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Prevention Effects Moderate the Association of 5-HTTLPR and Youth Risk Behavior Initiation: Gene × Environment Hypotheses Tested via a Randomized Prevention Design

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A randomized prevention design was used to investigate a moderation effect in the association between a polymorphism in the *SCL6A4*(*5HTT*) gene at 5-HTTLPR and increases in youths' risk behavior initiation. Participation in the Strong African American Families (SAAF) program was hypothesized to attenuate the link between 5-HTTLPR status and risk behavior initiation. Youths (N = 641, M age = 11.2 years) were assigned randomly to a SAAF or control condition. Risk behavior initiation across 29 months was linked positively with the 5-HTTLPR genotype and negatively with SAAF participation. Control youths at genetic risk initiated risk behavior at twice the rate of SAAF youths at genetic risk and youths not at genetic risk in either condition.

In an article published previously in this journal (Brody et al., 2004), we described the theoretical bases and an empirical test of a family-centered preventive intervention for rural African American families with a son or daughter in early adolescence. The Strong African American Families Program (SAAF) was designed to prevent the initiation of a cluster of risk behaviors that included alcohol use, marijuana use, and sexual activity. The literature consistently indicates that earlier onset of risk behavior is associated with greater likelihood of problematic outcomes in adolescence and adulthood (Brook & Newcomb, 1995; Choi, Gilpin, Farkas, & Pierce, 2001) and non-normative developmental trajectories that include low educational and occupational attainment (Sanford et al., 1994), reduced prosocial behavior in adulthood (Ackerman, Zuroff, & Moskowitz, 2000), and impaired mental health functioning (Windle & Windle, 2001). Accordingly, substantial effort has been devoted to the development of preventive interventions that delay the initiation of risk behaviors. SAAF was the first such intervention to have demonstrated efficacy for preventing the initiation of risk behaviors among rural African American youths (Brody Murry, Gerrard, et al., 2006).

The development of SAAF followed an approach recommended by the Institute of Medicine (1994) and the National Institute of Mental Health (1998). Both reports described a preventive intervention cycle in which longitudinal developmental research conducted with the targeted population is applied in deriving an etiological model of the problem's development, including the protective factors that may prevent its development. In the next phase of this cycle, the theoretical model for the intervention is constructed; malleable protective factors—those that can be modified—are identified as proximal targets for prevention efforts and a program is designed to change them. We proposed the SAAF randomized, longitudinal trial not only as a means of testing an intervention's effectiveness in preventing the initiation of risk behaviors but also as a test of the theory on which the developmental hypotheses were based. In studying contextual influences on children and families, intervention research is

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one of the only means through which variables can be appropriately manipulated while allowing an experimental investigation of causality. Evaluations of SAAF have confirmed its efficacy in preventing the initiation of risk behaviors (Brody, Kogan, Chen, & Murry, 2008; Brody et al., 2004; Brody, Murry, Gerrard, et al., 2006; Brody, Murry, Kogan, et al., 2006; Gerrard et al., 2006) and have also supported the developmental hypotheses included in its theoretical model (Brody, Murry, Chen, Kogan, & Brown, 2006; Brody et al., 2005; Brody, Murry, Gerrard, et al., 2006; Murry et al., 2005).

Randomized prevention trials also present a unique opportunity to test hypotheses about a theoretically and substantively important area emerging in developmental science, the interaction of genetic predispositions with contextual processes to create variations in phenotypes over time. Such transactions are termed Gene × Environment (G×E) interactions, which occur when genetic variation alters an individual's sensitivity to specific environmental effects or when environmental effects exert differential control over genetic effects (Kendler & Eaves, 1986). Typically, G×E interactions have been studied using both contemporaneous and longitudinal epidemiological research designs in which genotypes, environmental risk factors, and outcomes are observed as they unfold over time in the population. These studies have tested the hypothesis that an interaction between genotype and environmental risk accounts for unique and nontrivial proportions of the outcomes in focal populations (Moffitt, Caspi, & Rutter, 2006).

Like all methodological approaches, the study of G×E interactions via the epidemiological approach has some limitations. A primary concern is the difficulty in identifying a true environmental exposure or effect, particularly if the exposure occurs over an extended period of time. The use of intervention strategies such as randomized prevention trials is one means of determining whether an environmental factor has attained causal status. Through the implementation of such trials, a causal relationship between an environmental manipulation and the alteration of the course of a targeted outcome can be identified (Rutter, 2005). Randomized prevention designs also rule out an alternative rival explanation for G×E interactions, gene–environment correlations that occur when genetic influence on participants' probability of exposure to environmental factors (e.g., life stress, relationship conflict) contaminates measures of the environment (Rutter, 2007). For example, genetics contribute to extroversion and introversion (Rutter & Silberg, 2002). Extroverted individuals may seek social environments that differ from the environments that introverted individuals seek. Differences in the selected environments may interact with genes to create the impression that outcomes arise from G×E interactions when they are actually attributable to gene-environment correlations. Random assignment of participants to environmental conditions in an intervention trial rules out this type of self-selection.

Random assignment has the additional advantage of ruling out confounds which, in epidemiological designs, may be taken for environmental effects. These include history (unmeasured events, such as an economic downturn, which co-occur with measured events), maturation (natural change across time, such as the onset of puberty), repeated testing (effects of prior assessments on responses to subsequent assessments as participants become familiar with the instruments), and statistical regression (a subsequent shift toward the population mean following an initial low or high assessment). Finally, the testing of G×E hypotheses using experimental designs, such as randomized prevention trials, enhances statistical power as much as fivefold over epidemiological approaches (McClelland & Judd, 1993); consequently, fewer participants may be needed to obtain a detectable G×E interaction.

The present research was designed to help fill the need in the literature for studies in which randomized prevention designs are used to test G×E hypotheses. The primary hypothesis of this study concerned a moderation effect in the association between a genetic vulnerability factor, a variable nucleotide repeat polymorphism in the promoter region of the SLC6A4 gene (*5HTT*) referred to as the 5-HTTLPR, and the initiation of risk behaviors (alcohol use, marijuana use, and sexual intercourse) during early adolescence among African American youths. We predicted that participation in SAAF would ameliorate the link between the 5-HTTLPR polymorphism and risk behavior initiation. In the following sections, we describe the theoretical and empirical bases for this hypothesis.

