Published in final edited form as:
J Health Soc Behav. 2013 March ; 54(1): . doi:10.1177/0022146512468591.

Genetic sensitivity to peer behaviors: *5HTTLPR*, smoking, and alcohol consumption*

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Keywords

5HTTLPR; gene-environment interactions; cigarette smoking; alcohol drinking; peer effects

This paper investigates whether the serotonin transporter linked polymorphic region (*5HTTLPR*), a gene associated with environmental sensitivity, moderates the association between smoking and drinking patterns at adolescent's schools and their corresponding risk of smoking and drinking themselves. Drawing on the school-based design of the National Longitudinal Study of Adolescent Health (Add Health) in conjunction with molecular genetic data for roughly 15,000 respondents (including over 2,000 sibling pairs), we show that adolescents smoke more cigarettes and consume more alcohol when attending schools with elevated rates of tobacco and alcohol use. More importantly, an individual's susceptibility to school-level patterns of smoking or drinking is conditional upon the number of short alleles she or he has in *5HTTLPR*. Overall, the findings demonstrate the utility of the differential susceptibility framework for medical sociology by suggesting that health behaviors reflect interactions between genetic factors and the prevalence of these behaviors in a person's context.

Why do some adolescents drink alcohol and smoke cigarettes while others avoid substance use? A large body of sociological and public health research on this topic has focused on causal and selective (Brechwald and Prinstein 2011) social influences within adolescents' schools (Eisenberg and Forster 2003). Yet it is quite clear that not all adolescents who attend high-smoking and high-drinking schools smoke or drink themselves, suggesting that certain characteristics may render adolescents more or less susceptible to these social influences. Recent evidence suggests that genetic factors may provide clues about individual differences in overall environmental sensitivity (Simons et al. 2011). A polymorphism within the

*This research uses data from Add Health, a program project directed by Kathleen Mullan Harris and designed by J. Richard Udry, Peter S. Bearman, and Kathleen Mullan Harris at the University of North Carolina at Chapel Hill, and funded by grant P01-HD31921 from the Eunice Kennedy Shriver National Institute of Child Health and Human Development, with cooperative funding from 23 other federal agencies and foundations. Special acknowledgment is due Ronald R. Rindfuss and Barbara Entwisle for assistance in the original design. Information on how to obtain the Add Health data files is available on the Add Health website (http://www.cpc.unc.edu/addhealth). Additional support was provided by the following NIH/NICHD grants: R01 HD060726, R01 HD061622, and R24 HD066613.

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serotonergic system (*5HTTLPR*; an insertion/deletion producing short or long alleles) has been shown to influence environmental sensitivity (Caspi et al. 2003) but previous research has only focused on putatively risky and stressful social environments (Belsky and Pluess 2009a;Simons et al. 2011). Although it is an important concept, stress exposure is just one aspect of adolescents' lives that may influence their health behaviors through a gene-environment interaction (GxE) mechanism.

Often overlooked in GxE research is the notion that behaviors may diffuse in a population (e.g., reflecting shared norms, opportunities, and customs) and thus the prevalence of smoking and drinking behaviors in schools may be a particularly relevant feature of school social life. For example, social scientists have detailed the fundamental role played by expectations in adolescent health behaviors such as drinking and smoking (Alexander et al. 2001; Ellickson et al. 2003) but, to date, these social factors have not been fully integrated into research on gene-environment interplay. Smoking and drinking behavior, and especially nicotine and alcohol dependence, have been shown to be highly heritable Kendler et al. 1999; Li et al. 2003; Maes et al. 1999)[1] and a number of genetic markers have been linked to individual differences in these behaviors (McHugh et al. 2010; Munafo et al. 2004;), albeit sometimes inconsistently (McHugh et al. 2010; Munafo et al. 2004).

This research has been extended recently to demonstrate that the heritability of smoking and drinking behaviors varies across schools (Boardman et al. 2008; Harden et al. 2008) suggesting interplay between genetic and school compositional factors. In one study, genetic factors linked to smoking were shown to be higher for students who attended schools in which the most popular students also smoked the most (Boardman et al. 2008). To date, however, no molecular genetic marker has yet been identified to explain these patterns, which would permit studying this question using an allele-by-environment, rather than heritability-by-environment, approach. The purpose of this paper is to begin to examine the utility of the differential susceptibility GxE model for understanding the link between collective and individual behaviors in health research.

Gene-Environment Interactions in Differential Susceptibility to Environmental Influence

There is strong and consistent evidence that the collective behaviors of friends, neighbors, schoolmates, and colleagues are associated with the likelihood that an individual will engage in a healthy (or unhealthy) behavior in a particular place at a particular time. For example, friends' smoking and drinking habits (Alexander et al. 2001;Urberg et al. 1997), peer smoking and drinking rates (Alexander et al. 2001; Ellickson et al. 2003) and perceived peer smoking and drinking rates of peers (Chassin et al. 1984;Henry et al. 2005) all strongly predict individual smoking and drinking habits. The same has been shown for school smoking rates (Eitle and Eitle 2004) suggesting that individuals respond to contextual health behaviors even by those with whom they have no direct social connection.

Critically, some adolescents appear to be more susceptible to social influence than others, such that more susceptible youth are the most likely to adopt the risky or healthy social behaviors of those around them. Previous research has focused on social identities such as gender (Duncan et al. 2005; Erickson et al. 2000) or age (Gardner et al. 2008; Steinberg and Monahan 2007; Sumter et al. 2009) as the primary source of environmental sensitivity but it

[1]Li and colleagues (2003), in a meta-analytic review, suggest that the heritability of smoking behavior ranges from .37 to .59, depending on sex and whether one is measuring smoking initiation or persistence. Similarly, Dick and colleagues (2009) review previous research and estimate that genetic factors are responsible for approximately half of the variance in alcohol-related phenotypes.

is also possible that genetic factors may be an important source of environmental sensitivity. According to the *differential susceptibility hypothesis* (Belsky and Pluess 2009a;Conley et al. 2011; Ellis and Boyce 2008) persons with a certain genetic makeup will be relatively impervious to environmental influences, while others' outcomes strongly depend on their environmental context. Their model anticipates a cross-over effect such that those with more environmentally susceptible alleles engage in healthier behaviors in the healthiest social environments, and in less healthy behaviors in the least healthy social environments, than those with less susceptible alleles. Simons et al. (2012) found support for this perspective, showing that favorable social environments were associated with decreased aggression for carriers of the *5HTTLPR**S' or *DRD4**L (dopamine D4 receptor long) alleles (both of which are associated with higher environmental susceptibility) but not those without either susceptibility allele. Importantly, their analysis also demonstrated that carriers of environmentally sensitive alleles also had the highest aggression levels when they resided in the riskiest social environments.

