Gender Differences in Determinants of Smoking Initiation and Persistence in California Twins

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Abstract

Objective: **To determine the effects of genetic versus environmental influences on smoking initiation (SI) and smoking persistence (SP).**
Methods: **Native California twins (32,359 pairs), who completed a questionnaire in 1992 or 1998 to 2001, were studied. Standard epidemiologic and genetic analyses were conducted using multiple logistic regression and biometric models to determine factors related to smoking phenotype.**
Results: **The strongest influence on SI was having a co-twin who ever smoked; the adjusted odds ratio was 9.7 [95% confidence limits (CL), 8.8-10.6] among monozygotic twins and 5.7 (95% CL, 5.2-6.2) among dizygotic like-sex pairs. The risk of SP was also increased if the co-twin currently smoked [adjusted odds ratios, 3.5 (95% CL, 3.0-4.1) for monozygotic twins and 2.3 (95% CL, 2.0-2.7) for like-sex dizygotic pairs]. The proportions of variance due to genetic effects, shared environment, and individual environment for SI were 31.6% (24.2-39.1), 47.5% (41.1-53.7), and 20.9% (18.8-23.1) for females, and 71.2% (66.7-75.4), 12.0% (8.7-15.7), and 16.7% (15.0-18.7) for males. For SP, estimates were identical by gender: 54.6% (43.6-65.5), 8.6% (0-17.1), and 36.8% (32.9-40.9). Modification of SI by closeness between twins was found, but little difference was seen for SP by closeness, birth cohort, or age.**
Conclusions: **Gender differences in the pattern of genetic and environmental determinants of SI indicate that gender-specific approaches may be needed for smoking prevention efforts. Modification of genetic effects by closeness between twins and birth cohort suggests that environmental interventions could reduce a heritable propensity to smoke. However, the apparently heritable tendency to continue smoking is unaffected by gender, age, birth cohort, or closeness between twins.** (Cancer Epidemiol Biomarkers Prev 2006; 15(6):1189–97)

Introduction

A wide variety of environmental, psychosocial, and genetic factors influence the probability of smoking initiation (SI) and successful smoking cessation (1-8). Previous twin studies have estimated the heritability of various tobacco-related behaviors (1-4). Heritability estimates for SI have ranged from 32% to 70% among females, and from 31% to 61% among males; estimates of smoking persistence (SP) have ranged from 4% to 49% among females, and from 50% to 71% among males (5). Observations on 16 twin cohorts indicate weighted means of 56% for the heritability of SI and 67% for SP (6). The gender differences in these findings (7) indicate a need to use mixed-gender dizygotic pairs to study gender variation in genetic and environmental effects (8).

To understand the interaction between genetic and environmental effects, previous studies have examined tobacco use among twins reared together and apart (9), in different countries (10), and across birth cohorts as societal norms changed over time. Social-environmental factors such as antitobacco policies and social norms may influence the expression of genetic tendencies to use tobacco. One study found that heritability estimates did not vary significantly across birth cohorts, but they did vary significantly between the U.S. and Australia (1). This suggests that the social environment contributes to the expression of genetic tendencies to use tobacco. Because the tobacco-related social norms in California have changed so dramatically over the past century (11-14), studies in California offer a unique opportunity to examine the effects of large historical changes in the observed heritability of tobacco-related behaviors.

Understanding the genetic and environmental influences on tobacco use typically is obtained from twin studies and then extrapolated to the general population (15). However, it is not known whether twins are truly representative of tobacco use in the entire population. Because twins grow up with a same-aged sibling, the social influences on their decisions about smoking may be unique. In addition, maternal tobacco use may increase the likelihood of having a dizygotic twin birth (16), indicating that twinship could be confounded with prenatal or postnatal exposure to nicotine and tobacco smoke, as well as with parental smoking behavior. Information about the tobacco use of twins compared with that of the population is important for the translation of findings from twin studies into effective population-based smoking prevention and cessation programs. However, few studies have assessed whether tobacco use among samples of twins is similar to that among the overall population (17).

In this large cohort of >32,000 pairs of native California twins, we describe the prevalence of and risk factors for tobacco use, and the contributions of genetics, shared environment, and nonshared environment to ever-smoking (SI) and continued smoking among ever smokers (SP). We compare our results to smoking prevalence in the California population, and our large sample allows for the investigation of differences in the magnitude of effects across gender, social closeness between twins, age, and birth cohort.

