ORIGINAL ARTICLE

Effect of Team Sport Participation on Genetic Predisposition to Adolescent Smoking Progression

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Context: There is much to be learned about why some adolescents progress to a regular smoking habit and others do not.

Objective: To evaluate whether (1) team sport participation buffers the effect of having 2 smoking risk genotypes (the dopamine reuptake transporter [*SLC6A3*] and the dopamine D_2 receptor [*DRD2*]) or 1 of these risk genotypes vs having none on adolescent smoking progression and (2) the buffering effects of team sports were due to physical activity associated with team sport participation.

Design: Longitudinal cohort study. Survey data were collected annually from grade 9 to the end of grade 12. Self-report measures included smoking, team sport participation, physical activity, depression, smoking exposure, and alcohol and marijuana use. DNA was collected via buccal swabs. Data were analyzed using latent growth modeling.

Setting: Five public high schools in Virginia.

Participants: A total of 361 students of European ancestry.

Main Outcome Measure: Smoking progression.

Results: For adolescents participating in at least 1 team sport, but not for adolescents with no team sport participation, physical activity had a significant negative effect on smoking progression ($z=-3.85$, $P<.001$; $\chi^2_{1,N=361}=6.73$, $P=.009$). In addition, having 1 ($z=2.69$; $P=.007$) and 2 ($z=2.22$; $P=.03$) smoking risk genotypes had a positive effect on physical activity. These represented significant between-group effects ($\chi^2_{1,N=361}=6.29$, $P=.01$; $\chi^2_{1,N=361}=3.81$, $P=.05$, respectively). Thus, having 1 or more smoking risk genotypes was related to higher levels of physical activity, which, in turn, was related to lower levels of smoking progression for adolescents participating in at least 1 team sport but not for adolescents with no team sport participation.

Conclusions: This study provides the first evidence of an interaction between environmental influences and specific genes on adolescent smoking and may promote an understanding of important protective relationships in the environment.

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EXPERIMENTATION WITH CIGARETTE smoking usually begins in adolescence. Some, although not all, adolescents who experiment with cigarettes will progress to a regular smoking habit.[1-4] A critical question is why do some adolescents progress to a regular smoking habit and others do not progress beyond experimentation?

Environmental or behavioral factors, such as physical activity, seem to account for some of the variability in adolescent smoking progression. More physically active adolescents are less likely to smoke[5-8] and are half as likely to initiate smoking or to progress along the uptake continuum.[9] Furthermore, adolescents with decreasing or erratic team sport participation patterns are almost 3 times more likely to become regular smokers than adolescents with consistently high team sport participation.[10] These findings suggest that physical activity may be protective against adolescent smoking.

Individual differences in genetic susceptibility may also account, in part, for the variability in adolescent smoking progression. The heritability of smoking initiation and persistence has been well documented[11-14] and may be explained, in part, by genetic variation in the dopamine pathway.[15] For example, studies have linked smoking behavior in adults with polymorphisms in the dopamine D_2 receptor gene (*DRD2*)[16-18] and the dopamine reuptake transporter gene (*SLC6A3*).[19,20] There has been little research to evaluate specific genetic contributions to smoking acquisition in adolescents. A recent study[21] found that adolescents were almost 2 times more likely to progress to smoking for every

DRD2-A1 allele present and that this effect was accentuated by depression symptoms.

Twin studies indicate that the heritability of smoking can vary by environmental factors. For example, the importance of genetic effects on the risk of smoking initiation tends to be greater for males vs females,[22,23] whereas the genetic effects on the risk of becoming a smoker are greater for older vs younger adolescents.[24] Although studies have evaluated differences in the heritability of smoking based on environmental factors, to date, to our knowledge, no studies have evaluated the effects of interactions between the environment and specific genetic polymorphisms on smoking.

Although not yet investigated, sports participation may buffer the effects of genetic predisposition on smoking progression in adolescents. Evidence from animal models suggests that brain dopamine concentrations are increased as a function of exercise,[25-28] but more research in humans is needed.[29] Increases in dopamine levels caused by other behaviors, including physical activity and food intake, may be similar to smoking-associated increases in dopamine levels.[30-33] The ability of these behaviors to increase dopamine levels may make them substitutable. This may partially explain why physical activity decreases nicotine withdrawal symptoms and bolsters smoking cessation rates[34-36] and why food reward and food intake increase after smoking cessation.[37,38] Although the notion of substituting one rewarding behavior for another lends itself to the investigation of protective gene-environment interactions, there has been a lack of attention to environmental or behavioral factors that may buffer the effects of genes on smoking acquisition. Evaluating protective gene-environment interactions may inform the next generation of adolescent smoking prevention and intervention efforts.[39-41]

The present study sought to elucidate the interaction between behavioral and genetic influences on adolescent smoking. This study evaluated whether team sport participation interacted with polymorphisms in both *SLC6A3* and *DRD2* to affect adolescent smoking progression. We chose to investigate the role of these 2 dopamine genotypes on adolescent smoking acquisition because they have received the most attention in adult smoking practices.[42] We hypothesized that team sport participation would buffer the effects of having 1 or 2 smoking risk genotypes on adolescent smoking progression (vs having no risk genotypes) and that physical activity would be the mechanism explaining the buffering effect (ie, moderated-mediated effect).