To avoid the danger of false positives, it is critically important that we carefully select the genetic and environmental candidates for the present investigation based on prior empirical and theoretical research (Moffitt et al. 2005;Shanahan and Boardman 2009). Although a number of genes have been linked to alcohol and nicotine metabolism (Batra et al. 2003;Hill et al. 2004;Reich et al. 1998) and poor health behavioral patterns (Daw and Guo 2011; Eisenberg et al. 2007a; Salamone 1994), our interest in differential response to social cues suggested a potential role for the *5HTTLPR*. Importantly, this polymorphism has been linked to differential susceptibility but there is no consistent evidence that *5HTTLPR**S' is directly associated with the physiological process of nicotine or alcohol metabolism (McHugh et al. 2010; Munafo et al. 2004). As such, we believe that it is a strong candidate gene for our purposes. The lack of consistent main effects may have to do with the cross-over described above. Furthermore, it is not likely that individuals select schools as a function of their genotype; active gene-environment correlation is quite low. In ancillary analyses (results available upon request) we show that the distribution of school mean health behaviors is virtually identical across *5HTTLPR* genotypes. As such, we are confident that our results are not the product of gene-environment correlation; the environment is exogenous to *5HTTLPR* genotype.

Based on previous work that links the *5HTTLPR* to environmental sensitivity (Simons et al. 2011), we hypothesize that carriers of the short allele will smoke more cigarettes and drink more alcohol than carriers of the long allele when they attend schools in which a comparatively high amount of these substances is consumed. We also hypothesize that these same individuals will smoke or drink less than those with fewer copies of the *S'* allele when they attend schools in which mean smoking and drinking is fairly low. While we focus on this specific allele and these two important phenotypes, the implication of these hypotheses is broader: individuals adopt specific health behaviors based on their susceptibility to environmental influences and also the prevalence of those behaviors in their social settings.

The findings of this research will contribute to social scientific understanding of smoking and drinking patterns, social influence, and gene-environment interaction research in several ways. First, interactive effects between *5HTTLPR* genotype and school health behaviors would help to explain variable individual-level concordance with mean smoking and drinking behaviors at schools, contributing to understanding of both the social and genetic factors associated with smoking and drinking behavior. Second, while previous research has shown gene-age interactions with tobacco use (Guo et al. 2010), our paper is the first to focus on broad health contexts and the first to examined the serotonergic system as a mechanism of general vulnerability. The results of our study will help shed light on the

generalizability of differential susceptibility by *5HTTLPR* beyond the relationship between stressful life events, depression, or aggression.

Data and Methods

Data Source: The National Longitudinal Study of Adolescent Health

Data for this paper come from waves I and II of the National Longitudinal Study of Adolescent Health (Add Health), a widely used dataset for social and biological research on adolescents and young adults in the United States. These waves employed a school-based study design, in which high schools and feeder schools were selected from a national sampling frame, and in which all consenting students at the schools filled out a brief in-school questionnaire. A subsample of these students were then probabilistically selected for a more extensive in-home interview, and were subsequently re-interviewed a year later (excluding those who were seniors in wave I). Data from waves I and II were pooled in all analyses in order to maximize the statistical power of our analyses, using the sandwich estimator (Rogers 1993 to adjust for the resultant non-independence of observations.[2] No longitudinal modeling was employed; instead, both waves of data are employed to maximize the statistical power of the models. This sampling design ensures that basic information is available on the behaviors, attitudes, and networks of all consenting students in participating schools, whereas more detailed information is available on a significant research sub-sample. Additionally, genetic data were collected for the sibling sub-sample (in wave III), then the full sample (in wave IV) using Oragene or other buccal cell DNA collection technologies. This analysis uses the resultant wave IV genotypic marker data for *5HTTLPR*. See Harris and colleagues (Harris et al. 2009) for more details on the Add Health design and data.

The analytical sample consists of 14,560 respondents who participated in the survey and consented to have their DNA genotyped in the wave IV data collection. For fixed effects modeling (described below), this analytical sample is subset to the set of full siblings or dizygotic twins pairs who both consented to genotyping (Harris et al. 2006). Except for the descriptive statistics, mean-centered inverse-probability-of-selection weights are used in all analyses.[3]

Variables Used

Drinking—Individual drinking is measured in two different ways. First, a measure capturing the estimated *number of alcoholic drinks consumed* in the past 12 months multiplies the responses to two questions: “During the past twelve months, on how many days did you drink alcohol?” and “Think of all the times you have had a drink during the past 12 months. How many drinks did you usually have each time? (A ’drink’ is a glass of wine, a can of beer, a wine cooler, a shot glass of liquor, or a mixed drink.)” Responses to the first question were measured ordinally (values 0 to 6 were assigned to the responses “never,” “1 to 2 days in the past 12 months,” “once a month or less,” “2 to 3 days a month,” “1 to 2 days a week,” “3 to 5 days a week,” and “every day or almost every day”), and answer to the second were measured continuously. Although we refer to this measure as the number of drinks consumed in the previous 12 months, this measure is unfortunately

[2]As a robustness check, we also specified multilevel models that include an individual-level random intercept component. In no case did doing so change the substantive conclusions (results available upon request).

[3]As a robustness check, we also specified all models without sampling weights. In no case did doing so change the substantive conclusions (results available upon request). Finally, we also specified models that included level-2 weights constructed by averaging school-specific individual, grand-mean-centered weights. In one case doing so does affect the substantive conclusions of the analysis – the interaction term predicting drinking frequency becomes statistically significant in the expected direction, which is not the case in the results we present below.

imprecise, and values should not be interpreted strictly as such. Second, we employ the measure of the frequency of alcohol consumption independently from the measure of the typical number of drinks consumed as a robustness check.

Smoking—Individual smoking behavior is measured in two different ways. First, estimates of the *number of cigarettes smoked* by the respondent in the past month was derived by multiplying responses to the following two questions: “During the past 30 days, on how many days did you smoke cigarettes?” and “During the past 30 days, on the days you smoked, how many cigarettes did you smoke each day?” Multiplying the first response by the second results in an approximation of the total number of cigarettes smoked by the respondent in the past month. Although this measure is more precise than the parallel measure for alcohol consumption, it should be kept in mind that this measure, too, is only an approximation. Second we also employ the smoking frequency measure alone as a dependent variable to check for the robustness of our findings.

