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Faculty of Social Sciences

SIW5901 Master's Thesis

Perceived Neighborhood Collective Efficacy and Adolescent Mental Health Problems

A Behavioral Genetic Study of Gene-Environment Interactions

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Summary

Background: Perceived neighborhood collective efficacy is known to buffer the impact of diverse social-environmental risk factors on adolescent mental health problems. However, it is unknown whether collective efficacy also moderates individual genetic propensity for these disorders.

Objectives: To examine whether perceived neighborhood collective efficacy moderates the genetic influences on adolescent internalizing and externalizing problems and smoking initiation and assess whether these G×E interactions differ across sex.

Design: Quantitative behavioral genetic study design examining twin pairs stratified by zygosity and sex. Structural equation modeling was used to estimate latent genetic and environmental sources of variance in the three traits and the sex-specific moderation of these variance parameters by perceived neighborhood collective efficacy.

Setting: In-home structured interviews of adolescents recruited from a stratified random sample of high schools and middle schools in the U.S.

Participants: A nationally representative sample of 762 twin pairs (282 monozygotic and 480 dizygotic), aged 12–19 years (mean 16.0, S.D. 1.60).

Main outcome measures: Symptom-based scales of internalizing (depressive and anxiety) and externalizing (rule-breaking and aggressive) problems, and a binary measure of having ever smoked a cigarette.

Results: Perceived neighborhood collective efficacy moderated the genetic influences on internalizing only, and these G×E interactions followed distinct patterns in females and males. There was no evidence for G×E interactions in externalizing and smoking initiation.

Conclusion: High levels of perceived neighborhood collective efficacy attenuated the genetic influences on internalizing symptoms in females, following the diathesis-stress model. In males, the genetic influences were negligible at intermediate levels of perceived neighborhood collective efficacy but increased at both high and low levels of the latter, suggesting a differential-susceptibility process. These G×E findings help integrate bioecological

perspectives in the collective efficacy theory, which may aid in developing more robustly informed community interventions for youth mental health.

Keywords: Adolescent mental health problems; Neighborhood collective efficacy; Gene-environment interactions; Sex limitation; Bioecological model.

PART – A

Introductory Chapter

I. Background

Adolescence, the development stage between ages 10-19 years (World Health Organization, 2020a), is the period during which most mental health problems first emerge (Paus et al., 2008) and set the stage for psychiatric disorders later in life (Copeland et al., 2009). Epidemiologic studies suggest that, in any given year, one out of every four to five youth in the general population suffers from at least one mental disorder (Patel et al., 2007). Mental health problems are estimated to account for 16% of the global disease burden, or disability-adjusted life years (Murray, 1994), among adolescents (World Health Organization, 2020a). Besides causing individual distress, financial impairment, and an increased risk of premature mortality, youth mental disorders also exact profound societal costs, both economic and social, extending well into adulthood (Patton et al., 2016). Even though early, effective interventions for promoting and protecting adolescent mental health were heralded as both a "global public health challenge" (Patel et al., 2007) and a "best buy" (McGorry et al., 2007) over a decade ago, there is still a pressing need for more comprehensive theories of youth mental health, which may better inform these interventions (Azzopardi et al., 2019).

Most common adolescent psychiatric problems can be broadly grouped under "Internalizing" (mainly comprising mood and anxiety problems) and "Externalizing" (including antisocial and aggressive behaviors) disorders (Achenbach, 1966, 2017). Internalizing disorders are relatively more prevalent in females, while externalizing disorders are more common in males (Rutter et al., 2003). Adolescent males and females also show differences in the antecedents, correlates, comorbidities, and trajectories of these problems, which are attributable, at least partly, to biological, psychological, and social variations across sex (Zahn-Waxler et al., 2008). These differences suggest that adolescent mental health problems should be studied separately in males and females (King et al., 2004).

In addition, adolescent mental health problems also include substance use behaviors. Although clinical substance use disorders are uncommon in youth, substance use initiation during adolescence is, in and of itself, a crucial, preventable risk factor for problematic substance use during adulthood (Dodge et al., 2009). Smoking initiation is a pivotal event during adolescence, as tobacco remains the leading preventable cause of morbidity and mortality worldwide, killing over eight million people annually (World Health Organization, 2020b). Approximately 80% of adult smokers initiate cigarette smoking before age 18 (U.S. Department of Health and Human Services, 2012), and younger age at smoking initiation is

associated with an increased risk of daily smoking and nicotine dependence later in life (Dierker et al., 2012).

Adolescent mental health outcomes, including internalizing, externalizing, and smoking initiation, are complex, multifactorial traits. Therefore, a thorough understanding of the underlying risk and resiliency factors, whether social, psychological, or biological, is crucial for designing evidence-informed preventive interventions. These problems are attributed to a variety of social-environmental influences, ranging from more proximal, such as adverse childhood experiences, socioeconomic status, family, and peers, to more distal, such as neighborhood, state policies, and culture (Bronfenbrenner, 1986; Burt, 2014; Patel et al., 2007). Scientific evidence on the latter group of factors is particularly relevant for informing community-level interventions and policies to foster youth mental health.

Established neighborhood-level risk factors include structural characteristics, such as neighborhood poverty, housing, and inequality (Burt, 2014). For example, youth growing up in socioeconomically disadvantaged neighborhoods are more likely to develop internalizing and externalizing disorders (Sundquist et al., 2015) and substance use problems (Mennis & Mason, 2012). These structural neighborhood characteristics likely influence youth mental health through more proximal processes, including institutional resources, relationships, and norms/collective efficacy (Leventhal & Brooks-Gunn, 2000). Of these intermediary processes, the one supported by the most substantial evidence is “perceived neighborhood collective efficacy” (e.g., Maimon & Browning, 2010; Sampson et al., 1997; Xue et al., 2005). Perceived neighborhood collective efficacy indicates the degree of social cohesion among neighborhood residents, combined with their ability to exercise informal social control and monitor youth behavior collectively (Sampson et al., 2002). However, despite the wealth of research on these direct and indirect neighborhood influences, these factors have small effect sizes (0.10–0.20) and explain only a small portion of heterogeneity in individual mental health outcomes (Leventhal & Brooks-Gunn, 2000).

Contemporary bioecological theories (e.g., Bronfenbrenner & Ceci, 1994) emphasize a complex interplay between the contextual environment (“nurture”) and individual biology (“nature”), which underpins why some adolescents experience considerable mental health problems, while others do not (Guyer, 2020). Behavioral genetic research conceptualizes these nature-nurture transactions as Gene-Environment interactions (G×E), wherein, besides their additive effects on mental health outcomes, environmental factors also moderate the

expression of an individual's genetic liabilities (Manuck & McCaffery, 2014; Sameroff, 2009). There is extensive evidence on the role of genetic influences in the development of adolescent internalizing (Hatoum et al., 2018; Middeldorp et al., 2005; Patterson et al., 2018), externalizing (Burt, 2009; Dick et al., 2005; Hicks et al., 2007), and smoking initiation (Bares et al., 2015; Maes et al., 1999). However, studies examining whether neighborhood factors moderate these genetic influences have been few and far between. Further, the handful of previous studies on Gene-Neighborhood interactions have primarily looked into interactions with structural characteristics, such as neighborhood socioeconomic deprivation (Beaver et al., 2011; Cleveland, 2003; Tuvblad et al., 2006). Therefore, there is a dearth of evidence on whether perceived neighborhood collective efficacy also moderates the genetic influences on adolescent internalizing, externalizing, and smoking initiation.

With the aim to fill this critical knowledge gap, this study examined data from a nationally representative sample of U.S. adolescent twins using quantitative behavioral genetic methods. The scientific article communicating this study is written for the *Twin Research and Human Genetics* journal of the International Society for Twin Studies.

Research Question 1. Does perceived neighborhood collective efficacy moderate the genetic influences on three adolescent mental health problems: Internalizing, Externalizing, and Smoking initiation.

Research Question 2. Do the purported Gene × Perceived Neighborhood Collective Efficacy interactions differ between adolescent females and males?

By integrating the collective efficacy theory with behavioral genetic theories and methodology, this research may add to our understanding of the dynamic interplay between genetic liabilities and the neighborhood context in which youth and their families are embedded. This empirical integration of "nature" and "nurture" may contribute to re-envisioning the neighborhood-level theories of youth mental health from a bioecological perspective (Bronfenbrenner & Morris, 2007). Secondly, this research may also help expand the evidence on gene-environment interactions in adolescent mental health problems from micro-level influences, such as adverse childhood experiences and peer-affiliations, to broader environmental moderators in the community (Burt, 2009).

II. Literature Review

Empirical analyses of typical adolescent mental disorders support two symptom-based, dimensional scales: Internalizing and Externalizing (Cosgrove et al., 2011; Krueger, 1999; Snyder et al., 2017). Internalizing problems represent inward distress and include disorders with depressive, anxiety, and somatic symptoms, whereas Externalizing disorders map the outward expression of distress and comprise disruptive conduct, antisocial behaviors, and impulse-control problems (Achenbach, 1966; Cosgrove et al., 2011). Smoking initiation in adolescents may be considered an act of rule-breaking and, thus, essentially an externalizing problem (Audrain-McGovern et al., 2009). Smoking may, however, also be initiated in the context of internalizing disorders, without any associated externalizing behaviors, as is purported by the self-medication hypothesis of smoking (Khantzian, 1997). Therefore, the current study examined adolescent smoking initiation as a distinct mental health construct.

Evidence from behavioral genetic studies illustrates that both genetic liabilities and environmental factors contribute to adolescent internalizing (Middeldorp et al., 2005; Patterson et al., 2018), externalizing (Burt, 2009; Dick et al., 2005; Hicks et al., 2007), and smoking initiation (Maes et al., 2017). Further, these genetic and environmental influences typically do not act separately but rather interact to impact mental health outcomes (Kendler & Eaves, 1986). A variety of social-environmental factors (e.g., adverse childhood experiences, poverty, antisocial peer-affiliation, and parenting) have been shown to moderate the genetic liabilities for adolescent internalizing (Dunn et al., 2011; Hicks et al., 2009), externalizing (Button et al., 2008; Feinberg et al., 2007; Samek et al., 2017), and smoking initiation (Do & Maes, 2016).

Empirical evidence also highlights sex differences in the epidemiology of adolescent mental disorders. To wit, internalizing problems show a marked female preponderance, while externalizing problems have an evident male preponderance (Rutter et al., 2003). These differences may be attributed, at least partly, to sex differences in the biological, psychological, and social correlates of these problems, suggesting possible differences in the underlying etiological mechanisms in adolescent females and males (Zahn-Waxler et al., 2008). Indeed, some behavioral genetic studies have reported sex differences in the relative contributions of genetic and environmental influences. For adolescent internalizing, genetic factors likely contribute more to the variation in females than in males (Wright & Schwartz,

2021), while for externalizing, genetic influences play a greater role in males than in females (Newsome et al., 2016).

Another methodological challenge is the substantial correlation (0.66–0.72) between internalizing and externalizing disorders, likely due to their common underlying genetic and environmental factors (Cosgrove et al., 2011). Expectedly, adolescent smoking initiation also shares genetic and environmental influences with externalizing (Korhonen et al., 2012) and internalizing disorders (Leventhal et al., 2011; McCaffery et al., 2008). Therefore, using multivariate behavioral genetic designs for accounting for their covariance (Posthuma et al., 2003) may help parse the underlying mechanisms into factors common and specific to these traits.

