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# *FKBP5* and *CRHR1* Polymorphisms Moderate the Stress–Physical Health Association in a National Sample

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***Objective:*** Stressful life events experienced during childhood and as an adult negatively impact mental and physical health over the life span. This study examined polymorphisms from 2 hypothalamic–pituitary–adrenal axis-related genes previously associated with posttraumatic stress disorder—*FKBP5* and *CRHR1*—as moderators of the impact of child abuse and adult stress on physical health. ***Method:*** A national, community-based subsample of non-Hispanic European American respondents ($n = 527$) from a prospective longitudinal 3-year study of stress and coping ($N = 2,729$) provided saliva for genotyping. ***Results:*** FKBP5 (rs1360780) and *CRHR1* (rs12944712) polymorphisms significantly interacted with child abuse and adult stress to predict increases in physical health ailments over 3 years. Child abuse and adult stress were strongly related to physician-diagnosed physical ailments among individuals with the risk alleles of both single nucleotide polymorphisms. Individuals carrying the low-risk homozygotic genotypes were protected from the long-term negative health implications of experiencing both child abuse and adult stress. ***Conclusion:*** Consistent with theories linking the hypothalamic–pituitary–adrenal axis with stress-related disease, hypothalamic–pituitary–adrenal axis polymorphism genotypes moderated the association between exposure to child abuse/adult stress and long-term physical health outcomes in a national sample.

*Keywords:* hypothalamic-pituitary-adrenal axis (HPA axis), polymorphisms, stress, health, gene-environment interaction

*Supplemental materials:* http://dx.doi.org/10.1037/a0033968.supp

Child abuse substantially increases the risk for impaired physical and psychological health in adulthood (Dong et al., 2004; Repetti, Taylor, & Seeman, 2002). Although several factors are likely to affect the relationship between early abuse and subsequent physical health ailments, one of the more potentially damaging factors involves the impact of abuse on a child's developing brain (Lupien, McEwen, Gunnar, & Heim, 2009). That is, child abuse may increase vulnerability to mental and physical health

problems by altering biological processes, such as increasing the risk of dysfunctional growth, development, or activation of the brain's stress response system—the hypothalamic–pituitary–adrenal axis (HPA; Tyrka et al., 2009). The negative impact of child abuse on physiological stress response systems may, in turn, be exacerbated by preexisting genetic vulnerabilities (Binder et al., 2008; Bomyea, Risbrough, & Lang, 2012). A growing body of research suggests that the effects of child abuse are unique, and that other stressful events experienced during childhood may have a less negative effect on biological development. Although childhood trauma other than abuse (e.g., parental divorce, death of a loved one) might be expected to negatively impact development, the most robust research to date points to child abuse, domestic violence, and related family/interpersonal stress as predictors of a wide range of later psychological and physical health problems (Dong et al., 2004; Dube, Felitti, Dong, Giles, & Anda, 2003; Repetti et al., 2002).

Adult stressful life events (SLEs) have also been implicated as predictors of later physical health ailments (Juster, McEwen, & Lupien, 2010; Lupien et al., 2006; Tosevski & Milovancevic, 2006). Indeed, uncontrollable stressors often elicit HPA axis responses associated with long-term hormonal dysregulation (Dallman et al., 2004). In the normal stress response, elevations of cortisol associated with acute stress serve to downregulate HPA function through a negative feedback mechanism. During chronic stress, cortisol becomes dysregulated, resulting in abnormal levels of cortisol and increased inflammation (Shonkoff, Boyce, & McEwen, 2009). As a result, the cumulative burden of SLEs may

threaten physical health over time through persistent physiological changes associated with a dysregulated stress response. Growing evidence supports this theory: Chronic stress-related activation of the HPA axis, with concomitant increase in cortisol, has been linked to a wide range of negative physical health outcomes, including visceral obesity, hypertension, hyperlipidemia, insulin resistance, periodontal disease activity, and increased risk for chronic conditions such as cardiovascular disease, diabetes, and atherosclerosis (Dong et al., 2004; Juster et al., 2010; Lupien et al., 2006; Shonkoff et al., 2009).

The impact of child abuse and adult stress on physical health is thought to be moderated by HPA dysfunction (Lupien et al., 2006; Shonkoff et al., 2009; Tosevski & Milovancevic, 2006; Watts-English, Fortson, Gibler, Hooper, & De Bellis, 2006). Genetic polymorphisms in genes regulating glucocorticoid receptor activity may influence HPA axis response/regulation and in so doing exacerbate the health risks posed by child abuse and adult trauma. One such gene implicated in the HPA stress response system is the *FKBP5* gene, which codes for FKBP506 binding protein, a protein that modulates glucocorticoid receptor activity and helps regulate HPA axis response (Ising et al., 2008; Koenen, 2007; McEwen, 2008). Individuals with the minor risk allele of an *FKBP5* single nucleotide polymorphism (SNP) had slower cortisol recovery after a psychosocial stressor (i.e., the Trier Social Stress Test; Ising et al., 2008). Several SNPs from the *FKBP5* gene (e.g., rs1360780, rs3800737, rs9296158, rs9470080) have been shown to moderate the association between child abuse or other childhood adversity and the risk of developing posttraumatic stress disorder (PTSD) symptoms during adulthood (Binder et al., 2008; Xie et al., 2010). *FKBP5* has also been associated with an increased risk of depression during adulthood among individuals who suffered from child abuse (Appel et al., 2011). Similarly, SNPs from the corticotrophin-releasing hormone receptor (*CRHR1*) gene, which helps mediate HPA axis response to stress, have been linked to the onset and course of PTSD in children (Amstadter et al., 2011), as well as increased risk of developing PTSD symptoms and depression during adulthood (Boscarino, Erlich, Hoffman, & Zhang, 2012; Bradley et al., 2008; Polanczyk et al., 2009; Ressler et al., 2010).