School-level smoking and drinking—School-typical smoking and drinking behaviors were measured using school-specific, mean responses to the following items in the in-school questionnaire: “During the past twelve months, how often did you smoke cigarettes?” and “During the past twelve months, how often did you drink beer, wine, or liquor?” For both items, responses were recorded as “never,” “once or twice,” “once a month or less,” “2 or 3 days a month,” “once or twice a week,” “3 to 5 days a week,” and “nearly everyday,” which were quantitatively coded as values equal to 0 to 6, respectively. These items were administered to nearly every student at each school in the study.[4] The resultant means of these school census data are therefore highly representative of the level of drinking and smoking typical at the respondent’s school.

Controls—Because patterns of drinking and smoking are strongly related to demographic characteristics, many analyses are adjusted for respondents’ racial, ethnic, sex, and age characteristics. Race/ethnicity was measured by self-report in the Add Health survey. Respondents were invited to indicate all racial categories to which they belonged. These responses were recoded in this analysis into five categories: non-Hispanic white alone, non-Hispanic black alone, non-Hispanic Asian alone, Hispanics of any race, and a residual category of other racial categories and multiracial persons. Sex was measured using interviewers’ report during the wave I in-home interview. Age was measured by the difference in years between the respondent’s self-reported date of birth and the date on which the interview took place.

Additionally, all regression models included controls for measures of home access to, and school penalties for, alcohol and tobacco, matched to the dependent variable. Access to tobacco and alcohol are separately measured dichotomously by self-report in response to the question, “[Are cigarettes/Is alcohol] easily available to you in your home?” Data on school penalties for alcohol and tobacco use are measured using school administrator survey data in response to the question, “In your school, what happens to a student who is caught [smoking at school/possessing alcohol/drinking alcohol at school], [first/second] occurrence?” The observed response values for each of these six measures range from 3–7, representing “verbal warning,” “minor action,” “in-school suspension,” “out-of-school suspension,” and “expulsion” responses respectively. The tobacco measures for first and second occurrences are summed together, while the four alcohol measures are summed together and divided by two (so that the scale is comparable to tobacco).

[4]Students who were absent on the day of the in-school questionnaire or whose parents directed that their children not participate did not respond to this questionnaire. See http://www.cpc.unc.edu/projects/addhealth/design/wave1 for further details. Accessed 2/27/12.

5HTTLPR Genotype—A polymorphic region of the promoter region of the serotonin transporter gene (SLC6A4), *5HTTLPR* has been linked to a wide range of mental health outcomes. We focus on the most commonly studied polymorphism in this gene, *5HTTLPR*. The Add Health genotyping method is a modification (Anchordoquy et al. 2003) of the method of Lesch and colleagues (Lesch et al. 1996) using the primer sequences (600 nM) from Gelernter and colleagues (Gelernter et al. 1999), which yield products of 376 (Short, S) or 419 (Long, L) for the two most common alleles. Additional extra-long alleles are found rarely as detailed by Nakamura and colleagues (Nakamura et al. 2000). According to their nomenclature, the most common S and L alleles contain 14 or 16 repeat units, respectively. Extra-long alleles contain 18, 19, 20 and 22 repeat units. For this paper the analysis of the used 14R alleles as "S" and alleles equal to or greater than 16R as "L". See Smolen and colleagues (Smolen et al. 2012) for details on Add Health Wave IV genotyping methods.

Importantly, Hu and colleagues (Hu et al. 2005) reported that a SNP (rs25531, A/G) in the Long form of *5HTTLPR* may have functional significance: The more common L_A allele is associated with the reported higher basal activity, whereas the less common L_G allele has transcriptional activity no greater than the S. These investigators suggest that in tests of association the L_G alleles should be analyzed along with the S alleles (Hu et al. 2006). For the analysis of the "triallelic *5HTTLPR*" we coded the S and L_G alleles as S' and the L_A and extra-long alleles as L' to denote their respective putative activity levels. Note that throughout the remainder of the text we refer to L' and S' as "alleles" for consistency in comparing the biallelic and triallelic analyses, realizing that these are actually grouped by their genetic activity and not individual alleles *per se*.

Methods

Exploratory Analyses

The nature of the interactive relationships of *5HTTLPR*, school-typical smoking and drinking, and individual smoking and drinking were initially evaluated in a series of steps. First, average tobacco and alcohol use is calculated separately by school smoking or drinking quartile and respondent *5HTTLPR* genotypes. The purpose of this analysis is to assess the key relationships of interest with maximum analytical simplicity. Separately, two-way ANOVA is used to indicate the statistical significance of the main and interactive effects of school mean substance use and *5HTTLPR*. The differential susceptibility hypothesis predicts that those with more *5HTTLPR**S' alleles would show evidence of stronger responsiveness to higher school-level smoking and drinking rates. Furthermore, this hypothesis predicts that those with *5HTTLPR**S'/L' and *5HTTLPR**S'/S' genotypes will have lower levels of smoking and drinking in schools with the lowest levels of smoking and drinking, and higher levels of smoking and drinking in schools with the highest levels of smoking and drinking, than those with the *5HTTLPR**L'/L' genotype. The results of these analyses are presented in Table 2 and are discussed below.

Regression Models

Three different sets of regression models are employed. First, multilevel linear regression models predicting tobacco and alcohol use as a function of *5HTTLPR*, school-level smoking or drinking, the cross-level interaction of the genotype and health behavioral environment, and a set of controls, are estimated using the full Add Health in-home sample in which respondents are nested within schools. These models are specified to include random intercepts and coefficients for the effect of *5HTTLPR* at the school level.[5] As described above, two waves of data are used for each respondent and the standard errors are adjusted to reflect the non-independence of observations across waves using the clustered sandwich estimator (Rogers 1993. One-tailed tests are employed to test the statistical significance of

the gene-environment interaction terms because we had an a priori directional hypothesis for this coefficient; two-tailed coefficients were used to test the statistical significance of other terms because we did not have directional hypotheses for these coefficients. These analytical decisions were made before commencing with the analysis.

Second, we also estimate fixed effects models within sibships so that siblings' difference in number of *5HTTLPR* *S' alleles is used to predict their difference in tobacco and alcohol use, interactively with the school-level tobacco and alcohol measures. In addition to adjustments for population stratification, fixed effects regression also protects against bias due to all sources of unobserved heterogeneity shared by members of a sibship. For both reasons, and because fixed effects regression results provide a more stringent test than standard cross-sectional regressions, the results of this test will provide additional protection against spurious inference. Because the interaction of these genes and the school-level variables vary between sibling, these variables may still be modeled in fixed effects regression without bias (Allison 2005. Third, because the fixed effects models can only be estimated on sibling subsample and this subsample may differ systematically from the full sample, the multilevel linear regression model is also estimated separately on the sibling subsample alone. In this way it will be clearer whether any differences between the results from the multilevel and fixed effects models is due to the subsetting to the siblings.

