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Authors

Pampel, Fred C
Boardman, Jason D
Daw, Jonathan
et al.

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Life Events, Genetic Susceptibility, and Smoking among Adolescents

Fred C. Pampel[a,*], **Jason D. Boardman**[a], **Jonathan Daw**[b], **Michael C. Stallings**[c], **Andrew Smolen**[c], **Brett Haberstick**[c], **Keith F. Widaman**[d], **Tricia K. Neppl**[e], and **Rand D. Conger**[f]

[a]Institute of Behavioral Science, University of Colorado Boulder

[b]Department of Sociology, University of Alabama Birmingham

[c]Institute of Behavioral Genetics, University of Colorado Boulder

[d]Department of Psychology, University of California Davis

[e]Department of Human Development and Family Studies, Iowa State University

[f]Department of Human and Community Development, University of California Davis

Abstract

Although stressful life events during adolescence are associated with the adoption of unhealthy behaviors such as smoking, both social circumstances and physical traits can moderate the relationship. This study builds on the stress paradigm and gene-environment approach to social behavior by examining how a polymorphism in the serotonin transporter gene 5-HTTLPR moderates the effect of life events on adolescent smoking. Tests of interaction hypotheses use data from the Family Transitions Project, a longitudinal study of 7th graders followed for 5 years. A sibling-pair design with separate models for the gender composition of pairs (brothers, sisters, or brother/sister) controls for unmeasured family background. The results show that negative life events are significantly and positively associated with smoking. Among brother pairs but not other pairs, the results provide evidence of gene-environment interaction by showing that life events more strongly influence smoking behavior for those with more copies of the 5-HTTLPR S allele.

Keywords

adolescent smoking; negative life events; stress; gene-environment interaction; 5-HTTLPR

[*]Address correspondence to Fred Pampel, Institute of Behavioral Science, University of Colorado, Boulder CO 80309-0483. Phone (303)-492-5620; Fax (303)-492-6924; fred.pampel@colorado.edu..

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1. Introduction

Tobacco use has obvious practical and policy importance as a topic of study because of its standing as the single largest source of preventable mortality in the United States. Recent estimates attribute 480,000 deaths per year to smoking in the United States (USDHHS, 2014, p 659), and 12% of all deaths at ages 30 and over (about 5 million) across the globe (WHO, 2012). Despite considerable success from decades of anti-smoking messages, rising taxes on tobacco products, restrictions on the purchase and use of cigarettes, and social norms that shame and stigmatize smokers, the problem persists. According to the latest figures for the United States, 18% of adults report being current smokers (CDC, 2014) – a high level given societal opposition and public health concerns. Without a sudden and drastic change in behavior, current prevalence will translate into continued high levels of smoking-related mortality and morbidity.

To understand the problem, much research has appropriately focused on the causes of smoking initiation during adolescence. Virtually all cigarette smoking begins before age 18 (USDHHS, 2014, p. 708). As teens tend to discount the difficulty of quitting, the early addiction to nicotine in adolescence often leads to a life-long habit (Slovic, 2000). Enforcement efforts to restrict the access of minors to cigarettes have had some success (DiFranza, 2012), as have programs to prevent initiation and promote quitting among young people (Jacobson et al., 2001). Still, among high school students, about 20% of males and 16% of females report smoking (USDHHS, 2014, p. 720). The unambiguous benefits of understanding and preventing teen smoking underscores the importance of investigating its determinants.

In addition to its public policy and health importance, smoking has special theoretical importance for sociology and other social sciences: It reflects an intriguing mix of both social and biological influences. On one hand, social position (Link, 2008) and group-based norms (Cockerham, 2000) greatly influence social patterns and population trends in smoking. For example, smoking has become concentrated among socioeconomically disadvantaged groups in recent decades (Pampel, 2005), thereby reinforcing other sources of health disparities (Miech et al., 2011). Among teens, the contexts of schools, neighborhoods, and peers similarly reflect the importance of social influences on smoking (Ellickson et al., 2003; Henricksen et al., 2008). On the other hand, smoking frequently involves physical addiction to nicotine, a stimulating substance that links the behavior to biological or genetic traits (Brody, 2006; Hecht, 2012). The addictiveness of nicotine has been well substantiated (USDHHS, 1988), and a large literature on biological mechanisms (Bock and Goode, 2006; Brunzell, 2008), genetic predispositions (Sullivan and Kendler, 1999), and related psychological attractions to smoking (Zuckerman, 2007) helps explain individual differences.

With some exceptions, literatures treat the two classes of tobacco initiation risk as separate and independent. The social approach tends to assume that social patterns of smoking similarly affect persons with varied genetic propensities, while the genetic approach tends to assume that individual propensities to addiction remain invariant across social contexts. On the surface, the assumptions appear reasonable. Largely stable genetic traits cannot explain

changes in the social distribution of smoking, and changes in smoking prevalence do little to affect genetic traits.

In other ways, however, assumptions of independence may be flawed. Social conditions may facilitate or inhibit genetic propensities for addiction and smoking, and genetic influences may depend on social conditions (Boardman, Blalock, and Pampel, 2010). Understanding patterns of smoking (as well as other aspects of health with biological components) requires combined attention to both social context and genetic propensities. This perspective follows from the emphasis on gene-environment behavior interactions in the Institute of Medicine's (2006) report "Genes, Behavior and the Social Environment: Moving Beyond the Nature-Nurture Debate." This report stresses the need for interdisciplinary collaborations among social, behavioral, and medical researchers to address the complex interactions among genetic endowments, social structures, and individual behaviors. Until recently, however, relatively little research has bridged these tracks to examine the joint influence of biological and environmental determinants of tobacco use.

In this paper, we seek to understand the combined influence of genetic predispositions and one key social component of early smoking – adolescent stress. We ask if genetic influences shape the harm of negative life events for smoking and if the gene-environment interplay varies by gender. The effort gives new insight into a persistent problem of unhealthy behavior among teens and to the combined influences of biology and environment on social behavior. Toward that end, we specify interactive hypotheses about the links between social stress, genetic traits, and smoking during adolescence, and we test the hypotheses with prospective longitudinal data and sibling fixed-effects models.