Materials and Methods

The California Twin Program. The methods of cohort recruitment and its representativeness of the California Twin

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Program have been previously published (18, 19). Briefly, records of 265,516 live multiple births in California between 1908 and 1982 were obtained from the California Department of Vital Statistics and linked to the records of the California Department of Motor Vehicles to obtain address information (successfully for 136,156 individuals). Of those located, 51,609 subsequently completed a 16-page risk factor questionnaire (crude overall response rate, 37.9%).

The questionnaire assessed demographic characteristics (age, sex, education, occupation, and marital status), zygosity (20), growth and development, reproductive history, medical service utilization, dietary preference, disease experience (including cancer), and lifestyle (smoking, alcohol consumption, exercise, and sun exposure). For some questions, participants were asked to provide information about themselves and about their co-twin (e.g., ''How much taller or shorter than you is your twin?''). Zygosity (monozygotic or identical twins and dizygotic or fraternal twins) was determined from responses to validated questions (20). Questionnaires were sent to the cohort during two time periods based on birth year (in 1992 to twins born before 1956, and in 1998 to 2001 to twins born from 1957 to 1982).

Our crude response rate (37.9%) exceeds that of almost every other similar study (18). A substudy of reasons for nonresponse (18) indicated that 15% of those sent a questionnaire likely did not receive it, and would not have been identified by postal returns, resulting in an adjusted response rate of 44.6% based on the estimated number of twins who received a questionnaire. There were some differences in response rate by age and gender with higher response rates among females and older twins. However, older females, due to inability to match on maiden name, were less often located than younger females for whom an a.k.a. name was also available (due to a change in Department of Motor Vehicles procedures). As a result, more older males than older females participated, but (due to higher response rates among females) more younger females than younger males participated.

Comparison with California Census Data. We compared the birth and respondent cohorts to the 1990 population of California-born current California residents using the Integrated Public Use Microdata Series (http://www.ipums.umn.edu; ref. 21). The respondent cohort was similar to the population from which it was drawn in terms of age, sex, race, geographic distribution, and occupation, but had a lower percentage with a college degree than the general population (18). The distribution of males and females by age group differed, with more females in the younger ages and more males in the older ages as previously indicated. Thus, these analyses are age- and gender-specific.

Smoking Questions. Ever smoking, or SI, was defined as a positive response to the question: ''Have you smoked at least 100 cigarettes in your life?'' If affirmative, the twin was asked about the age when they started smoking regularly and the number of cigarettes per day usually smoked. Proxy information on the co-twins' smoking was also obtained (''Has your twin smoked at least 100 cigarettes in his/her life?''). Ever smokers (smoked at least 100 cigarettes) were asked if they currently smoked (''Have you smoked in the last 6 months?'') and if not, the age when they had quit. SP was defined as ever smoking, as above, *and* current smoking. No additional information was available on the number of cigarettes currently smoked per day or on the number of previous quit attempts. SP for the co-twin was obtained from analogous proxy questions. From pairs in which both twins responded, we determined that the proxy response closely matched the self-report; allowing us to analyze pairs in which only one twin responded. Kappa, an indication of the degree of nonrandom agreement between the self and proxy report, was 87.1 [95% confidence limits (CL), 86.2-87.9] for ever-smoking and 78.9 (95% CL, 77.2-80.6) for current smoking.

Sample Size. These analyses are based on 32,359 pairs of known zygosity (self-reported) for which at least one member completed the questionnaire (both members completed the questionnaire for 38% of the pairs). For the analyses of the prevalence of SI and SP, and determination of risk factors and biometric models associated with SI, the full sample was used, consisting of 4,783 monozygotic male-male pairs, 5,835 monozygotic female-female pairs, 5,559 dizygotic male-male pairs, 6,231 dizygotic female-female pairs, and 9,951 dizygotic male-female pairs. For the analysis of risk factors and biometric models associated with SP, only the pairs in which both members had ever smoked were used, including 1,535 monozygotic male-male pairs, 1,457 monozygotic female-female pairs, 1,742 dizygotic male-male pairs, 1,448 dizygotic female-female pairs, and 2,443 dizygotic male-female pairs.

Statistical Methods. The prevalence of SI and SP was calculated by age group at the time of questionnaire response, by gender, and zygosity. The twins surveyed in 1992 were ages 36 and older when they responded, whereas the group surveyed between 1998 and 2001 ranged in age from 19 to 42 at the time of the survey. Thus, twins aged 35 to 44 were surveyed at both time points, enabling the comparison of smoking prevalence in two 5-year age groups between these two time periods.