Results

Descriptive Statistics

How much tobacco and alcohol do adolescents use, how much between-school variation is there for these behaviors, and what is the distribution of genotypes for the *5HTTLPR*? As shown in Table 1, adolescents smoked an average of 46.9 cigarettes and consumed an average of 7.4 alcoholic beverages[6] over the last 30 days and 12 months, respectively.[7] Turning to frequency, the adolescents smoked an average of 4.7 days in the past month, and consumed alcohol on 1–2 days in the last 12 months. Schools reported an average smoking or drinking once or twice in the previous 30 days or twelve months, respectively. The least-smoking and drinking schools report mean values of nearly 0, and the highest smoking and drinking schools report means a little higher than "once a month or less." Schools account for a modest proportion of the variance in smoking and drinking behavior, as the intra-class correlation for the in-school measure of smoking and drinking is .044 for smoking and .014 for drinking behavior. For the *5HTTLPR* locus, the S' allele is more common and is considered the susceptibility allele. In our sample, 72% have at least one L' allele whereas 77% have at least one S' allele. This sample is 53% female, 55% white, 22% black, 16% Hispanic, and 6% Asian. The average age in the analytical sample is 16.4 years old, with a range between 11 and 22.

5HTTLPR, Average School Drinking, and Estimated Alcohol Consumption—

How does one's expected smoking covary interactively with mean smoking at the school and one's *5HTTLPR* genotype? Table 2 presents weighted mean levels of individual

[5]As a robustness check we conducted likelihood ratio tests using our models (excluding the gene-environment interaction) to assess whether specifying a random coefficient for *5HTTLPR* improved model fit compared to a null model including a school random intercept only. For models predicting estimated number of cigarettes smoked and alcoholic beverages consumed, the likelihood ratio test results were not statistically significant; for models predicting tobacco and alcohol use frequency, they were. We nonetheless employ random coefficients in all models, but this decision did not affect the substantive conclusions of the analysis (results available upon request).

[6]As discussed above, the alcohol consumption measure is not so cleanly interpretable as an estimated measure of the number of discrete units consumed as is the case with the tobacco use measure. However, we discuss the results as though it were for rhetorical convenience.

[7]These estimates overstate typical tobacco and alcohol use, however, as 63% and 47% of respondents did not smoke and drink respectively in the measured time periods. Furthermore, these distributions are right-skewed.

smoking and drinking by the level of smoking and drinking within schools and *5HTTLPR* genotype for all respondents. This table provides some initial evidence for differential response to environmental forces as a function of genotype. The upper half of Table 2 reports findings for the interactive effects of *5HTTLPR* and the average drinking at one's school on one's drinking. Findings show that attending a school in the fourth quartile of school drinking, compared with one in the first quartile, is associated with a 5.80 increase in the amount of alcohol consumption reported for those with the *5HTTLPR**L'/L' genotype, 5.63 for those with the *5HTTLPR**S'/L' genotype, and a 8.68 increase for those with the *5HTTLPR**S'/S' genotype. Furthermore, those with the *5HTTLPR**S'/S' genotype report lower average drinking than those with the L'/L' genotype in the lowest quartile, and report higher average drinking in the highest quartile. This pattern of differential effects of school drinking prevalence by genotype, including a crossover in outcomes, is consistent with the differential susceptibility hypothesis. The ANOVA results (not shown) show that there are no statistically significant main effects of *5HTTLPR* (p=.87), but there are statistically significant effects of school drinking (p=.00) and the interaction of school drinking and *5HTTLPR* (p=.03).

***5HTTLPR*, Average School Smoking, and Estimated Cigarette Use—**The lower half of Table 2 presents results identical to the upper half, but for tobacco use. These results show a difference between the first and fourth school-level smoking quartiles by genotype, as the expected number of cigarettes smoked increases by 75.8 for *5HTTLPR**L'/L', 78.85 for *5HTTLPR**S'/L', and 94.73 for *5HTTLPR**S'/S'. The data thus show evidence of an increase in the amount of smoking reported by the average smoking at the school, which ANOVA analyses show is statistically significant (p=.00). Furthermore, the effect of school smoking prevalence is descriptively highest for those with the *5HTTLPR**S'S' genotype; comparing the L'/L' and the S'/S' genotype, the difference in the increase between the 1st and 4th quartile is roughly equivalent to an additional 19 cigarettes per month. ANOVA analyses show that this interactive effect is marginally statistically significant (p=.052). The main effect of *5HTTLPR* genotype is not statistically significant (p=.79).

In summary, Table 2 provides descriptive evidence in favor of the hypothesis that *5HTTLPR* structures adolescents' responsiveness to school-level smoking and drinking patterns, in a manner consistent with the differential susceptibility hypothesis. In the next sections, the analysis tests whether this conclusion is robust to controls for demographic characteristics, measures of substance access and sanction, and population stratification.

Patterns of Alcohol Consumption

Table 3 reports the results of eight multilevel, linear regression models predicting tobacco and alcohol use consumption and frequency using Add Health data, estimated separately using the full sample and sibling subsample for reasons discussed above. The left side of Table 3 provides the results of fitting a multilevel, random-intercept and -coefficient regression model of alcohol consumption and frequency. Average school-level drinking is not significantly related to alcohol consumption in the full or sibling samples, but is statistically significantly and positively associated with drinking frequency in this model for the full (but not sibling) sample. The interactive effect of *5HTTLPR**S' and school drinking environment is positive and, for alcohol consumption (not frequency), statistically significant in the full sample analysis. This effect is marginally significant (p=.055) in the sibling sample for drinks consumed and drinking frequency. Additionally, there is no statistically significant association of *5HTTLPR**S' and drinking behavior for either measure, though it is negatively and marginally significantly related to alcohol consumption in the sibling subsample.

An additional question in this analysis is the degree to which school mean drinking levels explain overall school variation in the association of 5HTTLPR and alcohol consumption and frequency. Underneath each model just discussed in Table 3 is an indication thereof. The first row at the bottom of the table indicates the standard deviation in the 5HTTLPR*S' coefficient across schools in a model like that depicted but without the cross-level interaction; the second row shows the same figure with the cross-level interaction; and the third row indicates the percentage reduction in the school-level variation. School mean alcohol behavior is a major determinant of school-level variability in the association of *5HTTLPR* and drinking behavior. In the full sample models comparing this variability in models with and without the cross-level interaction between *5HTTLPR* and school mean drinking, this cross-level interaction accounts for 15% of the school-variability in this component for alcohol consumption and 17% of the variability in this component for drinking frequency.