METHODS

STUDY POPULATION

Participants consisted of 361 students in 9th grade of European ancestry who were enrolled in 1 of 5 public high schools in Virginia. These adolescents participated in a longitudinal cohort study of biobehavioral determinants of adolescent health habits. Of these 361 adolescents, 177 (49%) were male and 184 (51%) were female. This sample is a subset of a larger cohort that was drawn from 2393 students identified through class rosters at the beginning of 9th grade. Students were ineligible to participate if they had a special classroom placement. The cohort was formed in the 9th grade and was followed until the end of the 12th grade.

Based on the cohort selection criteria, a total of 2120 students (89%) were eligible to participate. The parents of 1533 students (72%) provided a response. Of these 1533 parents, 1151 (75%) consented to their teen's participation in the study, yielding an overall consent rate of 54%. An analysis of differences between parents who consented and those who did not consent to their teen's participation in the study revealed a race × education interaction. The interaction indicated that the likelihood of consent was significantly greater for white parents with more than a high school education than for those with a high school education or less (89% vs 77%).[43]

Participation in the study also required student assent. Fifteen students declined participation. An additional 13 students did not participate in the baseline administration owing to absence. The final baseline sample size (year 2000) was 1123 of the 2120 eligible students. The rates of participation at the 3 spring follow-ups in the 10th (2001), 11th (2002), and 12th (2003) grades were approximately 96% (n=1081), 93% (n=1043), and 89% (n=1005), respectively. The Georgetown University and University of Pennsylvania institutional review boards approved the study protocol.

To limit potential bias due to ethnic admixture, the analyses were limited to adolescents of European ancestry (n=714). Of the 714 adolescents, 413 had at least 1 puff of a cigarette. We included only those adolescents who had at least 1 puff of a cigarette because never smokers would not have had the opportunity for the genetic predisposition to nicotine reward to be expressed.[44-46] Separating never smokers from those who have smoked has been considered an important step in refining smoking phenotypes.[47] Fifteen adolescents with rare *SLC6A3* alleles (ie, other than 9- or 10-repeat alleles) were excluded from the analyses. Approximately 37 adolescents had missing data on at least 1 covariate. The primary variables of interest were smoking, team sport participation, physical activity, and the *SLC6A3* and *DRD2* genotypes. Depression, smoking exposure, alcohol use, marijuana use, and sex served as controlling variables. The data presented herein are based on 361 adolescents of European ancestry with "all available data" (a pairwise missing data strategy used when data are missing at random that capitalizes on the data available for each wave for each participant) for these variables, although this method does not include participants with data missing on the covariates.

PROCEDURES

Data were collected on-site in a classroom common to all students. A member of the research team distributed the survey. Each student received a survey with a subject identification number. The survey contained a front page with the student's name. The front page was removed when the survey was given to the student. The completed survey contained only an identification number. A member of the research team (J.A.-M.) read aloud a set of instructions, emphasizing confidentiality to promote honest responding, and encouraged questions if survey items were not clear. Surveys took approximately 30 minutes to complete.

Biological samples were collected using buccal swabs as previously described,[19,20] and DNA was extracted using standard phenol-chloroform techniques. Genotyping was performed as in previous studies.[48] The assays were validated by confirming a polymorphic inheritance pattern in 7 human family lines that encompassed 3 generations (data not shown; National Institute of General Medical Sciences Human Genetic Mutant Cell Repository, Coriell Institute, Camden, NJ). Quality control pro-

cedures included positive and negative controls with each assay and independent repeated genotyping for 20% of the results. The discordant rate was less than 5%, and ambiguous or discordant results were considered missing data.

MEASURES

Smoking Status and Progression

An ordered categorical variable was generated from responses to a series of standard epidemiologic questions regarding smoking, including, "Have you ever tried or experimented with cigarette smoking, even a few puffs?" Have you smoked at least 1 whole cigarette?" "Have you smoked a cigarette in the past 30 days?" "How many cigarettes have you smoked in your lifetime?"[49-54]

Based on participant responses to these items, adolescents were categorized as (1) never smokers (never having smoked a cigarette, not even a puff), (2) puffers (not ever having smoked a whole cigarette), (3) experimenters (smoked ≥1 whole cigarette but <100 total in a lifetime), (4) current smokers (smoked on <20 of the past 30 days and >100 cigarettes in a lifetime), and (5) frequent smokers (smoked on ≥20 of the past 30 days and >100 cigarettes in a lifetime). These categories for smoking status have been used in previous studies.[9,55] The smoking progression variable was designed to capture any progression from never to frequent by assessing smoking at each wave. Adolescents who reported not smoking in the past 30 days but having more than 100 cigarettes in a lifetime were classified as experimenters (n=2).