To evaluate risk factors related to SI and SP, adjusted odds ratios (OR) for the multiple factors that predicted each of these outcomes were calculated using two separate multivariate logistic regression models (using SAS Proc Logistic). Because the responses of co-twins are correlated, one twin from each pair was randomly selected to evaluate variables related to SI. Those selected were treated as individuals in the regression model, which included familial variables (i.e., co-twin's smoking habit, zygosity, parental smoking habits and education) and individual variables (i.e., educational achievement, age, and gender). The logistic regression model to assess factors related to SP was based only on those pairs in which both twins had ever smoked. Thus, the outcome variable was dichotomized between those who continued to smoke versus those who had quit. In addition to the variables included in the SI model (with the substitution of the co-twin's current smoking status for the ever smoking status), the model for SP included whether the twin lived with a smoker, the amount usually smoked (20+ cigarettes/d versus less), the age at initiation (<21 years of age or later), alcohol use (number of drinks in the preceding 2 weeks: none, 1-9, 10-19, 20+), and depression (whether respondent felt ''really depressed or blue'': never, sometimes for a day or so, sometimes for weeks, or almost always). Alcohol use and depression were included in the models for SP because they have been identified as risk factors for smoking (22-28). Each model used a forward stepwise selection method to determine the significant variables remaining in the final model.

To assess the effect of the co-twin's smoking status (ever versus never smoking for SI, former versus current smoking for SP) on the likelihood of the respondent twin having ever smoked or continuing to smoke, and to compare these effects on the same scale between zygosities and genders, a combined variable was created for each model that used individuals with a monozygotic nonsmoking co-twin as the referent for the SI model and those with a monozygotic former, but currently nonsmoking co-twin, as the referent for the SP model. Thus, the OR's for dizygotic and monozygotic twins could be compared directly within each model.

Results were also stratified on the degree of social closeness between co-twins as one method to assess the validity of the ''equal environment'' assumption, i.e., the assumption that twins share a common environment to the same extent

regardless of zygosity. Were this assumption to be violated, greater similarity between monozygotic pairs than between dizygotic pairs may be incorrectly attributed to a genetic effect, rather than to a greater sharing of environmental factors (29). Although this measure of social closeness does not directly assess sharing of specific factors (e.g., peers in common), it represents a proxy measure for them. If the results across strata of ''closeness'' are similar, then such closeness between pair members is not an influential determinant of SI or SP (thus providing support for the equal environment assumption). The measure used was based on the frequency of communication between co-twins in adulthood (''How often do you see, call, or write each other? Daily, weekly, monthly, every few months, at least yearly, or less than yearly''). Those communicating at least weekly were considered ''close'' and those communicating less often as ''distant.'' This dichotomy was based on practical as well as theoretical considerations because daily contact was rather uncommon among male and unlike-sex pairs. A similar dichotomy has been used in a previous study (18). Using such a definition, the percentage of pairs considered ''close'' varied by zygosity and gender, with 78% of monozygotic female pairs, 64% of dizygotic female pairs, 56% of monozygotic male pairs, 35% of dizygotic male pairs, and 32% of unlike-sex pairs so classified.

Birth cohort (before 1950 versus later) was also stratified to assess differences in the effect of societal influence on smoking behavior within twin pairs. The year 1950 was selected as an important turning point in the societal view of the harmfulness of smoking because those born in the 1950s reached their teenage years at the time of release of the 1964 Surgeon General's report. A genetic predisposition to smoke may be more fully expressed when society condones the behavior compared with a time period when it does not. Because those born before 1950 were older at the time of survey response than those born later, we also stratified the twins according to age at response (<40 and 40+); thus, dividing the sample approximately in half and allowing more direct comparison with other studies.

In addition to a standard epidemiologic approach, classical twin methods using structural equation models were applied to determine the proportion of total phenotypic variance of SI and SP attributable to additive genetic factors or heritability (h^2), shared environmental factors (c^2) or individual-specific (nonshared) environmental factors (e^2), using the Mx software (30). These models are based on the assumption that the equal environment assumption is true, and the proportion of variance attributed to genetic effects may be overestimated if the equal environment assumption is violated. Univariate biometric models were fit to twin pair contingency tables for same-sex monozygotic and dizygotic twin pairs (monozygotic female, monozygotic male, dizygotic female, and dizygotic male) and for opposite-sex dizygotic pairs (dizygotic male-female). Model fit was based on maximum likelihood methods with χ^2 goodness of fit statistics. Differences in the magnitude of h^2, c^2, and e^2 variable estimates between sex were tested by equating variables across sex and testing the fit of the reduced model against the general model, using a likelihood ratio χ^2 difference test. The significance of each of the genetic and environmental variables was similarly tested by equating each to zero and testing the fit of the reduced model against the general model. A significant deterioration of model fit, indicated by a significant χ^2 difference test ($P < 0.05$), suggested that the imposed constraints could not be retained. The most parsimonious model was the one that fit the data with the fewest estimated variables. Analyses were conducted for the whole sample and stratified by twin pair closeness, birth cohort, and age at response.