Figure 1 depicts these results graphically for the full sample analysis. As shown, the results are consistent with the prediction of the differential susceptibility hypothesis that those with more *5HTTLPR**S' alleles will show stronger positive responses to school-level drinking rates than their counterparts. The predicted level of alcohol consumption is lower for those with the *5HTTLPR**S'/S' genotype compared to those with the *5HTTLPR**L'/L' genotype in the low-drinking environment and higher in the high-drinking environment.

Within-Sibship Differences in Alcohol Use

The left side of Table 4 presents the results of a two fixed effects regression models predicting alcohol consumption and frequency of drinking in the past 12 months. The results are consistent: in both cases, there is a negative, statistically insignificant effect of *5HTTLPR**S' and statistically significant, positive interaction of *5HTTLPR**S' and school-level drinking. This effect is only marginally statistically significant (p=.068) for alcohol consumption. The results of this analysis are consistent with the hypothesis that the effect of school drinking on individual drinking is contingent on *5HTTLPR*, and that this interaction is robust to controls for all sources of unobserved heterogeneity common to siblings, including population stratification.

Patterns of Cigarette Smoking

The right side of Table 3 provides the results of multilevel regression models predicting two measures of tobacco use in the full and sibling subsamples of the Add Health dataset. Evidence is found in favor of a gene-environment interaction between *5HTTLPR* and school tobacco use environments such that more *5HTTLPR**S' alleles are associated with a stronger response to the school health behavioral environment. In the full sample analyses, the models predicting cigarette consumption and tobacco use frequency both show evidence of a statistically non-significant main effect of *5HTTLPR*, a positive and statistically significant main effect of the school smoking environment, and a positive and statistically significant gene-environment interaction between the two. Analyses of the sibling subsample largely conform to these patterns; however, the main effect of school smoking on cigarette consumption and the interactive effect on smoking frequency are not statistically significant in these models at the $p \leq .05$ level. Finally, the main effect of school smoking on smoking frequency is only marginally significant (p=.086) in the smoking frequency model.

For the cigarette consumption model, including the cross-level interaction nearly completely eliminates school variability in this association, suggesting that the school mean smoking measure nearly completely captures the source of school heterogeneity in this association between *5HTTLPR**S' and smoking . For smoking frequency, however, this only captures

25% of this variability. Both values, however, suggest that school mean smoking is a major source of heterogeneity in the association of *5HTTLPR* and smoking behavior.

Figure 2 depicts these results graphically. As shown, the full sample regression results are consistent with the differential susceptibility hypothesis that those with more *5HTTLPR**S' alleles smoke less than their counterparts in low-smoking schools, and smoke more than their counterparts in high-smoking schools. These differences in predicted cigarette consumption are statistically significant at both extremes of the school smoking range.

Within-Sibship Differences in Cigarette Smoking

As with drinking behavior, the right side of Table 4 presents the results of a sibling-wave fixed effects model of both the estimated number of cigarettes smoked and smoking frequency in the last 30 days. The results are consistent with a positive interaction of *5HTTLPR**S' and school-level smoking – both dependent variables have a negative and statistically significant coefficient for *5HTTLPR**S' and a positive coefficient for the interactive effect. However, the interactive coefficient is not statistically significant in either model. While the direction of the coefficients confirms the general pattern described in Table 3, these more strict models suggest that caution is warranted in the interpretation of the association of *5HTTLPR*, school-level smoking, and individual smoking behavior as causal in nature. It is likely that this change in significance is at least partially due to the lesser power and efficiency of the fixed effects estimator, but it may also indicate that the interactive finding is spurious due to population stratification or some other source of sibling-level unobserved heterogeneity bias.

Discussion

Studies of smoking and drinking behavior have long looked to the school health behavioral environment as a partial explanation of individual variation in these important health behaviors during adolescence. Based on recent developments in psychological theory (Belsky and Pluess 2009a), we hypothesized that social influences were partially dependent on *5HTTLPR* genotype such that possession of more *5HTTLPR**S alleles was associated with stronger susceptibility to the influences of school-level smoking and drinking patterns. The findings suggest that the school health behavioral environment remains a strong determinant of individual substance use behaviors for persons of all genotypes, but also partially explains why, among those in high cigarette and alcohol use environments, some take up similar behaviors and others do not. Our findings indicate that variation in *5HTTLPR* genotypes partially explains these patterns. Furthermore, the results of our analysis, like meta-analyses of the literature (McHugh et al. 2010; Munafo et al. 2004), show little evidence of main effects of *5HTTLPR* on smoking and drinking behavior. Rather, the effect of *5HTTLPR* variation is contingent on the health behavioral environment at adolescents' schools. Importantly, these findings are supported by fixed effects regression analyses that account for possible biases stemming from population stratification and other potential sources of unobserved heterogeneity bias shared by siblings. In this model, the interactive effect in the drinking models was both positive and statistically significant, providing very strong evidence of the differential susceptibility hypothesis in the case of drinking behavior. Furthermore, although the interactive effect of *5HTTLPR* and school-level smoking was statistically insignificant, the estimated interactive coefficient was in the theoretically expected direction.

Previous research on the differential susceptibility hypothesis and the *5HTTLPR* has focused primarily on the role of stressful living conditions and *5HTTLPR* in understanding depression and aggression (Belsky and Pluess 2009a;Caspi et al. 2003). In this analysis, we examine a very different environment (school mean smoking and drinking) and behavior

(individual smoking and drinking). It is remarkable that very similar results – contingency of environmental effects on *5HTTLPR* genotype – hold for this very substantively different set of phenotypes and environments. Although much work remains to be done to confirm this, these results are consistent with the view that *5HTTLPR* structures individual susceptibilities to the influence of a more general set of environments than have heretofore been tested. These findings also provide new information about social factors in smoking and drinking behaviors. Although it has long been thought that school health environments influence individual health behaviors, this is the first analysis to show an interactive influence of the health behavioral environment by respondent genotype. That the linkage between contextual and individual health behaviors is genetically contingent is a novel finding. More generally, research which investigates what other characteristics, either social or genetic, modify this association should contribute to sociological understanding of the diffusion of poor health behaviors through a population.