Perceived neighborhood collective efficacy is an individual-level indicator of two interlinked social processes in the neighborhood: *social cohesion* (the "collectivity" component) and *informal social control* (the "efficacy" component). "Social cohesion" is a measure of social ties, mutual trust, and solidarity among neighborhood residents. Meanwhile, "informal social control" indicates the willingness of residents to monitor neighborhood social environment, including youth behavior, and intervene according to their shared values and expectations (Sampson et al., 2002). Sampson and colleagues (1997) first demonstrated that perceived neighborhood collective efficacy was negatively associated with externalizing traits in youth and mediated much of neighborhood disadvantage's effects on these outcomes. Since then, a growing number of empirical studies have supported the protective influence of perceived neighborhood collective efficacy on adolescent externalizing (Maimon & Browning, 2010; Sampson et al., 2002) and internalizing (Donnelly et al., 2016; Xue et al., 2005) problems.

Additionally, perceived neighborhood collective efficacy has also been shown to buffer the negative impact of other social-environmental factors on externalizing (Delany-Brumsey et al., 2014; Derauf et al., 2015; Sharma et al., 2019; Silk et al., 2004), internalizing (Browning et al., 2013; Delany-Brumsey et al., 2014; Du & Kim, 2020; Sharma et al., 2019), and substance use in adolescents (Fagan et al., 2014). There is also some conflicting evidence of sex differences in these protective influences, with some reporting perceived neighborhood collective efficacy to attenuate neighborhood disadvantage's impact on internalizing in females only (Browning et al., 2013), while others have reported this effect to be significant in males only (Sharma et al., 2019).

However, there is limited evidence on whether perceived neighborhood collective also moderates the genetic influences on these youth mental health outcomes. Connolly (2014) found that higher levels of perceived neighborhood collective efficacy were associated with increased genetic influences on externalizing in a sample of U.S. adolescent twins. To my knowledge, this twin study is the only study of these gene-environment interactions in adolescents. There is some additional extrapolative evidence from candidate-gene analyses in adults, wherein higher perceived neighborhood collective efficacy reduced externalizing problems only in those with high-risk genotypes (Lei et al., 2014). Therefore, further research is required to obtain more conclusive evidence on the G×E interactions between perceived neighborhood collective efficacy and adolescent externalizing behaviors.

Moreover, since the genetic and environmental influences on externalizing problems overlap with the factors underpinning internalizing and smoking initiation, it is plausible that similar G×E interactions with perceived neighborhood collective efficacy also exist for the latter two traits. However, these G×E interactions are yet to be studied in adolescent internalizing problems and smoking initiation. For smoking initiation, there is some suggestive evidence from a study examining polygenic risk scores in adults, which found social cohesion to attenuate the association between genetic risk and smoking (Meyers et al., 2013).

Based on the reviewed literature, I aimed to examine whether perceived neighborhood collective efficacy moderated the genetic influences on adolescent internalizing, externalizing, and smoking initiation, using a behavioral genetic approach. Evidence for such G×E interactions would add to the literature by illustrating possible biological mechanisms underlying the protective effect of perceived neighborhood collective efficacy on these mental health outcomes. Given the likely sex differences in the genetic and environmental influences on adolescent mental disorders and the protective effects of perceived neighborhood collective efficacy, I also explored the differences between females and males in the purported G×E. Moreover, as adolescent internalizing, externalizing, and smoking initiation also share, to some extent, the underlying genetic and environmental factors, I chose to use multivariate models to parse the gene-environment interactions specific to each trait.

III. Theoretical Framework

The "bioecological model" (Bronfenbrenner & Ceci, 1994) provides a testable theoretical framework for empirically examining gene-environment interactions in adolescent mental health outcomes. This model postulates that specific organism-environment interactions, called proximal processes, facilitate the expression of genetic factors. The genetic influences estimated in behavioral genetic studies reflect the "actualized" genetic potential, while the non-actualized genetic potential remains unknown, and this actualized genetic potential is hypothesized to increase as the magnitude of conducive proximal processes increases. Applying this theoretical framework to negative behavioral traits, the "diathesis-stress" model posits that adverse ecological contexts increase the actualized genetic liability for mental health problems and, thus, the estimated genetic variance (Monroe & Simons, 1991; South et al., 2017). This conceptualization of gene-environment interactions is well illustrated by empirical studies of adolescent internalizing (Dunn et al., 2011; Hicks et al., 2009), externalizing (Button et al., 2008; Samek et al., 2017), and smoking initiation (Do & Maes, 2016).

Perceived neighborhood collective efficacy is proposed as one of the proximal processes mediating neighborhood influences on individual mental health (Sampson et al., 1997). This theory argues that close social ties and solidarity among residents promote neighborhood cohesion, such that residents get along well with each other, share common values, and trust and help each other. This social cohesion strengthens the residents' ability to realize informal social control in the neighborhood, as indicated by their willingness to intervene collectively for the common good, including monitoring adolescent behavior and activities (Sampson et al., 1997). Therefore, cohesive and organized neighborhoods are believed to create an optimal social climate for promoting and protecting adolescent mental health. Thereby, perceived neighborhood collective efficacy can also be viewed as a "social capital" (Coleman, 1988), which provides adolescents with social resources, including information channels, obligations and expectations, and social norms, that help promote their psychological wellbeing. Accordingly, higher perceived neighborhood collective efficacy is hypothesized to be associated with fewer mental health problems among adolescents.

In this study, I endeavored to combine perspectives from the collective efficacy theory (Sampson et al., 1997) with the bioecological model (Bronfenbrenner & Ceci, 1994) and examine whether perceived neighborhood collective efficacy modifies the actualized genetic

liability for internalizing, externalizing, and smoking initiation in adolescents. Given the limited evidence on Gene × Perceived Neighborhood Collective Efficacy in adolescent mental disorders, the purported G×E interactions were hypothesized to follow the "diathesis-stress" model, which is demonstrated to apply across diverse environmental variables (Hicks et al., 2009) and mental disorders (South et al., 2017). As perceived neighborhood collective efficacy is theorized to be a pro-social variable indexing lower environmental stress, I expected that higher perceived neighborhood collective efficacy would be associated with reduced genetic variation (the actualized genetic liability) in the three adolescent mental health problems.

IV. Methodological Considerations

Study sample

For this study, I examined secondary data from the twin sub-sample ($N = 762$ twin pairs) of the National Longitudinal Study of Adolescent Health ("Add Health") – a nationally representative study of U.S. adolescents (Harris, 2013). Add Health initially surveyed a stratified random sample of over 90,000 high-school and middle-school students (grades 7–12) in 1994-1995. A random sub-sample of over 20,000 adolescents and one of their resident parents completed an in-home structured interview in 1995 ("Wave I"). The in-school survey allowed Add Health to oversample twins from this nationally representative frame for in-depth personal interviews (Harris et al., 2006). Twin zygosity was determined based on self-report and four questionnaire items concerning confusability of appearance, which are shown to have over 92% agreement with DNA-based zygosity determinations (Spitz et al., 1996). The final analytic sample included 282 monozygotic (MZ) and 480 dizygotic (DZ) twin pairs aged 12-19 years at the time of interview.

Add Health Wave I provided a representative twin sample of U.S. adolescents across regions, urbanicity, school type, race/ethnicity, and socioeconomic status, along with rich data on health, behaviors, and multiple levels of environment. A potential limitation of this sample was that the data were collected in 1995 when adolescents presumably experienced a social environment much different from today's youth. However, meta-analyses of twin studies suggest minimal changes in the relative contributions of genetic and environmental influences on most human traits over the past fifty years (Polderman et al., 2015).

Measures

1. Mental health problems

Internalizing symptoms were assessed using 27 items, comprising 19 depressive symptoms from a modified Center for Epidemiologic Studies – Depression scale (CES-D; Radloff, 1977) and six physiological anxiety symptoms (Supplementary Table S1). To aid interpretation, I transformed these scores into a standardized scale. On the other hand, the externalizing measure included 15 items of rule-breaking and aggressive behaviors, such as physical fighting, lying, stealing, burglary, and group fights. Due to its markedly non-normal distribution ($\text{skew} = 2.70$, $\text{kurtosis} = 11.64$), I transformed externalizing score using rank-

based Inverse Normal Transformation (Blom, 1958), which first created a fractional rank for each subject and then back-transformed the rank variable to a phenotype score that approximated a standard normal distribution. This transformation is shown to optimize biometrical model selection in genetic studies (van den Oord et al., 2000). Both internalizing and externalizing scales showed good internal consistency, with a Cronbach's α of 0.88 and 0.84, respectively.

Smoking initiation was assessed with a binary measure of whether the participants had ever smoked a cigarette, even if just one or two puffs.

2. Perceived neighborhood collective efficacy

Consistent with recent studies (e.g., Jensen, 2020), I computed a nine-item total score of perceived neighborhood collective efficacy, which included five items on "social cohesion" reported by the adolescent and four items on "informal social control" reported by their parent. The scale had adequate internal consistency ($\alpha = 0.57$) and was standardized before analyses. Although this measure was conceptually consistent with the original operationalization by Sampson et al. (1997), I had to combine youth and parent reports, given the questionnaire structure in Add Health, which may explain its less-than-ideal Cronbach's α.

Analytic Strategy

For this study, I used biometrical twin modeling to partition the variance in the three trait phenotypes (internalizing, externalizing, and smoking initiation) and the environmental moderator (perceived neighborhood collective efficacy) into additive genetic (A), shared environmental (C), and unique environmental (E) factors (Figure 1), employing structural equation modeling (Rijsdijk & Sham, 2002). Quantitative behavioral genetic studies estimate these latent genetic and environmental sources of variance based on the shared genetic and environmental influences and the observed degree of similarity between twins reared together (Neale & Cardon, 1992). On average, MZ twins share 100% of their genetic variation, while DZ twins share 50%. Therefore, if genetic variation contributes to a phenotype, the MZ correlations would be greater than DZ correlations. Environmental influences shared by both twins make siblings more similar, making the DZ correlations more than half the MZ correlations. Finally, environmental factors unique to each twin (including measurement error) make siblings more different, such that MZ correlations are less than 1.0. I did the

structural equation modeling using the *OpenMx* package in R (Neale et al., 2016) and included all 762 twin pairs in the analyses. There were missing data on smoking initiation in eight twin pairs, which I accounted for using Full-Information Maximum Likelihood estimation (Enders & Bandalos, 2001).

To allow for the testing of sex differences in G×E, I initially evaluated sex-limited, univariate ACE models to estimate the additive genetic (a^2), shared environmental (c^2), and unique environmental (e^2) variances in the four variables. These models tested both "scalar sex limitation," indicating quantitative sex differences in the magnitude of latent variance parameters, and "non-scalar sex limitation," meaning sex differences in sets of genes influencing a phenotype. These sex differences were tested using nested models that constrained the relevant parameters to be equal across sex.

The next step was to test the hypothesized G×E by estimating how the ACE variance components in a trait changed depending on the measured environmental moderator included on each component's path. These G×E models needed to account for any gene-environment correlations between the traits and the moderator to prevent false-positive G×E results (Purcell, 2002). There are two modeling options to address this issue: either a bivariate G×E model (Figure 2A), which explicitly models any shared genetic variance between the trait and the moderator, or an extended univariate model (Figure 2B) that includes the environmental moderator of both twins as covariates in each twin (van der Sluis et al., 2012). The latter model is more powerful of the two but assumes no moderation of the shared variance between the trait and the moderator (van der Sluis et al., 2012). For the present study, I used the latter method after testing that the required assumptions were met in all three traits.

The main G×E models were multivariate ACE models (Figure 3) for internalizing, externalizing, and smoking initiation, with quantitative sex differences and the hypothesized moderation by perceived neighborhood collective efficacy. The models included as covariates age, sex × age, perceived neighborhood collective efficacy of each twin and their co-twin, and sex × perceived neighborhood collective efficacy of either twin. I tested for moderation using sequential nested models, which first examined moderation on the whole model using omnibus tests, and then on each phenotype separately for each sex. Significant tests of moderation were followed by tests of sex differences in moderation as well as tests of each moderation parameter individually. For comparing the goodness of fit of nested models, I assessed the differences in log-likelihood (Δ-2LL), which are asymptotically distributed as χ^2.