We hypothesized that functional polymorphism in the promoter region of the *5HTT* would affect the likelihood of the youths' initiation of risk behavior. *5HTT* is a key regulator of serotonergic neurotransmission, localized to 17p13 and consisting of 14 exons and a single promoter. A well-characterized polymorphism in the promoter region results in two variants, a short and a long allele, with the short allele resulting in lower serotonin

transporter availability. The short variant contains 12 copies of a 22-bp repeat element and the long variant has 14 copies of the repeat element. An important limitation of existing genetic research is its almost exclusive focus on populations of northern European descent to the exclusion of other ethnic groups. Genetic variation exists across ethnic groups at loci known to be responsible for moderating environmental risk mechanisms. For example, greater diversity in the distribution of loci of *5HTT* is generally found in the African American population than in the European American population (Disotell, 2000).

Youths with one or two copies of the *5HTT* ''short'' allele are hypothesized to display greater risk behavior initiation than youths with two copies of the ''long'' allele. Findings from different literatures converge to support this hypothesis. Genetic association studies indicate that the short allele of 5-HTTLPR is a risk factor for alcohol dependence and other drug use among adults (Kreek, Nielsen, Butelman, & LaForge, 2005) and it was recently found to forecast increased substance use across early adolescence (Brody et al., 2009). The short allele variant of 5-HTTLPR is also associated with alcohol consumption among college students (Herman, Philbeck, Vassilopoulos, & Depetrillo, 2003), maltreated youths (Kaufman et al., 2007), and adults in a large, representative community sample from the United Kingdom (Munato, Lingford-Hughes, Johnstone, & Walton, 2005).

Other studies provide a different kind of support for the hypothesized link between the 5-HTTLPR short allele and the initiation of risk behaviors. Rather than examining the direct association between 5-HTTLPR and risk behaviors, researchers examined associations between 5-HTTLPR and indicators of low self-control, a risk factor for a cluster of risk behaviors that include alcohol use and early sexual activity (Brody & Ge, 2001; Mezzich et al., 1997; Miller & Brown, 1991; Rutter et al., 1997). The 5-HTTLPR polymorphism is associated with high activity, low attentiveness, and high levels of negative affect in children (Auerbach, Faroy, Ebstein, Kahana, & Levine, 2001; Propper & Moore, 2006; Suomi, 2004) and with disregard for rules, impulsivity, and high levels of negative affect in adults (Burt, 2006; Headley & Wearing, 1989; Kendler, Gardner, & Prescott, 2003; Kreek, Nielsen, & LaForge, 2004). These studies converge to support consideration of *5HTT* variation as a predictor of risk behavior initiation across early adolescence.

Studies that include assessments of *5HTT* and psychosocial experiences suggest a focus on moderation. A noteworthy example is Caspi et al.'s (2003) research, in which a sample drawn from the Dunedin Longitudinal Study was used to test the hypothesis that the level and severity of depressive symptoms in early adulthood would be a product of maltreatment during childhood and the presence of one or two copies of the short-allele variant at the 5-HTTLPR locus. A significant and substantial G×E effect confirmed the hypothesis. This prospective finding is notable in theoretical terms because it demonstrated that genetic variability at *5HTT* altered individuals' reactivity to the psychosocial experience of childhood maltreatment.

Several attempts have been made to replicate the Caspi et al. (2003) findings, with the preponderance yielding similar results. The replication studies were designed to test moderation effects between the short-allele variant of 5-HTTLPR and indicators of psychosocial risk that indexed negative life events (Dick et al., 2007; Eley et al., 2004; Gillespie, Whitfield, Williams, Heath, & Morton, 2005; Grabe et al., 2005; Kaufman et al., 2004; Kendler, Kuhn, Vittum, Prescott, & Riley, 2005; Surtees et al., 2006; Taylor et al., 2006; Wilhelm et al., 2006; Zalsman et al., 2006) and low SES (Manuck, Flory, Ferrell, & Muldoon, 2004). As in Caspi et al.'s study, the criterion variable was the severity of depressive symptomatology. All but Gillespie et al. (2005) and Surtees et al. (2006) replicated Caspi and associates' findings that the short variant of 5-HTTLPR increased reactivity to psychosocial adversity, resulting in elevated depressive symptomatology.

A recent series of findings is particularly germane to this report. In a study involving children (Kaufman et al., 2007) and two studies involving adults (Covault et al., 2007; Nilsson et al., 2005), G×E interactions between the 5-HTTLPR genotype and life stress were associated with alcohol consumption. Participants with the short allele variant of 5-HTTLPR who reported high levels of life stress drank more frequently and consumed more alcohol than did participants experiencing similar levels of life stress who did not carry this variant.

Although these studies have shown with relative consistency that the short-allele form of 5-HTTLPR moderates the effects of exposure to psychosocial adversity, they did not address an equally important question in developmental science: Can participation in a preventive intervention ameliorate the risk that variation in 5HTT is hypothesized to confer on risk behavior initiation across early adolescence? Although a credible basis exists for hypothesizing protective moderation effects, little, if any, research has explored the possibility that

environmental changes resulting from participation in an efficacious prevention program can moderate genetic risk. The present research addressed this question by examining the SAAF program's protective capacity.

The primary purpose of this study was to test the G×E hypothesis that random assignment to the SAAF prevention group versus a control group would interact with genetic risk to predict youths' risk behavior initiation. Specifically, we predicted that (a) youths at genetic risk from one or two copies of the short-allele variant at the 5-HTTLPR who were assigned randomly to the control condition would initiate more risk behaviors compared with youths at genetic risk assigned randomly to the SAAF prevention condition, (b) youths at genetic risk assigned to the control condition would initiate more risk behaviors than would youths without genetic risk assigned randomly to the prevention or control condition, and (c) youths at genetic risk assigned to the prevention condition would not initiate more risk behaviors than would youths without genetic risk assigned to either the prevention or control condition.

The aforementioned study hypotheses were based on Rutter's (1985) thesis that protective processes have their greatest effects on youths at highest risk; presumably, protective processes augment at-risk youths' inhibitory controls and provide competencies that occasion positive developmental outcomes. In SAAF, parents learned caregiving practices that have been found to deter African American youths from initiating high-risk behaviors. These practices include racial socialization, high levels of vigilance and monitoring along with high levels of emotional support, clearly articulated norms and expectations for risk behavior, and bidirectional family communication (Brody, Flor, Hollett-Wright, & McCoy, 1998; Brody & Ge, 2001; Brody, Ge, Katz, & Arias, 2000; Brody, Chen, et al., 2006; DiClemente et al., 2001; Miller, Kotchick, Dorsey, Forehand, & Ham, 1998; Perrino, González-Soldevilla, Pantin, & Szapocznik, 2000). We conjectured that enhancing these protective caregiving practices via SAAF would mitigate the risk conferred by the short version of 5-HTTLPR by decreasing the likelihood that youths would encounter circumstances that provide opportunities to initiate and engage in risk behaviors.