2. Stress, Negative Life Events, and Smoking

We begin with the literature on stress and tobacco use. In general, the concentration of acute social stressors is associated with social environments characterized by high levels of smoking. Previous research has shown that work-related stress (Otten, Bosma, and Swinkels, 1999), unemployment (Fagan et al., 2007), family stressors (Miller and Volk, 2002), negative life events (Balk, Lynskey, and Agrawal, 2009), poor school performance (Johnson and Hoffman, 2000), poverty combined with single-parent childrearing (Graham, 1995; Marsh and McKay, 1994), socioeconomic disadvantage (Lynch et al., 1997), neighborhood deprivation (Duncan, Jones, and Moon, 1999), and everyday life strains (Liu, 2003) are linked with smoking behavior.

In the stress paradigm, difficult social circumstances are both a source of adversity and a drain on the capacity to cope (e.g., Pearlin, 1989). Stress involves physiological and emotional arousal that, when prolonged, leads to changes in the immune system and brain (Lantz et al., 2005). In the face of stress and the bodily changes that result, smoking (as well as overeating, inactivity, alcohol abuse, and other unhealthy behaviors) represents a form of pleasure and relaxation that helps regulate mood (Lantz et al., 2005, Layte and Whelan, 2009, Wilkinson, 1996). The coping or self-medicating function of these behaviors raises the costs of giving them up and limits the ability to adopt healthy but challenging behaviors.

For adolescents, the transition from childhood to adulthood presents special stressors that can contribute to early substance use (Pampel, Mollborn, and Lawrence, 2014). Adolescence is a period of new transitions, roles, and responsibilities that involve physical maturation, newfound freedom and desires, vulnerability to social and peer interactions, and resistance to continued parental, school, and community restrictions (Colten and Gore, 1991; Kim et al., 2003; Steinberg, 2001). As a result, teens may experience more stress or qualitatively different stress than adults and react in more impulsive and self-destructive ways (Hoffman and Su, 1997; Van Gundy and Rebellon, 2010). Tendencies to use substances to cope with stressful problems of living are reinforced by peers who use the substances and exert pressures or serve as models for smoking (Kobus, 2003).

Several studies have focused more specifically on negative life events as a source of stress during adolescence. The events are common for teens, with 53% of adults in a national survey reporting that they had experienced one or more stressful life events before age 18 (Green et al., 2010) such as parental divorce (17.5%), family violence (14%), economic adversity (11%), parental death (10%), and mental illness (10%). Further, negative life events are associated with adolescent alcohol dependency (Enoch, 2011), drug use (Oliva, Jimenez, and Parra, 2009; Van Gundy and Rebellon, 2010), addictive behavior (Lee et al., 2012), and externalizing behaviors (Kim et al., 2003). Studies of smoking similarly suggest a relationship with negative life events (Cheney et al., 2014).

However, the relationship between stressful negative life events and substance use outcomes is far from perfect. It can be moderated or buffered by social factors (Oliva, Jimenez, and Parra, 2009; Thoits, 2010). The stress paradigm explicitly incorporates protective factors that can moderate the harm of negative experience on health outcomes (Pearlin, 1989). Among adolescents, positive role models, strong ties to family and school, and a variety of positive coping strategies may moderate the harm of stress (Seiffge-Krenke, 2011). Much the same may occur for smoking, as personal and social circumstances may direct outlets for stress in healthier directions for some youth but lead to reliance on tobacco and other substances for coping among other youth.

3. Moderation and Genetic Influences

Much as in the stress paradigm, the gene-environment approach posits a process of moderation, only with a focus on how genetic traits shape the response to social experiences (Boardman, Blalock, and Pampel, 2010). Previous studies, mostly of adolescents, have suggested the value of the approach, particularly in relation to 5-HTTLPR, a polymorphism related to serotonin transport. It has two common variations in humans, a short (S) and a long (L) allele that combine into SS, SL, and LL and are related to social behavior. Consistent with arguments of differential genetic susceptibility (Belsky and Pluess, 2009; Ellis and Boyce, 2008), short allele carriers appear more sensitive to their environment than others. With life course data from childhood though young adulthood, Caspi and colleagues (2003) demonstrated a gene-environment interaction between 5-HTTLPR, negative life events, and depression outcomes such that the effect of stressful events on depression is significantly stronger for persons with an increasing number of S alleles in 5-HTTLPR. In a study of body weight during adolescence, Wickrama, O'Neal and Lee (2013) found that the

influence of community adversity on BMI growth was greater for those with more sensitivity alleles in four genetic polymorphisms (including 5-HTTLPR) than those with fewer sensitivity alleles. In examining the relationship between adolescent peer cigarette smoking behavior, 5-HTTLPR, and individual cigarette smoking, Daw et al. (2013) demonstrate that persons with the SS genotype have *lower* smoking levels in low-smoking schools, and *higher* smoking levels in high-smoking schools, compared to their counterparts with the LL genotype. Subsequent research (Daw et al., 2014) used an independent dataset and found a similar pattern for the interaction of neighborhood peers and *5HTTLPR*. This result suggests that those with the short alleles are more strongly influenced by their social environment.

Given findings of gene-environment interaction on adolescent depression, obesity, and smoking, it follows that negative life events may interact with 5-HTTLPR to predict adolescent cigarette smoking. As others have pointed out (Shanahan and Boardman, 2009), specific gene-environment models that incorporate the contingent influence of social and institutional forces may be more relevant to the study of adolescence than other points of the life course. Adolescents have far less control over their exposure to stress than do adults, and this helps to minimize active forms of gene-environment correlation in which heritable characteristics shape environment exposure. Given this form of potential bias, directly studying the social and institutional environments for teens, rather than assuming gene-environment interplay is the same as among adults, contributes to the literature.

Additionally, previous research suggests that gene-environment interactive effects vary by gender (Perry et al., 2013; Uddin et al., 2011), although the relationships have been little studied among adolescents. Men smoke at higher rates than women (Kulis et al., 2008) and the smoking behavior of both men and women is associated with psychological distress (Peiper and Rodu, 2013), but there is evidence that the effects of stress on cigarette use behavior is stronger for women than for men (McKee et al., 2003). Despite some exceptions (Todd, 2004; Booker et al., 2008), the bulk of research has shown that negative life events, especially financial shocks, have a more robust relationship with smoking onset among women and smoking levels among women smokers compared to men (McKee et al., 2003).

