "moderator" variable that was putatively environmental (but often had some genetic influence as well). These biometric moderation models resulted in different heritability estimates at different levels of the moderator; they were interpreted as the clearest analogy to Gene × Environment (G×E) interaction. Much of this research was conducted in child or adolescent samples but was also extended to adult twin samples (e.g., Jarnecke & South, 2014; Racine et al., 2011; Young-Wolff et al., 2011). Previous work demonstrated that the estimated genetic influences on internalizing psychopathology (a latent factor encompassing variance that is common to major depressive disorder symptoms, generalized anxiety, panic, and the personality trait of neuroticism) were greatest among individuals in a distressed or conflicted marriage (h = 29%) but decreased linearly such that in a good marriage, genetic influences were almost nil (i.e., 5%; South & Krueger, 2008).

The different patterns of findings from this work closely mapped to different theoretical models of the etiology of personality and psychopathology (Dick, 2011; South et al., 2017). For instance, the heritability of phenotypes such as externalizing behavior is higher in "risky" environments such as negative peer groups or poor child-parent relationships or low socioeconomic status (Hicks et al., 2009; Tuvblad et al., 2006), which follows a diathesis-stress model of psychopathology. The work cited above on internalizing would also fit a diathesis-stress framework because it could be interpreted to suggest that genetic influences on psychopathology are "expressed" in the context of a distressed marriage. Another pattern of G×E that has been empirically observed is one in which genetic influences are greatest in the most advantaged (or least stressful) environments (see South & Krueger, 2011), a model often called *social push*. Finally, it is possible for genetic influences to be high at both ends of the environment (stressed and advantaged) and lowest at mean levels. This has been conceptualized as differential susceptibility (Belsky & Pluess, 2009; Ellis & Boyce, 2008) such that what is inherited is not propensity to psychopathology per se but a predisposition to malleability to the environment.

Proceeding roughly in tandem with studies of quantitative G×E were studies of measured candidate G×E. The history of candidate G×E studies is too long to cover adequately here, but reviews in the past decade generally concluded that the field is one of inconsistent replication at best when attempted, failed replication, or no replication attempts at all (Duncan et al., 2014; Duncan & Keller, 2011). More recently, researchers have turned to examining G×E interaction using PRSs. These scores are calculated by using the results from genome-wide association studies (GWASs), which look for significant (family-wise error-corrected) associations between phenotypes and common SNPs (aka, point mutations) across all chromosomes. The results of these GWAS findings are then used in separate samples to create a PRS; the presence or absence of individual SNPs (chosen on the basis of specific p values) and associated effect sizes are multiplied and summed to

create an individual PRS for each person, providing an individual-level genetic proxy for a phenotype (Choi et al., 2020). The PRSs tend to explain statistically significant but small amounts of variance (e.g., 0.46% in depression score; Colodro-Conde et al., 2018). Thus, researchers have begun to examine whether the PRS can explain greater variance in a phenotype at different levels of a moderator variable.

Several examples of these PRS × Environment interactions have now appeared in the literature, many focusing on depression. In these studies, researchers have used environmental stressors such as stressful life events (Arnau-Soler et al., 2019; Colodro-Conde et al., 2018; Mullins et al., 2016; Musliner et al., 2015), social support (Colodro-Conde et al., 2018), and childhood trauma (Mullins et al., 2016; Peyrot et al., 2018). Findings have been mixed; some studies have found significant interactions (Arnau-Soler et al., 2019; Colodro-Conde et al., 2018), some have reported no interactions (Musliner et al., 2015; Peyrot et al., 2018), and one reported an interaction in the unexpected direction (childhood trauma and lower PRS associated with depression; Mullins et al., 2016). No study that we know of has used romantic relationship functioning as a moderator of the PRS-phenotype link for depression or any other mental health phenotype. In a recent study, however, relationship status (in a relationship of any length) as a moderator of the PRS-phenotype link was used. In that study (Barr et al., 2019), there was a significant interaction between relationship status and PRS for each of the three phenotypes—drinking frequency, intoxication frequency, and dependence symptoms—such that not being in a relationship increased the association between the PRS and each phenotype. This would suggest that aspects of romantic relationship functioning as a moderator in PRS × Environment interaction studies may be a fruitful area for further research.