V. Findings

Preliminary analyses (Table 1) revealed that, consistent with the available literature, internalizing symptoms were, on average, higher in females than in males, while externalizing symptoms were higher in males than in females. There were minimal sex differences in smoking initiation and perceived neighborhood collective efficacy (hereafter referred to as "collective efficacy" for brevity). Bivariate correlations (Table 2) reflected the expected negative relationship between collective efficacy and internalizing symptoms in both females and males, while the correlation between collective efficacy and externalizing symptoms was significant in females but not in males. There was no significant correlation between collective efficacy and smoking initiation in either sex. Lastly, there were moderate, positive pair-wise correlations between internalizing, externalizing, and smoking initiation.

A series of sex-limited, univariate ACE models showed no evidence of qualitative sex differences in any of the four variables, but there were significant quantitative sex differences in internalizing, externalizing, and collective efficacy (Supplementary Table S2). These models estimated that the additive genetic variance in internalizing symptoms was moderately high in females ($a^2 = 0.47$; Table 3) but near-zero in males ($a^2 = 0.01$). Contrarily, externalizing symptoms were estimated to have markedly higher genetic variation in males ($a^2 = 0.41$) than in females ($a^2 = 0.10$), as did collective efficacy ($a^2 = 0.22$ in males, *vs.* $a^2 = 0.10$ in females). Smoking initiation was estimated to have moderate heritability ($a^2 = 0.40$) across sex.

The hypothesized G×E were finally tested using multivariate ACE models with collective efficacy-moderation of the latent variance factors in internalizing, externalizing, and smoking initiation (Table 4). The base model estimated all variance and moderation parameters freely for males and females to account for the quantitative sex differences revealed by the initial sex-limited univariate models. Subsequent nested models first suggested that neither the additive genetic nor the shared environmental influences could be dropped from the full model, and neither the moderation coefficients nor the variance parameters could be constrained to be equal across sex. Testing for G×E indicated significant collective efficacy-moderation of the variance parameters specific to internalizing in females (Δ-2LL = 8.98, p = 0.030) and males (Δ-2LL = 8.47, p = 0.037), and these moderation effects could not be equated across sex (Δ-2LL = 15.61, p = 0.001). However, there was no significant moderation of the variance parameters in externalizing and smoking initiation.

Further examination of the individual variance parameters for internalizing showed a significant moderation of the additive genetic component in females and males. Collective efficacy-moderation of shared environmental influences was significant in females but not in males. Moderation of unique environmental variance was not statistically significant in either sex. Estimating and plotting these variance parameters across levels of collective efficacy (Table 5; Figure 4) indicated that as collective efficacy increased, the additive genetic influences on internalizing in females decreased, while the shared environmental influences increased. In males, the additive genetic variance in internalizing was close to zero at intermediate levels of collective efficacy but increased at both high and low levels of the latter.

VI. Discussion

In this study, I aimed to examine whether perceived neighborhood collective efficacy moderates the genetic influences on three adolescent mental health problems: internalizing problems, externalizing problems, and smoking initiation. Secondly, I aimed to assess whether these gene-environment interactions (G×E) differ between females and males. I examined these G×E through behavioral genetic analyses in a nationally representative sample of U.S. adolescent twins. The results from a series of sex-limited, multivariate ACE models supported the hypothesized collective efficacy-moderation in internalizing symptoms, but not in the other two traits, and the G×E interactions differed between females and males.

Gene × Perceived Neighborhood Collective Efficacy × Sex

Among females, the G×E interactions followed the hypothesized *diathesis-stress* model: with increasing levels of collective efficacy and the implied reduction in environmental stress, the estimated genetic influences on internalizing decreased markedly. This pattern of G×E provides empirical evidence for the applicability of the diathesis-stress model to pro-social environments (such as high collective-efficacy neighborhoods), which some researchers refer to as "social control" or "social compensation" of genetic risk (Shanahan & Hofer, 2005; South et al., 2017). Just as environmental stress is expected to increase the expression of genetic diathesis for mental disorders, a more supportive environment would reduce the expression of the genetic risk. From the bioecological perspective (Bronfenbrenner & Ceci, 1994), low collective efficacy, on the other hand, would increase the actualized genetic risk of internalizing in adolescent females.

Among males, the gene-environment interaction did not follow the expected diathesis-stress process. The additive genetic influences on internalizing in males were negligible when collective efficacy was at intermediate levels but increased when the latter was either very high or very low. This pattern may be explained by the *Differential-Susceptibility* model (Belsky & Pluess, 2009), which posits that genetic predispositions make some individuals more susceptible to environmental influences, for better and for worse. The genetic influences on the affected trait are hypothesized to increase in non-normative environmental contexts, whether unusually positive or unusually negative. Consequently, individuals who have genetic diathesis for experiencing mental problems upon exposure to adverse environments (as in the diathesis-stress model) would likely benefit the most from positive environments. In the

current analyses, this model implies that genetic influences in males function as a risk factor at low collective efficacy (with a resultant increase in internalizing) but a resiliency factor at high collective efficacy, contributing to a decrease in internalizing.

Besides G×E, there was also evidence that high collective efficacy increased the shared environmental influences on internalizing symptoms, although only in females. This increase in the impact of the environment within the family and its broader ecological context (including neighborhood) could be directly related to the high social cohesion and informal social control (Sampson et al., 2002). Moderating factors at play here could be interpersonal resources, such as positive neighborhood relationships, and what Coleman (1988) calls social capital, including information channels, obligations and expectations, and social norms. The lack of evidence for similar collective efficacy-moderation of shared environment in males is aligned with the sex differences previously reported (Browning et al., 2013), likely due to differences in how adolescent females and males respond to and are influenced by social-environmental factors (Zahn-Waxler et al., 2008).

Policy Implications

These findings demonstrate the complex gene-environment interactions between collective efficacy and adolescent internalizing problems. Accounting for the genetic influences and gene-environment interactions may improve the explanatory power of collective efficacy and other neighborhood-level theories of adolescent mental health and, thus, provide more robust evidence for community interventions to prevent youth mental health problems. The evident collective efficacy-related buffering of the genetic liability for internalizing in females and activation of genetic resiliency in males give impetus to the need for policies and interventions to strengthen social cohesion and control in neighborhoods. Possible strategies could include community education programs that emphasize adolescent empathy and communication (Carlson et al., 2012) and community trust, collaboration, and relationship building (Weisburd et al., 2015). However, these social actions would not minimize the need for interventions aimed at improving structural neighborhood characteristics, for neighborhood collective efficacy is also shaped, to a great extent, by socioeconomic status, housing, and inequalities in the neighborhood (Duncan et al., 2003; Sampson et al., 2002).

Limitations and Further Research

These results should be seen in the light of this study's possible limitations. First, the study's modest sample size resulted in imprecise parameter estimates; therefore, an essential next step is to attempt to replicate these findings in different, larger samples. Sample size may have limited this study's power, which likely explains why, unlike prior research (Connolly, 2014), I did not find evidence for G×E in externalizing. Secondly, this study only examined G×E with individual-level perceived neighborhood collective efficacy, which may conceivably differ for within- and between-neighborhood variations in collective efficacy. Future research should explore these multilevel G×E interactions using neighborhood-level aggregates of the individual-level measure, which would better inform relevant neighborhood interventions.

Furthermore, as alluded to earlier, the composite measure of collective efficacy followed the original operationalization by Sampson et al. (1997). However, it is possible that the two sub-processes, social cohesion and informal social control, differentially interact with genetic influences, which future studies should discern. Finally, this study's policy implications remain limited by the dearth of scientific literature on Gene × Collective Efficacy interactions in adolescent mental health. Expanded research is still needed to examine potential variations in these G×E interactions across population groups, developmental ages, and measurement specifics.

Conclusion

Despite its limitations, this study adds to the literature by demonstrating the role of gene-environment interactions in the protective influence of perceived neighborhood collective efficacy on adolescent internalizing problems. Specifically, high collective efficacy attenuated the expression of the genetic risk of internalizing in adolescent females, besides enhancing the social-environmental influences shared in the family and its broader community (including the neighborhood). Among males, high collective efficacy increased the expression of genetic factors conferring resiliency against internalizing problems. These empirical findings help incorporate bioecological perspectives in the collective efficacy theory of adolescent mental health, which may help develop more robustly informed community interventions.

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PART – B

Scientific Article

Examining Sex-dependent Gene-Environment Interactions between Adolescent Mental Health Problems and Perceived Neighborhood Collective Efficacy

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Abstract

Background: G×E research on youth mental health problems has seldom examined interactions with protective environments. One such pro-social environmental factor is perceived neighborhood collective efficacy, which is shown to buffer the influence of diverse ecological risk factors on adolescent psychopathology. The current study examined whether collective efficacy also moderates the genetic influences on three adolescent mental health outcomes – internalizing, externalizing, and smoking initiation – and explored the sex differences in these G×E interactions using biometrical twin modeling. ***Method:*** Data from 762 adolescent twin pairs (aged 12-19) from the National Longitudinal Study of Adolescent Health were examined using sex-limited, multivariate variance-decomposition models for gene-environment interactions between perceived neighborhood collective efficacy and the three phenotypic traits. ***Results:*** Collective efficacy moderated the genetic influences on internalizing only, and these G×E interactions differed across sex. Among females, higher collective efficacy attenuated the additive genetic variance in internalizing, while the shared environmental influences increased. Among males, the additive genetic variance was negligible at intermediate levels of collective efficacy but increased at both very high and very low levels of the latter. There was no evidence for collective efficacy-moderation of variance parameters in the other two traits. ***Conclusion:*** Perceived neighborhood collective efficacy likely moderates the genetic influences on adolescent internalizing problems, with distinct mechanistic processes across sex. In females, these G×E interactions follow the diathesis-stress mechanism, while males demonstrate a differential-susceptibility process, where genetic influences increase in non-normative environmental contexts. These findings also lend support to G×E protective interactions with pro-social environments in adolescent psychopathology.

Introduction

Most mental disorders begin to develop during adolescence, even if first diagnosed later in adulthood (Costello et al., 2005). In a nationally representative sample of U.S. adolescents, the overall prevalence of mental disorders with severe distress or impairment was reported to be 22.2% (Merikangas et al., 2010). Besides causing suffering, functional impairment, and an enhanced risk of premature death, youth mental disorders also profoundly impact economic and social outcomes extending into adulthood (Patel et al., 2007).

Internalizing-Externalizing Disorders

Symptoms-based factor-analytic studies support a higher-order, bi-factor Internalizing-Externalizing model of psychopathology (Achenbach et al., 2016), empirically validated in adolescents (Lahey et al., 2008). *Internalizing* maps the propensity to express psychological distress inwards and comprises depressed mood, anxiety, social withdrawal, and associated physiological symptoms. In contrast, *externalizing* is the propensity to express distress outwards and manifests as disorders with conduct problems, antisocial behaviors, impulse-control disturbances, and aggression.

Behavioral genetic research has well illustrated the multifactorial etiology of these disorders, with genetic liabilities, social-environmental influences shared in the family and its broader community, as well as individual-specific experiences jointly contributing to internalizing (Hatoum et al., 2018; Middeldorp et al., 2005; Patterson et al., 2018) and externalizing (Burt, 2009; Dick et al., 2005; Hicks et al., 2007) disorders. Typically, internalizing problems are more common in females, while externalizing disorders are more prevalent in males (Rutter et al., 2003). These variations are likely attributable to sex differences in the relative contributions of and interactions between genetic and environmental influences (Zahn-Waxler et al., 2008). Moreover, although adolescent internalizing and externalizing are conceptualized as distinct factors, there is significant comorbidity between the two, likely due to common genetic and environmental factors (Cosgrove et al., 2011; Mikolajewski et al., 2013).