Given that the association between stress and cigarette smoking appears to be stronger among women than men, the gene-environment interactions could operate in two different directions, one showing greater sensitivity among females and one showing greater sensitivity among males. First, as noted by Boardman et al. (2011), a diathesis-stress exacerbation model of the gene-by-environment paradigm typically focuses on causal models in which the environment triggers otherwise small latent genetic associations. Caspi et al. (2003) posit this kind of influence. Conversely, the environment may, at times, control or suppress genetic associations for behaviors like smoking, such as when legislative efforts limit who can smoke and where they can smoke (Boardman, 2009). While these two models focus on different processes, they both treat the environment as a causal precursor to genetic associations. With respect to gender, the causal gene-by-environment stress-diathesis model anticipates that the interaction between stress sensitivity polymorphisms and stress exposure may be higher among women compared to men. Given a stronger link between stress and

smoking among women compared to men, sensitivity alleles will enhance the likelihood of smoking among women in the face of stress.

Second, and alternatively, two gene-by-environment models are characterized as non-causal because the basic biological processes are not altered. Rather, small genetic associations are simply easier to identify in certain environments. The social push model (Raine, 2002) differentiates between typical and extreme social contexts and posits that genetic factors will appear more important within typical environments, whereas social influences dominate within extreme environments. The social distinction model is similar but, unlike the social push model, posits stronger genetic influences in extreme rather than typical environments. Based on these non-causal arguments, social factors related to gender may control smoking behaviors in the face of stress more so for women and thus limit the ability to detect small gene-by-environment associations. In this case, the stress-coping behavior of smoking will be more evident among men. That is, for women social stressors alone may be sufficient to increase the likelihood of smoking, whereas for men, social stressors *and* biological sensitivity to social stressors may both be required to produce this outcome.

4. Hypotheses

Based on the gene-environment approach and previous literature on life events and unhealthy beahviors, we propose three hypotheses:

1. Gene-environment interaction: The presence of one or two short (S) 5-HTTPLR alleles makes youth more susceptible to the influence of negative life events on the propensity to initiate and continue tobacco use.
2. Diathesis-stress exacerbation: Because adolescent girls are more likely to smoke in response to stress compared to boys, genetically oriented sensitivity to negative life events will likely be greater for females compared to males.
3. Social push and social distinction. Because social factors structure the relationship between stress and smoking for females more than males, the genetic sensitivity to stress will be more strongly associated with smoking for males compared to females.

5. Method

5.1. Data

We test these hypotheses with the first six waves of longitudinal data from the Family Transitions Project (FTP), which extends two earlier studies: The Iowa Youth and Families Project (IYFP) and the Iowa Single Parent Project (ISSP). The IYFP collected data annually from 1989-1992 and included both a target youth (n=451) and a sibling born within 4 years of the target adolescent (n=451). When interviewed in 1989, the target youth were in 7th-grade classes of 34 public and private schools in an eight-county area of Iowa (Conger and Elder, 1994). Eligible youth were living with both biological parents and were originally recruited for a study of family economic stress in the rural Midwest. Due to the rural nature of the study, the recruitment area had very few minority families. Human subjects approval

for gathering survey data and the genetic sample came from the IRB at the University of California Davis (protocol 219416).

The ISSP began in 1991 when the target youth were age 15 and in the same year of school as the IYFP cohort of target youth. Participants included the target youth (n=108) along with their closest aged sibling (n=108) and their single-parent mothers. These families were headed by a mother who had experienced divorce within 2 years prior to the study. The participants were Caucasian and lived in the same geographic area as the IYFP families (Simons et al., 1995). ISSP families participated in three waves of data collection, 1991, 1992, and 1993.

In 1994, families from the ISSP were combined with the IYFP to create the FTP. At that time, the target youth from both studies were in the 12^{th} grade. In 1994, the target youth participated in a survey with their parent(s) and siblings. In 1995, parents and siblings participated via telephone interview. Beginning in 1995, each target adolescent (1 year post high school) participated in the study with a romantic partner or friend; and in 1997, the study was expanded to include the first-born children of the youth. Therefore, in order to include information on both the target youth and his or her sibling, data collected from 1989 to 1995 were used in the current analyses. For these six waves, the sample sizes for targets and siblings with data on all variables under study are as follows: 1) the 1989 IYFP wave of 360 targets and 326 siblings; 2) the 1990 IYFP wave of 342 targets and 313 siblings; 3) the 1991 IYFP wave of 328 targets and 301 siblings combined with the age-matched 1991 ISPP wave of 73 targets and 65 siblings; 4) the 1992 IYFP wave of 327 targets and 301 siblings combined with the age-matched 1992 ISPP wave of 72 targets and 64 siblings; 5) the 1994 FTP wave of 410 targets and 338 siblings that combines the age-matched samples from the IYFP and ISPP studies; and 6) the 1995 FTP wave of 405 targets that combines the age-matched samples from the IYFP and ISPP studies but does not have smoking data for siblings. The loss of data in 1989 for the original samples results primarily from the lack of genetic data, which were collected between 2007 and 2011.

Because of the fairly weak replication history with the candidate gene-environment interaction studies (Risch et al., 2009) and questions about power and type-II error (Duncan and Keller, 2011), we examine the sensitivity of our results with increasingly conservative modeling strategies and the removal of outliers. Most importantly, given the size of our sample, we also simulated data to estimate the power and minimal detectible effect size for the analysis (results available on request). Our results suggest that the design is well powered (.98) when the effect of stress on smoking is large in magnitude (e.g., r = .5) for those with the SS genotype. The power drops to a moderate level (.66) when the effect is weaker (e.g., r = .3) in magnitude. Because the sample size requires a relatively large effect for significance, the tests of the hypotheses are conservative. Accordingly, we believe that we are adequately powered to detect true gene-environment interaction effects.