Current Study

The goal of the current study was to determine whether marital quality may serve as an important context for the expression of genetic influences on psychopathology. Specifically, we examined whether marital satisfaction moderates the association between the PRSs and measured phenotypes across a range of mental health syndromes. We focused on phenotypes for major depressive disorder, generalized anxiety, the personality trait of neuroticism, and alcohol use. Depression and generalized anxiety are two of the strongest correlates of marital quality; they are also common, highly prevalent disorders in the population (Kessler et al., 2005) and are highly comorbid with each other, and they form a lower-order factor of "distress" within a hierarchical, dimensional taxonomy of psychopathology (Kotov et al., 2017; Watson, 2009). Problematic alcohol use has been robustly associated with relationship problems (Leonard & Eiden, 2007). Neuroticism, although not a mental health phenotype per se, has been extensively modeled as an indicator of the internalizing spectrum of psychopathology (Hettema et al., 2006; Kotov et al., 2017), to the point of being considered the "core" of that domain (Clark, 2005). In fact, neuroticism is ubiquitous in its relations with almost all forms of psychopathology (Lahey, 2009).

We also decided to conduct exploratory analysis of a gender effect on the moderating effect of marital satisfaction. We had no a priori hypothesis as to how the moderating effect of marital satisfaction on the association between PRS and phenotype would differ between men and women. These analyses were conducted because there are important gender differences in the variables used in the current analyses. There is evidence of gender differences in the prevalence (e.g., depression is almost twice as prevalent in women than men; Kessler et al., 2005) and in the average levels (e.g., women have higher levels of neuroticism; South et al., 2018) of the phenotypes of interest. There are also very small but significant gender differences in levels of marital satisfaction (odds ratio = 1.07, women lower; Jackson et al., 2014). As others have noted, if men and women "differ in their exposure to environments that promote [mental illness risk] . . . G×E will contribute to gender differences in" that risk (Young-Wolff et al., 2011, p. 813). Thus, we tested the following hypotheses. First, for each of these phenotypes examined (depressive symptoms, anxiety symptoms, alcohol use and neuroticism), overall marital quality would moderate the association between PRS and phenotype such that the association between the PRS score and the phenotype will be stronger among those will low overall marital quality. Second, in an exploratory manner, we examined whether gender affects the interaction between PRS and marital satisfaction on the phenotype (three-way interaction).

Method

Participants and procedure

Data were drawn from the Midlife in the United States (MIDUS) project (Barry, 2014; Ryff & Krueger, 2018), a study of health and well-being that recruited individuals ranging in age from 25 to 74 years. MIDUS I, the first wave of data collection, lasted from 1995 to 1996 and consisted of 7,108 individuals; MIDUS II was conducted approximately 9 years later, from 2004 to 2006, and retained 4,963 (64.7%) of the original participants; a

third wave (MIDUS III) was conducted in 2013. At all waves of data collection, participants completed a computer-assisted phone interview and were sent questionnaires that they answered independently that took approximately an 90 min to complete. Questionnaire response rates at each wave were 89%, 80%, and 83% for MIDUS I through III, respectively. Participants were compensated for completion of each wave. A refresher project was conducted in 2011 with the goal of increasing the sample size of the MIDUS cohort by collecting the same measures on a new sample of individuals (N = 3,577). More information on the MIDUS project and data sets is available at http://midus.wisc.edu/index.php.

For the current analyses, we used data on mental health phenotypes, PRSs for those phenotypes, and relationship satisfaction collected at MIDUS II and in the MIDUS Refresher project. A subsample of MIDUS II and MIDUS Refresher participants completed a biomarker project that consisted of self-report questionnaires and a lab visit for a variety of biological markers of health. PRSs were computed from genetic analyses conducted on blood samples drawn from participants completing the biomarker project (N = 2,118). We eliminated one twin pair from each family to remove the nonindependence inherent in those observations and eliminated individuals with less than 90% European ancestry as determined by genetic principal components analysis, leaving a sample of 1,189 individuals with PRS data.

We then limited the sample to individuals who reported being currently married or living with a romantic partner because the self-report questionnaire instructions for the marriage or close relationship items instructed participants to answer if they were "married or living with a partner in a marriage-like relationship." We also limited the sample to participants who completed at least 19 of the 21 items comprising the relationship functioning items. The final sample used for the current analyses (N = 898) was 45.4% female (N = 408) with an average age of 54 years (SD = 12.21, range = 25–83[1]). Most participants had an associate's degree or higher for self-reported education. Average total household income was $98,677 (MIDUS caps total household income at "$300,000 or more"). Almost all participants reported their current relationship status as "married" (95.2%).

Measures

Sociodemographic characteristics. Participants reported on age (in years), gender (male, female), education level, current relationship status (e.g., married, divorced), and whether they were currently cohabiting with a romantic partner (yes/no).

