Running Head: GENETIC SENSITIVITY TO PREP

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Genetic Sensitivity Predicts Long-Term Psychological Benefits of a Relationship Education Program for Married Couples

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Abstract

Objective: Relationship education programs have proven effective in promoting relationship quality and preventing divorce among married couples. However, according to theories of *Environmental Sensitivity*, people differ for genetic reasons in their sensitivity to environmental influences with some more affected by both negative and positive experiences, including psychological interventions.

Method: Here we test in two studies whether the positive effects of the established *Prevention and Relationship Education Program* (PREP) are moderated by two different polygenic scores (PGS) for environmental sensitivity, one based on nine established candidate genes and one based on several thousand variants across the genome, derived from recent genome-wide association study (GWAS) results. Analyses were conducted in a randomized controlled study on PREP (N = 242) and then repeated in an independent replication trial (N = 183).

Results: Several significant PREP-X-PGS interactions indicated moderation of long-term treatment effects across the two studies, most of them involving the genome-wide score. Generally, higher genome-wide genetic sensitivity was associated with stronger intervention effects on almost all measures of relationship quality across the follow-up period.

Conclusions: Findings provide further evidence that people differ substantially in their response to the positive effects of psychological intervention as a function of individual differences in genetic sensitivity, with more sensitive participants potentially benefitting more from relationship education.

Keywords: Differential Susceptibility; Environmental Sensitivity; Genetics; Relationships; Marriage; Relationship Education; Military Couples

Author Note

Data from the two included studies are not available due to ethical reasons concerning the sensitive and dyadic nature of the data (informed consent). Study materials and analysis code can be requested from the corresponding author. The reported analyses were not preregistered.

Public Health Significance Statement

This study provides new but preliminary evidence that people differ in their sensitivity to the positive effects of psychological intervention due to their genes. Higher genetic sensitivity was associated with a stronger positive response to an established relationship intervention. Biologically-based differences in sensitivity may need to be considered as important factors in treatment response.

Introduction

Distressed and dysfunctional interpersonal relationships are associated with both mental and physical health problems (Donoho, Crimmins, & Seeman, 2013; Dush & Amato, 2005; Whisman, 1999). Given these health risks, couple-intervention programs seek to prevent romantic-relationship distress (Markman & Rhoades, 2012; Parke & Ooms, 2002; Seefeldt & Smock, 2004). One of the most established and empirically evaluated interventions is the *Prevention and Relationship Education Program* (PREP), initially designed in the late 1970s (Markman & Floyd, 1980) and revised repeatedly since then (Ragan, Einhorn, Rhoades, Markman, & Stanley, 2009). PREP significantly increases communication skills, improves relationship quality, and prevents divorce among married couples (Allen, Stanley, Rhoades, Markman, & Loew, 2011; Kaiser, Hahlweg, Fehm-Wolfsdorf, & Groth, 1998; Markman, Floyd, Stanley, & Storaasli, 1988; Stanley, Allen, Markman, Rhoades, & Prentice, 2010). What has not been considered before—and will be for the first time herein—is the theoretically derived proposition that participants' positive response to the program may vary as a function of individual differences in their genetic sensitivity to environmental influences.

According to the frameworks of *Differential Susceptibility* (Belsky & Pluess, 2009), *Biological Sensitivity to Context* (Boyce & Ellis, 2005), and *Sensory Processing Sensitivity* (Aron & Aron, 1997), referred to from this point onward more broadly using the umbrella term of *Environmental Sensitivity* (Pluess, 2015), people differ fundamentally in their sensitivity to their experiences. Consequently, some are generally more and others less influenced by both negative *and* positive exposures. Importantly, genetic factors have been found to account for some variation in environmental sensitivity (Assary, Zavos, Krapohl, Keers, & Pluess, 2020; Belsky & Pluess, 2009, 2013). In this two-study report, we evaluate whether genetic sensitivity, measured with two different polygenic scores, one based on a number of *candidate genes* and one on *genome-wide data*, moderates the well-established

positive effects of PREP in one of the largest randomized controlled trials on the effectiveness of PREP. In light of known challenges regarding the robustness of gene-environment interaction studies (Duncan & Keller, 2011), we then seek to replicate findings in an independent study. In what follows, we first provide information on PREP and its efficacy, then introduce the notion of environmental sensitivity and its genetic basis, before presenting the current study and hypotheses.

The Prevention and Relationship Education Program (PREP)

PREP is a relationship education program based on behavioral and social learning models of marital therapy (Markman, 1979; Markman & Floyd, 1980) as well as research on conflict and communication in couples (e.g., Birchler, Weiss, & Vincent, 1975; Gottman, Markman, & Notarius, 1977) and commitment (Stanley, Lobitz, & Dickson, 1999; Stanley & Markman, 1992). Since its inception, it has been continuously revised and refined based on new research on couple processes and predictors of distress and divorce (Markman, Rhoades, Stanley, Ragan, & Whitton, 2010; Stanley et al., 1999). In randomized controlled trials (RCTs), PREP participation has been compared to no-intervention controls (Stanley et al., 2014) as well as to marriage preparation provided by religious organizations (Stanley et al., 2001). Compared to no treatment at all, PREP increases communication skills (Allen et al., 2011; Markman et al., 1988) and relationship satisfaction (Markman et al., 1988); it also prevents divorce (Stanley et al., 2010) within two to three years after intervention.

However, results of PREP and similar programs (Johnson & Bradbury, 2015) are sometimes inconsistent, with treatment effects varying as a function of various characteristics of participants. For example, one study indicated that PREP was most effective for couples who had experienced infidelity compared to those who had not (Allen, Rhoades, Stanley, Loew, & Markman, 2012). Another investigation documented stronger impacts of reducing divorce for those who were *less* at risk prior to marriage in terms of their communication

patterns and history of physical aggression (Markman, Rhoades, Stanley, & Peterson, 2013). Notably, no research has yet evaluated whether intervention efficacy of relationship-education programs varies due to biologically-based individual differences, as expected according to the aforementioned theories of environmental sensitivity.