Smoking Initiation

Both externalizing and internalizing problems are associated with a high prevalence of substance use in youth (Colder et al., 2013; King et al., 2004), of which smoking initiation is

of particular public health significance. Tobacco remains the leading preventable cause of morbidity and mortality in the U.S. (Centers for Disease Control and Prevention, 2012), and around 80% of adult smokers initiate cigarette use before age 18 (U.S. Department of Health and Human Services, 2012). Moreover, smoking initiation at a younger age is associated with a heightened risk of progressing to daily smoking and nicotine dependence (Dierker et al., 2012). Smoking initiation, therefore, is a pivotal event in an adolescent's life, and its variation is attributable to additive genetic, shared social-environmental, and individual-specific environmental influences (Maes et al., 2017). Furthermore, multivariate behavioral genetic studies suggest that adolescent smoking initiation's co-occurrence with externalizing (Korhonen et al., 2012) and internalizing disorders (McCaffery et al., 2008) is primarily due to common underlying environmental and, to a lesser extent, genetic influences.

Gene-Environment Interactions

Genetic and environmental factors likely do not act independently but rather interact to influence these complex behavioral traits (Plomin et al., 1977). Gene-environment interactions (G×E) are conceptualized either as moderation by the environment of the expression of genetic influences or as moderation by genetic influences of an individual's sensitivity to the environment (Reiss et al., 2013). However, as Burt (2011) highlights, much of the extant literature on G×E in adolescent psychopathology has focused on social-environmental "pathogens" (e.g., antisocial peer-affiliation, childhood neglect, stressful life events, and poverty), following the long-standing *Diathesis-Stress* conceptualization of G×E in psychopathology (Monroe & Simons, 1991; South et al., 2017). Typically, the genetic risk is expressed more fully upon exposure to adverse environments, leading to increased adolescent internalizing (Dunn et al., 2011; Hicks et al., 2009), externalizing (Button et al., 2008; Feinberg et al., 2007; Samek et al., 2017), and smoking initiation (Do & Maes, 2016).

Another likely but less extensively studied process of G×E is the protective interactions with pro-social environments, rather than just the absence of adversity, which may contribute to individual resiliency against adolescent psychopathology (Burt, 2011). Recent G×E studies on the role of positive/warm parenting in adolescent externalizing (Feinberg et al., 2007; Henry et al., 2018) and internalizing (Hankin et al., 2011) illustrate these protective G×E, wherein genetic influences are diminished under particularly warm/positive parenting. Conceivably, similar G×E may also occur with the broader social contexts, such as neighborhood, as youth mental health is impacted not only by the micro-

level influences, such as parenting, but also the ecological contexts in which the families are embedded (Bronfenbrenner, 1986). These distal social contexts likely influence youth psychosocial outcomes through individual-level "proximal processes" (Bronfenbrenner & Morris, 2007). One such process through which structural neighborhood characteristics may influence adolescent mental health is neighborhood collective efficacy (Leventhal & Brooks-Gunn, 2000; Sampson et al., 1997).

Perceived Neighborhood Collective Efficacy

The Search Institute (2007) explicates 40 "developmental assets" for healthy youth development, two of which include "caring neighborhoods" (adolescents have caring relationships with their neighbors) and "neighborhood boundaries" (neighbors monitor adolescent behavior). These pro-social processes are reflected in the two central domains of neighborhood collective efficacy: social cohesion and informal social control, respectively (Sampson et al., 1997). Social cohesion, the *collectivity* component, is the degree to which neighborhood residents get along, share values, and trust each other. Informal social control, the *efficacy* component, is the willingness of neighborhood residents to regulate youth behavior and activity according to their shared values and expectations. The two processes are conceptually interlinked, as the realization of informal social control in the neighborhood would be predicated, in large part, on mutual trust and solidarity among residents (Sampson et al., 2002).

Empirically, social cohesion and informal social control may be indexed together using an individual-level composite measure of "perceived neighborhood collective efficacy" (Sampson et al., 1997). Prior research indicates that high levels of perceived neighborhood collective efficacy (henceforth abbreviated as "collective efficacy") are associated with lower levels of externalizing (Maimon & Browning, 2010; Sampson et al., 1997) and internalizing (Donnelly et al., 2016; Xue et al., 2005) problems in youth. Besides these independent influences, collective efficacy is also shown to attenuate the impact of a range of social-environmental risk factors on adolescent externalizing (Delany-Brumsey et al., 2014; Derauf et al., 2015; Sharma et al., 2019; Silk et al., 2004) and internalizing problems (Browning et al., 2013; Delany-Brumsey et al., 2014; Du & Kim, 2020; Sharma et al., 2019), and polysubstance use (Fagan et al., 2014). Some studies have also highlighted sex differences in these protective effects, albeit inconsistently. Browning et al. (2013) reported collective efficacy to attenuate the impact of neighborhood disadvantage on internalizing in females

only, whereas Sharma et al. (2019) found this effect significant in males only. Together these studies suggest a buffering action of collective efficacy against environmental risks across ecological levels, from individual (e.g., victimization, racial discrimination) to family (e.g., maternal depression, hostile parenting) and neighborhood (e.g., social disorder, poor neighborhood ecology).

However, it is not well studied whether collective efficacy also moderates the genetic influences underlying adolescent psychopathology. Connolly (2014) demonstrated an increased genetic variance in externalizing behaviors at higher levels of collective efficacy in a sample of U.S. adolescent twins. Another study using candidate-gene analyses in adult women reported that higher collective efficacy attenuated the risk of externalizing behavior in those with high-risk genotypes (Lei et al., 2014). Further research is still needed to garner more conclusive evidence for G×E between collective efficacy and adolescent externalizing. Moreover, since the genetic and environmental influences on externalizing likely overlap with the factors underlying internalizing (Cosgrove et al., 2011) and smoking initiation (Korhonen et al., 2012), the Gene × Collective Efficacy in externalizing may plausibly also exist for the latter two traits. For example, prior research indicates that greater social cohesion diminishes the association between genetic risk (polygenic risk score) and cigarette smoking in adults (Meyers et al., 2013). However, these G×E interactions remain to be studied in adolescent internalizing and smoking initiation.

Current Study

The present study used a behavioral genetic approach to examine gene-environment interactions between collective efficacy and three measures of adolescent mental health problems (internalizing, externalizing, and smoking initiation) in a nationally representative U.S. sample. Given the likely sex differences in the genetic and environmental influences on adolescent psychopathology (Zahn-Waxler et al., 2008) and the buffering action of collective efficacy (Browning et al., 2013; Sharma et al., 2019), this study also explored whether the purported G×E differed between females and males.

Due to the limited evidence on G×E specific to collective efficacy, the hypotheses were based on the *Diathesis-Stress* model, which is the most widely seen pattern of G×E in psychopathology (South et al., 2017) and applies across diverse environmental risks (Hicks et al., 2009). Under this model, the genetic influences on a trait increase as the degree of

environmental stress increases. In the present study, collective efficacy was conceptualized as a pro-social neighborhood environment that indexed lesser environmental stress. Therefore, it was hypothesized that the genetic influences on the three traits would decrease at higher levels of collective efficacy. Moreover, as prior research suggests some degree of common genetic and environmental factors underlying adolescent internalizing, externalizing, and smoking initiation, these interactions were examined using multivariate models to parse G×E interactions specific to the three traits.

Materials and Methods

Participants

Data for this study come from the National Longitudinal Study of Adolescent Health (Add Health) – a nationally representative, prospective longitudinal study of health and health behaviors in U.S. adolescents. For detailed study design and protocols, see Harris (2013). In brief, Add Health used a stratified random sample of U.S. high schools, each coupled with a feeder middle school (more than 70% of targeted schools agreed to participate). The study conducted an initial in-school, confidential survey of over 90,000 students from grades 7–12 in 1994-95. Of these respondents, a randomly selected sub-sample of over 20,000 adolescents completed a comprehensive, 90-minute in-home interview in April-December 1995 ("Wave I"). Additionally, one of the parents, usually the resident mother, also completed a 30-minute questionnaire at Wave I.

The in-school questionnaire allowed Add Health to oversample twins from this nationally representative frame for in-depth personal interviews (Harris et al., 2006). Both members of the twin pair were recruited to the study, even if one of them did not attend the schools selected in the original probability sample. Twin zygosity was determined based on self-report and four questionnaire items concerning confusability of appearance. Such twin-similarity questionnaires have been widely utilized in twin research and are shown to have greater than 92% agreement with zygosity determinations based on DNA (Spitz et al., 1996).

This study used the twin data subset from Add Health Wave I ($N = 762$ twin pairs). The final analytic sample included 282 monozygotic (MZ) twin pairs, including 140 MZ female (MZF) and 140 MZ male (MZM) pairs, and 480 dizygotic (DZ) pairs comprising 147 female-female DZ (DZF), 137 male-male DZ (DZM), and 196 opposite-sex DZ (DZO) twin pairs. Participants were aged 12-19 years at the time of interview (mean age 16.05, S.D. 1.60) and represented approximately 54% Non-Hispanic Caucasian, 25% Non-Hispanic African American, 14% Hispanic, 4% Asian American, 2% Native American, and 1% other racial/ethnic groups.

Measures

The study analyzed three phenotypic traits of adolescent mental health problems (internalizing, externalizing, and smoking initiation) and one environmental moderator

(perceived neighborhood collective efficacy). Demographic variables of age at the time of interview and self-reported sex were used as covariates.

Internalizing

Internalizing problems were assessed using a composite measure of depressive and anxiety symptoms (Supplementary Table S1).

Depressive symptoms. Add Health Wave I used a 19-item Feelings Scale, which included 18 of the 20 items in the Center for Epidemiologic Studies – Depression Scale (CES-D; Radloff, 1977), along with an additional question, *"You felt like life was not worth living."* The CESD-based Feelings Scale mapped the frequency of depressed affect, somatic complaints, interpersonal difficulties, and positive affect (reverse coded) experienced during the preceding week. Each item was scored from 0 ("never") to 3 ("daily"), and the sum score ranged from 0 to 57, with higher scores indicating greater depressive symptoms.

Anxiety symptoms. Eight items in the General Health section of Add Health questionnaire were used to construct a physiological symptoms-based anxiety scale, similar to prior research (Jacobson & Newman, 2016; Li et al., 2018). Each item was scored from 0 ("never") to 4 ("every day"), and the sum score had a metric of 0–32, with higher scores indicating greater anxiety symptoms.

A composite measure of internalizing symptoms was then created by aggregating the depressive and anxiety symptom scores. The items in this internalizing scale were analogous in content to Achenbach's Youth Self-Report (Achenbach, 2017), a widely used empirical assessment tool for broad-band internalizing psychopathology comprising anxious/depressed, withdrawn/depressed, and somatic complaints. The 27-item internalizing total score had a metric of 0–89 ($\text{mean} = 16.5$, $\text{S.D.} = 9.35$, $\text{skew} = 0.84$, $\text{kurtosis} = 0.89$) and good internal consistency (Cronbach's $\alpha = 0.88$). (The depressive symptom sub-scale had $\alpha = 0.86$, and the anxiety symptom sub-scale had $\alpha = 0.72$.) For easier interpretation, the scores were transformed into a standardized scale.