Mental health phenotypes. We included the following phenotypes: depressive symptoms, symptoms of generalized anxiety disorder, two measures of alcohol use, and a measure of neuroticism. All questions except those from neuroticism were captured in the telephone interview. The symptoms of depression and generalized anxiety were taken from the Composite International Diagnostic Interview Short Form scales (CIDI-SF; Kessler et al., 1998). The CIDI-SF has good sensitivity and specificity compared with diagnoses based on the full CIDI (Kessler et al., 1999). The CIDI-SF uses a stem-branch logic such that answers to a small number of initial questions is used to weed out individuals least likely to meet full diagnosis. For depressive symptoms, if an individual reported feeling sad, blue, or depressed in the past 2 weeks, they were asked seven follow-up questions (e.g., "lost interest in most things," "feel down on yourself"). If they did not report sadness but did report losing interest in most things, they were asked six follow-up questions (all same as above but not including "lost interest in most things"). Items were answered on a binary scale (yes/no) and summed. The total depressive symptoms score was a combination of answers to the follow-up questions (after reporting either sadness or anhedonia) and ranged from 0 to 7.[2]

Symptoms of generalized anxiety disorder (GAD; criteria from the third edition of the *Diagnostic and Statistical Manual of Mental Disorders*; American Psychiatric Association, 1980) were also assessed with the CID-SF. A total of 10 items were queried (e.g., "restless because of your worry," "were irritable because of your worry"). A symptom count was created by totaling the number of symptoms that were experienced "most days"; in addition, individuals had to report that they worry a lot more than most people, that they worry "every day, just about every day, or most days," and that they worry about more than one thing or have different worries at the same time.

Two measures of alcohol use were included. First, frequency of drinking was captured by the item "During the past month, how often did you drink any alcoholic beverages?" (1 = *never drink*, 2 = *less than one day a week*, 3 = *1 or 2 days a week*, 4 = *3 or 4 days a week*, 5 = *5 or 6 days a week*, 6 = *every day*). Second, maximum drinks was captured by the item "During that year you drank most, about how many drinks would you usually have on the days that you drank?"

Neuroticism was measured using four adjectives ("moody," "worrying," "nervous," and "calm," reverse-scored) included in the self-report questionnaire. Items were rated on a scale from 1 (*a lot*) to 4 (*not at all*). Items were averaged to create a total score after reverse-coding items such that higher scores represented higher levels of neuroticism. This measure of neuroticism is

both internally reliable and has demonstrated measurement invariance across age and gender (Mann et al., 2019; Zimprich et al., 2012). Data on all mental health phenotypes were available for all participants, except for frequency of drinking, which was available for 626 of the participants in the final analytic sample.

PRS for mental health phenotypes. As part of the Biomarker project in MIDUS II and the MIDUS Refresher, DNA was extracted from blood draws or saliva samples and genotyped using the Illumina Omni Express array. PRSs are calculated using the effect sizes of SNPs that were significantly associated with a phenotype in a GWAS.[3] A PRS therefore represents an individual's genetic propensity for a phenotype. Polygenic risk scores were calculated using PRSice (Version 2.0; Choi et al., 2020). Participant ancestry was estimated using the Admixture software (Alexander et al., 2009) using all five superpopulations as a basis for estimation with a 1000 Genomes data (Phase 3) reference. After linkage disequilibrium pruning of SNPs at a R^2 threshold of .2, ancestry component scores were calculated: European, East Asian, admixed American, Southeast Asian, and African. Because discovery GWASs have almost exclusively used participants of European ancestry, the effect sizes of individual SNPs are reliably known only for individuals of European ancestry. Therefore, polygenic scores are considered valid only for participants with predominantly European ancestry, and samples with less than 90% estimated European ancestry were excluded. Biological sex can be determined from the genotype data because the Illumina OmniExpress arrays tag a sufficient number of variants on the X and Y chromosomes (e.g., 17,707 SNPs on X chromosome and 1,367 on Y for array version 1.1). Data were also excluded if self-reported sex did not match genotype biological sex (n = 13).

Genotypes were imputed using the Haplotype Reference Consortium panel on the Michigan Imputation Server with minimac3 (Das et al., 2016) and Eagle (Loh et al., 2016). Before imputation, SNPs with more than 5% missing calls, ambiguous strand orientation, or Hardy-Weinberg equilibrium $p < .001$ were excluded. SNPs with minor allele frequency below 0.01 or an average call rate below 0.9 were excluded after imputation. Plink (Version 1.9) was used to handle all genetic data (Purcell & Chang, 2018; Purcell et al., 2007). We used the following PRSs available in the MIDUS data set: depressive symptoms, major depressive disorder, number of drinks per week, anxiety, and neuroticism.