Individual Differences in Environmental Sensitivity

It is quite evident that people differ in how strongly they are affected by their experiences. Traditionally, the fields of psychology and psychiatry have been particularly interested in such variation in response to adverse experiences, as reflected in the *Diathesis-Stress* model (Monroe & Simons, 1991). According to this established person-X-environment framework, some individuals are considered more vulnerable than others for the development of problems in response to adversity due to individual characteristics, be they select psychological traits or genetic factors. However, this model does not make any predictions about variation in response to positive exposures such as psychological interventions (Belsky, Bakermans-Kranenburg, & van IJzendoorn, 2007; Belsky & Pluess, 2009)

Over the last years, new theories emerged which all stipulate that individuals most negatively affected by adversity may also benefit most from positive and supportive experiences. For example, according to the theory of *Differential Susceptibility* (Belsky & Pluess, 2009), individuals differ in their susceptibility to environmental influences with more susceptible ones developing more problems in unfavorable environments but also more competences in supportive environments. This has been found in studies on infant temperament with a meta-analysis providing evidence that infants with more difficult and negatively emotional temperaments proving more vulnerable to negative parenting but also benefit more from positive parenting (Slagt, Dubas, Dekovic, & van Aken, 2016).

Similarly, the framework of *Biological Sensitivity to Context* (Boyce & Ellis, 2005) implicates heightened physiological stress reactivity as a sensitivity factor, with evidence

indicating, for example, that highly reactive children manifest the most and least prosocial behavior when they have experienced, respectively, low versus high levels of adversity (Obradovic, Bush, Stamperdahl, Adler, & Boyce, 2010). Furthermore, BSC theorizing stipulates that early environmental conditions influence stress reactivity, making children exposed to especially adverse or supportive conditions more sensitive to positive and negative environmental effects than other children.

The theory of *Sensory Processing Sensitivity* (Aron, Aron, & Jagiellowicz, 2012) suggests that about 20-30% of the population are characterized by a stable personality trait of high sensitivity and more affected by their experiences due to a heightened sensitivity to sensory input and deeper processing thereof. Importantly, the personality trait of sensitivity can be measured with questionnaires, with evidence showing that people scoring higher on this trait are indeed more vulnerable to the negative effects of stressful experiences but also more responsive to positive exposures such as positive mood induction (Pluess, Lionetti, Aron, & Aron, 2020).

Finally, the notion that people differ significantly in their response to positive experiences has been described more specifically in the *Vantage Sensitivity* model (Pluess & Belsky, 2013). According to this model, some individuals benefit more from positive exposure (such as psychological interventions) due to individual sensitivity factors whereas others do less or not at all. For example, in one study detecting a Vantage Sensitivity pattern, only children who scored high on the self-reported trait of sensitivity showed improvement in their mental health in response to a school-based anti-bullying intervention (Nocentini, Menesini, & Pluess, 2018).

Recently, these different—and independently developed—theories have all been integrated into the overarching umbrella framework of *Environmental Sensitivity* (Pluess, 2015), according to which individual differences in sensitivity have a genetic basis but are

also shaped by the developmental context, and eventually reflected behaviorally and psychologically in people's ability to perceive and process information about the environment. Extensive evidence now documents individual differences in sensitivity to environmental quality as a function of genetic, physiological, and psychological factors (for review, see Belsky & Pluess, 2009, 2013; de Villiers, Lionetti, & Pluess, 2018; Obradovic & Boyce, 2009).

Genetic Sensitivity

A substantial number of gene-environment interaction studies indicate that variability in specific candidate genes (usually investigated individually and selected due to their specific associated biological function), such as the serotonin transporter (HTTLPR, van IJzendoorn, Belsky, & Bakermans-Kranenburg, 2012) and the dopamine receptor D4 (DRD4, Bakermans-Kranenburg & van IJzendoorn, 2011) gene, account for differences in sensitivity to both negative *and* positive environmental influences (van IJzendoorn & Bakermans-Kranenburg, 2015). Especially notable is that many of these candidate genes have been found to moderate intervention effects. For example, adolescents from high-risk families randomly assigned to a preventative intervention evinced fewer "vulnerable" cognitions and reduced escalation in drug use more strongly when they carried the DRD4 7-repeat allele than when they did not (Brody, Yu, & Beach, 2015). Similarly, infants carrying the HTTLPR short allele proved more likely to develop a secure attachment when randomly allocated to a home-visiting intervention program compared to infants with different genotypes (Morgan et al., 2017). Much of this work, initially designed to test Diathesis-Stress hypotheses, contributed to the development of differential susceptibility thinking (Belsky et al., 2009).

Importantly, the observation that different candidate genes (associated with different biological systems and functions) proved related to environmental sensitivity led to the understanding that sensitivity is most likely a polygenic trait involving multiple biological

systems. Consequently, researchers began to combine several candidate genes associated with different biological functions into genetic scores when investigating genetic sensitivity (Belsky & Beaver, 2011; Keers & Pluess, 2017; Masarik et al., 2014). Importantly, these candidate genes scores tend to vary across studies and no single composite has been established yet. For example, a polygenic score based on five candidate genes associated with sensitivity has been shown to moderate the positive effects of an established parenting program with reduction in externalizing behaviors being strongest in boys carrying more sensitivity genes (Chhangur et al., 2017). (Important to mention, findings of candidate gene interaction studies generally need to be considered in light of the often small and statistically underpowered samples featured in such investigations (Duncan & Keller, 2011).)

More recently, this polygenic approach has been extended from the combination of a few well known candidate genes to that of many genes based on data-driven approaches considering the whole genome. What is critical to appreciate is that whereas candidate genes were typically selected based on thinking or evidence linking the putative genetic moderator to the outcome being predicted (i.e., genotype-phenotype considerations), identification of moderator genes using the whole genome was based on the proposition that there exist genes for plasticity or susceptibility to environmental influence (Zhang & Belsky, 2020). The latter work was further stimulated by the discovery that common traits are usually the function of thousands of gene variants that each make a tiny contribution to psychological-behavioral phenotypes rather than reflecting a small selection of candidate genes (Nagel et al., 2018; Okbay et al., 2016).

The first such differential-susceptibility related genome-wide association study (GWAS; a data-driven approach that is completely agnostic to the biological function of genes) relied on an innovative and novel design based on monozygotic twins (all of white ethnicity). It took advantage of the fact that some identical-twins are quite different from their

fellow twin, in contrast to pairs that are quite similar. Theorizing that this difference reflected the former's greater sensitivity to non-shared environmental experiences, and thus sensitivity to the environment, it identified genes that distinguished twin pairs more and less similar in terms of emotional problems in order to create a polygenic score for sensitivity featuring several thousand gene variants (Keers et al., 2016). The individual weights of these variants in distinguishing pairs more and less similar to each other were summed to create a polygenic score for sensitivity. Evidence of the validity of the polygenic plasticity index emerged from research showing it moderated effects of observed parenting quality on children's emotional development (Keers et al., 2016), explained variation in the efficacy of different types of Cognitive Behavioral Therapy (CBT) for child anxiety disorders (Keers et al., 2016), and explained variation in effects of a family intervention on children's internalizing symptoms (Lemery-Chalfant, Clifford, Dishion, Shaw, & Wilson, 2018). Most recently, the same polygenic score accounted for variability in effects of stressful life events on adults' depression symptoms (Davidson et al., Submitted).