5.2. Measures

The outcome measure of smoking at each wave comes from responses to questions about the use of cigarettes and other tobacco products in the past year. The response alternatives changed slightly across the waves, but were made comparable with four categories: (0)

never, (1) less than 1-2 times per week (or occasionally), (2) 1-2 times per week (or regularly), and (3) 3 or more times per week (or frequently). An alternative dichotomous outcome scale contrasts never users with the other three categories. The measure does not obtain the exact timing of starting and stopping during a year, but the data on tobacco use over the past year provide, with the exception of 1992 to 1994, a continuous yearly record for the period of study. The negative life events scale was calculated as the percentage of approximately 40 negative events that a respondent reported experiencing in the past year. The measure used the 1989 and 1991 scores. The first year of available data for the IYFP subjects was 1989, and the first year of available data for the ISPP subjects was 1991. The average is used when IYFP subjects have both years of data

DNA was collected via saliva/buccal samples from all study participants between November 2007 and August 2014 utilizing Oragene™ (DNA Genotek, Ontario, Canada) collection kits. Genotyping was conducted at the University of Colorado's Institute for Behavioral Genetics. Genomic DNA was isolated with Agencourt DNAdvance™ DNA Isolation Kits (Beckman Coulter, Brea, CA) using a Beckman-Coulter Biomek® FX workstation according to company protocols. Detailed methods for genotyping 5-HTTLPR are described in Whisman, Richardson, and Smolen (2011). Genotyping yielded two alleles for the 5-HTTLPR locus: a short (S) allele (14-repeat VNTR) and a long (L) allele (16-repeat VNTR). Although other extra-long alleles have been observed (Nakamura et al., 2000), they are rare and were not observed in the FTP sample. Allele frequencies for the S and L alleles were f(S) = 0.41 and f(L) = 0.59, which is consistent with expectations for European and European-American populations (Noskova et al., 2008). However, Hu and colleagues (Hu et al., 2005) reported that a SNP (rs25531, A/G) may cause the L_G allele (L allele with a G allele for rs25531) to have transcriptional activity no greater than the S allele. They suggest that in tests of association L_G alleles should be analyzed along with the S alleles (Hu et al., 2006), and we follow this advice. The frequency of the G allele for SNP rs25531 was 6% in the FTP sample. Taking rs25531 genotype into account, the 'functional' allele frequencies were: f(S, L_G) = 0.48, f(L) = .52. The call rate was 98.2% and observed Mendelian inconsistencies were less than 0.5%. Tests of Hardy Weinberg Equilibrium were also nonsignificant ($p > .05$). Genotypes for the 5-HTTLPR polymorphism were scored assuming an additive model and reflecting the number of short (S or L_G) alleles (i.e., 0 = no S alleles, 1 = one S allele, 2 = two S alleles). Likelihood ratio tests indicate that genotype coding (using dummy variables to represent the three categories) did not improve our analyses over the single additive coding.

Finally, covariates include age (measured in years and centered around the mean of 15.6), gender (females = 1), target/sibling (target = 1), and GPA reported in 1989 and 1991 (0 = F, 4 = A).

5.3. Models

The analysis pools the data by targets and siblings so that each individual counts as a separate case. It also pools the data by waves so that each case consists of a person/wave. This strategy maximizes power but assumes relationships are invariant across waves and requires adjustments for clustering by family and wave. With the pooled data, ordered

logistic regression is used for the ordinal categories of the tobacco use measure, but we also checked the estimates with linear regression and logistic regression.

The models control for wave and family-specific influences by using wave and family fixed effects (or dummy variables for each wave and each family). By equalizing differences between families with fixed effects, the models estimate between-sibling effects. The between-sibling estimates compare those who share similar genetic backgrounds while controlling for shared family backgrounds and parental characteristics that are stable over time.

Three different samples may be appropriate for the fixed effects models. (1) Full Sample, an approach that maximizes the number of cases by including any subject with data for a least one wave; (2) Paired Sibling Sample, an approach that includes a subject only if there is also a sibling with valid data for at least one wave, but it allows for different waves for sibling pairs (e.g., if one sibling had data for all six waves from 1989 to 1995 but the other sibling data for only 1991, all seven person/waves were included); and (3) Paired Sibling/Wave Sample, a final approach that allows for a more precise comparison of siblings by including a subject in a wave only if a sibling has data for the same wave. Because both smoking and the influence of the 5-HTTLPR gene likely differ by gender, the models were estimated for three groups of siblings: two brothers, one brother and one sister, and two sisters. A likelihood ratio test shows significant improvement from allowing the predictors to have varied effects across the three groups.

6. Results

Table 1 presents descriptive statistics for the results averaged across all waves and for the first and last wave. The sample includes only those subjects with valid data on the measures used in the models. For the 4392 cases, 824 individuals had data on an average of 5.3 waves (minimum of one wave and maximum of six). Of the 824 individuals, 433 were targets (with 2317 person/waves) and 391 were siblings (with 2075 person/waves). The ages ranged from 9.5 to 23.6 and increased by 1-2 years across each wave. As expected for adolescents, the trajectory in smoking produces a decrease in never smokers from 85% to 54% and an increase in frequent or daily smoking from 2% to 27%. However, the subsamples more closely match targets and siblings. When subjects without a sibling are dropped, it leaves a total of 3538 cases, 652 individuals who had data on an average of 5.4 waves, and 326 pairs of siblings. When waves without both a subject and sibling were dropped, a total of 3482 cases remained, with 652 individuals who had data on an average of 5.3 waves, and 326 pairs of siblings.

Table 2 lists the fixed effects ordered logistic regressions estimates for three samples (all cases, paired siblings, paired siblings/waves) and three groups (brothers, mixed, sisters). Smoking increases as a function of age, particularly for brothers, and as an inverse function of GPA, particularly for sisters. With controls, targets and siblings did not differ significantly in smoking. The key tests for the gene-environment interactions revealed significant coefficients for brothers, but not for brothers and sisters or for sisters (further tests using a pooled sample and linear probability models appropriate for comparison of

coefficients [Mood, 2010] show that the interaction coefficients for brothers differ significantly from the other two groups). For brother-sisters and for sisters, negative life events were significantly and positively associated with smoking (e.g.,β=0.231, Z=7.66; β=0.110, Z=2.90), but the effects were no different for those with and without short alleles. For brothers, the positive interaction coefficients mean that the addition of a short allele increased the initially negative, insignificant coefficient of negative life events on the logged odds of being in a higher smoking category by .106 to .114 (Z = 3.38 to 3.59). As shown by the additive term, negative life events had little influence on the smoking of those with no short alleles (e.g., β= − .058, Z = −1.22 with a score of 0 on the 5-HTTLPR measure). These associations are in line with Hypothesis 3 (the social distinction and social push perspectives).