In sum, the minor alleles of SNPs from the *FKBP5* and *CRHR1* genes appear to increase the risk of negative mental health outcomes after child abuse or other adult-onset SLEs. Yet, despite clear evidence implicating stress-related HPA axis dysfunction in the development of chronic disease (Lupien et al., 2009; Shonkoff et al., 2009), little has been done to examine whether SNPs from these HPA axis-related genes buffer the impact of child abuse and adult SLEs on *physical* health outcomes. Given that child abuse and adult stress are associated with both heightened HPA axis dysregulation and multiple physical ailments (e.g., cardiovascular, endocrine, immune, musculoskeletal; Tsigos, Kyrou, & Chrousos, 2004), and that SNPs from the *FKBP5* and *CRHR1* genes help modulate HPA axis response (Ising et al., 2008; Tyrka et al., 2009), we would expect SNPs from these genes to render some individuals more vulnerable to the negative health impact of childhood and adult stress. Moreover, unlike models suggesting that psychological responses to stress mediate the path by which stress enhances vulnerability to physical health ailments (Schnurr, Green, & Kaltman, 2007), we suspect a direct genetic vulnerability to physical health ailments through SNPs linked to HPA axis function.

This study examined whether a SNP from each of two HPA axis-related genes (*FKBP5*, *CRHR1*) would moderate the associ-ation between child abuse/adult SLEs and the development of physical ailments over a 3-year period. The candidate gene approach was used for several reasons. First, although several *FKBP5* SNPs have been linked with mental health effects of stress, recent in-depth biological research has documented the molecular mechanisms linking rs1360780 to HPA axis-related sensitivity to early trauma, making it the ideal *FKBP5* SNP for this study (Fani et al., 2013; Klengel et al., 2013; Menke et al., 2013). Indeed, the detailed findings from this work have translational value through identification of new pathways to target for treatment.

Second, although less is known about SNPs from the *CRHR1* gene, the *CRHR1* SNP rs12944712 has been associated with the onset and course of PTSD in children (Amstadter et al., 2011). Moreover, this SNP appears to contribute to the modulation of the cortisol stress response in young children (Sheikh, Kryski, Smith, Hayden, & Singh, 2013), a finding that is theoretically consistent with the presence of a genetically based developmental vulnerability to environmental stress. Third, the currently available genome-wide association study chips do not characterize either of these SNPs, making it impossible to study them with the that approach. Finally, this study is drawn from a large national sample of respondents who participated in a 3-year prospective longitudinal study of coping following collective stress (the September 11, 2001, terrorist attacks). The original study includes baseline measures of physical health with annual follow-up assessments, measures of lifetime stress, and critical potential confounds (e.g., ongoing stress). The prospective longitudinal nature of this larger study made it a compelling, unique sample in which to test our theory-driven questions.

In sum, evidence is mounting to support the theory that HPA axis response and specific SNPs from genes regulating its function govern processes that contribute to the mental and physical health consequences of stress (Juster et al., 2010; Klengel et al., 2013; Shonkoff et al., 2009). In light of this evidence, we chose to use a candidate gene approach targeting SNPs known to impact HPA axis function to examine our hypotheses in a unique, prospective longitudinal study.

The hypotheses were as follows:

*Hypothesis 1:* Child abuse and adult exposure to SLEs will each predict increases in reports of physician-diagnosed physical ailments over a 3-year period, controlling for baseline physical ailments.

*Hypothesis 2:* The minor allele variants of the *FKBP5* SNP rs1360780 and the *CRHR1* SNP rs12944712 will each predict increases in reports of physician-diagnosed physical ailments over a 3-year period, controlling for baseline physical health ailments.

*Hypothesis 3: FKBP5* and *CRHR1* will moderate the effects of childhood abuse and adult SLEs on physical ailments. Specifically, child abuse and high levels of adult SLEs will not be associated with increases in physical ailments for respondents homozygotic for the low-risk allele of these SNPs. However, child abuse and high levels of adult SLEs will be associated with increases in physical ailments for respondents carrying minor alleles of rs1360780 and rs12944712.

## Method

### Participants and Procedure

Participants were drawn from a 3-year prospective longitudinal study conducted in collaboration with Knowledge Networks, Inc. (KN, now known as GfK), a survey research firm that recruited, maintained, and conducted surveys with a nationally representative panel using anonymous Web-based methodology. KN used multistage probability sampling with random-digit-dialing telephone methods to recruit and maintain their panel. KN provided free Internet service and a WebTV appliance for recruits who had no Web access to ensure representativeness of their panel. Surveys were administered on the Web. Panel members were notified of surveys via e-mail to a KN-provided, password-protected account. Participation in every survey was voluntary, and panel members could withdraw from participation at any time. The study design and sampling have been detailed elsewhere (Holman et al., 2008; Silver et al., 2006). The survey data used in this study include a baseline health assessment collected before 9/11/2001 and follow-up assessments conducted annually for three years thereafter.

Participants were recruited from the original national sample of 2,729. KN recontacted 1,296 available panelists from the original study in June 2008 to request their participation in this follow-up study. Consenting participants provided saliva samples using Oragene kits mailed to their homes. Kits were marked with respondents' identification numbers from the original study so genetic results and preexisting survey data could be merged. Of the total kits sent, 711 respondents (527 self-reported non-Hispanic European Americans) returned them (55% return rate). The University of California, Irvine Institutional Review Board reviewed and approved all procedures from the original and current studies.

The sample of 527 non-Hispanic European Americans was 50.9% female and 69.4% married; 9.5% had not completed high school, 37.1% had completed high school or the equivalent, 23.6% had completed some college, and 29.7% had a 4-year college degree. Ages ranged from 18 to 88 years ($M = 51.9$ years, $SD = 15.4$). Median annual household income was between $40,000 and $49,999. Individuals who participated in the genetic sample ($n = 527$) did not differ from non-Hispanic European American nonparticipants from the larger study ($n = 1,425$) with regard to pre- and post-9/11 mental health, gender, household income, education level, recent stress, or child trauma. However, genetic study participants were older than nonparticipants (mean age = 52 vs. 48 years; $p < .001$) and more likely to be married than widowed (odds ratio [OR] = 0.39, 95% CI [0.22, 0.69], $p = .001$). Adult trauma (OR = 1.03, 95% CI [0.99, 1.06], $p = .07$) and baseline physical ailments (OR = 1.03, 95% CI [0.99, 1.08], $p = .09$) approached but did not reach significance in these analyses.

### Measures

**Genotyping.** The Center for Applied Genomics (http://www.tcag.ca) in Toronto, Canada, performed DNA extraction and genotyping. DNA was extracted from Oragene saliva self-collection kits (DNA Genotek, Ottawa, Canada) using the AUTOPURE LS system and PUREGENE chemistry (Gentra Systems, Minneapolis, MN) following the manufacturer's protocol.