Summary of the Present Research

This study was conducted with rural African American youths and their caregivers who participated in a randomized, longitudinal prevention trial using procedures that have been shown to yield reliable data in the study of the development of risk behaviors. These procedures included computer-based interviewing, matching of interviewers and participants by ethnicity, and extensive reassurances concerning confidentiality of the data (Murry & Brody, 2004; Patrick et al., 1994). Youths provided data on risk behavior initiation and opportunities for risk behavior, and caregivers provided data on intervention-targeted parenting practices. Genetic data were obtained from youths using procedures developed in partnership with rural African American community members (Brody et al., 2009). We predicted that youths with one or two copies of the short-allele variant of 5-HTTLPR who were randomly assigned to the control condition would initiate more risk behaviors over a period of 2 years and 5 months than would youths at similar risk who were randomly assigned to the prevention condition or youths without genetic risk who were randomly assigned to either condition. Support for this hypothesis would demonstrate the utility of using randomized prevention designs for testing G×E hypotheses while highlighting prevention programs' protective capacity for ameliorating genetic risk.

Method

Data were collected as part of the evaluation of the SAAF family-based preventive intervention study. The data reported in this article were collected from families randomly assigned to the prevention or control condition. The initiation of risk behaviors was assessed when the youths were 11 (pretest), 12 (posttest), and 14 (long-term follow-up) years old. Data on intervention-targeted parenting practices and risk opportunity were obtained at the pretest and posttest assessments; genetic data were obtained 2 years after the long-term follow-up assessment. Below, we briefly describe participant recruitment and enrollment, intervention implementation and fidelity, and data collection procedures; these procedures are described extensively in earlier reports on SAAF's efficacy (Brody et al., 2004; Brody, Murry, Chen, et al., 2006; Brody, Murry, Kogan, et al., 2006; Brody et al., 2008).

Participants

Participants in the SAAF trial included 641 African American families who resided in rural Georgia. From each family, a youth who was 11 years

old when recruited (58% girls) and the youth's primary caregiver, typically the biological mother, provided data. At the first data collection session, youths' mean age was 11.21 years (*SD* = 0.41) and caregivers' mean age was 37.7 years (*SD* = 7.62). Of the mothers, 36.6% were married and living with their husbands, 2.3% were married but separated, 7.1% were cohabiting with a significant other, 20.1% were in a significant relationship but not cohabiting, and 32.7% were not in a significant relationship. Mean household gross monthly income was $2,109 (*SD* = $1,443) and mean per capita gross monthly income was $509 (*SD* = $411). Although 74% of the mothers were employed outside the home and worked an average of 39.7 hr per week, 41% of the families lived below federal poverty standards and another 26% lived within 150% of the poverty threshold; they could be described as working poor (Boatright & Bachtel, 1999). As reported elsewhere, throughout the study the youths reported, on average, relatively close relationships with their primary caregivers, moderate levels of self-esteem and academic competence, and low rates of conduct problems (Brody et al., 2009).

Schools in four rural Georgia counties provided lists of 11-year-old students, from which youth participants were selected randomly (see Brody et al., 2004). Families were contacted and enrolled in the study by community liaisons who resided in the counties where the participants lived. Community liaisons were African American community members, selected on the basis of their social contacts and standing in the community, who worked with the researchers on participant recruitment and retention. The liaisons sent letters to the families and followed up with phone calls to the caregivers, during which the community liaisons answered any questions that the caregivers raised. Families who were willing to participate in the pretest were told that a research staff member would contact them to schedule the administration of the assessment in the families' homes. Parents gave written consent to their own and the youths' participation, and youths gave written assent to their own participation. Each family was paid $100 after each of the three assessments. The sample for the present study included 350 families randomly assigned to receive the SAAF intervention and 291 randomly assigned to the control condition; families assigned to SAAF were oversampled.

Of the families who provided data at the pretest assessment, 91% provided data at the posttest and at the long-term follow-up assessment conducted 29 months after the pretest. Two years after the long-term follow-up (4.5 years after the pretest), we attempted to recontact the study families to obtain youths' DNA from saliva samples. Of the original sample assessed at pretest, 84% (*n* = 539) of the families were relocated; in the relocated families, 86% (*n* = 461) of the youths agreed to provide DNA. Two equivalence analyses were executed to determine whether any differences existed on demographic characteristics (monthly per capita income, number of children in the household, target gender, and maternal marital status) or the study variables (risk behavior initiation, regulated-communicative parenting, and risk opportunities) between: (a) the families with pretest data (*n* = 641) and the sample with long-term follow-up data (*n* = 539; see Table 1) and (b) the families of target youths who did (*n* = 461) and did not (*n* = 78) agree to provide DNA (to conserve space, the means and standard deviations for these tests are not presented). For these analyses, *t* tests were used to compare all of the demographic and study measures except gender and maternal marital status, for which chi-square tests were used. No differences emerged on demographic or study variables between the families with pretest data and those with long-term follow-up data. Neither did any differences emerge between families or youths who did or did not agree to provide DNA.