Figures 1a-1c depict the predicted values (on the scale from 0-3) from linear regression and the non-linear probabilities obtained from ordered logistic regression for the full sample of brothers. Each graph compares the predicted smoking of subjects with short/short and long/long alleles by negative life events. To more clearly illustrate the differences, this figure only displays the two homozygous groups (i.e., having two identical alleles of a particular gene, in this case SS or LL of the 5-HTTLPR); the heterozygotes (i.e., the SL alleles) fall in between these two groups. Two observations are worth noting: 1) in all three cases the likelihood of smoking among the LL group is not strongly associated with stress whereas the SS group shows a marked response to increasing levels of stress; 2) the divergence of lines occurs at higher rather than lower levels of stress exposure. The first observation is in line with our hypothesis that carriers of the short allele tend to be more sensitive to environmental exposures related to substance use behaviors. The second observation provides more support for the stress-diathesis gene-environment interaction model compared to the differential susceptibility model. Specifically, in Figure 1a, the lines diverged significantly at .4 standard deviations above the mean but overlap at lower values. Figure 1b plots the non-linear predicted probability of frequent smoking (i.e., the highest category in the measure) from the ordered logistic regression. Again, divergence again occurred at high levels of negative life events, with the short/short subjects having significantly higher probabilities once they experienced stress levels that were at least 1.2 standard deviations above the mean and the divergence was weaker at the lower end. Figure 1c plots the non-linear probabilities from the ordered regression for never smoking and affirms the evidence of differential susceptibility. Subjects with short/short genotypes had significantly *higher* probabilities of not smoking at low levels of negative life events compared to long/long genotypes but significantly *lower* probabilities of not smoking at high levels of stress (at 1.2 to 4.4 standard deviations above the mean). This genetically oriented susceptibility to environmental stress denotes a protective factor for boys in the least stressful environments but a risk for boys in the most stressful environments.

To check the sensitivity of the results to estimation methods, measures, and influential cases, we examined a variety of alternate models. For these models, Table 3 lists only the coefficients and z-ratios for the interaction term of negative life events by the HTTLPR measure and only for brothers, the group with a significant interaction in the basic model. As shown in Table 3, the interaction remained significant with binary logit, a logged measure of

negative life events, and linear regression. A time-averaged linear regression in which measures were averaged across all waves and modeled cross-sectionally shows that the interactions remained significant. To check for influential cases, the four pairs of siblings with the largest positive dfbeta values for the interaction term were dropped one at a time from the sample. As listed in Table 3, each interaction remained significant.

7. Discussion

These results suggest that negative life events have a contingent relationship with adolescent smoking for young men but not for young women. The gene-environment interaction for 5-HTTLPR applies to male sibling pairs, but not to sibling pairs that include women. This result for men is consistent with previous research demonstrating the association of stressful life events with smoking behavior (Daw et al., 2103; Peiper and Rodu, 2013; Hu et al., 2006) and depression (Caspi et al., 2003). Why do we see this relationship among brother pairs of adolescents but not sibling pairs that include females? This result is best understood in light of previous research showing that the smoking behavior of women is more strongly associated with life stress than is true for men (Peiper and Rodu, 2013). If men are subject to a gene-environment interaction in this outcome such that persons with certain genotypes are much more environmentally responsive than others, but women are not, this would dilute the overall effect of the environment for men compared to women. Thus, these results are consistent with the explanation that the weaker association between stress and smoking for men compared to women is partially attributable to the presence of a gene-environment interaction for men but not for women.

The interaction findings imply something more than the heightened sensitivity of brothers with SS alleles to high levels of negative life events. At low levels of negative life events, there is some evidence that those with SS sensitivity are less likely to smoke. This finding is in line with the gene-by-environment approach (Belsky and Pluess 2009) in at least two ways. First, the crossover at the lowest level of stress suggests that not only are the SS carriers more likely to smoke in the most stressful environments but they are significantly less likely than others to smoke in the most healthy environments. Second, the less sensitive genotypes for this configuration show a muted response to smoking across the continuum. That is, carriers of two long alleles at 5HTT have a slope in all three models that is consistently flatter than the SS genotypes. Whether this denotes resilience as a protective trait or simply a muted response is unclear but it is still important to note that the divergence of the lines is most evident in the most highly stressful environments.

Although the findings apply to one cohort of youth, the long-term population decline in tobacco use in the United States suggests that the moderating influence of genetic characteristics may increase in the future. With lower smoking in general and lower initiation among adolescents in particular, the development of the habit likely becomes increasingly concentrated among youth with genetic propensities toward nicotine addiction (Boardman et al., 2011). Social factors once encouraged smoking among all youth but more recently have discouraged smoking, making genetic factors a more dominant influence on the attraction to tobacco initiation. The gene-environment interaction results we found for stress and smoking apply to the FTP cohort born in the 1970s and reaching adolescence in

the 1980s. They entered adolescence during a period of growing anti-smoking environmental influences, which may have served to increase the importance of genetic factors (Boardman et al. 2010). For younger cohorts, the continued decline in smoking suggests that genetic characteristics may become even more influential in moderating the influence of stress on smoking.

These results are limited to the single, though critically important public health outcome of smoking. As a check, we estimated these same models with different dependent variables, substituting measures of antisocial behavior and depression, and found no evidence for the gene-environment interaction or main effect of negative life events for either of these phenotypes (results available upon request). The fact that no informative results were derived from these phenotypes suggests that any mechanisms underlying the primary findings of this analysis is specific to cigarette smoking itself, not its psychological precursors. It is possible that cigarette smoking may be a high prevalence behavior in stressful social environments, and persons in these contexts simply turn to this behavior when they feel stressed (but not anti-social or depressed). This last point is important because we do not contextualize the source of the stress or the availability of coping resources. As previous research has linked genetic sensitivity to neighborhood level processes (Meyers et al., 2013), we encourage future research to expand our specific focus on gender and stress to the GxE research in the area of neighborhoods.