We believe that future research should investigate the generality of this finding across outcomes and datasets. For example, models of formal and informal socialization are linked to a broad range of phenomena including political participation (Dalton 2008, racial ideology (Bonilla-Silva 2006), gender identity (Schrock and Schwalbe 2009), and other central aspects of general social scientific inquiry. Sociologists have long recognized individual-level differences in the internalization of norms related to health behaviors (Pampel et al. 2010) and have made great efforts to characterize the social contexts in which expected behaviors are developed and maintained (Frohlich et al. 2002), but to date, there is very little information about the source of these individual differences. In other words, the correspondence between the local environment and an individual's behavior is never one to one. If schools with high levels of smoking or drinking correspond to normative environments in which these behaviors are viewed to be more permissible, then our findings suggest that individual variation in *5HTTLPR* may partly underlie these differences in patterns of norm internalization. Whereas the bulk of the work in this area has characterized the population as composed of 'orchids' and 'dandelions' (Conley et al. 2011) , this framework typically focuses on risky compared typical environments in which the former is characterized as stressful in nature. But when describing typical behaviors, attitudes, or perceptions of environments, then it may be equally useful to consider that many individuals are more likely to resemble 'chameleons' than others; chameleons' behavioral profiles simply tend to match those of others in a common social environment. In other words, one the key points of our findings is that those with more *5HTTLPR**S' alleles were more likely to conform to the smoking and drinking patterns of the students around them than were those with fewer *5HTTLPR**S' alleles.

Limitations

One limitation of the present analysis is that school-level smoking and drinking levels are highly correlated, at .84 (not shown), whereas they are much less strongly related at the individual level (r=.25). As such it is difficult to separate out the independent effects of each of these on individual smoking and drinking behavior respectively. In another sense, however, this finding highlights the strong commonalities in social patterns underlying smoking and drinking behavior, as reflected in the very similar results our analysis documents for each health behavior. This suggests that differential susceptibility by *5HTTLPR* to these high-substance-use environments may reflect general patterns of health behaviors which should be further investigated in future research.

Similarly, in light of high profile research on the interaction of stressful life events with *5HTTLPR* in predicting depression, one might suppose that the present results reflect similar processes in which alcohol and tobacco use indicate self-medication to cope with stress

common to all students at a school. While this possibility cannot be ruled out, there is no straightforward association between alcohol use, tobacco use, and stress (Cooper et al. 1992), and no research of which we are aware addressing the role of school-level stressors in this process. As such, in light of our analysis's controls for home access and school penalties for substance use, we believe that differential susceptibility to the school health behavioral environment is the most compelling interpretation of these results.

Conclusion

This research offers a number of important contributions to the literatures on adolescent smoking and drinking, gene-environment interplay, and social context. These results reinforce the emerging, interdisciplinary conclusion that the answer to the nature-nurture debate is neither 'nature' nor 'nurture,' but both. Contextual smoking and drinking levels are related to individual smoking and drinking, certainly, but the effect is stronger for those with more *5HTTLPR**S' alleles. Combined with previous research, this finding is consistent with the view that *5HTTLPR* structures individual susceptibility to environmental influence for a range of phenotypes. By accounting for genotypic variation, we can better account for environmental influence, and vice versa, particularly for drinking behavior.

Furthermore, research on gene-environment interplay increasingly provides an answer to one of the more puzzling outcomes of human genetic research: heritability estimates for smoking and drinking behavior in twin and other family-based decomposition models is generally found to be high (Kendler et al. 1999; Li et al. 2003; Maes et al. 1999), yet the influence of individual genetic markers on these phenotypes is nearly invariably found to be small (Yang et al. 2010). However, the twin models used to estimate broad-sense heritability do not separately apportion variation due to gene-environment interactions, the effects of which would be counted in favor of the heritability component. As such, our findings suggest that the strong gene-environment interactions for these behaviors we have documented may help to explain this 'missing heritability' puzzle.

In sum, considering individual differences in the *5HTTLPR* sheds light on the reasons for incomplete link between group and individual smoking and drinking behavior. Alongside many other influences, having more *5HTTLPR**S' alleles is associated with a steeper response curve to higher levels of school-level smoking and drinking, such that those with more S' alleles have lower rates of regular smoking and drinking at low levels of school smoking and drinking, but higher levels thereof in high smoking and drinking schools, than their counterparts with fewer S alleles. This suggests that genetics partly underlie differential susceptibility to peer influences.

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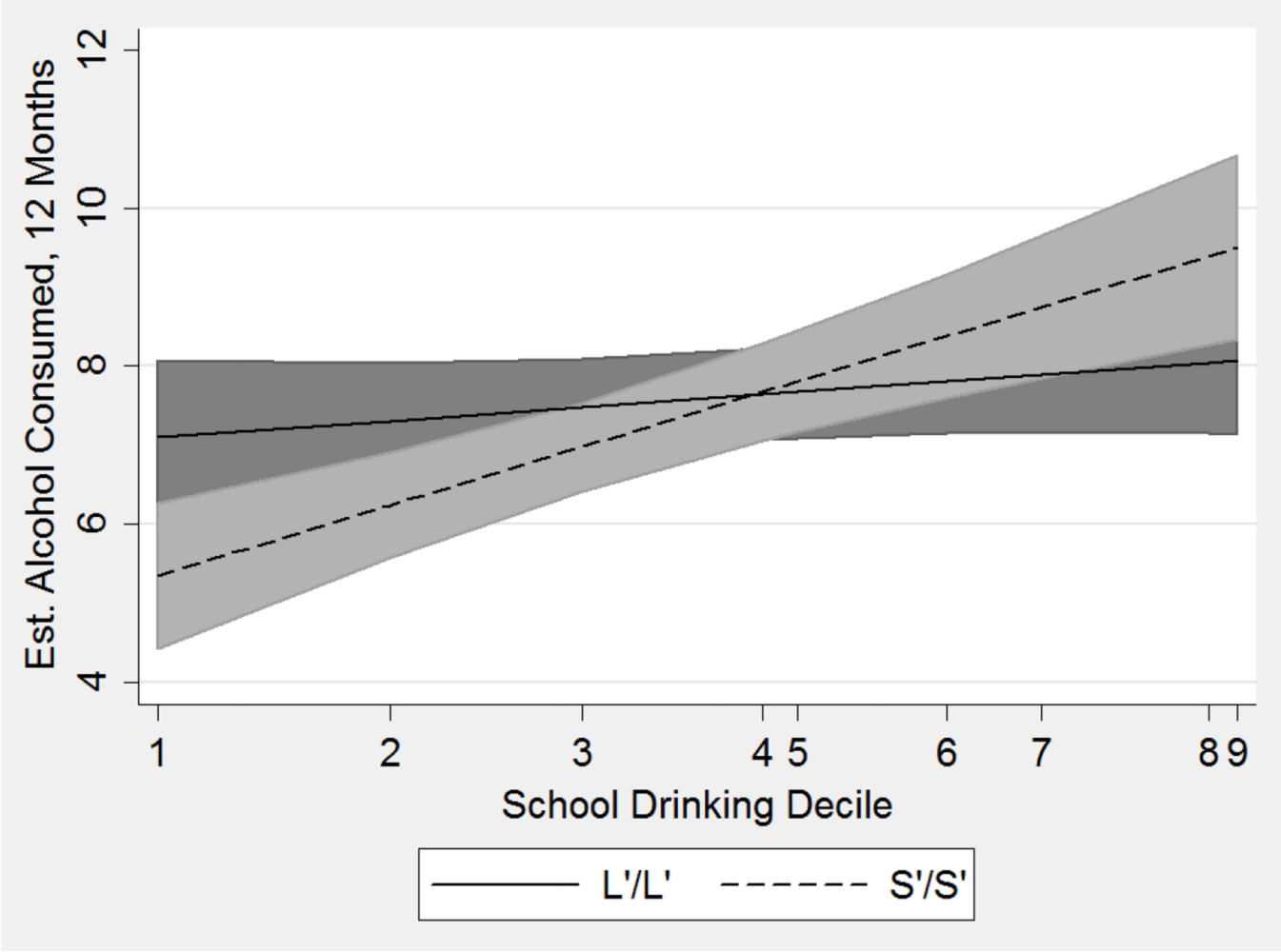