Preparation for the Collection of Genetic Data

Several steps were taken to prepare for the collection of genetic data. The researchers, who included a development psychologist, a clinical psychologist, and a family scientist, all of whom specialized in family processes; a psychiatrist who specialized in human genetics; and a biostatistician who specialized in the analysis of genetic data, met regularly over a 2-year period to review the genetic and family process literature. Their meetings resulted in the formulation of the hypotheses tested in this report. In addition, two focus groups of rural African Americans, 10 parents and 10 adolescents, each met for 2 hr to help the investigators understand any concerns that might arise about DNA collection and to develop procedures for dealing with these concerns. The concerns that arose involved procedural clarity, the possibility of individual identification, and potential benefits. Many focus group members wanted a clear explanation of the procedures for obtaining DNA and they wanted to know how DNA collection would advance knowledge about African American youths' development. This feedback was incorporated into a brochure

Table 1
Equivalence of Pretested and Long-Term Follow-Up Samples

	Pretested sample (n = 641)			Long-term follow-up samples (n = 539)				
Descriptive measure	*M*	*SD*	%	*M*	*SD*	%	*t*	χ^2
Per capita income, $/month	518.09	383.84		524.79	414.90		1.53	
Number of children in household	2.65	1.34		2.86	1.50		1.45	
Female youths			52.90			52.00		.03
Single-mother-headed families			56.40			55.40		.03
Regulated-communicative parenting	25.14	2.80		24.69	2.87		−1.48	
Risk opportunity	0.17	0.62		0.30	0.91		1.45	
Risk behavior initiation	0.30	1.02		0.48	1.96		0.89	

(available from the first author) in which straightforward answers to frequently asked questions are provided. A copy of the brochure was given to each participating family to provide them with written information that they could consult in addition to the verbal description of the protocol that accompanied DNA collection.

A pilot study was conducted to assess the viability of DNA collection from saliva versus whole blood (Philibert, Zadorozhnyaya, Beach, & Brody, 2008). As predicted, concentrations of DNA were higher in blood than in saliva; nevertheless, saliva samples contained adequate amounts of DNA to permit genotyping. We concluded that the ease and economy of DNA collection from saliva made it appropriate for the research questions we planned to address.

Intervention Implementation and Fidelity

The SAAF prevention program consisted of seven consecutive meetings held at community facilities, with separate parent and youth skill-building curricula and a family curriculum. Each meeting included separate, concurrent training sessions for parents and youths followed by a joint parent–youth session during which the families practiced the skills they learned in the separate sessions. Concurrent and family sessions each lasted 1 hr; thus, parents and youths received 14 hr of prevention training. During the weeks when the intervention families participated in the prevention sessions, the control families received three leaflets via post mail: One described various aspects of early adolescent development, another dealt with stress management, and the other provided suggestions for encouraging youths to exercise.

Parents in the prevention condition were taught regulated-communicative parenting processes, which included the consistent use of nurturant-involved parenting practices along with high levels of monitoring and control, adaptive racial socialization strategies, strategies for communication about sex, and the establishment of clear norms and expectations for the use of alcohol and other substances. Youths learned the importance of having and abiding by household rules, adaptive behaviors to use when encountering racism, the importance of forming goals for the future and making plans to attain them, and the similarities and differences between themselves and age mates who use alcohol. Together, family members practiced communication skills and engaged in activities designed to increase family cohesion and the youth's positive involvement in the family.

Ten three-person teams of African American group leaders, each of whom had received 40 hr of training, conducted 38 intervention groups that ranged in size from 3 to 12 families (M = 10). Families attended a mean of 4.7 sessions. Approximately 68% of the families took part in four or more sessions, 37% attended all seven sessions, 10% attended one or two sessions, and 14% attended no sessions. To preserve the random nature of the group assignment, the analyses reported here included all families who completed the pretest, posttest, and long-term follow-up regardless of the number of prevention sessions that they actually attended (an intent-to-treat analysis). Although this may have reduced the magnitude of the differences between the prevention and control group, we retained these families in the analysis to preclude the introduction of self-selection bias into the findings.

All sessions were videotaped to assess fidelity to the prevention program. For each group, two parent, two youth, and two family sessions were selected randomly and scored by three raters for

adherence. Interrater reliability checks were conducted on 23% of the adherence assessments; mean coverage of the prevention curriculum components was 90% for the parent, youth, and family sessions.

Procedure

To enhance rapport and cultural understanding, African American students and community members served as home visitors to collect pretest, posttest, and long-term follow-up data. During the pretest, posttest, and long-term follow-up data collections, field interviewers who were blind to the families' group assignments made one home visit lasting 2 hr to each family. The posttest was conducted in both the prevention and control conditions an average of 3 months after the end of prevention programming. The time from pretest to posttest averaged 8 months; the long-term follow-up took place an average of 29 months after the pretest. Informed consent forms were completed at all data collection points. Caregivers consented to their own participation and the youths' participation in the study, and youths assented to their own participation. During the home visits, self-report questionnaires were administered to caregivers and youths in an interview format. Each interview was conducted privately, with no other family members present or able to overhear the conversation.

Measures

The measures were selected for their relevance to the evaluation of the preventive intervention program. They were derived from previous research, which included focus group meetings and pilot testing followed by construct validation of the instrument (Brody, Stoneman, Flor, & McCrary, 1994; Brody, Stoneman, Flor, McCrary, Hastings, et al., 1994; Brody et al., 2004). Parenting data were collected from caregivers and risk opportunity, risk behavior initiation, and DNA data were obtained from youths.

Demographics. Youth age and gender, maternal age, maternal employment, and monthly income were recorded. Each caregiver reported the number of children and adults living in the home and her marital/significant relationship status.

Caregivers' regulated-communicative parenting. Caregivers reported on their nurturant-involved parenting, racial socialization, communication about sex, and clear communication of expectations about the use of alcohol and other substances. Nurturant-involved parenting was assessed via an instrument that we have used in our previous research with rural African American families (Brody et al., 2001; Brody et al., 2003; Ge, Brody, Conger, Simons, & Murry, 2002). The scale is composed of 19 items rated on Likert-type scales that assess the frequency, ranging from 1 (*never*) to 5 (*always*), of parental behaviors concerning involvement, inductive discipline, consistent discipline, consistent rules, and monitoring. As in our prior research (Brody et al., 2001; Brody et al., 2003), responses to these subscales were summed to form the nurturant-involved indicator. Cronbach's alphas for the pretest and posttest assessments exceeded .70. The Racial Socialization Scale (Hughes & Johnson, 2001) includes 15 items rated on Likert-type scales ranging from 1 (*never*) to 3 (*3–5 times*). Caregivers reported how often during the past month they had engaged in specific racial socialization behaviors, such as talking with youths about discrimination. Cronbach's alphas at pretest and posttest exceeded .75. The Parental Communication About Sex Scale (Gerrard, Gibbons, & Gano, 2003; Wills, Gibbons, Gerrard, Murry, & Brody, 2003) consists of nine items rated on a Likert-type scale ranging from 0 (*no*) to 2 (*yes, quite a bit*), indicating whether and how much a parent has discussed various aspects of sexuality, such as sexually transmitted infections and HIV/AIDS, with a youth. Cronbach's alphas exceeded .80 at pretest and posttest. The establishment of clear expectations about alcohol use was assessed using two items, rated on a Likert-type scale ranging from 0 (*not true*) to 2 (*very true* or *often true*): ''I have told my child exactly what I feel about alcohol and drugs,'' and ''I remind my child that very few children his or her age get involved with alcohol and drugs.'' The correlation between the items was .51 at both pretest and posttest.