Genotyping was performed using Applied Biosystems' Taqman SNP genotyping technology (see Supplementary Table 1 for de-

tails). The 10 μl reaction mix consisted of 5 μl Taqman Genotyping Master Mix (Applied Biosystems, Life Technology, Carlsbad, CA), 0.15 μl of 40× combined primer and probe mix, 5.0 μl water and 50 ng of DNA template. Cycling conditions for the reaction were 95 °C for 10 min, followed by 40 cycles of 95 °C for 15 s and 62 °C for 1 min, and one final cycle of 10 °C. Samples were analyzed using the ABI 7900HT Sequence Detection System and genotype calls were made using SDS v2.3 software.

The *FKBP5* rs1360780 genotype distribution was 234 GG, 229 AG, 57 AA, with a call rate of 98.7% (520/527), and it was in Hardy–Weinberg equilibrium ($\chi^2 = 0.01$, $p > .10$). The *CRHR1* rs12944712 genotype distribution was 153 GG, 254 AG, 115 AA, with a call rate of 99.0% (522/527), and it was in Hardy–Weinberg equilibrium ($\chi^2 = 0.24$, $p > .10$). To ensure sufficient power for the analyses, we coded genotypes 0 for the common homozygote (GG) and 1 for heterozygotes and high-risk homozygotes (AG/AA). Neither the *FKBP5* nor the *CRHR1* genotype was associated with age, gender, income, marital status, or education ($ps > .15$).

**SLEs.** Lifetime exposure to stressful events was assessed by asking participants whether they had ever experienced each of 37 negative events (e.g., natural disaster, divorce), and if so, how old they were when it happened. The Diagnostic Interview Schedule Trauma section was modified to include a wider variety of stressful events (Holman, Silver, & Waitzkin, 2000; Robins, Helzer, Croughan, Ratcliff, & Seyfried, 1981). The measure has provided rates of specific events comparable to those in other community samples (Breslau et al., 1998; Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995). A count of the total number of stressful events occurring during adulthood (over the age of 17) was created. Two stressful events directly related to physical health (i.e., suffered a serious accident or injury, suffered a serious illness) were excluded from analyses to avoid confounding stress and health outcomes.

**Child abuse.** As part of the stressful event assessment, participants were asked to report whether they had experienced physical, sexual, or emotional abuse during their childhood (up to 17 years old). A count reflecting all reported incidents of physical, sexual, or emotional abuse during childhood was created.

**Recent stress.** Recent stressful events were assessed annually at three time points postbaseline using the measure of life events described above modified to elicit events that had occurred over the previous year. Stressful events directly related to physical health were excluded from analyses to avoid confounding stress and health outcomes (i.e., suffered a serious accident or injury, suffered a serious illness). For the analyses, a longitudinal variable was created reflecting reports of ongoing/recent stress over 3 years postbaseline.

**Baseline and follow-up health.** Once recruited onto the KN panel (between June 2000 and September 2001 for this sample), panelists completed a health survey modeled after the Centers for Disease Control's National Center for Health Statistics annual National Health Interview Survey (U.S. Department of Health and Human Services, 2000). Respondents indicated whether a medical doctor had ever diagnosed them as suffering from any of 35 physical and mental health ailments. When compared with estimates from the 2000 National Health Interview Survey, data from 25,000 KN health surveys indicated that for several major health problems (e.g., diabetes, cancer, stroke) and health behaviors (e.g., smoking) the average difference was less than 1.5%, supporting the validity of these data (Baker, Bundorf, Singer, & Wagner, 2003). A simple count of 33 physical health items provided a baseline of pre-9/11 physical ail-

ments. Comparable annual surveys were readministered over the next 3 years to all available respondents. Data were missing information about physician-diagnosed ailments for approximately 8–9%, 6–7%, <1%, <1% of respondents across the four time points (at baseline and at 1-year, 2-year, and 3-year follow-ups), respectively. Missing data were imputed within age groups using the expectation maximization method for pre- and 1-year post-9/11 health data as missing-completely-at-random tests for these data were nonsignificant (Little & Rubin, 1987). A total count of physician-diagnosed physical ailments was created for each time point: baseline, and 1-, 2-, and 3-year follow-ups.

## Data Analytic Plan

The main study variables were initially examined in PASW Statistics 18.0.3 (formerly SPSS). As the outcomes were count variables, we used longitudinal generalized estimating equations with Poisson distributions for hypothesis testing in STATA Version 11.2. Given that the longitudinal data had a two-level hierarchical structure with yearly survey responses (Level 1) nested within persons (Level 2), we accounted for the within-person correlations between yearly physical ailment assessments by using an autoregressive covariance matrix. Because Poisson techniques may violate assumptions about dispersion of residuals (e.g., overdispersion), which leads to inflated goodness-of-fit tests and erroneously reduced standard errors, we examined the three outcome assessments of physical ailments (1, 2, and 3 years after baseline) to confirm that they followed a Poisson distribution. The deviance goodness-of-fit tests for the overdispersion of physical ailments were all nonsignificant. Interaction terms were computed from dummy-coded genotype variables and centered counts of child abuse or adult SLEs. For graphing purposes, zero and two counts of child abuse were used as "low" and "high" levels, respectively. For adult SLEs, 1 standard deviation below and above the mean value was used as the "low" and "high" levels, respectively. All analyses were adjusted for significant demographics, a longitudinal variable reflecting ongoing stress over 3 years post-baseline and baseline physical health ailments. We examined whether age as a quadratic term would more accurately reflect the development of physical ailments in our sample. However, this term was nonsignificant in all analyses, so it was not included in the final models.

## Results

### Preliminary Analyses

The means, standard deviations, and intercorrelations among study variables of interest are shown in Table 1. Adult stress was more strongly associated with the count of physician-diagnosed physical ailments than was child abuse at all four time points. The *CRHR1* rs12944712 risk alleles were associated with higher rates of physical ailments 1 year after baseline.

### Child Abuse, Adult Stress, and Genetic Vulnerability to Physical Ailments

Longitudinal generalized estimating equation models controlling for age, gender, marital status, recent SLEs, and baseline physician-diagnosed physical ailments revealed that child abuse and adult SLEs were both highly significant predictors of physician-diagnosed physical ailments over time (see Model 1, Table 2). The *FKBP5* and *CRHR1* SNP risk alleles were also significant predictors of physical ailments. To test whether genotype buffered the association between child abuse/adult SLEs and physical health, we created interaction terms for child abuse and adult SLEs with each of the SNPs. These interaction terms were added individually in separate generalized estimating equation models. All four of the two-way interactions were significant (see Models 2–5, Table 2). Lastly, to test whether the interaction between genotype and adult stress was influenced by the earlier exposure to child abuse, we examined three-way SNP × Child Abuse × Adult SLE interactions (see Models 6 and 7, Table 2). All possible two-way interactions (SNP × Child Abuse, SNP × Adult SLEs, and Child Abuse × Adult SLEs) were included (Aiken & West, 1991). Both of these three-way interactions were significant (see Models 6 and 7, Table 2).