Externalizing

Externalizing symptoms were assessed using the 15-item Delinquency Scale from Add Health Wave I (Supplementary Table S1). Items comprising the scale included rule-breaking

and aggressive behaviors, such as lying, physical fighting, vandalism, stealing, shoplifting, burglary, and group fights. The frequency of engaging in each behavior in the past 12 months was scored from 0 ("never") to 3 ("5 or more times"). These 15 items were summed to obtain a measure of externalizing behaviors, which had a range of 0–45 ($\text{mean} = 4.0$, $\text{S.D.} = 5.1$, $\text{skew} = 2.70$, $\text{kurtosis} = 11.64$) with good internal consistency (Cronbach's $\alpha = 0.84$).

Given its markedly non-normal distribution with positive skewness, the externalizing symptom score was transformed using rank-based Inverse Normal Transformation (Blom, 1958). The transformation first created a fractional rank for each subject, based on their sample quantile, and then back-transformed the rank variable to a phenotype score that approximated a standard normal distribution. Using simulations, van den Oord et al. (2000) have shown this transformation to optimize biometrical model selection.

Smoking Initiation

Participants were asked if they had ever smoked a cigarette, even if just one or two puffs. The response was coded as $0 = No$ and $1 = Yes$, providing a binary measure of smoking initiation ($Yes = 54\%$).

Perceived Neighborhood Collective Efficacy

Following Sampson et al. (1997), individual-level perceptions of the "social cohesion" and "informal social control" components of neighborhood collective efficacy were measured using nine items. Consistent with recent studies (e.g., Jensen, 2020), five of these nine items were reported by the youth, while the remaining four items were reported by one of the resident parents (92% mothers, 8% fathers).

The five youth-report items mapped on to the perceived levels of social cohesion and included: *"People in this neighborhood look out for each other," "You know most of the people in your neighborhood," "In the past month, you have stopped on the street to talk with someone who lives in your neighborhood," "On the whole, how happy are you with living in your neighborhood,"* and *"If, for any reason, you had to move from here to some other neighborhood, how happy or unhappy would you be?"*

Four items measured parent-perceived informal social control and included: *"If you saw a neighbor's child getting into trouble, would you tell your neighbor about it," "If a*

neighbor saw your child getting into trouble, would your neighbor tell you about it," "In this neighborhood, how big a problem is litter or trash on the streets and sidewalks," and *"How much would you like to move away from this neighborhood?"*

All nine items were re-coded, where required, and summed such that higher scores indicated greater levels of perceived neighborhood collective efficacy. The possible sum score could range from 0 to 23 ($\text{mean} = 15.3$, $\text{S.D.} = 4.71$, $\text{skew} = -0.78$, $\text{kurtosis} = -0.11$) and had adequate internal consistency ($\alpha = 0.57$). To aid interpretation, the scores were standardized before analyses.

Analytic Strategy

This study used biometrical twin modeling to partition the variance in the three trait phenotypes (internalizing, externalizing, and smoking initiation) and the environmental moderator (perceived neighborhood collective efficacy) into additive genetic (A), shared environmental (C), and unique environmental (E) factors (Figure 1). The three variance parameters can be estimated based on the assumed shared genetic and environmental influences between twins reared together and the relative similarity of MZ and DZ twin pairs for a phenotype. The additive genetic factor reflects the cumulative effect of individual genes on each phenotype. MZ twins share 100% of their differentiating genes, while DZ twins share, on average, 50% of their genetic variation. If genetic variation (or heritability) contributes to a phenotype, then MZ correlations would be greater than DZ correlations. Environmental influences shared by both twins make the twins more similar, while environmental factors unique to each twin (including measurement error) make the twins more different. MZ correlations less than double the DZ correlations would imply the influence of shared environmental factors. Finally, if unique environmental effects contribute to the phenotype, MZ correlations would be less than 1.0. For a detailed review of structural equation modeling of twin data, see Rijsdijk and Sham (2002).

[*Figure 1 about here.*]

Preliminary analyses involved testing the assumptions of equal means and variances for the three scale variables (internalizing, externalizing, and perceived neighborhood collective efficacy) and equal thresholds for smoking initiation (binary variable) across twin order, zygosity, and sex. Since this study also aimed to test sex differences in gene-

environment interactions, initial sex-limited, univariate ACE models estimated the additive genetic (a^2), shared environmental (c^2), and unique environmental (e^2) variances in each of these four variables and tested whether these parameters varied across sex. Two types of sex differences (*Gene* × *Sex*) were examined: sex differences in the *magnitude* of additive genetic effects (*scalar sex limitation*) and differences due to different sets of genes contributing to the phenotype in males and females (*non-scalar sex limitation*). These sex differences were tested by constraining the relevant parameters to be equal across both sexes. These models included age and sex × age as covariates.

Biometrical *Gene* × *Environment* can be tested by estimating how the ACE variance components in a phenotype change depending on a measured environmental moderator (perceived neighborhood collective efficacy) included on the path for each component (Purcell, 2002). These G×E models must account for potential gene-environment correlations that could inflate the estimated moderation on A and give false-positive G×E results. To address this issue, Purcell (2002) proposed a bivariate G×E model (Figure 2A), which includes specific and common additive genetic components for the trait and the moderator, besides the moderation on the variance path estimates for the trait. Alternatively, van der Sluis et al. (2012) developed an extended univariate G×E model (Figure 2B), which collapses these shared variances into the means section by regressing each twin's mean on the environmental moderator levels in both twins. The latter method is more powerful than the model by Purcell (2002) but assumes that there is no moderation of the shared variance between the trait and the moderator (for a detailed review and mathematical proof, see van der Sluis et al., 2012). In the present study, preliminary analyses (results available on request) showed no evidence of moderation of the shared paths between the moderator and the three traits. Therefore, the more powerful van der Sluis et al. (2012) method was adopted for further G×E testing.

[*Figure 2 about here.*]

The main variance decomposition models in this study were multivariate models for internalizing, externalizing, and smoking initiation with scalar sex limitation, as well as the hypothesized sex-specific moderation by perceived neighborhood collective efficacy (Figure 3). The models included variance components specific to each trait and the cross-trait variance paths representing genetic and environmental influences common between traits. The models included as covariates age, sex × age, perceived neighborhood collective efficacy of each twin and their co-twin, and sex × perceived neighborhood collective efficacy of either twin. After

fitting the full ACE moderation model, simpler models were tested without shared environmental variance components (AE model) or additive genetic components (CE model). Scalar sex limitation was tested by constraining parameters to be equal across sex. Moderation was tested by first using omnibus tests on the whole model and then on each phenotype separately for each sex. Significant tests of moderation were followed up with tests of sex differences in moderation and tests of each moderation parameter individually. Supplementary analyses tested for moderating effects on shared variance components between traits for each sex.

[*Figure 3 about here.*]

The models were fit using the *OpenMx* package in R (Boker et al., 2011). Eight of the total 762 twin pairs had missing data (only for the smoking initiation variable). All twin pairs were included in the analyses, and the missing data were accounted for using Full Information Maximum Likelihood estimation (FIML; Enders & Bandalos, 2001). Nested models were compared by using the differences in log-likelihood, which are asymptotically distributed as χ^2.

Results

Preliminary Analyses

Table 1 presents the descriptive statistics for the study variables in twin pairs stratified by zygosity and sex. Consistent with the available literature, there was a higher average level of internalizing symptoms in females (range = 17.1–18.2) than in males (15.2–15.8) while externalizing symptoms were, on average, greater in males (4.1–5.0) than in females (3.0–3.5). There were minimal sex differences in smoking initiation or perceived neighborhood collective efficacy levels.

[*Table 1 about here.*]

Bivariate correlations (Table 2) indicated that collective efficacy was negatively related to internalizing symptoms in both females ($r = -0.12, p < 0.001$) and males ($r = -0.14, p < 0.001$). The correlation between collective efficacy and externalizing symptoms was significant in females ($r = -0.09, p = 0.012$) but not in males ($r = -0.04, p = 0.281$). Lastly, collective efficacy did not significantly correlate with smoking initiation in either females ($r = -0.08, p = 0.097$) or males ($r = -0.04, p = 0.366$). Additionally, there were moderate, positive pair-wise correlations amongst the three trait phenotypes.

[*Table 2 about here.*]

Twin correlations (Table 2) suggested that variances in the three traits were likely attributable to additive genetic, shared environmental, and unique environmental factors. Twin correlations for perceived neighborhood collective efficacy also suggested additive genetic influences, especially in males, besides the expected shared environmental and some unique environmental influences.

Preliminary saturated twin models indicated that the means and variances for internalizing, externalizing, and collective efficacy and the threshold for smoking initiation could be constrained to be equal across twin order, zygosity, and same-sex and opposite-sex pairs. These parameters could be equated across sex only in smoking initiation but not for the other two behavioral traits or collective efficacy (results available upon request).

Sex-limited Univariate ACE Models

Sex differences in the genetic and environmental influences on the four key variables were tested using sex-limited, univariate ACE models. Serial nested models showed no evidence of non-scalar sex limitation (qualitative sex difference) in any trait or collective efficacy (Supplementary Table S2). However, there was significant scalar sex limitation (quantitative sex differences) in internalizing and externalizing symptoms and perceived neighborhood collective efficacy, but not in smoking initiation.

The univariate ACE models (Table 3) estimated that the heritability for internalizing symptoms was moderately high in females ($a^2 = 0.47$) but close to zero in males ($a^2 = 0.01$). On the other hand, heritability for externalizing symptoms was estimated to be substantially higher in males ($a^2 = 0.41$) than in females ($a^2 = 0.10$). Smoking initiation, which showed no sex differences in additive genetic influences, was estimated to have a heritability of $a^2 = 0.40$. Furthermore, the environmental moderator – perceived neighborhood collective efficacy – also showed significant heritability that was greater in males ($a^2 = 0.22$) than in females ($a^2 = 0.10$).

[*Table 3 about here.*]

Sex-limited Multivariate Gene × Environment Interaction Models

The main G×E models tested for collective efficacy-moderation of the genetic and environmental variances in internalizing, externalizing, and smoking initiation in a series of multivariate variance decomposition models (Table 4).

[*Table 4 about here.*]

Based on the evidence from sex-limited univariate models, Model 1 included all variance components and scalar sex limitation, such that all variance and moderation parameters were estimated freely for males and females. Dropping the shared environmental component (Model 2) resulted in substantial decrease in model fit (Δ-2LL = 44.45, p = 0.007), as did dropping the additive genetic component (Model 3; Δ-2LL = 46.05, p = 0.004). Constraining the effect of collective efficacy to be equal across sex (Model 4) resulted in substantially poorer fit (Δ-2LL = 1808.96, p < 0.001), and constraining the variances components to be equal across sex (Model 5) also decreased the model fit (Δ-2LL = 50.32, p < 0.001). Therefore, Model 1 was used as the comparison model for testing moderation.

Dropping the moderation effects on all trait-specific and cross-trait shared variance pathways for both females and males (Model 6) was highly significant (Δ-2LL = 60.38, p = 0.007); therefore, subsequent tests of moderation were done for each trait individually. Dropping the moderation effects of variance pathways specific to internalizing resulted in a weak, but significant, decrease in model fit for both females (Model 7; Δ-2LL = 8.98, p = 0.030) and males (Model 8; Δ-2LL = 8.47, p = 0.037). Constraining these moderating effects to be equal across sex (Model 9) resulted in a significant reduction in model fit (Δ-2LL = 15.61, p = 0.001). Further examination of individual parameters for internalizing showed a significant moderation of the additive genetic component (A) in both females (β = -0.08, S.E. = 0.03) and males (β = 0.22, S.E. = 0.10). The moderating effects on shared environmental influences were significant in females (β = 0.21, S.E. = 0.07), but not in males (β = -0.02, S.E. = 0.08). Moderation on unique environmental influences was not statistically significant in either females (β = -0.02, S.E. = 0.04) or males (β < 0.01, S.E. = 0.03).