Risk opportunity. The risk opportunity scale consists of two items that have been used in previous research (Van Etten & Anthony, 1999). On a response scale ranging from 0 (*never*) to 4 (*7 or more times*), youth indicated how often during the past month they had the opportunity to drink alcohol and to smoke marijuana. Cronbach's alpha was .71 at both pretest and posttest.

Risk behavior initiation. Risk behavior initiation was evaluated using instruments that we have previously used with rural African American youths (Brody, Murry, Gerrard, et al., 2006; Wills, Gibbons, Gerrard, & Brody, 2000; Wills et al., 2003). Youths indicated whether they had ever drunk beer, wine, wine coolers, whiskey, gin, or other liquor (alcohol use); used marijuana; or had sexual intercourse.

Responses to these items were coded 1 for *yes* (ever used alcohol, used marijuana, or had sexual intercourse) and 0 for *no*. These risk behavior initiation scores were summed to form a risk behavior initiation index that could range from 0 to 3 at each assessment.

Genotyping. Youths' DNA was obtained using Oragene™ DNA kits (Genetek, Calgary, AB, Canada). Youths rinsed their mouths with tap water, then deposited 4 ml of saliva in the Oragene sample vial. The vial was sealed, inverted, and shipped via courier to a central laboratory in Iowa City, IA where samples were prepared according to the manufacturer's specifications. Genotype at 5-HTTLPR was determined for each youth as previously described (Bradley, Dodelzon, Sandhu, & Philibert, 2005). Of the sample, 6.4% were homozygous for the short allele (*ss*), 35.2% were heterozygous (*sl*), and 58.4% were homozygous for the long allele (*ll*). None of the alleles deviated from Hardy–Weinberg equilibrium ($p = .77$, *ns*). Consistent with prior research (Hariri et al., 2005), genotyping results were used to form two groups of participants: those homozygous for the long allele and those with either one or two copies of the short allele.

Results

Descriptive Statistics

As expected, prevalence rates for risk behavior initiation at pretest, when the youths were 11 years old, were low: 13.8% for alcohol use, 1.5% for binge drinking, 0.5% for marijuana use, and 3.2% for sexual intercourse. The mean risk initiation index score at pretest was 0.55 ($SD = 1.3$). Lifetime prevalence rates increased over time; at the long-term follow-up, when the youths were 14 years old, lifetime rates were 39.5% for alcohol use, 5.4% for binge drinking, 5.9% for marijuana use, and 18.0% for sexual intercourse. The mean risk initiation index score was 0.97 ($SD = 2.09$). These rates for African American youths are consistent with data from other studies (Johnston, O'Malley, Bachman, & Schulenberg, 2004).

Plan of Analysis for the Study Hypotheses

Latent growth modeling (Singer & Willett, 2003) was used to test the first two study hypotheses, that (a) compared with youths without genetic risk, youths with one or two copies of the short allele would evince a greater increase in risk behavior initiation over time, and (b) compared with youths assigned randomly to the SAAF condition, youths assigned randomly to the control condition would evince greater increases in risk behavior initiation over time. Planned group comparisons (Keppel, 1982; Kirk, 1982) were used to test the primary study G×E hypothesis: Youths at genetic risk who were assigned randomly to the control condition would evince greater mean risk behavior initiation at long-term follow-up than would (a) youths with genetic risk assigned randomly to the SAAF condition and (b) youths without genetic risk assigned randomly to either the SAAF or control condition. Moffitt et al. (2006) prescribed the use of planed group comparisons for testing G×E hypotheses when such hypotheses specify the precise patterning of group means. If the primary study hypothesis was empirically supported, we planned some *exploratory* analyses to explicate the findings. Focusing only on youths at genetic risk, we sought to determine (a) whether youths at genetic risk assigned to the SAAF condition would receive more intervention-targeted regulated-communicative parenting and report fewer risk opportunities than would youths at genetic risk assigned to the control condition and (b) whether the protective effect of assignment to SAAF on youths at genetic risk could be described in a conceptual model in which assignment to SAAF versus the control condition causes increases in regulated-communicative parenting that, in turn, forecast fewer opportunities for youths to engage in risk behaviors. We expected risk opportunities to forecast changes in risk behavior initiation from pretest to long-term follow-up.

Genetic Risk, Participation in SAAF, and Initiation of Risk Behaviors

We specified a latent growth model to test the predictions about the effect of the 5-HTTLPR and SAAF intervention on increases in risk behavior initiation. A test of the measurement model for the latent growth constructs was conducted, with the intercept specified by setting factor loadings for each of the observed values of the risk behavior initiation index to 1. The slope construct for three observed values of the risk behavior initiation index reflected the number of years after the first assessment at which each subsequent assessment was obtained. The measurement model displayed an excellent fit to the data, $\chi^2 = 0.21$, $df = 1$, $p = .65$, *ns*; comparative fit index (CFI) = 1.00. The mean intercept value was .29 was a variance of .54, both significantly different from 0, $p < .01$. The mean

slope value was .29 with a variance of .36, both significantly different from 0, $p < 01$. Thus, the data met the assumptions for latent growth modeling; risk behavior initiation demonstrated linear growth over time and participants varied significantly around the mean rate of growth.

A second conditional latent growth model was executed to test the hypothesis that genetic risk would predict the rate of growth in risk behavior initiation. Group membership was dummy coded; participants with *ss* or *sl* alleles were combined into a genetic risk group and assigned a code of 1, participants with *ll* alleles were assigned a code of 0, and the dummy code genetic risk predictor was regressed on the risk behavior initiation slope. Of the sample, 4.6% ($n = 21$) had the ''very long'' variant of 5-HTTLPR. As the activity of this variant on the hypothesized associations has not been well characterized, these individuals were excluded from the data analyses. The model demonstrated a good fit to the data ($\chi^2 = 1.84$, $df = 3$, $p = .61$, *ns*; CFI = 1.00). The results were consistent with our predictions: Genetic risk was associated with a higher rate of risk behavior initiation between the first and third assessments ($\beta = .19$, $p < .05$). These analyses were reexecuted with gender, monthly per capita income, marital status, and experimental condition (SAAF vs. control) added as exogenous predictors of growth in risk behavior initiation. Controlling for those covariates did not change the results.