*FKBP5*–stress interactions. The relationship between child abuse and physical ailments was significantly moderated by *FKBP5* rs1360780. For individuals who had not experienced child abuse, the *FKBP5* rs1360780 genotype was not associated with physical ailments. However, experiencing child abuse was associated with substantial increases in physical ailments for individuals with the *FKBP5*

Table 1
*Means, Standard Deviations, and Intercorrelations Among Study Variables*

| Variable | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | M (SD) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1. Child abuse | — | | | | | | | | | | | 0.73 (1.44) |
| 2. Adult stress | .31*** | — | | | | | | | | | | 5.30 (4.24) |
| Recent stress | | | | | | | | | | | | |
|   3. Year 1 | .14** | .29*** | — | | | | | | | | | 0.78 (1.35) |
|   4. Year 2 | .16** | .29*** | .28*** | — | | | | | | | | 0.66 (1.11) |
|   5. Year 3 | .21*** | .30*** | .24*** | .44*** | — | | | | | | | 0.93 (1.19) |
| 6. FKBP5 | −.01 | −.04 | −.01 | .06 | .01 | — | | | | | | 0.55 (0.50) |
| 7. CRHR1 | −.02 | .11* | .11* | .06 | .07 | −.01 | — | | | | | 0.71 (0.45) |
| Physician-diagnosed physical ailments | | | | | | | | | | | | |
|   9. Baseline | .04 | .26*** | .18*** | .15** | .13** | −.05 | .06 | — | | | | 3.65 (2.08) |
|   10. Year 1 | .12** | .33*** | .20*** | .18*** | .22*** | −.04 | .10* | .74*** | — | | | 3.64 (2.14) |
|   11. Year 2 | .10* | .25*** | .23*** | .23*** | .20*** | −.03 | .08 | .61*** | .72*** | — | | 3.69 (2.28) |
|   12. Year 3 | .20*** | .37*** | .22*** | .26*** | .36*** | .01 | .03 | .74*** | .79*** | .75*** | — | 4.74 (2.58) |

* $p < .05$. ** $p < .01$. *** $p < .001$.

Table 2

*Longitudinal Generalized Estimating Equation Models of Child Abuse, Adult Stressful Events,* FKBP5, *and* CRHR1 *on Physician-Diagnosed Physical Ailments*

| Variable | Model 1 | | Model 2 | | Model 3 | | Model 4 | | Model 5 | | Model 6 | | Model 7 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | IRR | $p$ | IRR | $p$ | IRR | $p$ | IRR | $p$ | IRR | $p$ | IRR | $p$ | IRR | $p$ |
| Intercept | 3.00 | .000 | 3.02 | .000 | 3.06 | .000 | 3.01 | .000 | 3.00 | .000 | 3.02 | .000 | 2.95 | .000 |
| Wave | 1.12 | .000 | 1.12 | .000 | 1.12 | .000 | 1.12 | .000 | 1.12 | .000 | 1.12 | .000 | 1.12 | .000 |
| Age | 1.01 | .000 | 1.01 | .000 | 1.01 | .000 | 1.01 | .000 | 1.01 | .000 | 1.01 | .000 | 1.01 | .000 |
| Gender | 1.06 | .087 | 1.07 | .102 | 1.08 | .055 | 1.08 | .073 | 1.08 | .080 | 1.07 | .102 | 1.07 | .099 |
| Marital status[a] | | | | | | | | | | | | | | |
| Single | 1.03 | .478 | 1.05 | .650 | 1.05 | .450 | 1.05 | .400 | 1.05 | .400 | 1.05 | .650 | 1.05 | .478 |
| Divorced | 0.86 | .028 | 0.88 | .014 | 0.88 | .018 | 0.89 | .027 | 0.90 | .048 | 0.88 | .014 | 0.89 | .039 |
| Widowed | 0.81 | .018 | 0.79 | .017 | 0.79 | .015 | 0.79 | .015 | 0.80 | .018 | 0.79 | .017 | 0.80 | .018 |
| Baseline physical ailments | 1.13 | .000 | 1.13 | .000 | 1.13 | .000 | 1.13 | .000 | 1.13 | .000 | 1.13 | .000 | 1.13 | .000 |
| Recent SLEs | 1.02 | .014 | 1.02 | .003 | 1.02 | .006 | 1.02 | .006 | 1.02 | .006 | 1.02 | .003 | 1.02 | .004 |
| Child abuse | 1.04 | .000 | 1.07 | .000 | 1.06 | .000 | 1.06 | .000 | 1.06 | .000 | 1.07 | .000 | 1.07 | .000 |
| Adult SLEs | 1.01 | .042 | 1.01 | .178 | 1.01 | .107 | 1.00 | .381 | 1.00 | .574 | 1.01 | .221 | 1.01 | .221 |
| FKBP5 | 1.12 | .012 | 1.08 | .012 | 1.04 | .108 | 1.07 | .035 | 1.07 | .018 | 1.06 | .027 | 1.06 | .027 |
| CRHR1 | 1.09 | .048 | 1.04 | .111 | 1.04 | .079 | 1.04 | .101 | 1.04 | .169 | 1.03 | .214 | 1.03 | .214 |
| FKBP5 × Child Abuse | | | 1.08 | .000 | | | | | | | 1.02 | .297 | | |
| FKBP5 × Adult SLEs | | | | | 1.02 | .006 | | | | | 1.03 | .080 | | |
| CRHR1 × Child Abuse | | | | | | | 1.04 | .009 | | | | | 1.01 | .481 |
| CRHR1 × Adult SLEs | | | | | | | | | 1.02 | .019 | | | 1.00 | .622 |
| Child Abuse × Adult SLEs | | | | | | | | | | | 1.00 | .117 | 1.00 | .096 |
| FKBP5 × Child Abuse × Adult SLEs | | | | | | | | | | | 1.01 | .001 | | |
| CRHR1 × Child Abuse × Adult SLEs | | | | | | | | | | | | | 1.01 | .001 |
| Model fit statistic: Wald $\chi^2$ | 1225.27 | .000 | 1232.66 | .000 | 1230.97 | .000 | 1231.90 | .000 | 1230.55 | .000 | 1247.65 | .000 | 1245.44 | .000 |

*Note.* IRR = incidence risk ratio; SLEs = stressful life events.
[a] Reference group = married.

rs1360780 minor allele when compared to respondents homozygotic for the major allele, $t(397) = 3.32$, $p < .001$ (see Figure 1).