Genotype

Genotyping was performed as in previous studies.[19-21] The *SLC6A3* genotype was classified as the number of 10-repeat alleles (0, 1, or 2), and the *DRD2* genotype was classified as the number of *A1* alleles (0, 1, or 2).[16,21]

Physical Activity and Team Sport Participation

Physical activity was assessed with 3 items from the Youth Risk Behavior Survey.[49] These items assessed intensity, duration, and frequency of physical activity, including vigorous, moderate, and strengthening/toning activity. Physical activity was treated as a latent variable with the 3 indicators (ie, vigorous, moderate, and strengthening/toning activity). Team sport participation was assessed with 1 item from the Youth Risk Behavior Survey.[49] The item requested the number of teams on which the individual played during the past 12 months.

COVARIATES

Depression symptoms were assessed using the Center for Epidemiological Studies Depression inventory at baseline.[56] The 20 items on this inventory are rated along a 4-point Likert scale to indicate symptom frequency during the past week (0=rarely or none of the time and 3=most of the time).

Exposure to smoking from family members and peers was evaluated as in previous studies.[57,58] Overall exposure was characterized as no exposure, family exposure only, peer exposure only, and both family and peer exposure.[58]

Past-month alcohol use was assessed with an item that asked, "During the past 30 days, on how many days did you have at least 1 drink (not just a sip) of alcohol?"[49] Marijuana use was assessed with an item that asked, "During your life, how many times have you used marijuana?"[49] The response options ranged from 1 (0 days or times) to 7 (≥100 days or times).

STATISTICAL ANALYSES

Univariate statistics were used to characterize the study variables, and bivariate statistics were used to create the correlation matrix. We design-coded risk genotypes with reference cell coding, with the 2 design variables representing 1 and 2 risk genotypes[59]; zero risk genotypes was the reference. We used latent growth curve modeling (growth modeling from a latent variable perspective[60,61]) to analyze for moderated and mediated effects in the longitudinal data. The latent variables represent baseline (initial level) and slope (ie, trend) and allow for the assessment of average trajectory shape (eg, linear or quadratic), developmental heterogeneity, and whether select covariates predict initial level and trends. Latent growth modeling also permits centering the level at any wave, permitting testing of the effects of covariates on a specific year's level while maintaining the longitudinal nature of the study.[61] In the present study, we centered level at grade 12. Thus, our measure of smoking progression by the end of 12th grade represents the accumulation of 4 years of smoking experience in a single latent variable.[61,62] To test for a team sport participation (0 vs ≥1 teams) by smoking risk–genotype interaction, we used multigroup modeling, dividing the sample by the number of team sports. Interactions occurred if differences in specific effects were significant between groups. We used a χ^2 difference test to assess between-group differences.[60] The mediating role of physical activity was evaluated by computing specific indirect effects, with delta method standard errors and associated z values.

Model fit was evaluated using χ^2 tests, the comparative fit index (CFI), root-mean-squared error of approximation (RMSEA), and standardized root-mean-square residual (SRMR). Suggested values are a nonsignificant χ^2, a CFI less than 0.95, an RMSEA less than 0.05 to 0.08 (including the upper limit of the confidence interval), and an SRMR below 0.08.[63-65] Finally, we evaluated the power of the results using a Monte Carlo analysis with 500 replications, using model parameter estimates resulting from our analysis as the population values. All multivariate analyses were conducted using M*plus* 3.13 software.[66]

RESULTS

Of the 361 participants, 253 (70%) had no *DRD2-A1* alleles (*A2/A2*), 94 (26%) had 1 *DRD2-A1* allele (*A1/A2*), and 14 (4%) had 2 *DRD2-A1* alleles (*A1/A1*). With respect to *SLC6A3*, 35 participants (10%) had no *SLC6A3* 10-repeat alleles (*9/9*), 127 (35%) had 1 *SLC6A3* 10-repeat allele (*9/10*), and 199 (55%) had 2 *SLC6A3* 10-repeat alleles (*10/10*). Neither the *SLC6A3* nor the *DRD2* alleles departed significantly from Hardy-Weinberg (HW) equilibrium ($P<.08$ and $P<.90$, respectively). The *DRD2* and *SLC6A3* genotype data were summarized into 3 categories of increasing risk for smoking: 107 participants (30%) had zero risk genotypes for smoking (*DRD2 A2/A2* and *SLC6A3 9/10* or *9/9*), 200 participants (55%) had 1 risk genotype for smoking (*DRD2 A2/A2* and *SLC6A3 10/10* or *DRD2 A1/** and *SLC6A3 9/10, 9/9*), and 53 participants (15%) had 2 risk genotypes for smoking (*DRD2 A1/** and *SLC6A3 10/10*).