Relationship functioning. The self-report questionnaire included in MIDUS II and the Refresher project included several items assessing aspects of the participant's romantic relationship. We used a summary score composed of 21 items measuring relationship disagreement (three items on a scale from 1 to 4; e.g., "How much do you and your spouse or partner disagree on the following issues – household tasks, such as what needs doing and who does it?"), spousal support (six items on a scale from 1 to 4; e.g., "How much does your spouse or partner really care about you?"), spousal strain (six items on a scale from 1 to 4; e.g., "How often does your spouse or partner make too many demands on you?"), relationship risk (two items on a scale from 1 to 5; e.g., "During the past year, how often have you thought your relationship might be in trouble?"), and relationship decision-making (four items on a scale from 1 to 7; e.g., "Things turn out better when I talk things over with my partner"; South & Krueger, 2008). A sum score was calculated (for participants missing less than three items) to create a total score. Higher scores indicated greater relationship satisfaction. A total of 16 individuals were missing data on the relationship satisfaction score. The overall scale had excellent internal reliability (α = .94, Ω = .94).

Analyses

Descriptive statistics and regression analyses were run in the R software environment (Version 3.6.3; R Core Team, 2020). All regressions controlled for age, age^2, gender, Age × Gender and Age^2 × Gender interactions, and the first five genetic principal components to take account of population stratification. For each mental health phenotype, predictors included the respective PRS, marital satisfaction, and PRS × Marital Satisfaction, PRS × Gender, Marital Satisfaction × Gender, and Gender × PRS × Marital Satisfaction interactions. The PRS and relationship functioning were first standardized before creating the interaction terms to produce a more easily interpretable coefficient. For count outcomes (i.e., total depressive symptoms, generalized anxiety symptoms, frequency of drinking), Poisson regression was used. As a sensitivity check, negative binomial regressions were also run on all of the skewed count outcomes (any differences between the two methods are reported in the main results below). From these regressions, we report estimated slopes, robust standard errors calculated using the *sandwich* package for R (Version 2.5-1; Zeileis et al., 2019), p values, and 95% confidence intervals. We also report McFadden's pseudo R^2. Maximum number of drinks was log-transformed to correct for positive skew and then analyzed using linear regression. Neuroticism was analyzed using linear regression (as a sensitivity check, we also log-transformed neuroticism to account for skew). The reported p values are uncorrected for multiple testing.

Table 1. Means, Standard Deviations, and Correlations for Marital Satisfaction and Phenotypic Outcome Variables

Variable	Mean	*SD*	Range		1	2	3	4	5
			Possible	Actual					
1. Marital satisfaction	80.89	12.13	23–97	21–98	—				
2. Depressive symptoms	0.54	1.61	0–7	0–7	−.17** [−.23, −.11]	—			
3. 1+ drinks	3.30	1.37	1–6	1–6	.02 [−.05, .09]	−.04 [−.11, .03]	—		
4. Maximum number of drinks	3.36	2.56	0–20[a]	0–20[a]	−.11** [−.17, −.05]	.07* [.01, .13]	.03 [−.04, .10]	—	
5. GAD symptoms	0.07	0.57	0–9	0–10	−.07* [−.13, −.01]	.19** [.13, .25]	−.02 [−.09, .05]	.03 [−.04, .10]	—
6. Neuroticism	2.02	0.63	1–4	1–4	−.19** [−.25, −.13]	.22** [.16, .28]	−.01 [−.08, .06]	.05 [−.02, .12]	.21** [.15, .27]

Note: Correlations are Spearman's correlations (except for the correlation between marital satisfaction and neuroticism, which is a Pearson correlation). Values in brackets are 95% confidence intervals. GAD = generalized anxiety disorder.
[a]This question was open-ended.
*$p < .05$. **$p < .01$.

Any significant interaction ($p < .05$) was decomposed and graphed using the plot_interaction function in the *interactions* package for R (Version 1.1.1; Long, 2019).

Results

Descriptive statistics

Table 1 displays the descriptive statistics and correlations among the mental health outcome variables and relationship satisfaction (mean and *SD* are shown for raw satisfaction score). Correlations are all Spearman's rank-order correlations to account for the skewed nature of the data, with the exception of a Pearson product-moment correlation between marital satisfaction and neuroticism. As shown, marital satisfaction was negatively and significantly related to all of the outcome variables except for frequency of drinking.