A third conditional latent growth model was executed to test the hypothesis that group assignment would predict the rate of growth in risk behavior initiation. The risk behavior initiation index was regressed on group assignment, with SAAF participants dummy coded as 1 and control group participants coded as 0. The model demonstrated a good fit to the data ($\chi^2 = 6.03$, $df = 3$, $p = .11$, *ns*; CFI = .99). The results were consistent with our predictions: Assignment to the SAAF condition was associated with a significantly slower rate ($\beta = -15$; $p < .05$) of risk behavior initiation across the 29 months between pretest and long-term follow-up. This analysis was reexecuted with the additional exogenous predictors of growth that were added to the previous analysis involving genetic risk without the group assignment predictor. Controlling for these covariates did not change the results.

Test for a Moderation Effect of SAAF Participation on Genetic Risk

Four groups were formed to test the hypothesis that participation in SAAF would moderate the association between youths' 5-HTTLPR status and their risk behavior initiation over time: (a) youths in the SAAF condition at genetic risk ($n = 105$), (b) youths in the SAAF condition without genetic risk ($n = 153$), (c) youths in the control condition at genetic risk ($n = 78$), and (d) youths in the control condition without genetic risk ($n = 104$). A one-way analysis of variance (ANOVA) was used to determine the four groups' pretest equivalence on the demographic and study variables, and chi-square tests were used to determine group equivalence on youth gender and maternal marital status. Only one equivalence comparison was significant. Youths in the SAAF condition at genetic risk experienced more risk opportunities at pretest than did youths in the other Genetic Risk × Prevention Conditions. Pretest levels of all variables in the following analyses were controlled because the analyses addressed change across time. The means and standard deviations for the demographic variables and the proportions of male youths and single-mother-headed households for each Treatment Condition × Genetic Risk group are presented in Table 2.

As stated previously, the G×E hypothesis was tested via a planned comparison contrast, which tested the hypothesis that the study means would be arranged in a precise pattern (Keppel, 1982; Kirk, 1982). We hypothesized that the risk behavior initiation mean at long-term follow-up for youths at genetic risk assigned to the control condition would be greater than the means for youths in the other three Condition Assignment × Genetic Risk combinations; we further hypothesized that the latter means would not differ from one another.

The first step in executing a planned comparison is to compute an omnibus analysis of variance to obtain within- and between-group error terms; these are necessary in the computation of the planned comparisons. In this study, we computed a one-way analysis of covariance (ANCOVA) on the four Prevention Condition × Genetic Risk groups. It is standard practice in analyses of prevention or intervention effects to adjust dependent measures for their pretest values, both to decrease error variance and to remove any systematic between-group differences on the outcomes. The result of the omnibus ANCOVA was also significant, $F(3, 435) = 4.36$, $p < .01$. The adjusted means are presented in Figure 1. As expected, the planned comparison contrast was significant, $t = 3.60$, $p < .001$.

The patterning of means conformed to the G×E prediction; youths at genetic risk assigned randomly

Table 2
Equivalence Data for Each Treatment Condition × Genetic Risk

	SAAF condition						Control condition							
	Genetic risk (n = 105)			No genetic risk (n = 153)			Genetic risk (n = 78)			No genetic risk (n = 104)				
Descriptive measure	*M*	*SD*	%	*M*	*SD*	%	*M*	*SD*	%	*M*	*SD*	%	*F*	χ^2
Per capita income, $/month	432.54	242.39		494.84	346.81		564.32	451.72		526.32	354.42		2.16	
Number of children in household	2.63	1.30		2.83	1.35		2.73	1.54		2.49	1.32		1.48	
Female youths			53.30			52.90			47.40			57.70		1.89
Single-mother-headed families			64.10			55.90			57.70			52.90		2.89
Regulated-communicative parenting	24.84	3.14		25.26	2.73		25.50	2.82		25.00	3.14		0.84	
Risk opportunity	0.38	1.07		0.12	0.45		0.13	0.44		0.09	0.46		4.53*	
Risk behavior initiation	0.43	1.18		0.27	0.84		0.18	0.53		0.24	0.53		1.70	

Note. SAAF = Strong African American Families Program.
*$p < .05$.

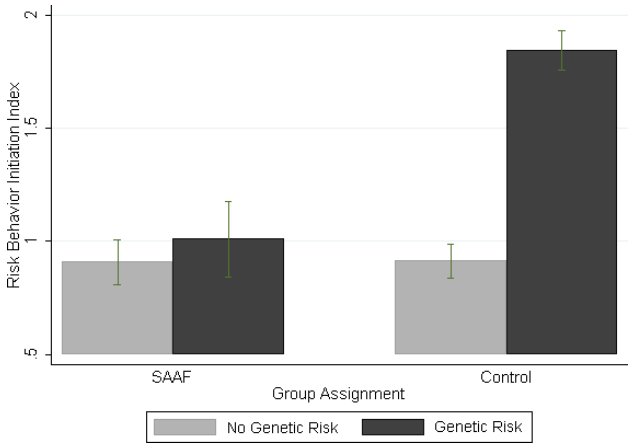

Figure 1. Mean risk behavior initiation for each Prevention Group × Genetic Risk condition at long-term follow-up, adjusted for pretest values.

to the control condition initiated significantly more risk behaviors at long-term follow-up than did those in the other three groups. This significant contrast had an effect size of .17; a post hoc power analysis using this effect size with the study sample size of 440 yielded a power estimate of .96 to detect the obtained effect size. The adjusted means for the four groups at long-term follow-up were as follows: SAAF, genetic risk = .90; SAAF, no genetic risk = .86; control, genetic risk = 1.91; control, no genetic risk = .93. These means are depicted in Figure 1 with standard error bars representing 95% confidence intervals.