The Current Study

On the basis of the work reviewed we investigated, in Study 1, whether individual differences in genetic sensitivity moderated the positive effects of PREP in a randomized controlled trial conducted with couples in the United States Army on outcomes assessed before and directly after treatment and then repeatedly every six months for up to two years following program termination. We examined interaction effects for both immediate (pre-post) and long-term effects by considering *trajectories of change* from the post treatment assessment through to the follow-up assessment two years later. We considered four relevant intervention outcomes from both partners of each participating couple, selected based on a previous evaluation of PREP using the same data (Stanley et al., 2014).

Two different polygenic scores were used to model genetic sensitivity. The first was based on nine candidate gene variants found to reflect increased responsivity to both low and high environmental quality in multiple observational and intervention studies of gene-environment interaction (Belsky & Pluess, 2013, 2016), none of which, notably, involved marital processes. Importantly, we only included candidate genes for which there were at least two or more independent studies providing evidence for the moderating effect of the gene as proposed by the framework of environmental sensitivity with the aim to combine as many candidate genes as possible that have been associated with sensitivity (but not considering their specific biological function). The second polygenic score was that developed by (Keers et al., 2016), as already described, and which included many thousand gene variants across the genome.

Given growing concerns that genetic findings often lack robustness (Duncan & Keller, 2011), we repeated an independent study to determine if findings from the first study proved replicable. Study 2 also featured a randomized controlled design with annual post-intervention assessments across 16 years and with couples in the United States assigned to PREP or naturally-occurring marriage preparation from religious organizations. We report in the Methods and Materials sections how we determined the sample size, all data exclusions (if any), all manipulations, and all measures in both studies.

We hypothesized that individuals with higher polygenic sensitivity scores would benefit most from the intervention. Furthermore, given evidence from prior studies that variation in treatment response due to genetic sensitivity emerged sometimes more clearly during follow-up assessments (Chhangur et al., 2017; Eley et al., 2012; Pluess & Belsky, 2015; Pluess & Boniwell, 2015), we expected the strongest moderation of treatment effects for change over time (i.e., trajectories) rather than immediate pre-post changes.

Study 1

Methods and Materials

Overview of the Study

This study used a sample of couples participating in a larger randomized controlled trial of PREP (vs. no treatment) delivered in the United States Army. Please see Stanley et al. (2014) for complete details (the CONSORT diagram for the original study is also provided in supplementary information, Figure S1).

Participants

Analyses are based on 116 male and 126 female participants (representing 154 unique couples) involved in the original RCT who provided DNA for the current project. Following common practice in the field of genetics, only White participants were included as the predominant ethnicity to avoid known confounding by genetic differences with minor ethnicities (see Table 1 for demographics).

Importantly, although the original randomized controlled trial was conducted across two sites in the southern United States, due to logistic issues that precluded collection of genetic samples, only participants who were recruited at one of these sites (Site 1) could be included in the subsample for the genetic study. In total, DNA collection kits were mailed to 570 participants; 271 returned these samples which resulted in a final sample of 242 with usable genetic data after processing in the lab. According to comparisons of all outcome variables between the final subsample (N = 242) and all other participants of the original study (N = 1,051), the genetic subsample had significantly higher marital satisfaction (M = 6.06, SD = 1.07, for included cases versus M = 5.80, SD = 1.24 for the remaining original sample, with t = 2.93, p <.01) and lower divorce proneness (M = .10, SD = .25, for included cases versus M = .18, SD = .33 for the remaining original sample, with t = -3.86, p <.01) at the immediate post treatment assessment.

Procedures

Prior to random assignment to PREP-treatment or no-treatment control groups, each spouse separately completed questionnaires. Approximately two weeks after PREP was completed (i.e., immediate post), each spouse separately completed the measures again, with these repeated online approximately every six months thereafter through two years post-intervention. Like the main outcome paper from this study (Stanley et al., 2014), the current analyses are based on data collected at pre- and immediate-post intervention and at four follow-up assessments. The genetic data were collected approximately seven years after the start of the study. Participants were each mailed a consent form together with a saliva sample kit and paid $50 for returning the samples. All procedures were approved by a university Institutional Review Board (University of Denver, 471733).

Intervention

PREP-treatment participants received a version of PREP adapted for use by Army chaplains with Army couples (Markman, Rhoades, et al., 2010; Markman, Stanley, & Blumberg, 2010; Stanley, Markman, Jenkins, & Blumberg, 2006; Stanley et al., 2014). It consisted of two parts totaling approximately 14.4 hours of training: a one-day, on-post training followed by a weekend retreat at an off-post location. PREP intervention modules addressed communication problem solving, negative affect-management, relationship dynamics, emotional support, stress and relaxation, commitment, fun/friendship, forgiveness, sensuality/sexuality, expectations, core beliefs, and deployment/reintegration issues.

Measures

We considered the same four intervention outcomes as in the original outcome study (Stanley et al., 2014).

Marital satisfaction was assessed using the reliable and valid three item Kansas Marital Satisfaction Scale (KMS; Schumm et al., 1986). It assesses satisfaction with the spouse and with the marriage (Cronbach's α =.94).

Communication skills were assessed with 10 Likert items from the longer Communication Skills Test (Jenkins & Saiz, 1995), with items avoiding PREP-specific terminology, including *"When discussing issues, I allow my spouse to finish talking before I respond," "When our discussions begin to get out of hand, we agree to stop them and talk later."* (Cronbach's α =.85).

Positive bonding was assessed by means of nine Likert items from the longer Couple Activities Scale (Markman, 2000) measuring partner friendship, intimacy, fun, felt support, and sensuality/sexuality such as *"We regularly have conversations where we just talk as good friends," "We have a satisfying sensual or sexual relationship," "I feel emotionally supported by my partner."* (Cronbach's α =.88).

Divorce proneness was assessed using three (binary: yes/no) items adapted from the short form of the Marital Instability Index (MII; Booth, Johnson, & Edwards, 1983) taping concern for marriage, and consideration and discussion of separation/divorce (Cronbach's α =.83).