Moderation analyses

Depression. We examined moderation of the association between PRS and depression phenotype by marital satisfaction. The model including PRS for depressive symptoms, marital score, and their interaction predicting depressive symptoms explained 11% of the variance. The PRS was not significant, marital score had a significant effect, and the interaction was not significant (see Table 2). The interactions between PRS and gender, between gender and satisfaction, and a three-way interaction among PRS, gender, and satisfaction were not statistically significant.

When depressive symptoms were predicted from the PRS for major depressive disorder, marital score, and the interaction, the full model explained 12% of the variance. The PRS was not significant, marital score had a significant effect, and the interaction was not significant (see Table 2). The interactions between PRS and gender, between gender and satisfaction, and a three-way interaction among PRS, gender, and satisfaction were not statistically significant.

Problem drinking. We examined two phenotypes related to drinking—how often participants had at least one drink a day and maximum number of drinks when they drank. Results for both are shown in Table 2. When the outcome variable was frequency of drinking at least one drink a day, the full model explained 10% of the variance. The effect of the PRS (drinks per week) was in the expected direction and met conventional thresholds for marginally significant, marital score was not significant, and the interaction was not significant. The interactions between PRS and gender, between gender and satisfaction, and a three-way interaction among PRS, gender, and satisfaction were not statistically significant.

When predicting the most-drinks phenotype from the PRS for drinks per week, the full model explained 12% of the variance. The PRS was not significant, the marital score was significant, but the interaction between PRS and marital score was significant. The interactions between PRS and gender, between gender and satisfaction, and the 3-way interaction among PRS, gender, and satisfaction were not statistically significant.[4]

Table 2. Regression Results Predicting Mental Health Outcomes

Outcome and predictor	*b*	*SE*	95% CI	*p*
Depressive symptoms				
PRS for depressive symptoms	0.17	0.16	[−0.15, 0.48]	.30
Marital satisfaction	−0.38	0.10	[−0.57, −0.19]	< .0001
PRS × Marital Satisfaction	0.12	0.09	[−0.06, 0.30]	.20
PRS × Gender	0.12	0.27	[−0.40, 0.64]	.65
Gender × Satisfaction	−0.12	0.15	[−0.43, 0.18]	.43
PRS × Gender × Satisfaction	0.04	0.16	[−0.28, 0.36]	.82
Depressive symptoms				
PRS for MDD	0.17	0.15	[−0.12, 0.46]	.25
Marital satisfaction	−0.33	0.09	[−0.50, −0.15]	< .0001
PRS × Marital Satisfaction	−0.06	0.08	[−0.22, 0.10]	.46
PRS × Gender	0.05	0.21	[−0.37, 0.46]	.82
Gender × Satisfaction	−0.07	0.14	[−0.35, 0.21]	.64
PRS × Gender × Satisfaction	−0.13	0.14	[−0.40, 0.14]	.35
Frequency of drinking				
PRS for drinks per week	0.04	0.02	[−0.01, 0.08]	.09
Marital satisfaction	−0.01	0.02	[−0.06, 0.04]	.65
PRS × Marital Satisfaction	−0.01	0.02	[−0.05, 0.04]	.75
PRS × Gender	−0.02	0.03	[−0.08, 0.05]	.64
Gender × Satisfaction	0.01	0.03	[−0.05, 0.08]	.71
PRS × Gender × Satisfaction	0.03	0.03	[−0.03, 0.08]	.39
Most drinks				
PRS for drinks per week	0.01	0.03	[−0.05, 0.07]	.57
Marital satisfaction	−0.06	0.02	[−0.10, −0.02]	.01
PRS × Marital Satisfaction	0.03	0.02	[−0.01, 0.07	.22
PRS × Gender	0.03	0.03	[−0.03, 0.09]	.32
Gender × Satisfaction	−0.01	0.03	[−0.07, 0.05]	.83
PRS × Gender × Satisfaction	−0.03	0.03	[−0.09, 0.03]	.33
Anxiety/anxiety				
PRS for anxiety symptoms	−0.20	0.21	[−0.62, 0.22]	.34
Marital satisfaction	−0.04	0.13	[−0.30, 0.22]	.75
PRS × Marital Satisfaction	−0.18	0.08	[−0.33, −0.03]	.02
PRS × Gender	0.30	0.27	[−0.23, 0.84]	.27
Gender × Satisfaction	−0.54	0.22	[−0.97, −0.11]	.01
PRS × Gender × Satisfaction	0.11	0.16	[−0.19, 0.42]	.47
Neuroticism				
PRS for neuroticism	0.05	0.03	[−0.01, 0.11]	.10
Marital satisfaction	−0.13	0.03	[−0.19, −0.07]	< .0001
PRS × Marital Satisfaction	0.02	0.03	[−0.04, 0.08]	.48
PRS × Gender	0.04	0.04	[−0.04, 0.12]	.36
Gender × Satisfaction	0.04	0.04	[−0.04, 0.12]	.30
PRS × Gender × Satisfaction	−0.04	0.04	[−0.12, 0.04]	.34

Note: All regressions controlled for age, age^2, gender, Age × Gender and Age^2 × Gender interactions, and the first five genetic principal components. *b* = unstandardized coefficient; PRS = polygenic risk score; MDD = major depressive disorder.