Figure 1. Regression-Based Response Curves for Alcohol Consumption by *5HTTLPR*

NOTE: Standard errors are depicted using 90% confidence intervals to represent the one-tailed nature of the statistical significance tests for the interactive effect in the regression models.

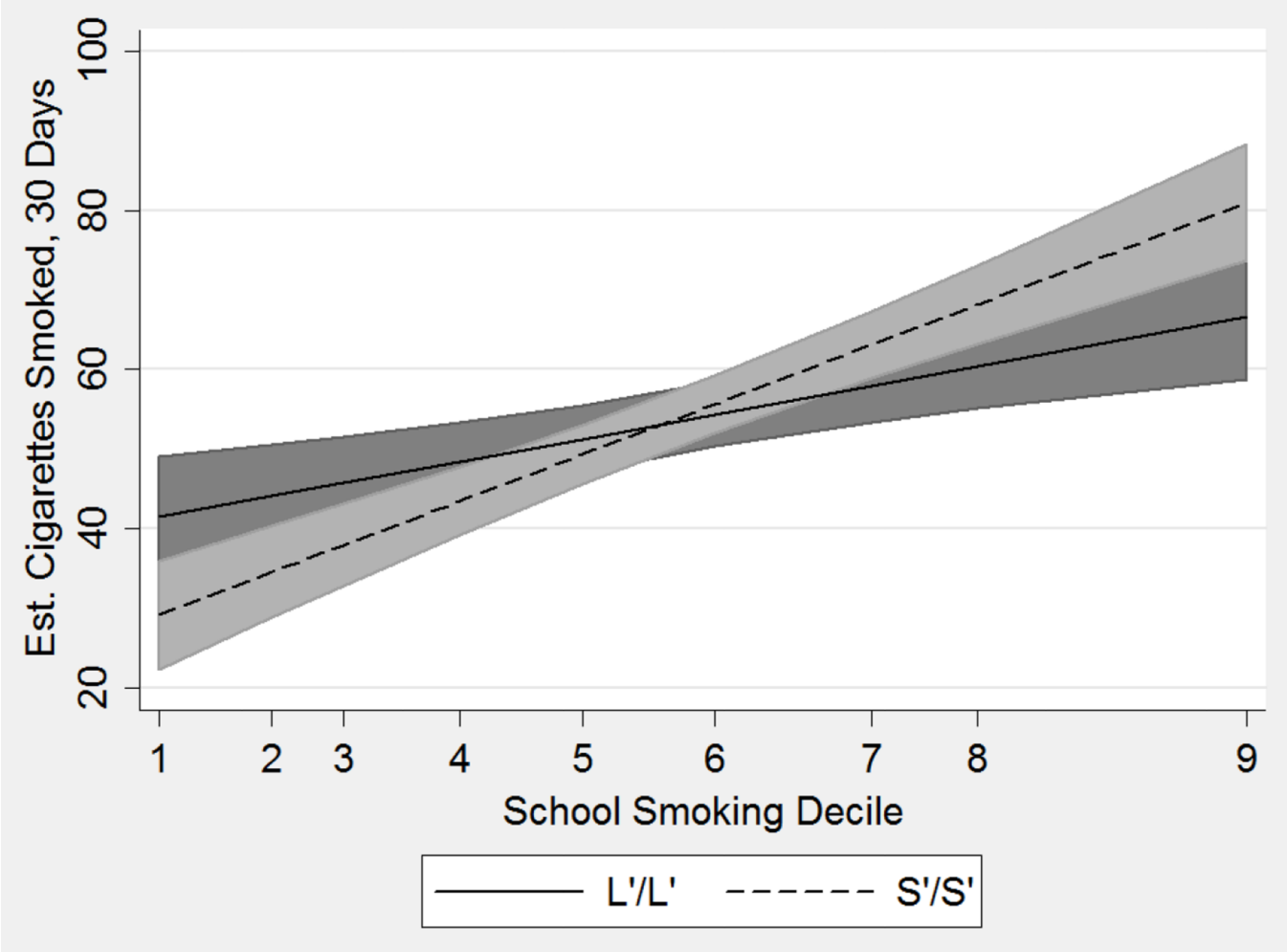

Figure 2. Regression-Based Response Curves for Cigarette Consumption by *5HTTLPR*
NOTE: Standard errors are depicted using 90% confidence intervals to represent the one-tailed nature of the statistical significance tests for the interactive effect in the regression models.

Table 1

Descriptive Statistics for all variables used in the analysis

Variable	Mean / Proportion	SD	Range
Cigarettes Smoked	46.87	147.81	(0,2850)
Alcoholic Drinks Consumed	7.36	21.67	(0,522)
Cigarette Frequency	4.71	9.96	(0,30)
Alcohol Frequency	1.08	1.48	(0,6)
Access to Cigarettes	.31	--	(0,1)
Access to Alcohol	.29	--	(0,1)
School Penalties for Smoking	1.96	1.37	(6,14)
School Penalties for Alcohol	12.47	.92	(8,14)
School Smoke Mean	1.16	.50	(.11,2.22)
School Drinking Mean	1.19	.38	(.14,2.05)
5HTTLPR			
L'/L'	.23	--	--
S'/L'	.49	--	--
S'/S'	.28	--	--
Age	16.34	1.68	(11,22)
Sex			
Male	.47	--	--
Female	.53	--	--
Race			
White	.55	--	--
Black	.22	--	--
Hispanic	.16	--	--
Asian	.06	--	--
Other	.01	--	--

NOTE: The full sample size is 14,560. These figures are unweighted.