More generally, the results illustrate the value of a gene-environment approach to understanding healthy behaviors among adolescents. The stress paradigm emphasizes the importance of moderating social factors in the relationship between stress and health outcomes. The potential for genetic factors to have a similar moderating influence suggests a fruitful extension of the stress paradigm. Cigarette smoking offers an ideal outcome for the study of genetic moderation because it is clearly influenced by both social and physical factors. The results presented on the combined influence of stress and genetic characteristics contribute to understanding the persistence of a harmful behavior despite strong social approbation.

Along with viewing genetics as moderating the influence of stress on smoking, one can view the results equivalently as showing that social circumstances – in this case stress – moderate genetic expression. Genetic sensitivity involving the 5-HTTLPR S allele is not deterministic but is contingent on the presence of stress among young men. The allele has little influence on smoking among brother pairs facing an average number of stressful life events, but many stressful life events facilitate the importance of genetic make-up. A full understanding of smoking thus requires attention to both social and genetic components of health behavior.

We also encourage future researchers to consider the specific sources of stress when considering our results. Booker et al. (2008) demonstrate that adolescent boys and girls are both more likely to smoke in the face of stressors but girls seem to respond to peer based stressors and boys respond to personal stressors. Further differentiating between the gendered source of stress and gendered coping behavior may enhance the conclusions of our current research.

This research is subject to a number of limitations. First, this is observational research, and we cannot eliminate the possibility that our results are non-causal in nature. However, the most common form of confounding in molecular genetic research, population stratification, is not a major concern for our findings because of our family fixed effects research design. Furthermore, the robustness of these results across alternative modeling strategies further buttresses our confidence in the validity of these findings. Second, although the Family Transitions Project is a well-designed study, it is not population representative, and its sample size is small compared to most datasets commonly employed to study cigarette use in adolescence. The interactive results may be sensitive to the particular sample and require replication with different and larger data sets. Still, the consistency of these results with previous research conducted using other datasets somewhat ameliorates these concerns.

8. Conclusion

This study links two separate literatures, one on stress and smoking and another on combined gene-environment influences on health. Longitudinal data from the Families in Transition Project on a cohort of adolescents similarly bring together measures of negative life events and smoking with measures of genetic characteristics. The findings first replicate previous studies showing an association between negative life events and youth smoking. In addition, they show that stress and negative life events have varied impacts on smoking prevalence during adolescence. Genetic differences among male siblings (but not female or mixed siblings) facilitate the influence of stress and negative life events. The results suggest that understanding healthy teen behavior should focus on stress-related risk factors but also recognize the genetic contingency of such environmental influences. They also suggest the value of a gene-environment approach that takes into account the synergistic influence of social and genetic influences on social behavior.

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Research Highlights

- Stress and negative life events have varied impacts on smoking initiation.
- Genetic differences among male siblings (but not female or mixed siblings) facilitate the influence of stress and negative life events
- Understanding healthy teen behavior should focus on stress-related risk factors but also recognize the genetic contingency of such environmental influences.

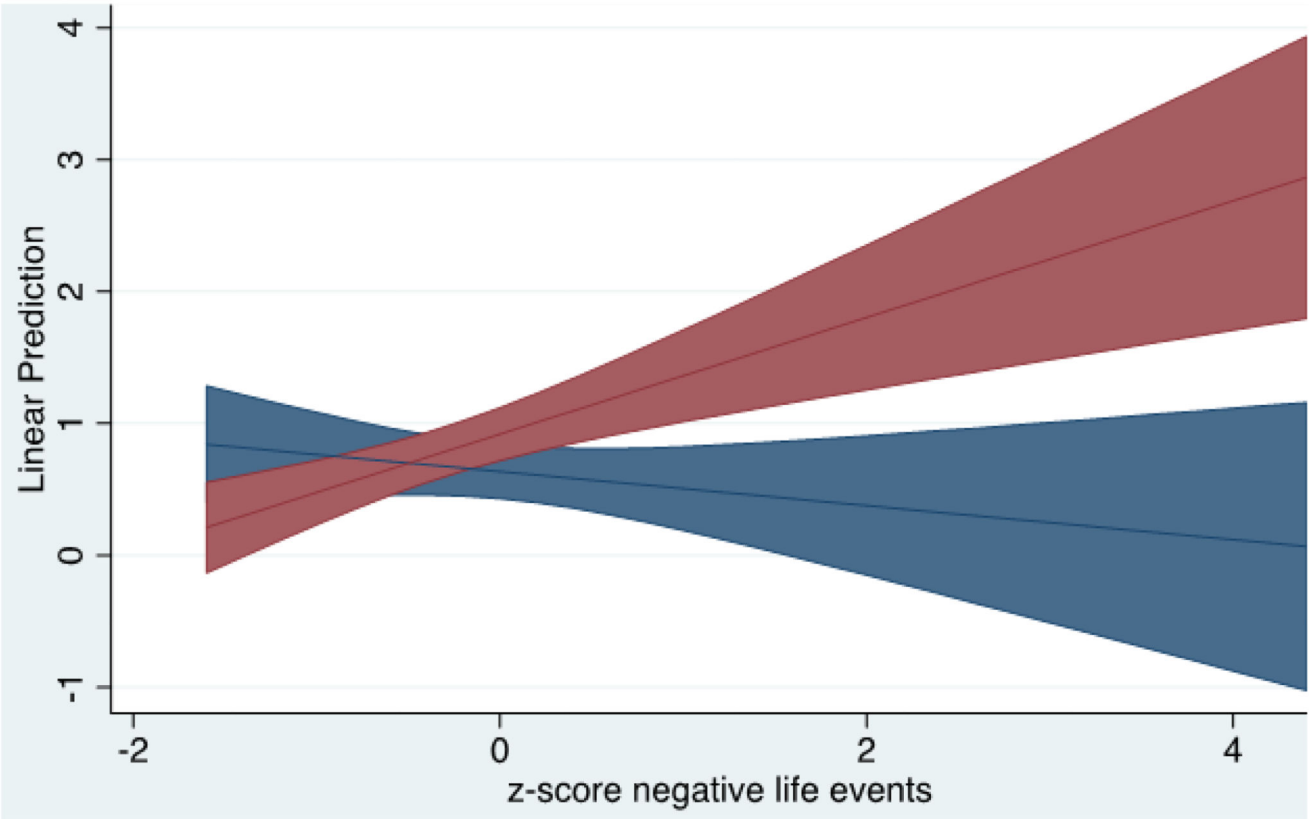

Figure 1a.
Predicted values from linear regression on 4-category measure of smoking among boys by stressful life events and 5HTTLPR genotype.