Anxiety. We examined marital satisfaction as a moderator of the association between PRS for anxiety and anxiety symptoms. When predicting the anxiety phenotype from the PRS for anxiety, marital score, and their interaction, the full model explained 11% of the variance. The PRS was not significant, marital score was not significant, but the interaction effect was statistically significant (see Table 2).[5] There was also a statistically significant interaction between gender and satisfaction, but the interaction between PRS and gender did not meet a conventional threshold for statistical significance, nor did the three-way interaction among PRS, gender, and satisfaction.[6]

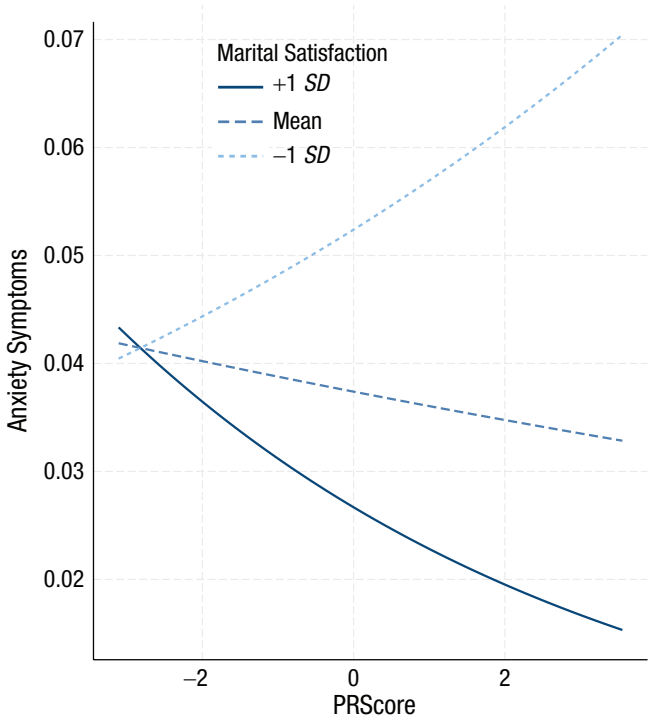

Fig. 1. Moderating effect of marital satisfaction on the association between polygenic risk score (PRS) for anxiety and generalized anxiety symptoms.

When the interaction between PRS and marital satisfaction was plotted, the association between PRS and GAD symptoms was positive for participants 1 *SD* below the mean of marital satisfaction; for participants who were 1 *SD* above the mean, the association between PRS and GAD symptoms was negative (see Fig. 1). The simple slopes revealed that the association between PRS and anxiety was not significant at the mean level of the moderator or at 1 *SD* above and below the mean.

Neuroticism. When predicting the neuroticism phenotype from the PRS for neuroticism, marital score, and their interaction, the full model was significant and explained 9% of the variance.[7] The PRS was not significant, marital score was significant, but the interaction was not significant (see Table 2). The interactions between PRS and gender, between gender and satisfaction and the three-way interaction among PRS, gender, and satisfaction were not statistically significant.

Discussion

The aim of the current study was to examine the role of marital satisfaction as a moderator of genetic influences on a variety of mental health phenotypes. The calculation and use of a PRS to represent a person's common genetic liability toward a phenotype is still relatively new but growing (see Wray et al., 2014). Only very recently, however, have researchers started to examine whether the association between PRS and phenotype may differ across a sample as a result of a third, moderator variable. This research has largely been confined to certain phenotypes and certain environmental stressors—particularly depression and life stress variables (e.g., Arnau-Soler et al., 2019; Colodro-Conde et al., 2018; Peyrot et al., 2018). To our knowledge, no study to date has examined how marital functioning may moderate the association between a mental health phenotype and a PRS for that phenotype.