Table 2

Mean Substance Use, by *5HTTLPR* and School Substance Use Quartile

5HTTLPR	School Drinking Quartile				
	Q1	Q2	Q3	Q4	Q4-Q1
L'/L'	4.57 (1628)	6.31 (1611)	9.33 (1518)	10.37 (1673)	5.80
S'/L'	4.08 (3339)	8.03 (3283)	9.66 (3276)	9.71 (3390)	5.63
S'/S'	3.09 (1896)	7.43 (1964)	8.78 (2051)	11.77 (1801)	8.68
5HTTLPR	**School Smoking Quartile**				
	Q1	Q2	Q3	Q4	Q4-Q1
L'/L'	21.77 (1644)	34.15 (1477)	53.50 (1591)	97.60 (1718)	75.83
S'/L'	16.02 (3313)	30.45 (3248)	57.04 (3357)	94.87 (3370)	78.85
S'/S'	12.84 (1900)	28.77 (2135)	48.03 (1913)	107.57 (1764)	94.73

NOTE: The first number in each cell is the mean smoking or drinking level; the number in parentheses is the cell size. Q4-Q1 is the difference of the Q4 proportion minus the Q1 proportion. These figures are weighted.

Table 3

Full and sibling sample estimates for the interaction between 5HTTS genotype and school-level drinking and smoking norms.

	Drinks Consumed		Drink Frequency		Cigarettes Smoked		Smoke Frequency	
	Full	**Sibling**	**Full**	**Sibling**	**Full**	**Sibling**	**Full**	**Sibling**
5HTTLPR*S’	.042	−1.716‡	−.005	−.083	−.538	−15.27‡	.019	−.847
	(.883)	(.053)	(.824)	(.186)	(.720)	(.082)	(.867)	(.103)
School Drinking	.903	−1.201	.346*	.274	--	--	--	--
	(.290)	(.633)	(.000)	(.176)	--	--	--	--
5HTTLPR*S’×School Drinking	1.491*	3.180‡	.041	.187‡	--	--	--	--
	(.016)	(.055)	(.201)	(.089)	--	--	--	--
School Smoking	--	--	--	--	16.06*	−15.68	1.792*	1.621
	--	--	--	--	(.002)	(.475)	(.000)	(.086)
5HTTLPR*S’×School Smoking	--	--	--	--	8.556*	33.96*	.454*	.679
	--	--	--	--	(.002)	(.015)	(.021)	(.200)
Age	1.577*	1.266*	.178*	.170*	12.54*	13.91*	.826*	.792*
	(.000)	(.000)	(.000)	(.000)	(.000)	(.000)	(.000)	(.000)
Sex								
Male (Ref.)	--	--	--	--	--	--	--	--
Female	−2.415*	−3.970*	−.099*	−.187*	−5.915*	−11.03	.456*	−.215
	(.000)	(.000)	(.000)	(.018)	(.032)	(.348)	(.050)	(.706)
Race								
White (Ref.)	--	--	--	--	--	--	--	--
Black	−3.726*	−3.512*	−.290*	−.405*	−43.16*	−44.71*	−3.954*	−3.362*
	(.000)	(.001)	(.000)	(.001)	(.000)	(.000)	(.000)	(.000)
Hispanic	.297	2.045	−.040	.050	−18.27*	−21.94	−1.350*	−1.272
	(.651)	(.228)	(.397)	(.706)	(.000)	(.133)	(.000)	(.169)
Asian	−3.640*	−4.123*	−.390*	−.443*	−23.09*	−9.909	−1.485*	−1.047
	(.000)	(.000)	(.000)	(.011)	(.000)	(.443)	(.002)	(.471)
Other	.0334	−5.205*	−.132	−.758*	2.45	−44.83*	.463	−2.322

	Drinks Consumed		Drink Frequency		Cigarettes Smoked		Smoke Frequency	
	Full	**Sibling**	**Full**	**Sibling**	**Full**	**Sibling**	**Full**	**Sibling**
	(.987)	(.024)	(.315)	(.016)	(.288)	(.001)	(.587)	(.111)
Intercept	−16.44*	−9.542	−1.540*	−1.930*	205.1	−179.7	−11.100*	−8.177
	(3.67e-06)	(.409)	(.000)	(.007)	(.000)	(.061)	(.000)	(.128)
SD(5HTTLPR*S'), No Int.	1.355	1.405	.125	.248	6.321	18.759	.688	1.591
SD(5HTTLPR*S'), Int.	1.154	.966	.104	.211	.000	7.309	.514	1.364
% Reduction	14.83	31.29	16.89	15.21	99.99	61.04	25.32	14.24
N (Unique)	13,040	1,154	13,085	1,155	13,329	1,182	13,335	1,182

*p<.05;

‡p<.10. All p-values are from two-tailed tests except for the interaction effects, which are one-tailed tests. All models control for measures of access to, and school penalties for, tobacco and alcohol, corresponding to the dependent variable. '% Reduction SD(5HTTLPR*S')' calculates the percentage reduction in the level-2 standard deviation in the 5HTTLPR*S' coefficient as a result of including the cross-level gene-environment interaction term in the model.

Table 4

Fixed Effects Regression Models of Estimated Cigarettes/Drinks Consumed and Smoking/Drinking Frequency

	Drinks Consumed	Drinking Frequency	Cigarettes Smoked	Smoking Frequency
5HTT*S’	−.820	−.0691	−24.39*	−1.568*
	(.389)	(.413)	(.004)	(.015)
5HTT*S’×School Smoking/Drinking	1.517‡	.253*	8.002	.0362
	(.068)	(.009)	(.300)	(.482)
Intercept	−8.459	−1.006	335.1	15.51*
	(.766)	(.588)	(.051)	(.005)
R^2	.01	.03	.01	.01
N (Unique)	1,154	1,155	1,182	1,182

*p<.05;

‡p<.10. All p-values are from two-tailed tests except for the interaction effects, which are one-tailed tests. All models include controls for measures of access to, and school penalties for, tobacco and alcohol, corresponding to the dependent variable.