Removing the moderating effects on externalizing did not alter model fit in females (Δ-2LL = 2.39, p = 0.496) and males (Δ-2LL = 4.84, p = 0.184). Likewise, dropping the moderation of variance in smoking initiation did not result in poorer model fit in females (Δ-2LL = 5.48, p = 0.141) and males (Δ-2LL = 0.66, p = 0.882). Therefore, Model 14 dropped the moderating effects on the variance components specific to externalizing and smoking initiation in both sexes.

Using the final simplified model with collective efficacy-moderation of genetic and environmental influences on internalizing, we estimated the mean levels of internalizing symptoms (on a standardized scale) and the associated additive genetic, shared environmental, and unique environmental variance components at varying levels of collective efficacy for each sex (Table 5). There was a negative direct relationship between collective efficacy and the mean internalizing symptom score, though the effect size was larger in females (β = -0.16) than in males (β = -0.04).

[*Table 5 about here.*]

Figure 4 presents the patterns of change in the raw and the proportional variance components for females and males. For internalizing symptoms in females, the additive genetic variance declined as collective efficacy increased. The shared environmental variance worked oppositely and increased as collective efficacy increased (except at very low levels of

the latter). For males, the additive genetic variance in internalizing symptoms was negligible at intermediate levels of collective efficacy but increased at both very high and very low levels of the latter.

[*Figure 4 about here.*]

Discussion

The present study used the nationally representative sample of U.S. adolescent twins from Wave I of Add Health to examine whether perceived neighborhood collective efficacy moderates the genetic and environmental influences on three adolescent mental health problems: internalizing and externalizing problems and smoking initiation. Additionally, this study aimed to explore whether these gene-environment interactions differ between females and males. This study found partial support for the hypothesized gene-environment interactions in a series of sex-limited, multivariate ACE models. There was evidence of collective efficacy-moderation for internalizing symptoms, but not for the other two traits. Further, the G×E between collective efficacy and internalizing followed distinct trends in females and males.

Gene × Collective Efficacy × Sex for Internalizing in Youth

Among females, as collective efficacy increased, the additive genetic influences on internalizing symptoms decreased substantially, supporting the hypothesized G×E analogous to the *Diathesis-Stress* mechanism (South et al., 2017). This decrease in the additive genetic variance suggests that collective efficacy likely buffers the genetic propensity for internalizing symptoms in adolescent females. This pattern of G×E protective interactions extends the diathesis-stress model to pro-social environments and also lends support to the conceptually similar model of "social control" or "social compensation" of genetic risk (Shanahan & Hofer, 2005; South et al., 2017). Here, a more supportive and cohesive environment may reduce the expression of the genetic risk of a negative behavioral trait.

On the other hand, G×E among adolescent males followed a pattern different than the expected diathesis-stress process. In neighborhoods with intermediate levels of collective efficacy, additive genetic influences made minimal contribution to the individual differences in internalizing symptoms among males. However, in neighborhoods with either very high or very low levels of collective efficacy, the influence of additive genetic factors increased. This pattern may be explained by the *Differential Susceptibility* perspective (Belsky & Pluess, 2009), which proposes that underlying genetic predispositions in some individuals make a given trait more malleable to environmental influences, for better or worse. Consequently, the additive genetic variance is expected to increase in non-normative environmental contexts, whether unusually positive or unusually negative. Individuals who have a genetic

predisposition for experiencing a negative outcome upon exposure to adverse environments also benefit the most from positive environments.

Given the negative relationship between collective efficacy and internalizing symptoms and the observed G×E among males, the differential-susceptibility model would imply that genetic influences likely function as a risk factor at low levels of collective efficacy (with a resultant increase rise in internalizing), but as a resiliency factor at high levels of collective efficacy, contributing to the decrease in internalizing. Further, these individual differences imply that collective efficacy's protective influence against internalizing would be stronger in some males than others. Prior studies using candidate gene analyses have reported similar "differential susceptibility" of internalizing to the interparental relationship in children (Brock et al., 2017) and positive parenting in adolescents (Hankin et al., 2011). Thus, the present study adds to the literature by demonstrating a similar pattern of G×E in biometrical models between collective efficacy and internalizing symptoms in adolescent males.

Besides G×E, the results from this study also suggested that as collective efficacy increased, shared environmental influences contributed to more of the variance in internalizing symptoms, albeit only in females. Moderating factors at play here could include interpersonal resources, such as positive relationships in the neighborhood environment. From the "social capital" perspective (Coleman, 1988), collective efficacy would help youth accrue social capital, including information channels, obligations and expectations, and social norms, which may help promote the youth's psychological well-being. Additionally, families embedded in a socially cohesive and organized neighborhood might worry less about their children's welfare in the broader environment and ease parental monitoring of the youth (Noah, 2015), leading to more positive parenting and family processes. The lack of evidence for collective efficacy-moderation of the shared environmental influences on internalizing in males could be due to the differences in how adolescent females and males, on average, respond to and are impacted by social-environmental factors (Zahn-Waxler et al., 2008).

On average, individual differences in internalizing symptoms were attributable primarily to additive genetic and unique environmental influences among adolescent females and shared environmental and unique environmental influences among males, as indicated in the preliminary univariate ACE models. These quantitative sex differences were consistent with previous studies of Add Health data (e.g., Wright & Schwartz, 2021). Likewise, there were quantitative sex differences in externalizing. Consistent with prior research (e.g.,

Newsome et al., 2016), the variation in externalizing symptoms was primarily attributable to shared environmental and unique environmental influences among females and additive genetic and unique environmental factors in males.

Limitations

Some limitations temper the results from this study. First, the current study combined youth and parent responses to create the "perceived neighborhood collective efficacy" variable, unlike the original conceptualization that used responses only from adult neighborhood residents (Sampson et al., 1997). However, this combined measure aligned well with prior research examining the relationship between collective efficacy and youth mental health using Add Health data (Duncan et al., 2003; Jensen, 2020; Lee & Liechty, 2015). Secondly, although this measure was consistent with the collective efficacy theory (Sampson et al., 2002), it did not differentiate which of the component processes (social cohesion and informal social control) was more consequential in the observed G×E with internalizing. Furthermore, this study only examined individual-level perceptions of neighborhood collective efficacy. However, analyzing neighborhood-level aggregates of these measures with multilevel models may reveal different findings for within- and between-neighborhood variations in collective efficacy, which future research should explore. Finally, because of its modest sample size, this study yielded imprecise parameter estimates, which might also explain the lack of evidence for G×E in externalizing (previously reported by Connolly, 2014).

Conclusion

Despite its limitations, the present study adds to the literature by demonstrating the gene-environment interactions underlying the protective influence of perceived neighborhood collective efficacy on adolescent internalizing problems in the Add Health sample. Specifically, high collective efficacy attenuated the genetic risk of internalizing in adolescent females while enhancing the social-environmental influences shared in the family and its broader community (including the neighborhood). Among males, individual genetic differences in internalizing increased at both high and low levels of collective efficacy. Thereby, this study lends weight to the need for a greater emphasis on community-based initiatives that foster neighborhood social cohesion and informal social control. These findings also shed light on the diathesis-stress model's applications in G×E protective

interactions with pro-social environmental variables and how the same set of environmental moderators and behavioral phenotypes may have different mechanistic underpinnings in females and males (diathesis-stress *vs.* differential-susceptibility, respectively, in this study).

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Conflicts of Interest

The authors have no conflicts of interest to declare.

Author notes

This study was done while Singh was on a research placement at the University of Michigan. Parts of this study's results were presented as a poster at the Virtual World Congress of Psychiatric Genetics, 2020.

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Tables

Table 1

Descriptive Statistics for Twin Pairs Stratified by Zygosity and Sex

Twin pair type	N[a]	Mean (S.D.) / Prevalence				
		Age	Internalizing[b]	Externalizing[c]	Smoking Initiation	Collective Efficacy[d]
Monozygotic Females	141	15.57 (1.58)	17.10 (10.18)	3.25 (4.31)	56.07%	15.24 (4.70)
Monozygotic Males	141	15.79 (1.56)	15.83 (9.08)	5.04 (6.49)	55.87%	15.09 (4.76)
Dizygotic Females	137	15.33 (1.56)	18.17 (9.52)	3.53 (4.51)	48.90%	14.83 (5.06)
Dizygotic Males	147	15.57 (1.72)	15.16 (8.02)	4.45 (4.84)	60.82%	15.45 (4.56)
Dizygotic Opposite-sex	196	15.53 (1.64)	F: 17.34 (10.41)	F: 3.05 (4.05)	F: 49.49%	F: 15.88 (4.67)
			M: 15.69 (8.59)	M: 4.12 (4.12)	M: 49.74%	M: 15.84 (4.32)

Note. F = Female; M = Male (members of the opposite-sex dizygotic twin pairs)

a. N is the number of twin pairs.

b. Internalizing = Modified CESD scale + Physiological anxiety symptoms; Metric 0-89.

c. Externalizing = Non-violent and Violent Delinquent Behaviors; Metric 0-45.

d. Collective Efficacy [Perceived Neighborhood Collective Efficacy] = Youth-perceived Social cohesion + Parent-perceived Informal social control; Metric 0-23.

Table 2

Twin and Bivariate Likelihood-based Correlations

Variable	Univariate Twin Correlation					Within-twin Bivariate Correlation[a]			
	MZF (N=140)	MZM (N=140)	DZF (N=136)	DZM (N=145)	DZO (N=193)	1.	2.	3.[c]	4.
1. Internalizing	0.54 (0.06)	0.40 (0.07)	0.25 (0.08)	0.32 (0.08)	0.18 (0.07)	1 (0)	0.32 (0.03)	0.32 (0.04)	-0.12 (0.04)
2. Externalizing[b]	0.49 (0.06)	0.52 (0.06)	0.45 (0.07)	0.33 (0.07)	0.27 (0.07)	0.22 (0.03)	1 (0)	0.51 (0.04)	-0.09 (0.04)
3. Smoking Initiation[c]	0.79 (0.07)	0.74 (0.10)	0.62 (0.10)	0.59 (0.10)	0.46 (0.10)	0.20 (0.04)	0.54 (0.04)	1 (0)	*-0.08 (0.05)*
4. Collective Efficacy	0.85 (0.02)	0.83 (0.03)	0.82 (0.03)	0.68 (0.04)	0.75 (0.03)	-0.14 (0.04)	*-0.04 (0.04)*	*-0.04 (0.05)*	1 (0)

Note. MZF = Monozygotic females; MZM = Monozygotic males; DZF = Dizygotic females; DZM = Dizygotic males; DZO = Dizygotic opposite sex.

a. Bivariate correlation matrix: Females (n=748) are above the diagonal, and Males (n=765) below the diagonal.

b. Correlation estimated after Rank-based Inverse Normal Transformation of Externalizing scores.

c. Tetrachoric correlation for univariate twin correlations and Polyserial correlation for bivariate correlations.

Table 3

Standardized Univariate ACE estimates

Variable	a^2	c^2	e^2
Internalizing			
Females	0.47 [0.22, 0.62]	0.06 [0.00, 0.26]	0.47 [0.37, 0.59]
Males	0.01 [0.00, 0.31]	0.38 [0.11, 0.70]	0.62 [0.52, 0.76]
Externalizing			
Females	0.10 [0.00, 0.46]	0.38 [0.07, 0.54]	0.52 [0.41, 0.63]
Males	0.41 [0.14, 0.57]	0.09 [0.00, 0.33]	0.50 [0.40, 0.62]
Smoking Initiation[a]	0.40 [0.08, 0.72]	0.33 [0.06, 0.57]	0.27 [0.17, 0.39]
Collective Efficacy			
Females	0.10 [0.01, 0.20]	0.76 [0.66, 0.84]	0.14 [0.11, 0.18]
Males	0.22 [0.10, 0.34]	0.59 [0.48, 0.69]	0.19 [0.15, 0.24]

Note. Estimates indicate the proportion of total variance explained by additive genetic (a^2), shared environmental (c^2), and unique environmental (e^2) factors underlying each phenotype. 95% likelihood-based confidence intervals are shown in parentheses.

a. No statistically significant sex differences in the variance component estimates for Smoking Initiation.