The average amount of physical activity per week was 3.00, which corresponded to 2 days of physical activity of at least 20 to 30 minutes' duration (SD=1.85). The number of adolescents participating in team sports during the past 12 months was 118 on 0 teams (33%), 85 on 1 team (23%), 72 on 2 teams (20%), and 86 on 3 or

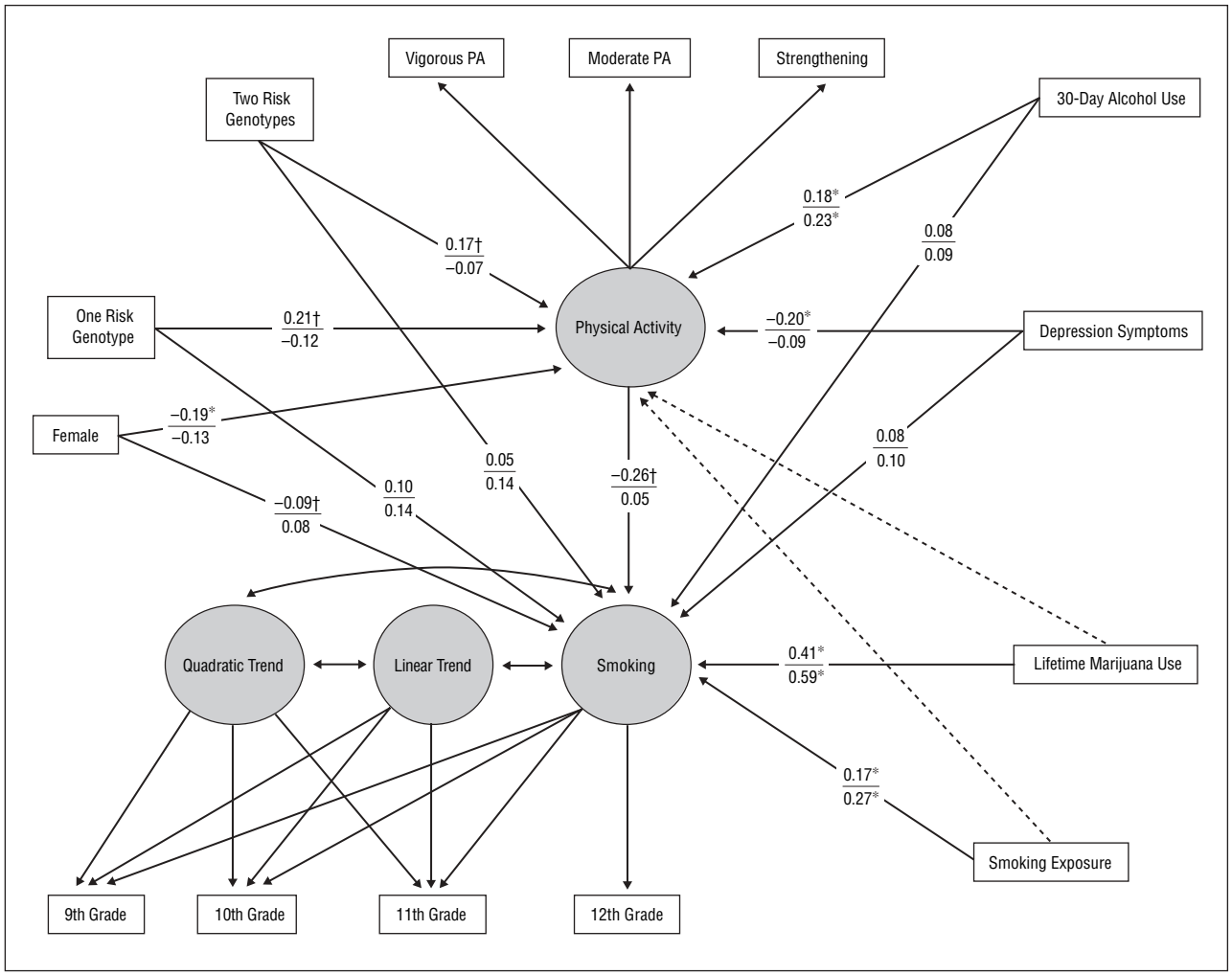

Figure. Two-group latent growth model for adolescent smoking progression by the end of 12th grade. Values above the horizontal dividing line are for adolescents participating in 1 or more team sports; values below the dividing line are for adolescents with no team sport participation. Zero smoking risk genotypes, *DRD2 A2/A2* and *SLC6A3 9/10* or *9/9;* 1 smoking risk genotype, *DRD2 A1/** and *SLC6A3 9/10, 9/9* or *DRD2 A2/A2* and *SLC6A3 10/10;* and 2 smoking risk genotypes, *DRD2 A1/** and *SLC6A3 10/10*. PA indicates physical activity; asterisk, significant within-group effect; and dagger, significant between-group effect.

more teams (24%). The mean (SD) Center for Epidemiological Studies Depression inventory score was 13.28 (9.47). Approximately 27% of the sample progressed in their smoking (any progression) during the 3-year follow-up period; 30% progressed to a regular habit (ie, current or frequent smoking).