We comprehensively examined whether a summary score of marital satisfaction, encompassing aspects of decision-making, conflict, and positive sentiment toward one's partner, would change the impact of a PRS on a respective phenotype. We examined several different mental health phenotypes as measured in the MIDUS study, including depressive symptoms, alcohol use, symptoms of generalized anxiety, and neuroticism. A summary of the results across PRSs and phenotypes is shown in Table 3. The most consistent finding was the effect of marital satisfaction on psychopathology. Marital satisfaction was robustly related to total depressive symptoms, maximum number of drinks, and neuroticism. This parallels work that reported moderate associations between both internalizing and externalizing psychopathology and marital satisfaction (South et al., 2011). The effects of PRSs on phenotypic outcomes were not as strong in the current study. These findings may be attributable to the difficulty of replicating the predictive effect of PRSs across samples that differ in the measurement of the phenotype (e.g., Bogdan et al., 2018).

We did find evidence that marital satisfaction moderated the association between PRS and the generalized anxiety symptom score phenotype. The PRS for anxiety was more strongly associated with the respective phenotype at low levels of marital satisfaction (although the simple slopes analysis showed that the association was not significant at 1 *SD* above and below average satisfaction). Relationship quality may have a potent effect on triggering genetic effects on anxiety because individuals with GAD report worrying more about family/interpersonal issues more than anything else (Roemer et al., 1997). The nature of the pathology in GAD is such that to guard against an increase in negative emotion, the individual uses worry as a compensatory mechanism that, in fact, prolongs negative emotionality and physiological reactivity (Newman et al., 2013). Having a high level of relationship satisfaction, however, seemed to buffer against the expression of the PR score on anxiety symptoms (see Fig. 1). Thus, our findings are in line with a susceptibility model for symptoms of generalized anxiety (i.e., worry and concomitant distress about that worry) such that genetic predisposition for anxiety is most likely to be triggered or

Table 3. Summary of Null-Hypothesis Significance Tests From Regression Analyses of PRS and Marital Satisfaction on Mental Health Phenotypes

Outcome (phenotype)	PRS	Effect of PRS?	Effect of marital satisfaction?	Two-way interaction?	Three-way interaction?
Depressive symptoms	Depressive symptoms	No	Yes	No	No
Depressive symptoms	MDD	No	Yes	No	No
Frequency of 1+ drinks per day	Drinks per week	No	No	No	No
Most drinks when drinking	Drinks per week	No	Yes	No	No
Anxiety symptoms	Anxiety	No	No	Yes	No
Neuroticism	Neuroticism	No	Yes	No	No

Note: All three-way interactions included gender, marital satisfaction, and PRS. Yes = statistically significant effect found at $p < .05$. PRS = polygenic risk score; MDD = major depressive disorder.

expressed among individuals with unsatisfying or conflict-laden intimate romantic relationships but buffered among individuals with very satisfying relationships.

Contrary to our expectations, we did not find a similar interaction effect on the other mental health phenotypes or neuroticism. This is in direct contrast to previous work that found heritability of internalizing psychopathology was highest among people with the lowest marital satisfaction (South & Krueger, 2008). One explanation for the failure to replicate, beyond generalized anxiety symptoms, is the difference in measure of genetic influence. Quantitative genetic studies, in which genetic influence is inferred from the relative resemblance of identical and fraternal twins, capture additive genetic effects, including both commons and rare variants, whereas PRSs capture only the influence of common variants. Thus, marital satisfaction may have a moderating effect on interactive (epistatic) genetic processes or rare variants. Another possible conclusion from our findings is that marital satisfaction is moderating the association between genetic liability for a broad-based phenotype encompassing several forms of internalizing pathology and the manifestation of that liability. Other work from molecular genetics also supports action at the level of latent factors and not individual syndrome manifestation (for a review, see Waszczuk et al., 2020). How genetic liability as captured by a PRS manifests (i.e., as worry, distress, and negative reactivity to potentially stressful situations) may also be a function of other personality traits or individual differences not captured in the current analyses.

In an exploratory manner, we examined gender as a moderator of the effect of PRS, marital satisfaction, and the PRS × Marital Satisfaction interaction on each mental health phenotype. We found no systematic or statistically significant effect of gender on any of these associations. The differences between men and women on both relationship satisfaction (Jackson et al., 2014) and psychopathology (Kramer et al., 2008) are primarily of mean differences. Furthermore, we have found that the association between psychopathology and relationship distress is equivalent across gender (South et al., 2011). We had only a handful of mental health phenotypes in the current analyses, and it is possible, of course, that the association between individual genetic risk and other phenotypes may differ as a function of gender and an environmental moderator (e.g., relationship distress). Another intriguing possibility is that, as we noted above, the real "action" for PRS and phenotype may be at the level of higher-order domains of psychopathology (see Dick et al., 2007). Environmental stress may affect the way that genetic risk manifests as a specific syndrome, and this effect may differ by gender. This is an important avenue for further research.