Table 4

Multivariate G×E moderation on Internalizing, Externalizing, and Smoking Initiation by Perceived Neighborhood Collective Efficacy

Model Description	EP	-2LL	df	AIC	Δ-2LL	Δdf	p	Comparison Model[a]
1. Full ACE moderation with scalar sex limitation	96	9774.02	4467	840.02				
Testing overall sex limitation								
2. No sex differences in ACE moderation	78	11582.98	4485	2612.98	1808.96	18	<0.001	1.
3. No sex differences in variances	78	9824.35	4485	854.35	50.32	18	<0.001	1.
Testing overall variance parameters								
4. Moderated AE with scalar sex limitation	72	9818.48	4491	836.48	44.45	24	0.007	1.
5. Moderated CE with scalar sex limitation	72	9820.08	4491	838.08	46.05	24	0.004	1.
Testing moderation on phenotypic variances								
6. No moderation on variances	60	9834.40	4503	828.40	60.38	36	0.007	1.
7. No moderation on INT in females	93	9783.00	4470	843.00	8.98	3	0.030	1.
8. No moderation on INT in males	93	9782.49	4470	842.49	8.47	3	0.037	1.
9. No sex differences in moderation on INT	93	9789.64	4470	849.64	15.61	3	0.001	1.
10. No moderation on EXT in females	93	9776.41	4470	836.41	2.39	3	0.496	1.
11. No moderation on EXT in males	93	9778.86	4470	838.86	4.84	3	0.184	1.
12. No moderation on SMK in females	93	9779.51	4470	839.51	5.48	3	0.140	1.
13. No moderation on SMK in males	93	9774.69	4470	834.69	0.66	3	0.882	1.
14. No moderation on EXT and SMK	84	9787.76	4479	829.76	13.74	12	0.318	1.
Supplementary tests of moderation on cross-trait shared liabilities								

15.	No moderation on INT-EXT in females	81	9794.95	4482	830.95	7.19	3	0.066	14.
16.	No moderation on INT-EXT in males	81	9790.73	4482	826.73	2.97	3	0.396	14.
17.	No moderation on INT-SMK in females	81	9789.98	4482	825.98	2.22	3	0.528	14.
18.	No moderation on INT-SMK in males	81	9789.36	4482	825.36	1.60	3	0.658	14.
19.	No moderation on EXT-SMK in females	81	9792.24	4482	828.24	4.48	3	0.215	14.
20.	No moderation on EXT-SMK in males	81	9792.32	4482	828.32	4.55	3	0.208	14.
21.	No moderation on shared liabilities	66	9813.13	4497	819.13	25.37	18	0.115	14.

Note. N = 762 twin pairs (monozygotic females = 141; monozygotic males = 141; dizygotic females = 137; dizygotic males = 147; dizygotic opposite sex = 196).

G×E = Gene-environment interactions; INT = Internalizing symptoms; EXT = Externalizing symptoms; SMK = Smoking initiation.

EP = number of estimated parameters; LL = log likelihood; df = degrees of freedom; AIC = Akaike Information Criterion; A = additive genetic variance factor; C = shared environmental variance factor; E = unique environmental variance factor.

All models controlled for Age, Age × Sex, Perceived Neighborhood Collective Efficacy of either twin, and Sex × Perceived Neighborhood Collective Efficacy. Externalizing scores were transformed with Rank-based Inverse Normal Transformation before the analyses.

a. Comparison Model was the model against which Δ-2LL was tested.

Table 5

Estimated Moderation of Raw Variance in Internalizing across Perceived Neighborhood Collective Efficacy

Collective Efficacy[a]	Females				Males			
	Mean[a]	a^2	c^2	$e^{2\,b}$	Mean[a]	a^2	$c^{2\,b}$	$e^{2\,b}$
-3	0.51	0.85	0.14	0.60	0.16	0.24	0.30	0.53
-2	0.38	0.71	0.03	0.57	0.07	0.08	0.28	0.53
-1	0.24	0.59	0.00	0.54	-0.01	0.01	0.26	0.53
0	0.10	0.48	0.06	0.52	-0.10	0.02	0.24	0.53
1	-0.04	0.38	0.20	0.49	-0.18	0.12	0.22	0.54
2	-0.18	0.29	0.43	0.46	-0.27	0.30	0.20	0.54
3	-0.32	0.22	0.74	0.44	-0.35	0.57	0.19	0.54

Note. a^2 = additive genetic variance; c^2 = shared environmental variance; e^2 = unique environmental variance

a. Perceived Neighborhood Collective Efficacy and Internalizing are both on a standardized scale.

b. Parameter without statistically significant interaction with Collective Efficacy

Figures

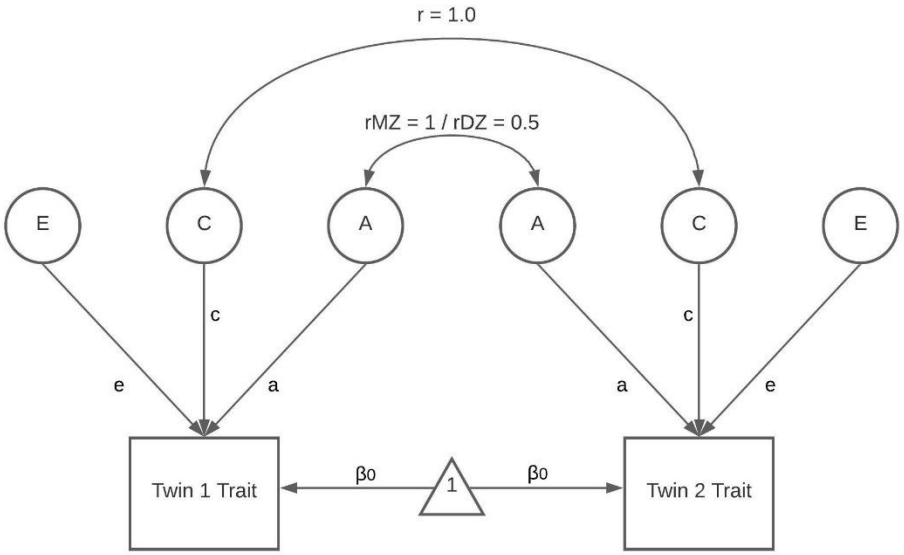

Figure 1. The classic univariate twin ACE model. The figure illustrates the partitioning of a trait's variance into additive genetic (A), shared environmental (C), and unique environmental (E) latent factors. Monozygotic (MZ) twins share 100% of their differentiating genes, while Dizygotic (DZ) twins share, on average, 50% of their genetic variation. Therefore, the correlation between A is constrained to be 1.0 for MZ twin pairs and 0.5 for DZ twin pairs. The correlation between C is fixed at 1.0 for both MZ and DZ twins. These shared environmental influences make the twins more similar, while environmental factors unique to each twin (E) make the twins less similar.

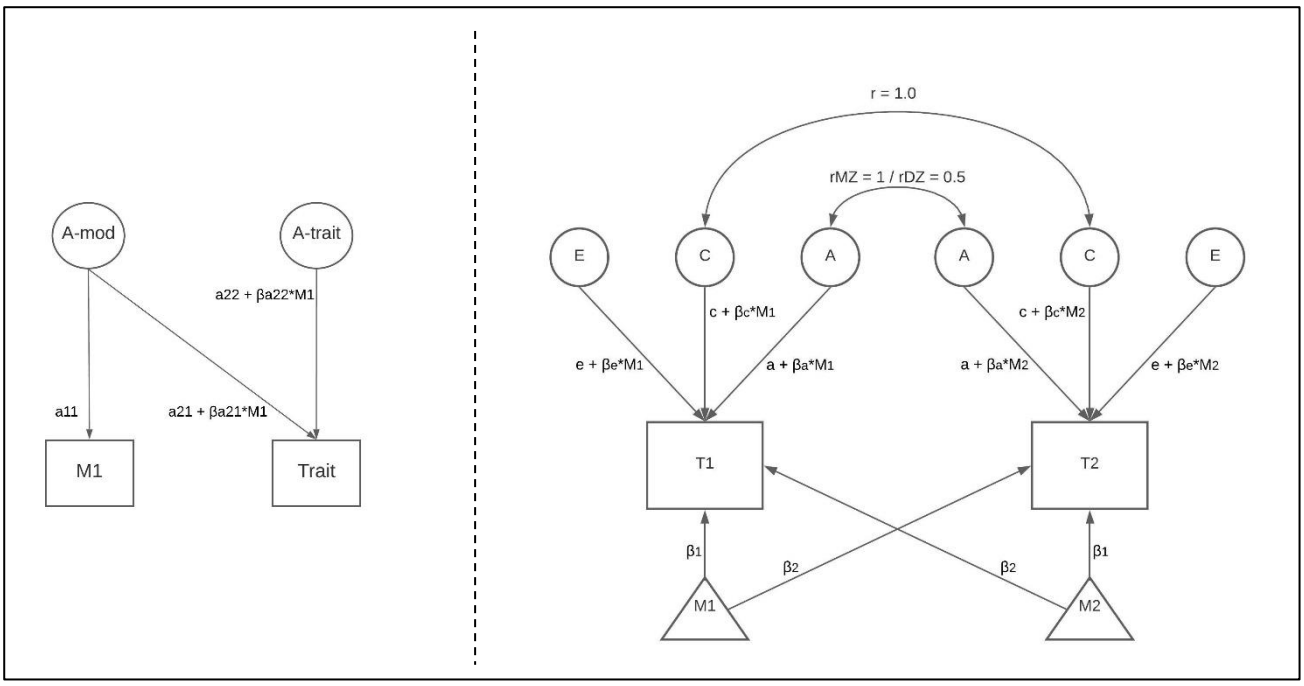

Figure 2. Biometric G×E in ACE models. **2A. (Left)** A simplified bivariate model with only the additive genetic components in Twin 1 shown for ease of display. Moderation can act both on the path unique to the trait (a22) and the path shared between the trait and the moderator (a21). Potential gene-environment correlations are accounted for by the shared paths. **2B. (Right)** The extended univariate model accounts for the gene-environment correlations by including the moderator levels of both twins (M1 and M2) as covariates for the trait mean in each twin. The shared paths between the trait and the moderator from the bivariate model are condensed into the means portion of the extended univariate model. In both models, the β coefficients on the a, c, and e paths estimate moderation.