Genetic sensitivity was assessed with two different polygenic sensitivity scores, one based on a *small number of candidate genes* that have been repeatedly associated with environmental sensitivity (Belsky & Pluess, 2009, 2013, 2016), and one based on *genome-wide data* (Keers et al., 2016). DNA was obtained from saliva samples, which was genotyped separately for selected candidate genes and genome-wide analyses at multiple labs in the UK following standard protocols. None of the selected candidate genes showed major deviations from the Hardy-Weinberg Equilibrium (HWE). The genotypes (i.e., combination of alleles) of the candidate gene were recoded "0" for those reflecting no sensitivity and "1" for those reflecting sensitivity. Whether sensitivity alleles were coded dominant or recessive was informed by previous studies in order to obtain sensitivity genotypes that have been most consistently and most strongly associated with sensitivity (e.g., for HTTLPR LS and LL were

coded 0, and SS as the sensitivity genotype was coded 1). Recoded genes were then summed up, with the resultant polygenic score ranging from 0-9. The few missing data for any gene variant were replaced by the mean of each individuals' score. Of all 271 samples that were returned by participants, 242 yielded polygenic scores. See Table 2 for detailed information on specific candidate genes, their frequencies, missing data and coding for inclusion in the polygenic score.

Genome-wide data were obtained using the Illumina GSA microarray to create a genome-wide polygenic score for sensitivity, initially developed and validated by Keers et al. (2016). To maximize the number of overlapping Single Nucleotide Polymorphisms (SNPs) between the prior study and this one, we first imputed (separately in Study 1 and 2) our data using the 1,000 genomes database (The Genomes Project Consortium et al., 2015). Following post-imputation quality control (including the removal of SNPs with an info score <.80) we had a total of 5,155,277 SNPs (build 37). Similar to Keers et al. (2016), polygenic scores for genetic sensitivity were calculated at different thresholds for SNP inclusion (p = .0001, p = .01, p = .05, p = .10, p = .50, and p = 1.00). However, in keeping with current thinking about the value of maintaining the broadest pool of loci for construction of genetic indices, the current analysis (and Study 2) used the p = 1.00 score to include all available SNPs associated with sensitivity in the Keers et al. (2016) study, but we also ran sensitivity analyses with the p = .05 score to test for robustness of findings. To account for population structure, we calculated principal components and regressed the first 10 principal components on the polygenic score in a multiple regression model; this yielded residuals with no influence of population structure that were used in all analyses.

Importantly, only four gene variants were shared between the candidate gene and the genome-wide polygenic scores (i.e., DRD2, BDNF, COMT, FKBP5). The remaining variants (i.e., HTTLPR, DRD4, MAOA, DAT1, OXTR) were unique to the candidate gene score.

Data Analysis

First, we generated bivariate correlations between the polygenetic sensitivity scores and treatment-group assignment (i.e., control/treatment) to determine whether genes and treatment proved independent of one another, as well as with gender. Next, the moderating effects of the two polygenic sensitivity scores were tested in the primary analysis, with three-level multilevel models using HLM 7.0 (Raudenbush, Bryk, Cheong, & Congdon, 2011). We ran separate models for each of the four outcomes. Following Atkins (2005) and others using this data set (Allen et al., 2012; Stanley et al., 2014), time-varying characteristics of individuals (e.g., marital satisfaction) were modeled at level 1, time-invariant individual characteristics (e.g., pre-intervention marital quality) at level 2, and couple characteristics (i.e., intervention group) at level 3. Importantly, this modeling approach, which was also applied in the original evaluation of PREP using these data (Stanley et al., 2014), accounts for the nesting of individual participants in couples. We controlled for pre-intervention marital quality measurements by including them at level 2. Time reflected months since the post intervention assessment and was not centered, so that the intercept could be interpreted as the estimated immediate post score. Group was coded 0/1 for control/intervention. Alpha was set at $p < .05$, two-tailed, for all analyses. In order to account for the testing of four different intervention outcomes, we applied False Discovery Rate (FDR) correction to the main models and report both uncorrected as well as corrected findings.

The statistical model (see supplementary information for the full equation) afforded evaluation of the interaction of polygenetic sensitivity and PREP for both immediate effects (i.e., post-intervention) on intervention outcomes and for trajectories of change thereafter through two years following the immediate post assessment (i.e., slope). We calculated effect sizes for interaction effects on slopes that survived correction for multiple testing in units of Cohen's *d* based on change in proportion of variance explained (PVE); this was done for

models with and without the slope interaction term. For illustrative purposes, we investigated simple slopes (i.e., +/- 1 standard deviation of the genome-wide polygenic score) following Aiken and West (1991) for the most general outcome (i.e., marital satisfaction), using the Johnson-Neyman technique using Preacher's (2006) online tool (figures for the remaining significant interactions are provided in supplementary documentation, see Figures S3-5). Importantly, models with the genome-wide polygenic score were rerun with a score made up of fewer SNPs (p = .05) to test for robustness of findings in sensitivity analyses. All analyses with both polygenic scores were then repeated in the Study 2 replication sample.

Due to the ethical constraints of the study, data are not available but study materials and analysis code can be requested from the corresponding author.

Results

Preliminary Analyses

Polygenetic sensitivity proved statistically independent of treatment group assignment and gender (all ps > .05). As expected, outcome variables were significantly correlated with one another with a range of r = |.43 to .79|.

Primary Analyses

Candidate Gene Polygenic Score. Genetic variation did not moderate effects of PREP on immediate post-treatment scores for any of the marital quality outcomes. Nevertheless, a significant interaction between PREP and genetic sensitivity emerged for divorce proneness (but none of the other outcomes) for the trajectory (of change) index: Greater genetic sensitivity was associated with a stronger treatment effect on the reduction of divorce proneness over time (see Table 3). However, after correction for multiple testing, this effect was no longer significant.

Genome-Wide Polygenic Score. Notably, reliance on the GWAS-based polygenic score yielded multiple significant interaction effects on all four outcome measures of change

(i.e., slope from post-test to 2 years following PREP), all of which survived correction for multiple testing (see Table 3 for results). However, there was no genetic moderation of immediate post-treatment scores. As predicted, greater polygenetic sensitivity was associated with a stronger positive treatment effect on post-intervention change in marital satisfaction (*B* = .019, *p* < .001, *d* = .13), divorce proneness (*B* = -.004, *p* = .03, *d* = .10), communication skills (*B* = .010, *p* = .03, *d* = .07), and positive bonding (*B* = .012, *p* = .02, *d* = .24). Thus, following treatment, individuals with higher genetic sensitivity improved more than those with lower sensitivity.

When measures of change for the marital satisfaction post intervention were evaluated at +/- 1 SD of genetic sensitivity (see Figure 1), none of the simple slopes were statistically significant. However, according to the obtained slopes and associated effect sizes the genetically high sensitive group manifested a somewhat steeper increase in marital satisfaction when allocated to PREP (*B* = .023, *p* = .19, *d* = .35) compared to their genetically sensitive counterparts in the control group (*B* = .007, *p* = .71, *d* = .17). The genetically low sensitive group showed almost no improvement in marital satisfaction when in the PREP condition (*B* = .002, *p* = .92, *d* = .10) but, surprisingly, appeared to increase in the control condition (*B* = .022, *p* = .23, *d* = .35). Figures of simple slopes for the remaining outcomes are provided in supplementary documentation (see Figures S3-5).