A supplementary analysis was executed to illustrate further the form of the hypothesized G×E

Table 3
Means and Standard Deviations for the Risk Behavior Initiation Index at Each Assessment

	Pretest		Posttest		Follow-up	
Intervention condition	*M*	*SD*	*M*	*SD*	*M*	*SD*
SAAF						
Genetic risk	0.44	1.18	.39	.71	0.91	1.73
No genetic risk	0.27	.84	.35	.71	1.01	1.66
Control						
Genetic risk	0.18	.53	.58	1.33	1.85	4.17
No genetic risk	0.24	.53	.58	1.18	0.91	1.48

Note. Scores on the Risk Behavior Initiation Index have a possible range of 0–3. SAAF = Strong African American Families Program.

effect. A 4 (group) × 3 (assessment: pretest, posttest, or long-term follow-up) ANOVA with repeated measures on the last factor was executed on the risk behavior initiation data. As expected, a significant Group × Assessment interaction emerged, $F(6, 872) = 4.18$, $p < .001$. Table 3 presents the risk behavior initiation means for each group at each assessment. Post hoc tests using the Bonferroni correction to adjust for multiple comparisons revealed the means to be similar for all groups at the pretest and posttest assessments and to diverge as expected at the long-term follow-up assessment. The mean risk behavior initiation index was significantly greater for youths at genetic risk in the control condition than for youths in the other three groups (all ps < .05). The effect size for the Group × Assessment interaction was .17, which

yielded a post hoc power estimate of .99 for detecting the obtained effect size.

Tests of Exploratory Hypotheses for the Genetic Moderation Effect

These analyses focused only on youths at genetic risk who were assigned randomly to either the SAAF or control condition. We tested two exploratory hypotheses, the first of which specified that participation in SAAF, compared with assignment to the control condition, would be associated with greater increases in protective regulated-communicative parenting and smaller increases in unsupervised opportunities for substance use across the 8 months that separated the pretest and posttest. A priori *t* tests were used to test this hypothesis. The planned contrast compared youths at genetic risk in the SAAF and control conditions while setting values on the dependent measure to 0 for youths without genetic risk, thereby excluding them from the contrasts. The results confirmed this hypothesis for both regulated-communicative parenting (M change SAAF = .22), $t(429) = 21.74$, $p < .001$, and unsupervised opportunities (M change control = −.15), $t(429) = 5.08$, $p < .05$. Control youths reported greater increases in unsupervised opportunities to engage in risk behavior ($M = .50$) than did SAAF youths ($M = .24$).

The second exploratory hypothesis posited that intervention-induced changes from pretest to posttest in protective regulated-communicative parenting would be linked to decreases in unsupervised opportunities from pretest to posttest. Changes in unsupervised opportunities, in turn, were predicted to forecast increases in risk behavior initiation across the 29 months from pretest to long-term follow-up. This hypothesis was tested using structural equation modeling (SEM). For this analysis, the pretest value of each indicator of regulated-communicative parenting was subtracted from the posttest value. The difference for each indicator was standardized and summed, which yielded a regulated-communicative parenting score that controlled for pretest values. The same procedure was used for the single indicators representing unsupervised opportunity and risk behavior initiation. All constructs in the SEM analysis presented below were fixed at unity.

Table 4
Intercorrelations of Research Variables

Variables	1	2	3	4
1. Group assignment: SAAF versus control	—			
2. Change in regulated-communicative parenting	.32	—		
3. Change in risk opportunity	−.20	−.26	—	
4. Change in risk behavior initiation	−.18	−.12	.32	—
M	0.57	0.06	0.17	1.04
SD	0.50	0.61	1.07	2.95

Note. All correlations with an absolute value of .18 or greater are significant at $p < .05$. SAAF = Strong African American Families Program.

Table 4 presents the correlations among the theoretical constructs, along with the construct means and standard deviations. Consistent with theoretical predictions, the exogenous variable (dummy coded 1 for assignment to the SAAF condition and 0 for assignment to the control condition) was significantly correlated with increases in regulated-communicative parenting and decreases in unsupervised opportunity and risk behavior initiation. As predicted, increases in regulated-communicative parenting were associated with decreases in unsupervised opportunities. These results indicated that a formal test of the model would be appropriate.

The Mplus software package (Muthén & Muthén, 2007) was used to test the theoretical model. The structural model was specified with assignment to SAAF or control as the exogenous construct, not predicted by any prior variable in the model. Changes in regulated-communicative parenting and unsupervised opportunities were specified as endogenous constructs, which can be predicted by prior variables in the model, and long-term change in risk behavior initiation was specified as the criterion construct. All indices showed that the structural model, presented in Figure 2 with

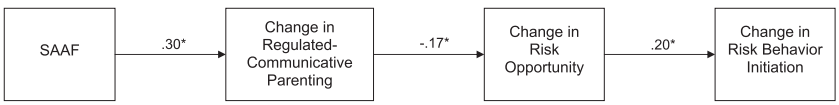

Figure 2. Structural model.
Note. $\chi^2(df = 3) = 4.84$, $p = .18$; comparative fit index = .91; root mean square error of approximation = .06. SAAF = Strong African American Families Program.
*p < .05.

standardized coefficients, fit the data well: $\chi^2(df = 3) = 4.84$, $p = .18$, *ns*; CFI = .91; root mean square error of approximation (RMSE) = .06. As hypothesized, the exogenous construct, SAAF or control assignment, forecast an increase in regulated-communicative parenting ($\beta = .30$), which was linked to fewer increases from pretest to posttest in unsupervised opportunities to engage in risk behaviors ($\beta = -17$). Unsupervised opportunities, in turn, forecast risk behavior initiation at long-term follow-up 21 months after posttest ($\beta = .20$). Separate analyses by gender demonstrated that the findings did not differ significantly for boys and girls. Taken together, the exploratory analyses support the hypothesis that participation in the SAAF prevention program increased parenting competence and control, which protected youth at genetic risk from initiating risk behaviors across early adolescence.

Discussion

Using a randomized prevention trial, we tested a G×E hypothesis about the genetic moderation of prevention effects on risk behavior initiation. The results indicated that (a) youths at genetic risk who were assigned to the control condition initiated risk behavior at higher rates than did youths at genetic risk in the SAAF condition and youths with no genetic risk in either the SAAF or control condition, and (b) exploratory analyses involving only youths at genetic risk suggested that SAAF's protective effects came from the increase it sponsored in protective parenting practices and the effects of such parenting on youths' unsupervised opportunities to engage in risk behaviors. To our knowledge, this is the first study to test a G×E hypothesis using a randomized prevention design.