The relationship between adult stress and physical health was also significantly moderated by *FKBP5* rs1368780. For individuals who had low levels of adult stress, the *FKBP5* rs1360780 genotype predicted similar levels of physical ailments. However, experiencing high levels of stress during adulthood was associated with significant increases in physical ailments for individuals carrying the minor allele but not for respondents carrying two major alleles, $t(397) = 3.57$, $p < .001$ (see Figure 2).

These findings are qualified, however, by a significant three-way interaction between *FKBP5* rs1360780, child abuse, and adult
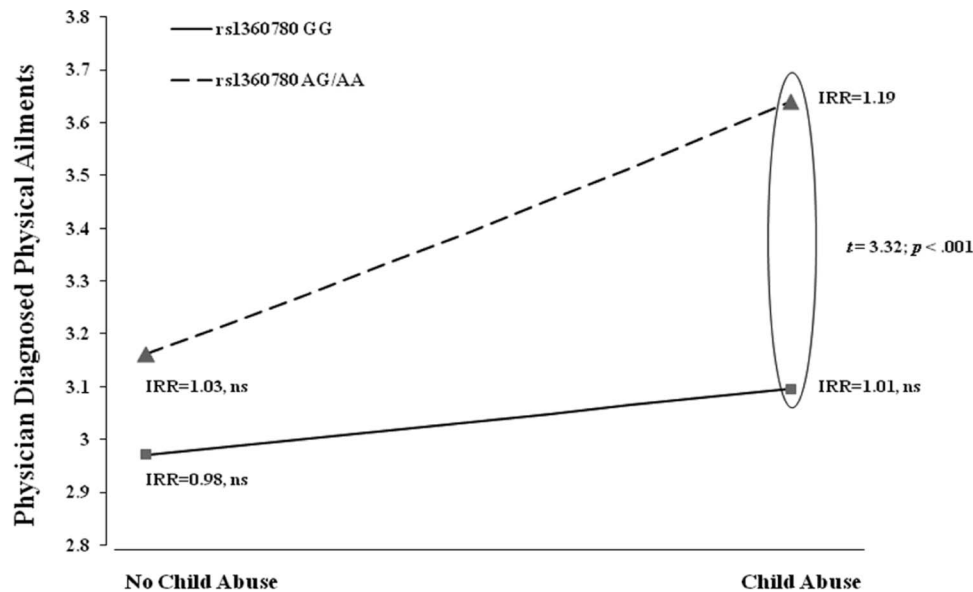


*Figure 1.* The moderating effect of *FKBP5* on the association between child abuse and reports of physician-diagnosed physical ailments over time. IRR = incidence risk ratio.
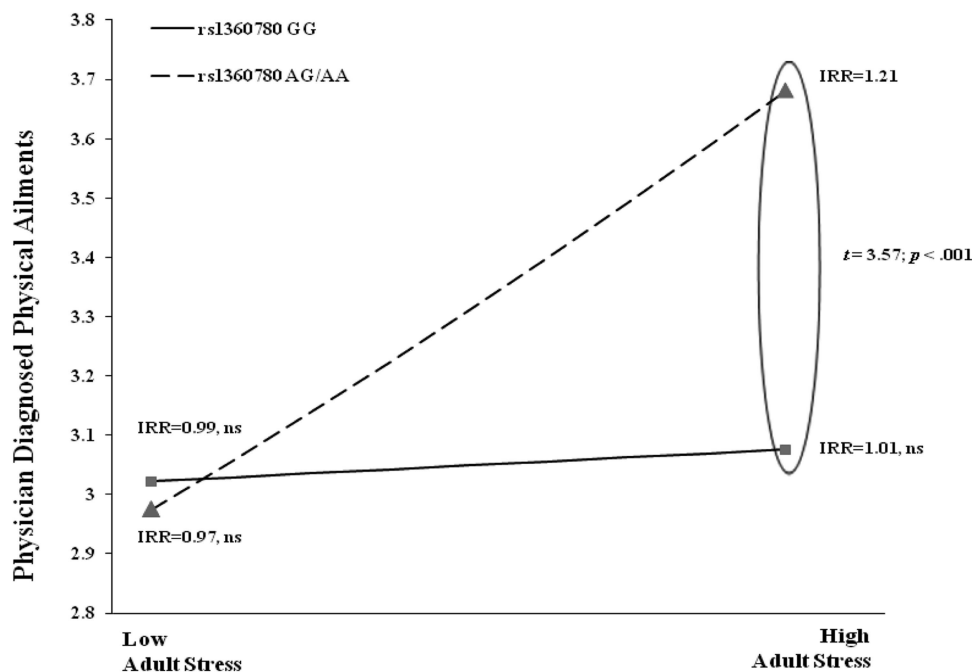
*Figure 2.* The moderating effect of *FKBP5* on the association between adult stress and reports of physician-diagnosed physical ailments over time. IRR = incidence risk ratio.

SLEs. For individuals who had not experienced child abuse, exposure to adult SLEs was associated with increases in physical ailments, regardless of genotype. However, for individuals abused as children, only those with a minor allele of *FKBP5* rs1360780 were at risk for increases in physical ailments from exposure to high levels of adult stress (see Figure 3).

**CRHR1–stress interactions.** The relationship between child abuse and physical health ailments was also significantly moderated by *CRHR1* rs12944712. For individuals who had not experienced child abuse, the *CRHR1* rs12944712 genotype predicted similar levels of physical ailments. However, experiencing child abuse was associated with substantial increases in physical ailments for individuals carrying a minor allele, but was not associated with increased risk of physical ailments for individuals with two major alleles, $t(396) = 3.24$, $p < .001$ (see Figure 4).

The relationship between adult SLEs and physical health was also significantly moderated by *CRHR1* rs12944712. For individuals who had low levels of adult stress, the *CRHR1* rs12944712 genotype predicted similar levels of physical ailments. However, experiencing high levels of stress during adulthood was associated with significant increases in physical ailments for individuals carrying a minor allele but not for individuals with two common alleles, $t(396) = 2.92$, $p < .001$ (see Figure 5).