Sensitivity Analysis

When rerunning analyses with a revised genome-wide polygenic score based only on SNPs at *p* =.05, which included significantly fewer SNPs than the one at *p* = 1.00 (i.e., 8,112 versus 64,964), all of the results were replicated, though the effect for divorce proneness was only marginally significant. Moreover, the genetic moderation effects for short-term pre-post changes related to communication skills became marginally significant with genetically more sensitive individuals declining in communication skills when allocated to the treatment

condition (see Table S1 in supplementary documentation). However, none of these findings survived correction for multiple testing.

Study 2

Methods and Materials

Overview of the Study

The replication sample includes 171 families in the USA who were initially recruited between 1996 and 2001 as part of different larger randomized controlled trial on PREP (Stanley et al., 2001). See supplementary information for a CONSORT diagram of the original study (Figure S2).

Participants

Analyses are based on 84 men and 99 women (representing 106 unique couples) who were involved in the original randomized controlled trial (at recruitment, all couples were about to marry) and agreed to donate DNA for the current project (83% White, see Table 1 for further demographics). T-tests contrasting individuals included in the genetic subsample (N = 183) and the remaining participants in the original trial (N = 328) did not reveal significant differences in the post treatment outcomes.

Procedures

Participating couples were randomly assigned to receive a 12-hour version of PREP (delivered either by the religious organization that would perform their wedding or at a university) or the naturally-occurring premarital training services at their religious organization, Couples completed a post assessment several weeks after intervention and then yearly assessments thereafter, for up to 16 years. Genetic data was collected during one of the more recent follow-up assessments in order to test for genetic moderation of treatment effects. All procedures were approved by a university Institutional Review Board (University of Denver, 472392).

Measures

Annual assessments included self-reports and videotaped interactions following intervention. Self-reports included various questionnaires relationship functioning such as marital satisfaction, and communication. We considered the same intervention outcomes as in the original study (Stanley et al., 2001).

Marital adjustment (self-report). The Marital Adjustment Test (Locke & Wallace, 1959) was used to assess marital quality. It is a 16-item measure that assesses several domains of marital quality, including disagreements, commitment, cohesion, and overall happiness. A total score was used and higher scores reflect greater marital quality (Cronbach's α =.65).

Negative communication (self-report). Negative communication was measured by self-report with the Communication Danger Signs Scale (Markman, Stanley, et al., 2010). This measure includes 7 items rated on a scale ranging from 1 (almost never) to 3 (frequently) scale. An example item is "My partner criticizes or belittles my opinions, feelings, or desires." An average of the 7 items was used and higher scores reflect more negative communication (Cronbach's α =.73).

Negative and positive communication (observed). The Interactional Dimensions Coding System, a global coding system for couples' discussions of relationship problems (Julien, Markman, & Lindahl, 1989; Kline et al., 2004), was used to code couples' videotaped problem discussions. Both the negative communication subscale (made up of individually-rated withdrawal, denial, conflict, dominance, and negative affect, as well as couple-level negative escalation (Cronbach's α = .86) and the positive communication subscale (made up of individually-rated communication skills, support validation, problem solving skills, and positive affect, with α = .90) were used.

Genetic sensitivity. We applied the exact same procedures as in the primary sample to create to polygenic scores for sensitivity. Importantly, all candidate genes were within the

Hardy-Weinberg equilibrium (for more information see Table 2). Of all 183 samples that were returned by participants, 160 could be included in the candidate gene polygenic score and in the genome-wide polygenic score (based on 5,247,880 SNPs after imputation and subsequent quality control).

Data Analysis

After considering bivariate correlations between genetic sensitivity scores and other variables, we tested genetic moderation of treatment effects across all 16 years of the follow-up data using the same multilevel models and statistical approach as with the primary sample. In addition, we reran analyses with the White-only subsample in order to test whether findings were biased by the ethnic differences in the sample.

Due to the ethical constraints of the study data are not available but study materials and analysis code can be requested from the corresponding author.

Results

Preliminary Analyses

The genetic scores were independent from each other (all *p*s > .05) to group assignment, as well as gender and race/ethnicity. Outcome variables were correlated with one another with a range of r = |.08 to .61|.

Primary Analyses

Candidate Gene Polygenic Score. No significant interaction effects emerged for immediate post-treatment scores or trajectories after treatment (see Table 4).

Genome-Wide Polygenic Score. Significant interaction effects for post-treatment trajectories (but none for immediate post-treatment scores) emerged for two of the four measures of marital quality which survived correction for multiple testing (see Table 4): marital adjustment (B = .692, p = .02, d = .14) and self-reported negative communication (B = -.015, p = .01, d = .14). For both, greater genetic sensitivity was associated with a stronger

(beneficial) treatment effect (i.e., increased marital adjustment, reduced negative communication).

Simple slopes for the interaction between group and genome-wide genetic sensitivity predicting the slope of marital adjustment are presented in Figure 2. Similar to Study 1, none of the simple slopes were statistically significant but the genetically high sensitive group showed a steeper increase in marital adjustment when allocated to PREP (B = 1.67, p = .09, d = 1.15) compared to the genetically sensitive individuals in the control group (B = 1.30, p = .21, d = .81). The genetically low-sensitive group showed the least improvement in marital adjustment of all groups when in the PREP condition (B = 1.17, p = .22, d = .90) but, similar to Study 1, appeared to increase in the control condition (B = 2.09, p = .05, d = 1.45). A figure of simple slopes for the outcome negative communication is provided in supplementary documentation (see Figure S6).

Sensitivity Analysis

Repeating analyses using the more stringent genome-wide polygenic score based on the smaller set of SNPs at p =.05, the two significant interactions replicated and an additional moderation effect emerged for short-term pre-post changes in relation to marital adjustment, with more genetically sensitive individuals' marital adjustment scores declining in the short term when allocated to the treatment condition (see Table S2 in supplementary documentation). Also in line with the primary analysis above and the findings from Study 1, the PREP-X-PGS interaction for the post-treatment trajectories for observed negative communication and observed positive communication proved marginally significant, with those with greater sensitivity showing a stronger treatment effect. After correction for multiple testing, interaction effects for marital adjustment and negative communication survived.