The results demonstrated the utility of using randomized prevention trials to test G×E hypotheses. By using a prevention program with established environmental effects (Brody, Murry, Gerrard, et al., 2006; Brody, Murry, Kogan, et al., 2006), we were able to test such hypotheses using an experimental design. Such demonstrations are rare in developmental sciences because families and children cannot be assigned randomly to different environments. The randomized prevention design also ruled out plausible rival hypotheses involving history, maturation, instrumentation, regression to the mean, and gene-environment correlations that must be considered when epidemiological longitudinal designs are used (Moffitt et al., 2006). Despite these advantages, diverse approaches are needed to advance understanding of the ways in which genes and environments interact to create phenotypic differences over time. Longitudinal, epidemiological studies, twin designs, and randomized trials all can make important contributions. This study, for example, was informed by epidemiologic investigations; we hope that the results will inform the conceptualization, design, and analysis of other approaches to exploring G×E effects.

The results of this study build on prevention researchers' findings that individuals with higher levels of sociodemographic risk and adjustment problems prior to program participation benefit most from the prevention experience (Brody, Chen, et al., 2006; Brody et al., 2008). As an aggregate, these results support Rutter's (1985) thesis that protective factors have their greatest impact on individuals at highest risk. Conceptually, the results of this study are identical to a protective interaction reported in the resilience literature, in which a resilience resource reduces the negative impact of a risk factor on the development of an outcome over time (Luthar, 2006). Program-induced risk reduction is important from a theoretical viewpoint because it demonstrates that the progression from risk factors, including genetic risk, to negative outcomes is not immutable. Furthermore, these G×E protective interaction effects emerged with an effective sample size of about 100 in each of the four Prevention × Genetic Risk groups. Post hoc power analyses indicated that this study was adequately powered to detect the hypothesized G×E interactions; power to detect these interactions equaled or exceeded .95. Other recent studies using observational research designs have also detected robust G×E interactions with cell sizes similar to those in this study (e.g., Kaufman et al., 2004; Kaufman et al., 2007; Sjöberg et al., 2006). The power to detect G×E interactions may be more robust than that required to detect either G or E main effects (Moffitt et al., 2006). Both the present study and other research support this conjecture.

SAAF was designed as a universal prevention program to reach the general population of all African American 11-year-olds in the sampled rural communities. Universal prevention programming is defined as administration of a single prevention curriculum and dosage to a general population rather than to clinical populations or participants with specific risk factors. In rural African American communities, this approach has several advantages. Research has shown that inclusion of youths from general populations in preventive interventions ultimately reaches greater proportions of potential

substance-abusing adults than does focusing only on at-risk or clinical populations (Offord, Kraemer, Kazdin, Jensen, & Harrington, 1998). This is critical in underserved rural communities where there are few or no resources for risk behavior prevention.

Equally important, the use of genetic screening to identify subgroups for preventive interventions has the potential to stigmatize youths and lead to concerns regarding genetic discrimination. When these concerns are superimposed on decades of racial discrimination, community members are unlikely to participate, or consent for their children to participate, in prevention programs that involve genetic screening. In contrast, the rural African American community has embraced SAAF and participation rates have been high (Brody et al., 2004). Furthermore, in any general population, the percentage of youth at genetic risk for substance use and risk behaviors is likely to be considerable. For example, we found that 42% of our sample had the short-allele variant of 5-HTTLPR that placed them at risk for the escalation of substance use across early adolescence. Similar proportions of the European American population also have been found to carry this variant (Kaufman et al., 2004; Kaufman et al., 2007). When other susceptibility genes not yet identified are added to the mix, the percentage of youths at risk for substance use due to genetic vulnerability is likely to become considerable. For these reasons, efficacious universal preventive interventions like SAAF offer the most promise for reaching youths who may carry a myriad of genetic risks while avoiding stigmatization, discrimination, and potential adverse psychological effects that could occur with selective programs that include genetic screening (Lerman, Patterson, & Shields, 2003).

In the present study, we conducted some exploratory analyses to investigate the locus of genetic moderation effects. The findings indicated that moderation was attributable to the prevention program's enhancement of regulated-communicative parenting and consequent decreases in opportunities for youths to engage in risk behaviors. Our finding of multiple loci for moderation is consistent with results from longitudinal, developmental research with rural African American youths conducted from an epidemiological perspective. These studies demonstrated that, when parenting includes high levels of control, vigilance, emotional support, and racial socialization, youths avoid risk-conducive situations, internalize parental norms for substance use, and do not affiliate with peers who are likely to engage in risk behavior (Brody et al., 2000; Brody et al., 2004; DiClemente et al., 2001; Kotchick, Dorsey, Miller, & Forehand, 1999). The results also are consistent with an emerging body of research indicating that 5-HTTLPR is sensitive to both positive and negative aspects of the environment. Youths in the present study with the high-risk genotype benefited more from positive factors in their environments, such as enhanced parenting practices, than did youths with the low-risk genotype. This conjecture is consistent with recent studies suggesting that those who carry the short-allele variant of 5-HTTLPR generally experience heightened reactivity to their environments, responding to a range of environmental stimuli with an increase in activity in the amygdala (Heinz et al., 2007).

Some aspects of the present research should be noted as limitations. First, only one genetic polymorphism was examined, which does not represent all the variation that conceivably could place youths at risk for initiation of problem behaviors. Many genetic variants may alter risk, the expression of which may only emerge in a particular environmental context. Future researchers may choose to examine different genes and the potential for participation in a preventive intervention to ameliorate their impact. Second, a corollary of this limitation is the perception that genes confer only risk. Genetic effects also may be protective, and what is conceptualized as a risk-promoting genetic effect may actually be the absence of protective genes. As protective genes are identified, future research could examine the potential for participation in prevention programming to compensate for the absence of those genes. Third, future studies should investigate the possibility that participation in prevention programs could have protective effects for caregivers whose genetic diatheses may contribute to variation in the provision of protective parenting practices. Currently, little is known about links between genotypes and parenting behavior. Fourth, SAAF was designed to meet a need in rural Southern communities for efficacious prevention programming for African American youths and their families. Prior to SAAF, empirically based programs designed to prevent youths' development of high-risk behaviors were unavailable for this population. Generalization of the findings in this report must be established through the use of randomized prevention designs to test G×E hypotheses with ethnically and socioeconomically diverse participants residing in urban and rural locations.

These cautions notwithstanding, the present study demonstrates the utility of using randomized

prevention trials to test G×E hypotheses. Of particular importance to developmental and prevention scientists, the results demonstrate the power of the contexts in which youths live to determine whether they initiate risk behavior.

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