Once again, these findings were qualified by a significant three-way interaction between the *CRHR1* rs12944712 genotype, child abuse, and adult SLEs. For individuals who had not experienced child abuse, exposure to adult SLEs was associated with increases in physical ailments regardless of genotype. However, for those with prior exposure to child abuse, only those with a minor allele of *CRHR1* rs12944712 were at risk for increases in physical ailments from exposure to high levels of adult stress (see Figure 6).

## Discussion

This study documents specific HPA axis-related genetic vulnerability to the risk of developing physical ailments after experiencing child abuse or adult stress. Consistent with the hypotheses, the negative health impacts of child abuse and adult stress were buffered by polymorphisms of *FKBP5* and *CRHR1* genes. The minor alleles of both HPA axis-related SNPs exacerbated the impact of child abuse and adult stress on physical health outcomes. This study also provides preliminary evidence that the early trauma of child abuse exacerbates the influence of *FKBP5* and *CRHR1* risk alleles on the health impact of later stressful events. That is, for individuals who did not experience child abuse, neither SNP genotype exacerbated the adult stress–physical health association. However, for individuals who were abused as children, the high-risk allele of both SNPs exacerbated the adult stress–physical health association, leading to significantly higher rates of physician-diagnosed physical ailments. In other words, child abuse appeared to sensitize risk allele carriers of both SNPs to the negative health impacts of later adult stress. However, low-risk homozygotic major allele carriers were protected from the additional health impact of experiencing both child abuse and adult stress.

These findings are consistent with those of the Adverse Childhood Experiences Study indicating that early abuse is associated with the development of later physical health problems such as heart disease (Dong et al., 2004). That work is extended, however, by providing evidence that genetic polymorphisms affecting HPA axis activity are involved in moderating the link between child abuse and the development of physical ailments decades later. HPA axis dysregulation brought on by childhood adversity and exacerbated by preexisting genetic vulnerabilities may increase allostatic load, overwhelming the body's ability to repair damage
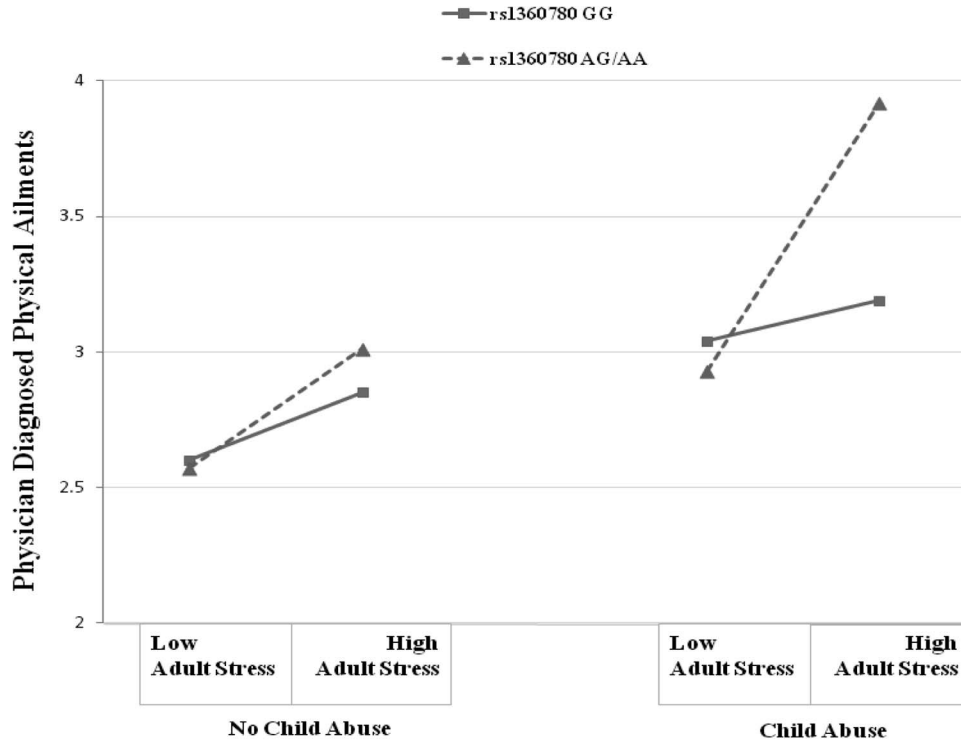
*Figure 3.* *FKBP5* single nucleotide polymorphism genotype and adult stress moderate the association between child abuse and increases in reports of physician-diagnosed physical ailments over time. IRR = incidence risk ratio.

and properly regulate various physiological systems (Shonkoff et al., 2009). Our current findings suggest that a genetically vulnerable child who is abused may be at even greater risk for the development of later health problems if exposed to stressors during

adulthood. Alternatively, childhood trauma may also affect DNA methylation, and in so doing, the function of genes later in life (Beach, Brody, Todorov, Gunter, & Philibert, 2011), especially those genes related to developmental processes (Suzuki & Bird,
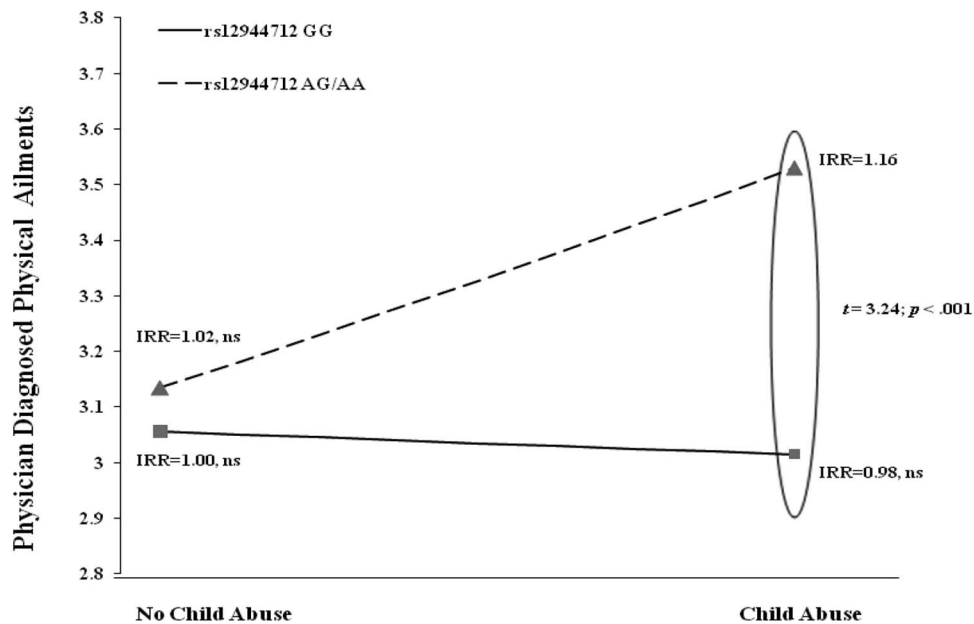