Finally, results of the main models remained unchanged when analyses were repeated in the White-only subsample. Sensitivity analyses with more stringent genome-wide polygenic score also yielded similar results in the subsample with the only exception that the interaction predicting negative communication (observed) was no longer marginally significant (p = .24 instead of p = .07).

Discussion

Relationship education programs such as PREP have proven effective in enhancing marital quality and promoting stability (e.g., Hawkins, Blanchard, Baldwin, & Fawcett, 2008). At the same time, it is widely appreciated that even effective interventions have heterogeneous effects, in that that there is variation in benefits achieved. Building on advances in our understanding of genetic sensitivity, we tested the hypothesis that some participants would benefit more from the positive effects of such interventions due to genetic make-up that confers heightened environmental sensitivity (Bakermans-Kranenburg & van IJzendoorn, 2015; Belsky et al., 2007; Belsky & Pluess, 2009; Pluess, 2015). In the current study, we tested whether two different polygenic scores for sensitivity moderated the previously documented positive (main) effects of the *Prevention and Relationship Education Program* (PREP), an established and evidence-based intervention. We hypothesized that individuals with higher genetic sensitivity would benefit more from PREP than those with lower genetic sensitivity. After testing hypotheses in our primary sample (Study 1), we repeated analyses in a replication sample (Study 2), finding notable, even if imperfect, support for these propositions in the case of post-intervention relationship trajectories.

While genetic moderation of intervention efficacy proved mostly absent for short-term effects (with exception of some sensitivity analysis results), the opposite proved true of longer-term ones. Consistent with predictions, several moderating effects emerged regarding change during the years following intervention (i.e., the slopes), with genetically more

sensitive participants, defined a priori, showing a stronger positive response to treatment. The candidate gene polygenic score moderated treatment effects only on one of four outcomes in Study 1 and not at all in Study 2, whereas the genome-wide polygenic score did so on all four outcomes in Study 1 and two of four in Study 2. Notably, only these genome-wide polygenic effects survived correction for multiple testing.

According to follow-up analyses, and consistent with our hypothesis, higher genetic sensitivity was associated with a stronger positive response to the PREP intervention compared to those with lower genetic sensitivity. However, although simple slopes differed in effect size, individual slopes were not statistically significant (most likely due to small sample size and arbitrary standard cut-off points). When running sensitivity analyses with a polygenic score that included fewer genetic variants, effects detected in the primary analyses replicated for the most part. However, we also detected additional genetic moderation of short-term changes between pre and post assessments for communication skills in Study 1 (which did not survive correction for multiple testing) and of marital adjustment in Study 2 (which survived correction for multiple testing). In both cases, higher genetic sensitivity was associated with an initial *reduction* in marital adjustment/communication skills when allocated to PREP (opposite to what was hypothesized).

Findings across the two studies and the multiple outcome measures of marital functioning proved consistent and provide further empirical evidence that genetic sensitivity can moderate the positive effects of psychological intervention with more sensitive individuals benefitting more from treatment than less sensitive ones (Pluess, 2017; Pluess & Belsky, 2015; van IJzendoorn et al., 2011). Beyond this general point, three observations deserve further discussion. First, genetic sensitivity most consistently moderated changes across the years following the intervention rather than shorter-term, though some pre-post treatment effects did emerge in sensitivity analyses. The fact that it was delayed rather than

immediate effects that principally revealed the moderating effect of genetic sensitivity is somewhat consistent with results of several other gene-X-intervention studies (e.g., Chhangur et al., 2017; Eley et al., 2012; Pluess & Belsky, 2015; Pluess & Boniwell, 2015). Such consistency may reflect the fact that it takes some time for sensitive individuals to integrate new skills before effects prove detectable. Additionally, sensitive individuals may also be more likely to internalize the content of interventions due to their deeper processing (Pluess, 2015), which then increases the continued application of acquired techniques and approaches well beyond the treatment duration.

Second, results were stronger and more consistent for the genome-wide polygenic score. This may suggest that genetic sensitivity is better represented by a large number of gene variants across the whole genome (Keers et al., 2016). In other words, sensitivity likely reflects the summed contribution of thousands of gene variants from multiple biological systems, consistent with much genotype-phenotype work (Howard et al., 2018). Alternatively, genome-wide polygenic scores may be more efficient than candidate gene scores with fewer variants when applied in small samples.

Third, and in respect to one particular result, findings proved entirely unanticipated. Here we are referring to those pertaining to participants in the control group. Relying on the example in the follow-up analyses of marital satisfaction in Study 1 and marital adjustment in Study 2, recall that low-genetic-sensitivity controls showed a similar increase over time as did high-sensitivity participants in the treatment group. In other words, low sensitive individuals appeared to be less responsive to treatment but did better under control conditions. According to theory (Aron et al., 2012; Belsky & Pluess, 2009; Boyce & Ellis, 2005; Ellis, Boyce, Belsky, Bakermans-Kranenburg, & Van IJzendoorn, 2011), the expectation was that low sensitive individuals would display a flat trajectory of change irrespective of treatment condition. Although it may be too speculative to interpret this

unanticipated result, especially given that most of the simple slopes were not statistically significant due, we believe, to low power, the observation that low sensitive individuals show an increase over time in outcomes of marital quality may indicate that their lower genetic sensitivity renders them less vulnerable to the typical relationship stressors that many couples tend to experience. (Alternatively, they may simply show greater responsiveness to assessment.) If replicated, the unexpected findings will be important both for a better understanding of low sensitivity as well as for guiding clinical intervention.

Strengths and Limitations

The research reported herein has a number of significant strengths, including the experimental design with participants randomized into control and treatment groups; multiple assessments over time up to several years after the intervention; replication in an independent sample with a comparable design; and use of both a polygenic score based on candidate genes and a recently developed genome-wide polygenic score for sensitivity. Despite these strengths, findings need to be considered in light of several limitations. First, not all participants included in the original studies provided genetic samples which means that the current samples likely suffer from selection bias in that they are not fully comparable to those in the original studies. This is in part explained by the fact that DNA was collected several years after the intervention. Notably, couples that had significant problems or got divorced before recruitment into the genetic study are less likely to be included in the current subsample, which may also explain why most of the simple slopes were positive; this latter observation is in contrast to the generally observed decline in marital satisfaction over time (e.g., Kurdek, 1998). Second, the samples of both studies were relatively small. According to a post-hoc power analysis using Optimal Design 3.0 software for multilevel models (Raudenbush, Spybrook, et al., 2011), there was sufficient power to detect effects of $d = 0.43$ for Study 1 and $d = 0.50$ for Study 2 with power set to 0.80. Hence, samples were

underpowered to detect small effects and findings should be considered preliminary until confirmed in future research featuring larger samples.