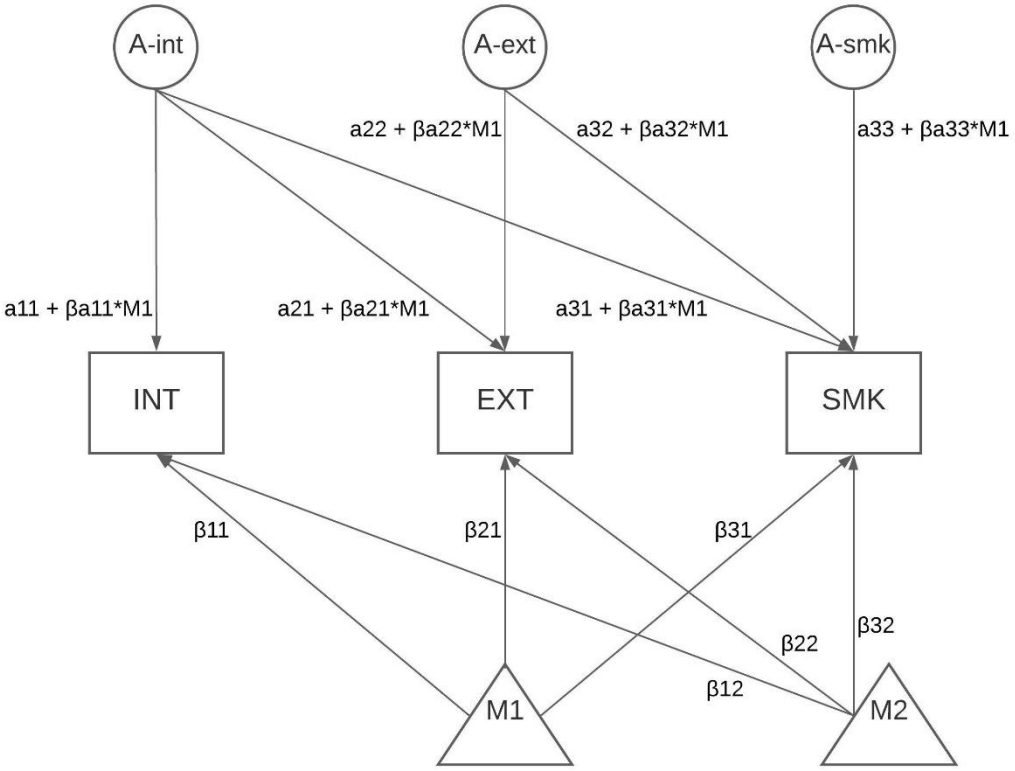

Figure 3. Multivariate ACE model of adolescent Internalizing (INT), Externalizing (EXT), and Smoking initiation (SMK), extended to include G×E with the measured environmental moderator – Perceived Neighborhood Collective Efficacy. For ease of display, only the additive genetic components in Twin 1 are shown. Adopting the model from Figure 2B, gene-environment correlations were accounted for by including as covariates the moderator levels of both twins (M1 and M2) on the trait means in each twin. The β coefficients on the *"a"* paths estimate G×E; for example, the β_{a11} coefficient estimates G×E specific to Internalizing.

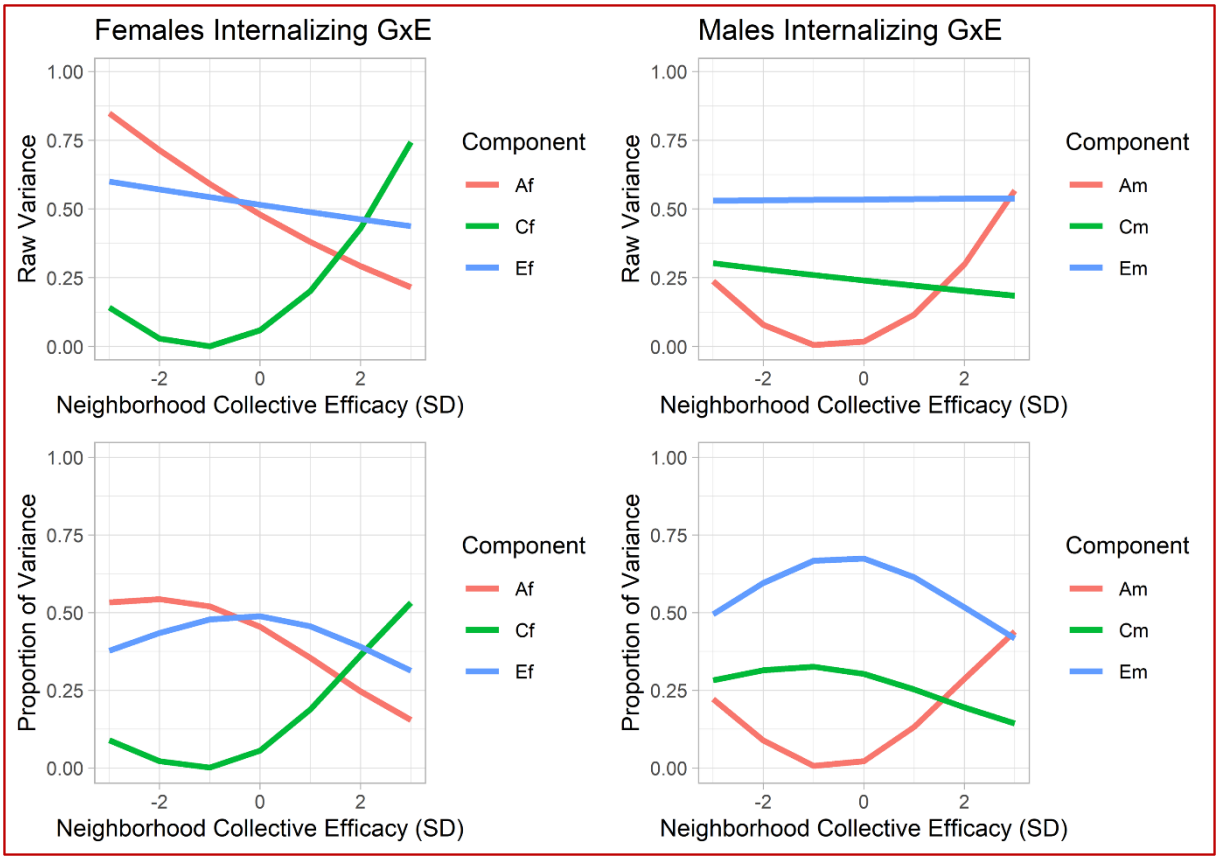

Figure 4. The estimated raw and proportion of variance in adolescent Internalizing attributable to the additive genetic (Af, Am), shared environmental (Cf, Cm), and unique environmental (Ef, Em) influences in females and males, across varying levels of Perceived Neighborhood Collective Efficacy.

Online supplement for ***Examining Sex-dependent Gene-Environment Interactions between Adolescent Mental Health Problems and Perceived Neighborhood Collective Efficacy*** by Singh et al.

Supplementary Table S1

Scale Items and Reliability Coefficients

Variable	Item	Cronbach's α
Internalizing Problem Scale		0.88
	Modified CES-D scale	0.86
	How often was each of the following things true during the past week?	
	1. You were bothered by things that usually don't bother you.	
	2. You did not feel like eating; your appetite was poor.	
	3. You felt that you could not shake off the blues, even with help from your family and your friends.	
	4. felt that you were just as good as other people. (reverse coded)	
	5. You had trouble keeping your mind on what you were doing.	
	6. You felt depressed.	
	7. You felt that you were too tired to do things.	
	8. You felt hopeful about the future. (reverse coded)	
	9. You thought your life had been a failure.	
	10. You felt fearful.	
	11. You were happy. (reverse coded)	
	12. You talked less than usual.	
	13. You felt lonely.	
	14. People were unfriendly to you.	
	15. You enjoyed life. (reverse coded)	
	16. You felt sad.	
	17. You felt that people disliked you.	
	18. It was hard to get started doing things.	

19. You felt life was not worth living.	
Physiological anxiety symptoms	0.72
Please tell me how often you have had each of the following conditions in the past 12 months.	
1. Feeling hot all over suddenly, for no reason.	
2. A stomach-ache or an upset stomach.	
3. Cold sweats.	
4. Dizziness.	
5. Chest pains.	
6. Trouble falling asleep or staying asleep.	
7. Trouble relaxing.	
8. Moodiness.	
Externalizing Problem Scale	0.84
In the past 12 months, how often did you…	
1. Get into a serious physical fight?	
2. Hurt someone badly enough to need bandages or care from a doctor or nurse?	
3. Take part in a fight where a group of your friends was against another group?	
4. Use or threaten to use a weapon to get something from someone?	
5. Paint graffiti or signs on someone else's property or in a public place?	
6. Deliberately damage property that did not belong to you?	
7. Go into a house or building to steal something?	
8. Take something from a store without paying for it?	
9. Drive a car without its owner's permission?	
10. Steal something worth more than $50?	
11. Steal something worth less than $50?	
12. Lie to your parents or guardians about where you had been or whom you were with?	
13. Run away from home?	
14. Sell marijuana or other drugs?	
15. Were you loud, rowdy, or unruly in a public place?	

Note. CES-D = Center for Epidemiological Studies – Depression Scale. See the Materials and Methods section for details.

Supplementary Table S2

Univariate Twin ACE Models with Sex Limitation (Gene × Sex)

Model Description	EP	-2LL	df	AIC	Δ-2LL	Δdf	p	Comparison Model[a]
Internalizing								
1. Saturated	27	4159.84	1497	1165.84				
2. ACE with non-scalar and scalar sex limitation	11	4184.11	1513	1158.11	24.26	16	0.084	1.
3. **ACE with scalar sex limitation**	10	4184.13	1514	1156.13	0.03	1	0.871	2.
4. ACE with no sex limitation	7	4205.22	1517	1171.22	21.09	3	<0.001	3.
5. AE with scalar sex limitation	8	4189.61	1516	1157.61	5.47	2	0.065	3.
6. CE with scalar sex limitation	8	4200.35	1516	1168.35	16.22	2	<0.001	3.
Externalizing								
7. Saturated	27	3911.32	1497	917.32				
8. ACE with non-scalar and scalar sex limitation	11	3925.60	1513	899.60	14.28	16	0.578	7.
9. **ACE with scalar sex limitation**	10	3925.72	1514	897.72	0.12	1	0.723	8.
10. ACE with no sex limitation	7	3934.88	1517	900.88	9.15	3	0.027	9.
11. AE with scalar sex limitation	8	3932.16	1516	900.16	6.44	2	0.040	9.
12. CE with scalar sex limitation	8	3935.12	1516	903.12	9.39	2	0.009	9.
Smoking Initiation								
13. Saturated	17	1885.83	1496	-1106.17				
14. ACE with non-scalar and scalar sex limitation	11	1899.33	1504	-1108.67	13.5	8	0.096	13.
15. ACE with scalar sex limitation	10	1900.64	1505	-1109.36	1.32	1	0.251	14.
16. **ACE with no sex limitation**	7	1901.57	1508	-1114.43	0.93	3	0.819	15.
17. AE with no sex limitation	6	1907.46	1509	-1110.54	5.89	1	0.015	16.
18. CE with no sex limitation	6	1907.43	1509	-1110.57	5.86	1	0.016	'16.

Perceived Neighborhood Collective Efficacy									
19.	Saturated	27	3544.89	1497	550.89				
20.	ACE with non-scalar and scalar sex limitation	11	3559.62	1513	533.62	14.73	16	0.544	19.
21.	**ACE with scalar sex limitation**	10	3561.30	1514	533.30	1.68	1	0.194	20.
22.	ACE with no sex limitation	7	3571.45	1517	537.45	10.15	3	0.017	21.
23.	AE with scalar sex limitation	8	3701.50	1516	669.50	140.20	2	<0.001	21.
24.	CE with scalar sex limitation	8	3575.38	1516	543.38	14.06	2	0.001	21.

Note. N = 762 twin pairs (monozygotic females = 141; monozygotic males = 141; dizygotic females = 137; dizygotic males = 147; dizygotic opposite sex = 196).

All models controlled for Age and Age × Sex. Externalizing scores were transformed with Rank-based Inverse Normal Transformation before analyses.

EP = number of estimated parameters; LL = log likelihood; df = degrees of freedom; AIC = Akaike Information Criterion; A = additive genetic variance factor; C = shared environmental variance factor; E = unique environmental variance factor.

a. Comparison Model was the model against which Δ-2LL was tested.