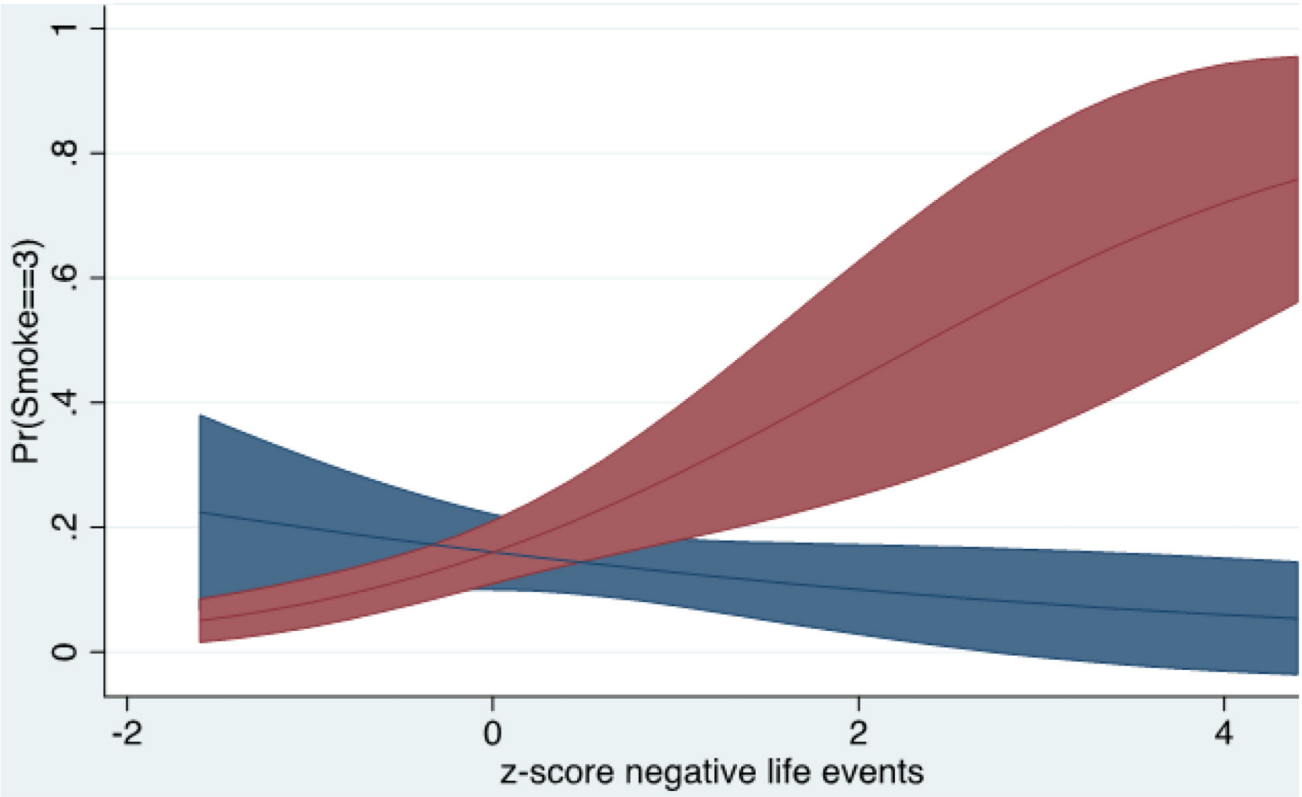

Figure 1b.
Predicted probability of frequent smoking among boys by stressful life events and 5HTTLPR genotype