It should not be forgotten, however, that even with low power, results were relatively consistent across the two studies and sensitivity analyses. Moreover, although effect sizes of interactions proved small (d = .07-.24), they are in line with other GXE interaction effects (for example, d = .28-.37 in meta-analysis by van IJzendoorn et al., 2012). Third, the computation of the genome-wide polygenic sensitivity score (Keers et al., 2016) as well as the analyses of Study 1 were based on white samples only (as is often the case with genetic studies). Hence, findings need to be replicated with other ethnicities. Finally, neither of the polygenic scores were created in order to reflect specific biological systems hypothesized to be implicated in environmental sensitivity. Future investigations should consider the creation and testing of more biologically informed polygenic scores for sensitivity. Similarly, the selection of variants included in candidate gene polygenic score for sensitivity tends to vary across studies (Belsky & Beaver, 2011; Keers & Pluess, 2017; Masarik et al., 2014), and results may differ as a function of included polymorphisms and coding thereof.

Implications

The results of our study have several implications. For example, given that not all people who participate in relationship programs would seem to benefit equally from such interventions, it may be helpful to distinguish those with low and high sensitivity, and to potentially offer alternative programs to those unlikely to respond to standard treatments. Before such guidance is followed, of course, results reported herein require replication, especially across different races and ethnicities. Additionally, there is the issue of what degree of genetic sensitivity, as operationalized in this report and based on monozygotic twins discordant for emotional problems (Keers et al., 2016), would distinguish those judged sensitive and those judged much less so. Then there is the fact that it is not known whether

those who proved low in genetic sensitivity in our research would also fail to benefit from different relationship (or other) interventions. Of note in this regard is that the Keers et al. (2016) GWAS-derived polygenic score for genetic sensitivity has now proven functional in two very different interventions, one with children suffering from high levels of anxiety and based on CBT and the current one with married couples. At the same time, new research on differential susceptibility addressing the issue of domain general vs. domain specific sensitivity is calling attention to the latter (Belsky, Zhang, & Sayler, 2021).

Importantly, although the current investigation relied on measures of genetic sensitivity, it may not be necessary to collect DNA samples from participants in order to assess such sensitivity. It may be more practical to use validated sensitivity questionnaires (Aron & Aron, 1997; Pluess et al., 2018; Pluess et al., 2020) which can be quickly and easily completed and captures heritable differences (Assary et al., 2020), even if they have not yet been administered in relationship programs. These sensitivity measures predict treatment response in previous studies of school-based resilience (Pluess & Boniwell, 2015) and anti-bullying programs (Nocentini et al., 2018), with more sensitive individuals benefitting most from these interventions. However, it remains to be determined whether similar moderating effects would emerge with questionnaire-based measures of sensitivity when applied to relationship education programs. Future research should aim to evaluate the moderating effect of the applied genome-wide polygenic score in further samples and in response to various psychological treatments, whilst also testing the association between the applied polygenetic sensitivity score and sensitivity questionnaires.

In conclusion, consistent with diverse theories of environmental sensitivity (Aron et al., 2012; Belsky & Pluess, 2009; Boyce & Ellis, 2005; Ellis et al., 2011; Pluess, 2015), we found across two independent studies that people differ in their response to the anticipated positive effects of an established relationship education program as a function of their genetic

make-up. Importantly, such genetic sensitivity was best captured with a broad, genome-wide polygenic score. However, findings need to be replicated in studies featuring larger samples before considering application of genetic sensitivity scores in practice.

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Conflict of Interests

None of the authors has any conflicts of interests to declare.

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Tables

Table 1

Sample Demographics (Study 1 and Study 2 Samples).

	Study 1 (*n* = 242)	**Study 2 (*n* = 183)**
Gender (% female)	52%	54%
Age	*M* = 28.8 (*SD* = 6.1)	*M* = 26.9 (*SD* = 5.4)
Race (% white)	100%	83%
College Degree (%)	30%	65%
Individual Income (median)	USD $20,000-$29,000	USD $20,000-$29,000
Relationship Length (years)	*M* = 7.4 (*SD* = 5.5)	*M* = 3.0 (*SD* = 2.2)
Marital Status (% married)	100%	89%

Table 2

Descriptive Statistics of Included Genetic Variants for the Candidate Gene Polygenic Sensitivity Score (Studies 1 & 2)

				Study 1				Study 2			
Gene	Variant	Coding	Example Study	N	MAF	HWE P	Genotypes	N	MAF	HWE P	Genotypes
SLC6A4	VNTR (5-HTTLPR)	SS = 1 (SL/LL = 0)	Hankin et al. (2011)	233	.19	.82	44/109/80	187	.17	.84	32/86/69
DRD4	VNTR (11p15.5)	7R allele = 1 (all others = 0)	Plak, Kegel, and Bus (2015)	230	.27	*NA*	62/168	175	.11	NA	20/155
DRD2	rs1800497	A1 (T) allele = 1 (CC = 0)	Brody, Chen, and Beach (2013)	248	.40	.89	14/84/150	189	.38	.99	9/63/117
DAT1	VNTR (5p15.3)	9R allele = 1 (10/10 = 0)	Lahey et al. (2011)	222	.35	.32	13/65/144	174	.48	.81	11/72/91
MAOA	VNTR (Xp11.23-11.4)	Low Activity =1 (high activity = 0)	Gorodetsky et al. (2014)	223	.22	*NA*	49/62/112	183	.36	NA	26/40/117
BDNF	rs6265	Met (A) allele = 1 (Val/Val = 0)	Gunnar et al. (2012)	247	.38	.15	5/89/153	190	.34	.99	7/57/126
COMT	rs4680	Val/Val = 1 (Met/Val & Met/Met = 0)	Hygen et al. (2015)	244	.18	.20	44/135/65	185	.31	.59	57/85/43
OXTR	rs53576	TT = 1 (TC & TT = 0)	Hammen, Bower, and Cole (2015)	243	.51	.92	20/104/119	190	.53	.91	17/84/89
FKBP5	rs1360780	A (T) allele = 1 (CC = 0)	Klengel et al. (2013)	243	.49	.08	31/89/123	185	.56	.57	16/87/82

Note. SLC6A4 = Serotonin Transporter gene polymorphism (5-HTTLPR), DRD4 = Dopamine Receptor D4, DRD2 = Dopamine Receptor D2, DAT1 = Dopamine Transporter gene (SLC6A3), MAOA = Monoamine Oxidase A, BDNF = Brain-Derived Neurotrophic Factor, COMT =

Catechol-O-Methyltransferase, OXTR = Oxytocin Receptor gene, and FKBP5 = FK506-Binding Protein 51, VNTR = Variable Number Tandem Repeat; NA = Not Applicable to these VNTRs; N = Number of participants with genotype data; MAF = Minor Allele Frequency; HWE P = Hardy-Weinberg Equilibrium p-value.