LATENT GROWTH MODEL OF SMOKING PROGRESSION BY THE END OF GRADE 12

A 2-group latent growth model with linear and quadratic trends was fit to the data. The **Figure** presents the model, with standardized regression coefficients for key regression paths. To ensure proper model fit, all the factors (ie, physical activity, smoking level, and the linear and quadratic trends) were regressed on the covariates. This model fit the data well ($\chi^2_{71,N=361}=84.29$, $P=.13$, CFI=0.99, SRMR=0.03, RMSEA=0.03 [95% confidence interval, 0.00-0.06]). Three error variances were constrained to zero owing to nonsignificant negative error variances. No post hoc modifications were made to this model to improve fit. **Table 1** provides the correlation matrices for both groups.

LONGITUDINAL ANALYSIS OF BUFFERING EFFECTS

Table 2 provides regression coefficients with standard errors and z test statistics for the effects of smoking progression by the end of 12th grade and physical activity by team sport participation. For adolescents participating in at least 1 team sport, having 1 ($z=2.69$; $P=.007$) and 2 ($z=2.22$; $P=.03$) risk genotypes had a positive effect on physical activity. For adolescents with no team sport participation, neither risk genotype had a significant effect on physical activity. This difference in the effect of smoking risk genotype on physical activity between the groups was significant for 1 and 2 smoking risk genotypes ($\chi^2_{1,N=361}=6.29$; $P=.01$ and $\chi^2_{1,N=361}=3.81$; $P=.05$, respectively). Thus, having 1 or more smoking risk genotypes was related to higher levels of physical activity for adolescents participating in at least 1 team sport but not for adolescents with no team sport participation. Physical activity, in turn, had a significant negative effect on smoking ($z=-3.85$; $P<.001$), but only for adolescents with team sport participation. This between-group difference in the effect of physical activity on smoking was significant

Table 1. Bivariate Correlation for All Measured Variables in the Model by Team Sport Participation*

	1	2	3	4	5	6	7	8	9	10	11	12	13	14
0 Team Sports (n = 118)														
1. Female	1.00													
2. 1 Risk genotype	–0.16	1.00												
3. 2 Risk genotypes	0.05	–0.44	1.00											
4. Smoking exposure	–0.02	–0.03	–0.04	1.00										
5. Depression symptoms	0.07	0.01	–0.05	0.17	1.00									
6. Lifetime marijuana use	–0.24	–0.08	–0.01	0.29	0.04	1.00								
7. 30-d Alcohol use	–0.14	–0.14	0.17	0.23	0.00	0.47	1.00							
8. Vigorous PA	–0.08	–0.10	0.02	0.03	–0.10	0.15	0.21	1.00						
9. Moderate PA	–0.08	0.01	–0.06	–0.05	–0.04	0.01	0.06	0.49	1.00					
10. Strengthening and toning	–0.29	–0.04	0.06	–0.13	–0.05	0.07	0.22	0.54	0.24	1.00				
11. Smoking (grade 9)	–0.10	0.01	0.11	0.24	0.09	0.28	0.34	0.00	–0.06	0.01	1.00			
12. Smoking (grade 10)	–0.13	0.04	0.05	0.33	–0.02	0.50	0.48	0.11	–0.02	0.06	0.73	1.00		
13. Smoking (grade 11)	–0.09	0.11	0.12	0.43	0.12	0.58	0.42	0.05	0.04	0.01	0.58	0.71	1.00	
14. Smoking (grade 12)	–0.09	0.00	0.06	0.43	0.13	0.65	0.41	0.13	0.04	0.01	0.44	0.65	0.78	1.00
Mean (SD)	1.55 (0.50)	0.49 (0.50)	0.17 (0.38)	2.98 (0.94)	14.57 (10.33)	3.71 (2.32)	2.44 (1.38)	2.27 (1.90)	2.21 (2.20)	1.60 (1.95)	2.34 (1.28)	2.70 (1.29)	3.02 (1.24)	3.44 (1.03)
≥1 Team Sports (n = 243)														
1. Female	1.00													
2. 1 Risk genotype	0.04	1.00												
3. 2 Risk genotypes	0.05	–0.48	1.00											
4. Smoking exposure	0.07	–0.03	0.04	1.00										
5. Depression symptoms	0.22	–0.02	0.11	0.09	1.00									
6. Lifetime marijuana use	–0.19	–0.02	0.12	0.28	–0.02	1.00								
7. 30-d Alcohol use	–0.01	–0.03	0.04	0.13	–0.02	0.47	1.00							
8. Vigorous PA	–0.17	0.07	0.06	0.01	–0.17	0.03	0.11	1.00						
9. Moderate PA	–0.13	0.04	0.07	–0.05	–0.12	–0.02	0.12	0.48	1.00					
10. Strengthening and toning	–0.11	0.16	–0.07	0.00	–0.21	–0.05	0.05	0.62	0.42	1.00				
11. Smoking (grade 9)	–0.04	–0.01	–0.01	0.14	0.09	0.33	0.12	–0.06	–0.07	–0.14	1.00			
12. Smoking (grade 10)	–0.01	0.03	0.07	0.15	0.11	0.35	0.10	–0.01	–0.12	–0.09	0.62	1.00		
13. Smoking (grade 11)	0.01	0.07	–0.03	0.26	0.05	0.45	0.24	–0.01	–0.10	–0.04	0.43	0.66	1.00	
14. Smoking (grade 12)	–0.08	0.03	0.05	0.30	0.12	0.52	0.26	–0.19	–0.18	–0.19	0.31	0.44	0.68	1.00
Mean (SD)	1.46 (0.50)	0.59 (0.49)	0.14 (0.34)	2.69 (0.96)	12.65 (8.94)	3.46 (2.14)	2.62 (1.28)	4.04 (2.19)	3.10 (2.26)	3.06 (2.14)	2.04 (0.96)	2.43 (1.06)	2.73 (1.08)	3.15 (0.94)