*Figure 4.* The moderating effect of *CRHR1* on the association between child abuse and reports of physician-diagnosed physical ailments over time.
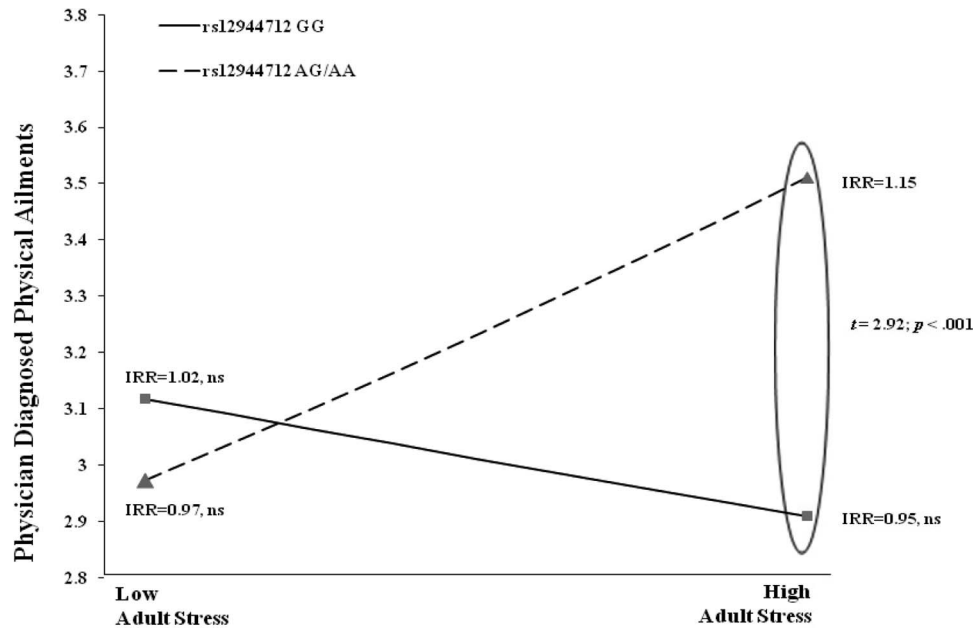
*Figure 5.* The moderating effect of *CRHR1* on the association between adult stress and reports of physician-diagnosed physical ailments over time. IRR = incidence risk ratio.

2008; van IJzendoorn, Bakermans-Kranenburg, & Ebstein, 2011). Recent research supports this interpretation as patterns of DNA demethylation for the *FKBP5* rs1360780 SNP have been linked to early childhood adversity and *FKBP5* gene function (Klengel et al., 2013). Our findings suggest that these changes may ultimately have implications for physical health.

The findings are largely consistent with prior research showing that the minor alleles of these *FKBP5* and *CRHR1* SNPs place individuals at higher risk for negative mental health outcomes and risky behaviors such as binge drinking after facing childhood or adult adversity (Binder et al., 2008; Schmid et al., 2010). However, they further suggest that genetic vulnerability to HPA axis dysregulation may be one of the mechanisms by which child abuse and adult stress increase one's risk of negative physical health outcomes as well. In so doing, these findings support the growing literature linking HPA axis response with trauma-related physical ailments as well as comorbid mental health problems.

Two potential pathways may account for these findings. First, in the presence of significant trauma or stress, the minor alleles of rs1360780 may increase the risk of pathological glucocorticoid dysfunction (Klengel et al., 2013). Indeed, a growing body of research implicates glucocorticoid dysfunction in the development of a variety of physical health ailments, including cardiovascular disease (Rosmond & Björntorp, 2001), metabolic syndrome and endocrine diseases (Chrousos, 2000), obesity (Spencer & Tilbrook, 2011), and other maladies (Charmandari, Kino, & Chrousos, 2004).

Second, studies have also implicated *CRHR1* SNPs in heavy alcohol use during adolescence (Blomeyer et al., 2008) and binge drinking (Treutlein et al., 2006), and *CRHR1* gene upregulation has been linked to the risk of relapse after cessation of drinking (Sommer et al., 2008). *CRHR1* SNPs also interact with stressful life events to predict heavy drinking among 19-year-olds (Schmid et al., 2010). Moreover, preliminary evidence suggests that epigenetic changes in genes reg-

ulating corticotrophin-releasing factor (e.g., *CRHR1*) are associated with behavioral responses to stress (Elliott, Ezra-Nevo, Regev, Neufeld-Cohen, & Chen, 2010). To the extent that rs12944712 also plays a role in regulating *CRHR1* function, perhaps it too could affect behavioral responses to stress that increase one's risk for physical ailments. In this situation, alcohol use, or some other maladaptive coping behavior, might mediate the relationship between *CRHR1*-related genetic vulnerabilities and stress-related physical health problems across the life span.