Table 3

Summary of Multilevel Models for PREP-X-PGS Interactions (Study 1)

	Candidate Genes PGS				Genome-Wide PGS			
	Post		Slope		Post		Slope	
	b	*p*	*b*	*p*	*b*	*p*	*b*	*p*
Marital Satisfaction	<0.001	>.999	-0.002	.624	-0.159	.156	**0.019**	**<.001**
Divorce Proneness	0.015	.485	-0.003	.043	0.019	.546	**-0.004**	**.027**
Communication Skills	0.001	.987	<0.001	.830	-0.073	.451	**0.010**	**.031**
Positive Bonding	0.051	.447	<0.001	.897	0.040	.691	**0.012**	**.018**

Notes. PGS = Polygenic Score; Genome-Wide PGS = Polygenic Score based on SNPs at p = 1.00; All models control for pre-treatment scores on the outcome of interest. Post = the interaction effect between polygenic scores and treatment group for pre-post changes (i.e., immediate treatment effect). Slope = the interaction effect between polygenic scores and treatment group for the trajectory from the first post-treatment assessment to follow-up four (two years later). Significant interactions that survived correction for multiple testing are marked bold.

Table 4

Summary of Multilevel Models for PREP-X-PGS Interactions (Study 2)

	Candidate Genes PGS				Genome-Wide PGS			
	Post		Slope		Post		Slope	
	b	*p*	*b*	*p*	*b*	*p*	*b*	*p*
Marital Adjustment	-0.734	.670	-0.116	.369	-4.563	.163	**0.692**	**.015**
Negative Communication (SR)	-0.053	.132	0.001	.569	0.096	.166	**-0.015**	**.009**
Negative Communication (OBS)	-0.003	.967	-0.003	.699	0.057	.719	-0.018	.318
Positive Communication (OBS)	-0.013	.900	-0.001	.907	-0.106	.614	0.014	.572

Notes. PGS = Polygenic Score; Genome-Wide PGS = Polygenic Score based on SNPs at p = 1.00; SR = Self-Report; OBS = Observed; All models control for pre-treatment scores on the outcome of interest. Post = the interaction effect between polygenic scores and treatment group for pre-post changes (i.e., immediate treatment effect). Slope = the interaction effect between polygenic scores and treatment group for the trajectory from the first post-treatment assessment to final (sixteen years later). Significant interactions that survived correction for multiple testing are marked bold.

Figure Legends

Figure 1.

Simple slopes and associated effect sizes for low and high genome-wide sensitivity (+/- 1 standard deviation from the mean), separately for control and treatment groups regarding outcome marital satisfaction. Post-treatment scores are adjusted for pre-treatment scores and slopes reflect the trajectory from the post-treatment assessment to follow-up assessment four (two years later).

Figure 2.

Simple slopes and associated effect sizes for low and high genome-wide sensitivity (+/- 1 standard deviation from the mean), separately for control and treatment groups regarding outcome marital adjustment. Post-treatment scores are adjusted for pre-treatment scores and slopes reflect the trajectory from the post-treatment assessment to follow-up assessment 16 years later.

Figures

Figure 1

Simple Slopes for Marital Satisfaction by Genetic Sensitivity in Study 1

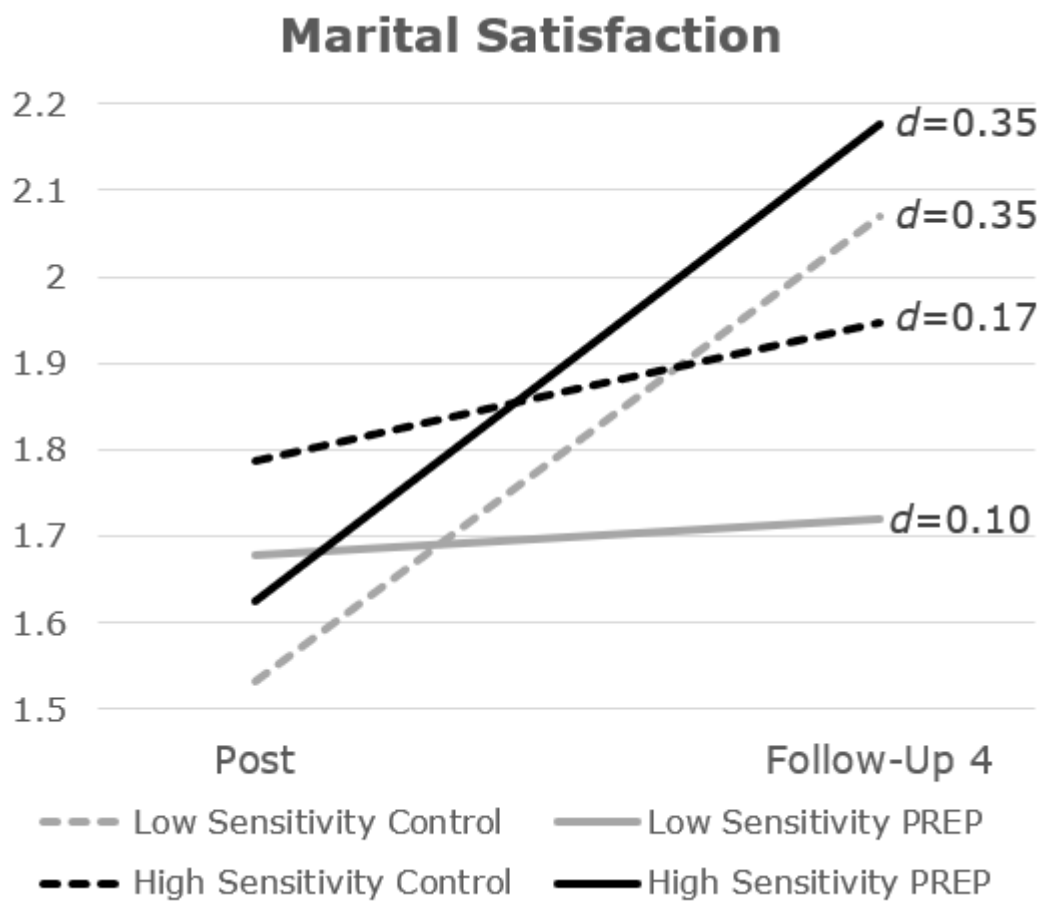

Figure 2

Simple Slopes for Marital Adjustment by Genetic Sensitivity in Study 2