Limitations

There are four main limitations to the study methodology that may affect our findings. First, this sample is limited in its generalizability. Like many studies that use genome-wide data, creation of PRSs was restricted to individuals of European ancestry. This is because the discovery GWASs that are used to create the SNP weights are based almost universally on participants of European ancestry. It is our hope that future GWASs will include more data from participants of non-European ancestry that can be translated to PRSs and that the current analyses can be replicated and extended in more racially and ethnically diverse populations. The sample is also predominantly middle-aged and married; thus, findings may not be generalizable to individuals across the life span or to individuals who choose to cohabitate rather than marry. Second, to handle the nested nature of a small portion of our sample (i.e., there is a twin subsample in the larger MIDUS sample), we chose to exclude one twin from each pair. Although necessary, this reduced our sample size, and it was the most conservative option for dealing with nested data. Indeed, our sample size, although not under our control because this was secondary data analysis, was small for

genetic analyses, particularly for the purpose of "gene-hunting" via a GWAS (but large for regression with interaction effects). Our hope is that in the future, larger studies will be available that include mental health phenotypes and measures of relationship functioning. Third, PRSs capture *common* genetic liability for phenotypes because of the additive effects of point mutations, but PRSs do not capture the potential influence of rare genetic variants, copy number variants, insertion, and deletions. Consequently, although PRSs capture genome-wide genetic liability, the totality of genetic influence is not fully captured. Finally, although the associations between marital satisfaction and mental health phenotypes were robust in the current study, even after accounting for the effects of PRSs, the non-experimental, cross-sectional nature of the data precludes establishing the temporal direction of estimated associations. Consequently, causal inference is not warranted.

Summary

In the current article, we present an extensive analysis of how relationship satisfaction moderated the association between PRSs and corresponding mental health phenotypes. Significant moderation was found such that the association between a PRS for anxiety and anxiety phenotype was greatest in distressed marriages. To our knowledge, this is the first study to examine marital quality as a moderator of the association between mental health phenotypes and genotypes as indexed by a PRS. Our findings suggest that for generalized anxiety, a genetic susceptibility to environmental influences on anxiety may be highly influenced by relationship quality.

Transparency

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Author Contributions

S. C. South and R. F. Krueger developed the study concept. S. C. South and F. D. Mann developed and performed the data analysis and interpretation of results. S. C. South drafted the manuscript, and R. F. Krueger and F. D. Mann provided critical revisions. All of the authors approved the final manuscript for submission.

Declaration of Conflicting Interests

The author(s) declared that there were no conflicts of interest with respect to the authorship or the publication of this article.

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MIDUS data is publicly available from the ICPSR at the University of Michigan (https://www.icpsr.umich.edu/web/pages/) or through the MIDUS Colectica portal (see http://midus.wisc.edu/data/index.php).

Notes

1. The MIDUS Refresher project had participants as young as age 20, thus the average age for the current sample included individuals as young as 25 when the data for these analyses were collected.
2. The MIDUS data set also includes separate scores for depressed affect and anhedonia based on summed responses to the items following report of sadness (range of scores = 0–7) or items following reported of anhedonia (range of scores = 0–6). We also analyzed these scores using Poisson regression and robust standard errors, and results of null hypothesis significance tests are consistent with what is reported for the total depression symptoms score in the main text.
3. More information on the specific discovery GWAS used in the calculation of the PRS is available in the MIDUS documentation, accessible through the Inter-university Consortium for Political and Social Research or the MIDUS Collectica portal: http://midus.wisc.edu/index.php.
4. These analyses were also run with a square root transformation of the drinks per week variable. Results were largely unchanged, although the effect of marital satisfaction on drinks per week was now significant at $p < .01$.
5. Although this interaction effect met conventional standards for statistical significance, we applied Benjamini-Hochberg to correct for multiple testing. Using the ranked p values for the six effects reported in Table 2, we found that the interaction between PRS score and satisfaction on anxiety survived correction when $Q = .10$ but just missed significance when $Q = .05$.
6. These analyses were also conducted using a negative binomial regression. The interaction between PRS score and satisfaction on anxiety trended toward significance at $p = .0767$, and the interaction between gender and satisfaction was $p = .052$.
7. The neuroticism score was slightly positively skewed (0.5). We reran the regression analyses using a log-transformed neuroticism variable, and results were virtually identical, although in this model, the PRS for neuroticism almost met a conventional threshold for significance, $p = .05$. We also ran a regression predicting neuroticism from the PRS, marital satisfaction, gender, and centered age (including age interactions with all main predictors). Substantive findings were identical to those reported in the text.

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