Studies using animal models have identified genetic vulnerabilities that increase the impact of psychosocial stressors on stress response and functioning, leading to a variety of physical health problems (Renz et al., 2011). Our findings extend this work by providing preliminary evidence that polymorphisms related to the development and function of the stress response system are also associated with physical health outcomes in human populations. Given the potential for using genetic analyses to identify people at risk for developing stress-related health problems, future research should examine the precise physiologic pathways by which these gene–environment interactions impact physical health. That is, understanding how the minor alleles of these SNPs potentiate the impact of child abuse and adult SLEs on disease processes (e.g., inflammation; Renz et al., 2011) could open avenues for possible pharmacologic or behavioral interventions to prevent or ameliorate stress-related disease. An important component of this work would be to look for developmental windows of opportunity during which early poststress interventions may be used to interrupt damaging physiologic processes before they become chronic and cause irreparable harm. In sum, designing pharmaceutical and/or behavioral interventions to short-circuit the development of dysregulated HPA functioning, thus reducing the long-term consequences of abuse and SLEs, would be an important goal for future research.
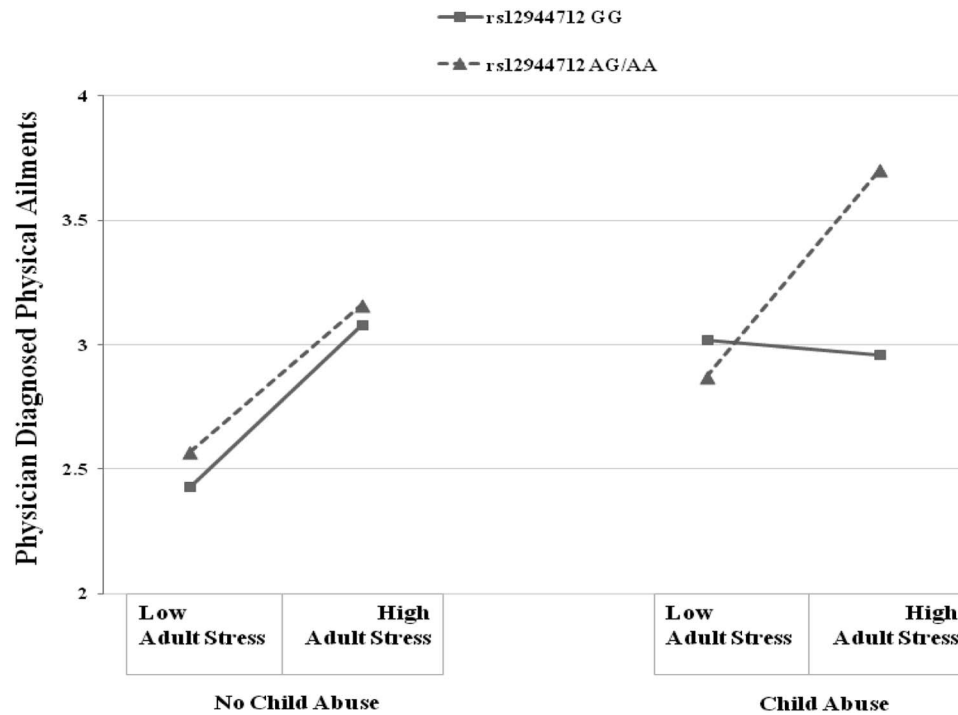
*Figure 6.* *CRHR1* single nucleotide polymorphism genotype and adult stress moderate the association between child abuse and increases in reports of physician-diagnosed physical ailments over time. IRR = incidence risk ratio.

Finally, although the current findings suggest that the minor alleles of *FKBP5* and *CRHR1* present a risk factor for more negative outcomes when individuals experience both child abuse and adult SLEs, research on other genes has suggested that gene–environment interactions may not be this simple. Some authors have argued that many alleles that increase risk for negative outcomes in poor environmental circumstances are also associated with better functioning in more positive environments (Belsky & Pluess, 2009; Taylor et al., 2006). Indeed, differential susceptibility theory may explain why some apparently high-risk alleles have been evolutionarily conserved (Belsky & Pluess, 2009). Perhaps, given a rich social environment during adulthood, the minor alleles of *FKBP5* and *CRHR1* may have beneficial effects, even for children who experience child abuse. A longer term prospective longitudinal study, beginning in early childhood, would be required to examine this possibility. It would be important to include assessments of broader context (e.g., family social environment, neighborhood characteristics, cultural and socioeconomic factors) that shape how individuals perceive and respond to the threat of specific types of stress.

## Contributions and Limitations

This study has several strengths. The respondents were part of a prospective 3-year longitudinal study that included assessments of physical health and ongoing stress in a national sample. Drawing the sample from this larger study allowed examination of the relationship between polymorphisms and stress as it occurs in its natural context. Moreover, the study addressed not only the direct role of *FKBP5* and *CRHR1* SNPs on physical health but, more important, their interaction with child abuse and adult SLEs, both

of which may lead to impaired physical health and functioning. The findings extend previous research on the link between these genetic vulnerabilities and mental health by providing strong evidence that *FKBP5* and *CRHR1* SNPs interact with child abuse and adult stress to produce negative physical health outcomes as well.

Nonetheless, the subsample for this study was older and reported marginally more physical health problems than did the original sample's respondents even though the original sample closely paralleled the U.S. population census. These differences limit the findings' generalizability. Moreover, self-report measures of physician diagnoses suffer from recall biases and are open to interpretation by respondents. Without medical record corroboration, we cannot assume that all individuals reporting physician-diagnosed physical ailments have true disease. And, although selection of candidate genes was theoretically based, the set of polymorphisms used in these analyses is not inclusive of all those known to influence stress responses. Given the profound impact of stressful environments on complex biological processes, future research should examine other genes/polymorphisms and combinations of SNPs that may influence the stress response system and that might impact physical as well as mental health (Juster et al., 2010). Similarly, it is important to understand whether and how different types of stress interact with SNPs from other stress-related physiologic systems (e.g., endocannabinoid) to produce disease-specific changes. Given recent advances linking *FKBP5* and *CRHR1* demethylation to glucocorticoid dysregulation (Elliott et al., 2010; Klengel et al., 2013), future research also needs to examine the role of methylation in the physiologic processes underlying the link between child abuse/adult SLEs and physical

health problems. Finally, these findings also need to be confirmed in future replication studies.

## Conclusion

This study provides strong evidence that long-term health outcomes of exposure to child abuse and later adult stress are substantially influenced by underlying genetic vulnerabilities. In the relative absence of stress during childhood and adulthood, the minor alleles of *FKBP5* and *CRHR1* do not appear to put individuals at higher risk for developing health problems when compared with homozygotic major allele carriers. However, when exposed to stressful experiences during either childhood or adulthood, individuals with minor alleles of *FKBP5* rs1360780 or *CRHR1* rs12944712 are at substantially increased risk not just for mental disorders, but for physical health ailments as well. We also provide important evidence suggesting a developmental sensitivity among individuals with minor alleles of rs1360780 and rs12944712: Individuals who are also exposed to child abuse and adult stress are at particular risk for developing more physical ailments later in life than individuals who do not carry a risk allele. Although future research is needed to identify the precise biological and behavioral pathways that mediate this association, this study suggests that understanding genetic vulnerabilities may provide insight into the pathways linking environmental psychosocial stress to the development of physical health ailments.

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