Abbreviation: PA, physical activity.

*Female (male = 0); 1 risk genotype (2 risk genotypes = 0, 1 risk genotype = 1, and 0 risk genotypes = 0); 2 risk genotypes (2 risk genotypes = 1, 1 risk genotype = 0, and 0 risk genotypes = 0); smoking exposure (1 = no exposure, 2 = family members only, 3 = peers only, and 4 = family members and peers). The final sample size for both correlation matrices was 361, representing adolescents smoking at least 1 puff of a cigarette by 12th grade. Thus, there were no never smokers in 12th grade, resulting in a smaller 12th-grade standard deviation.

($\chi^2_{1,N=361}=6.73$; $P=.009$). This result suggests that the protective effects of physical activity on smoking progression by the end of 12th grade are specific to adolescents with team sport participation.

For adolescents involved in at least 1 team sport, neither smoking risk genotype had a significant direct effect on smoking ($P>.10$); the effect was indirect through physical activity. The indirect effect of 1 and 2 smoking risk genotypes on smoking progression through physical activity was significant (1 risk genotype: $z=-2.20$; $P=.03$ and 2 risk genotypes: $z=-1.94$; $P=.05$). There was not a significant indirect effect of 1 and 2 smoking risk genotypes on smoking progression through physical activity for adolescents without team sport participation, although a direct effect approached significance ($z=1.75$; $P=.08$ and $z=1.67$; $P=.09$, respectively), indicating an increased risk of smoking progression by the end of 12th grade for adolescents with 1 and 2 risk genotypes.

Thus, having 1 or more smoking risk genotypes was related to higher levels of physical activity, which, in turn, was related to lower levels of smoking progression by the end of 12th grade for adolescents participating in at least 1 team sport but not for adolescents with no team sport participation.

STATISTICAL POWER TO DETECT EFFECTS

To test the statistical power of these results, we ran a Monte Carlo analysis based on the results of the 2-group latent growth model. Monte Carlo analyses assess the power of a sample to detect specific effects based on repeated samplings from a population with known parameters.[67] In the present case, the population parameters were those resulting from our analysis, and the population size was 361 adolescents. For the effect of physical activity on smoking in the group of adolescents participating in 1 or more team sports, the power was 0.99. For the effect of 1 and 2 smoking risk genotypes on physical activity in the same group, the power was 0.75 and 0.66, respectively.

Table 2. Linear Regression Coefficients, Standard Errors, and *z* Test Statistics for 361 Adolescents*