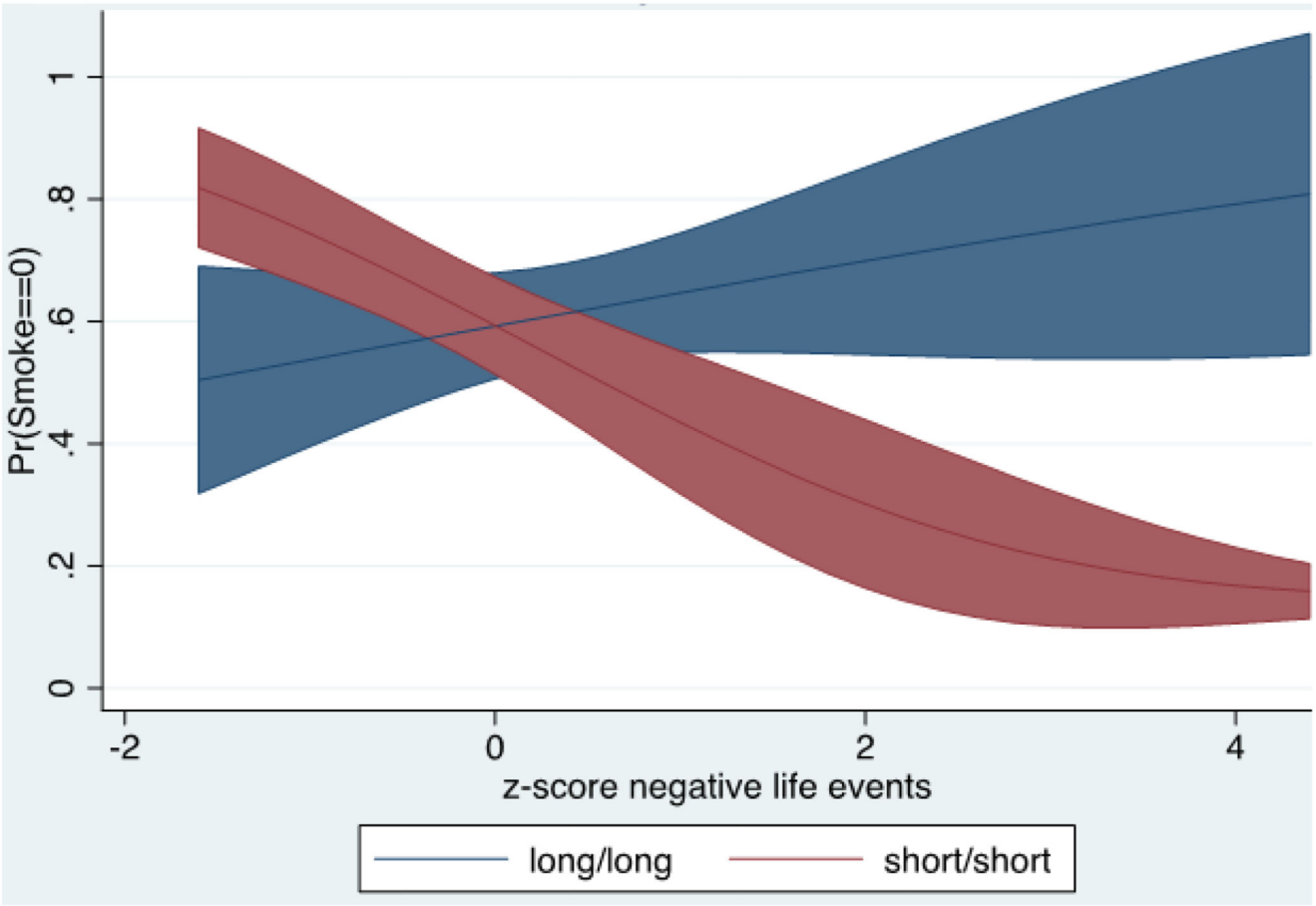

Figure 1c.

Predicted probability of never smoking among boys by stressful life events and 5HTTLPR genotype

Note: estimates derived from models in which smoking is a function of stressful life events and 5HTT genotype. The shaded area around each line describes the 95% confidence interval for the estimate as a function of stress and genotype.

Table 1

Descriptive Statistics

	All Waves					Mean By Wave	
	N	**Mean**	**SD**	**Min**	**Max**	**1989**	**1995**
Smokes							
Never	4392	0.70	0.46	0	1	0.85	0.54
Occasionally	4392	0.16	0.37	0	1	0.12	0.15
Regularly	4392	0.02	0.14	0	1	0.01	0.03
Frequently	4392	0.12	0.33	0	1	0.02	0.27
Age	4392	16.09	2.67	9.46	23.58	13.33	19.14
Female	4392	0.56	0.50	0	1	0.56	0.57
Target	4392	0.53	0.50	0	1	0.52	0.52
IYFP	4392	0.88	0.33	0	1	1.00	0.84
GPA	4392	3.03	0.73	0	4	3.06	3.02
Life Events	4392	13.33	7.92	0	63.83	12.54	13.65
Long/Long	4392	0.24	0.43	0	1	0.24	0.24
Short/Long	4392	0.54	0.50	0	1	0.53	0.55
Short/Short	4392	0.22	0.41	0	1	0.22	0.22
Brothers	4392	0.22	0.41	0	1	0.21	0.21
Mixed	4392	0.48	0.50	0	1	0.48	0.47
Sisters	4392	0.31	0.46	0	1	0.31	0.32

Table 2

Ordered Logistic Regression Coefficients and Z-Ratios

	Brothers					
	All		Pairs		Pairs/Waves	
	b	z	b	z	b	z
Age	0.356	3.91 **	0.341	3.83 **	0.329	3.67 **
Target	−0.333	−1.56	−0.316	−1.52	−0.317	−1.51
GPA	−0.568	−2.02 *	−0.532	−1.93	−0.564	−2.03 *
Life Events	−0.058	−1.22	−0.053	−1.14	−0.044	−0.93
5HTTLPR	−1.565	−2.64 **	−1.464	−2.53 *	−1.422	−2.44 *
LE*5HTTLPR	0.114	3.59 **	0.107	3.45 **	0.106	3.38 **
N Total	948		671		660	
Individuals	181		124		124	
Families	119		62		62	

	Brothers/Sisters					
	All		Pairs		Pairs/Waves	
	b	z	b	z	b	z
Age	0.165	3.04 **	0.16	2.99 **	0.162	2.97 **
Target	0.103	0.74	0.10	0.71	0.122	0.87
GPA	−0.665	−4.29 **	−0.65	−4.24 **	−0.706	−4.46 *
Life Events	0.231	7.66 **	0.23	7.57 **	0.230	7.52 **
5HTTLPR	0.675	1.86	0.66	1.83	0.614	1.69
LE*5HTTLPR	−0.032	−1.61	−0.03	−1.59	−0.029	−1.44
N Total	2087		1743			1712
Individuals	391		320			320
Families	231		160			160

	Sisters					
	All		Pairs		Pairs/Waves	
	b	z	b	z	b	z
Age	0.078	1.01	0.075	0.98	0.078	1.01
Target	0.162	0.84	0.151	0.79	0.172	0.89
GPA	−0.814	−4.04 **	−0.787	−3.96 **	−0.813	−4.04 **
Life Events	0.110	2.90 **	0.106	2.84 **	0.106	2.82 **
5HTTLPR	−0.768	−1.25	−0.733	−1.21	−0.808	−1.31
LE*5HTTLPR	−0.001	−0.03	−0.002	−0.07	0.001	0.02
N Total	1357		1124		1110	
Individuals	252		208		208	
Families	148		104		104	

* $p < .05$

** $p < .01$

Table 3

Interaction Terms Coefficients and Z-Ratios for Brothers under Varied Specifications

	Brothers		
	All	**Pairs**	**Pairs/ Waves**
Basic Model	0.114 3.59 **	0.107 3.45 **	0.106 3.38 **
Binary Logit	0.092 2.27 *	0.090 2.25 *	0.085 2.11 *
Logged Negative Life Events	0.917 2.16 *	0.865 2.09 *	0.900 2.15 *
Regression	0.035 3.33 **	0.035 3.33 **	0.033 3.20 **
Time Averaged Regression	0.028 2.06 *	0.031 2.35 *	0.029 2.24 *
Drop Outlier 1	0.108 3.35 **	0.102 3.23 **	0.104 3.28 **
Drop Outlier 2	0.103 3.19 **	0.096 3.06 **	0.095 2.99 **
Drop Outlier 3	0.098 2.65 **	0.093 2.58 **	0.094 2.58 **
Drop Outlier 4	0.090 2.40 *	0.085 2.31 *	0.081 2.17 *

* $p < .05$

** $p < .01$