Predictor Variable	0 Team Sports (n = 118) β	SE	*z* Value	≥1 Team Sports (n = 243) β	SE	*z* Value
Criterion Variable: Physical Activity						
Female	–0.44	0.36	–1.22	–0.73	0.27	–2.69†
Depression symptoms	–0.01	0.02	–0.85	–0.04	0.02	–2.87†
1 Risk genotype‡	–0.39	0.37	–1.07	0.80	0.30	2.69†
2 Risk genotypes§	–0.31	0.49	–0.64	0.96	0.43	2.22†
Smoking exposure	–0.13	0.19	–0.69	0.09	0.14	0.67
Lifetime marijuana use	0.02	0.08	0.20	–0.13	0.07	–1.85
30-d Alcohol use	0.27	0.14	1.98†	0.26	0.11	2.29†
Criterion Variable: Smoking Progression by 12th Grade						
Female	0.28	0.08	3.44†	0.17	0.06	3.08†
Depression symptoms	0.16	0.15	1.10	–0.17	0.11	–1.55
1 Risk genotype	0.28	0.16	1.75	0.20	0.12	1.65
2 Risk genotypes	0.35	0.21	1.67	0.13	0.17	0.79
Smoking exposure	0.01	0.01	1.30	0.01	0.01	1.40
Lifetime marijuana use	0.25	0.04	6.96†	0.18	0.03	6.35†
30-d Alcohol use	0.07	0.06	1.09	0.06	0.05	1.31
Physical activity‡	0.03	0.05	0.57	–0.13	0.03	–3.85†

*This model includes only adolescents who smoked at least 1 puff of a cigarette by 12th grade. Female (male = 0); physical activity is a latent variable, with vigorous physical activity, moderate physical activity, and strengthening and toning as its indicators; smoking exposure (1 = no exposure, 2 = family members only, 3 = peers only, and 4 = family members and peers); 1 risk genotype (2 risk genotypes = 0, 1 risk genotype = 1, and 0 risk genotypes = 0); 2 risk genotypes (2 risk genotypes = 1, 1 risk genotype = 0, and 0 risk genotypes = 0).

†Significant within-group effect, $P<.05$.

‡Significant between-group effect, $P<.05$.

§Significant between-group effect, $P<.10$.

ANALYSIS OF POPULATION SUBSTRUCTURE

The sample was examined for evidence of population stratification using the STRUCTURE program.[68] STRUCTURE is a clustering program that uses genotypes that may be out of HW equilibrium overall and that attempts to identify subpopulations that are at HW equilibrium internally. Based on the hypothesis that the sample population was not 1 population but 2 subpopulations, the program attempted to classify individuals as belonging to one population or the other using class probabilities. A stratified population would separate into a bimodal distribution of assignment probabilities, with values close to 0 or 1. Data for the analysis were genotypes of 42 randomly selected biallelic single-nucleotide polymorphisms (list available on request).

We tested HW equilibrium for each of the 42 single nucleotide polymorphisms using the GENHW routine in Stata (StataCorp, College Station, Tex). The routine generates a χ^2 value for each genotype. Our 42 random single nucleotide polymorphisms were at HW equilibrium. Results from the STRUCTURE program indicated a single population, as the probability of assignment to a subpopulation was clearly not bimodal. Having determined ahead of time to attempt to identify 2 subpopulations, the average probability of assignment to subpopulation 1 was 0.500, with the entire range of assignment probabilities from 0.476 to 0.527.

COMMENT

The present study provides the first evidence of interacting effects of environmental influences with specific genetic variants on adolescent smoking progression. Among adolescents participating in at least 1 team sport, having 1 or 2 smoking risk genotypes was related to higher levels of physical activity, which, in turn, was related to lower levels of smoking progression by the end of 12th grade. These effects were not present for adolescents with no team sport participation. Thus, team sport participation buffered the impact of smoking risk genotypes on adolescent smoking progression. The protective effects can be explained, in part, by the physical activity associated with team sport participation.

The interacting effects of genetic predisposition and team sport participation on adolescent smoking progression may be best explained in the context of the existing neurobiological research. The *A1* allele of the *DRD2* gene has been associated with altered receptor density and binding characteristics and thus less endogenous dopamine.[69-71] The 10-repeat allele of *SLC6A3* has also been associated with greater gene expression[72] and greater dopamine transporter reuptake protein levels, which results in greater clearance and less bioavailability of dopamine.[73] Thus, it is possible that adolescents who carry the *A1* allele of the *DRD2* gene or the 10-repeat allele of the *SLC6A3* gene may achieve greater reward from nicotine's effects on dopamine activity because they have less dopamine activity. Greater reward from the nicotine in cigarettes may promote further experimentation and progression to regular smoking. Consistent with this hypothesis are findings indicating that individuals with both the *SLC6A3-9* and the *DRD2 A2* genotypes are significantly less likely to be smokers,[19] and if they do smoke to have higher smoking abstinence rates and longer latency to smoking relapse.[74]

Evidence from animal models suggests that similar to nicotine in cigarettes, exercise increases brain dopamine concentrations and *DRD2* receptor binding,[25-28,75,76] which may help explain the reinforcing aspects of physical activity and why it may be protective against smoking progression. Research with humans has implicated the *DRD2* gene with annual levels of physical activity in women.[77] It is possible, as found in the present study, that specific genetic effects on smoking may also impact physical activity. A recent study[78] of adult male twins found that physical activity and smoking shared a common genetic component.

There are 2 possible explanations for the finding that team sport participation protects adolescents with 1 and 2 risk genotypes from progressing in their smoking. One mechanism, physical activity, was evaluated in the present study. This biologically based explanation suggests that the physical activity involved in team sport, or the physical activity habits of those involved in team sport, may increase dopamine levels in the brains of adolescents with genotypes associated with less available dopamine. Thus, the physical activity may provide a reward and make smoking less rewarding, or it may reduce the need for alternative methods to increase dopamine levels, such as smoking. The model evaluating physical activity as a mechanism accounted for 37% of the variance in smoking progression by the end of 12th grade, which suggests that there are other mechanisms that explain this relationship.

A more socially based explanation is that team sport participation has a component of social reinforcement derived from coaches and teammates. In addition, there are behavioral norms and rules for the athletic subculture (ie, athletes do not smoke and smoking is inconsistent with athletic performance) to which an adolescent may conform. These norms may also decrease smoking among teammates, which may protect against peer smoking influences.[79,80] These social influences may offset the genetic propensity to smoke. Both of these explanations are consistent with research showing that erratic and declining team sport participation is associated with the adoption of a regular smoking habit.[10]

Regarding adolescent smoking prevention, almost 25% of adolescents are regular smokers, and smoking prevalence increases across adolescence.[3,4] Whereas smoking prevalence increases, physical activity and team sport involvement decreases across adolescence. In fact, research has consistently shown that levels of physical activity from all sources, including team sports, declines 26% to 37% during adolescence and that physical inactivity tracks into adulthood.[8,10,81-86] Almost 20% of adolescents have both the *DRD2 A1/** and *SLC6A3 10/10* smoking risk genotypes, and at least 30% have 1 of these smoking risk genotypes. Thus, a significant subset of adolescents who would probably progress to a regular smoking habit could avoid the acquisition of a smoking habit through involvement in team sports, even 1 team sport a year. Successful adolescent smoking prevention efforts may focus on helping adolescents identify team sports to participate in and promoting consistent participation.

As the first investigation of the interacting effects of environmental factors and specific genes on adolescent smoking progression, this study has strengths and weaknesses. Strengths include the collection of DNA and behavioral data from a large sample of adolescents, the use of more refined longitudinal smoking phenotypes, and analysis of the potentially biasing effects of ethnic admixture as an alternative explanation for the study findings.[15,45,87,88] Disparate findings regarding the neurobiological features of *DRD2* and *SLC6A3* or their association with smoking phenotypes in adults[20,89-94] may be related, in part, to these methodological factors. It is important to point out that the functional significance of the 2 polymorphisms evaluated in the present study is not known. Thus, these polymorphisms may be in linkage disequilibrium with other functional variants, or it may be that variants downstream of the *DRD2* and *SLC6A3* loci could be affected by these polymorphisms.[95]

One potential limitation of this study is the parental consent rate for adolescent participation. Seventy-five percent of parents who responded provided consent, and the differences between those who provided consent and those who declined were relatively small and few.[43] However, some caution is warranted in generalizing the results of this study. Although the sample may not be representative of all adolescents in the United States, the sample is nationally and locally representative on basic demographic characteristics,[96-98] and the sample smoking rates are regionally and locally comparable with those found in national surveys. For example, data from our 2003 survey indicated that 10% are daily smokers compared with approximately 9% in the 2003 Youth Risk Behavior Survey and approximately 15% in the 2003 Monitoring the Future Survey.[3,4,98] In addition, 15% of the adolescents in our sample were current smokers compared with 13% in the 2003 Youth Risk Behavior Survey.

Another potential limitation is that an unmeasured factor associated with team sport participation and smoking accounted for the genotype interaction. Although we controlled for several key variables that could account for this association (eg, depression, family and peer smoking, alcohol use, and marijuana use), we cannot assume that another variable that we did not control for explained the interaction. Finally, there were insufficient numbers of adolescents in other racial or ethnic groups (eg, African American, Asian American, and Hispanic) to conduct analyses stratified by race.

Despite these potential limitations, the present study provides the first evidence of an interaction between environmental influences and specific genes on adolescent smoking acquisition. Although replication of these findings is necessary, these results, coupled with previous research,[9,10] provide more support for the role of team sport participation and physical activity in adolescent smoking prevention and may provide an increased understanding of why these behaviors may be protective.

Future research may include investigation of the social factors important to the buffering effect of team sport participation on the impact of genes on adolescent smoking progression. Furthermore, positron emission tomography studies of the immediate impact of physical activity on dopamine release in the brain that consider the role of habitual activity and smoking status/history on this relationship are also warranted.[25,27-29,99] Because adoles-

cent smoking often results in long-term smoking in adulthood, the medical and economic impact of preventing and reducing youth smoking could be significant.

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