Results

Prevalence of Smoking in the California Twin Program. The proportion of California Twin Program participants who smoked at the time of the survey did not vary by age or gender between 1992 and 2000 (Table 1). At neither time point was there were a statistically significant difference in current prevalence between the 35 to 39 year olds (24-25%) and the 40 to 44 year olds (23-25%). Overall, 23.1% in 1992 and 22.3% in 2000 were current smokers, a nonsignificant difference. The proportion who had ever smoked declined significantly between 1992 and 2000 in each age group, from 46% to 40% among 35 to 39 year olds and from 50% to 43% among 40 to 44 year olds ($P < 0.01$ for each age group), with similar findings by gender (Table 1).

Risk Factors Associated with SI. In a multivariate logistic regression analysis using one twin per pair (Table 2), White

Table 1. Percentage of respondent cohort currently smoking and ever smoking by age (at questionnaire response in 1992 and 2000) and gender (one respondent per pair included)

Age at response	Total, % (*n*)		Males, % (*n*)		Females, % (*n*)	
	1992	2000	1992	2000	1992	2000
Currently smoking						
<25	—	21.6 (3,634)	—	24.1 (1,229)	—	20.4 (2,390)
25-29	—	21.6 (2,793)	—	25.9 (989)	—	18.8 (1,770)
30-34	—	20.6 (3,640)	—	23.0 (1,337)	—	19.2 (2,217)
35-39	24.7 (4,624)	24.1 (4,950)	27.9 (2,013)	27.0 (2,014)	22.3 (2,601)	22.0 (2,859)
40-44	24.8 (4,740)	23.3 (2,854)	26.6 (2,193)	24.0 (1,155)	23.2 (2,533)	22.6 (1,669)
45-49	25.5 (2,972)	—	28.4 (1,566)	—	22.2 (1,402)	—
50-59	21.2 (2,097)	—	20.6 (1,492)	—	22.7 (600)	—
60+	12.5 (1,808)	—	12.3 (1,491)	—	13.3 (309)	—
Total	23.1 (16,241)	22.3 (17,871)	23.8 (8,755)	25.0 (6,724)	22.3 (7,445)	20.6 (10,905)*
Ever smoking						
<25	—	27.4 (3,665)	—	30.7 (1,241)	—	25.6 (2,409)
25-29	—	32.3 (2,836)	—	37.7 (1,010)	—	29.0 (1,792)
30-34	—	34.0 (3,715)	—	36.1 (1,362)	—	32.5 (2,263)
35-39	46.3 (4,634)	39.5 (5,037)*	49.3 (2,018)	40.8 (2,049)*	44.1 (2,606)	38.5 (2,910)*
40-44	50.5 (4,754)	42.7 (2,939)*	56.0 (2,199)	42.9 (1,190)*	45.8 (2,541)	42.5 (1,718)*
45-49	56.7 (2,982)	—	63.2 (1,572)	—	49.4 (1,405)	—
50-59	62.5 (2,106)	—	65.8 (1,499)	—	54.3 (602)	—
60+	63.0 (1,826)	—	66.1 (1,508)	—	47.7 (310)	—
Total	53.4 (16,302)	35.3 (18,192)*	59.1 (8,796)	38.0 (6,852)*	46.6 (7,464)	33.6 (11,092)*

*$P < 0.05$ for the difference between 1992 and 2000.

Table 2. Adjusted ORs for factors associated with SI (i.e., ever smoked): all twins and by gender

Selected variables	All twins*	Males	Females
	Adjusted OR (95% CL)	Adjusted OR (95% CL)	Adjusted OR (95% CL)
Co-twin's ever smoking status and zygosity			
Never smoked monozygotic	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Never smoked dizygotic same sex	1.19 (1.10-1.28)	1.27 (1.13-1.43)	1.12 (1.01-1.26)
Never smoked dizygotic opposite sex	1.56 (1.43-1.69)	1.76 (1.57-1.98)	1.37 (1.22-1.54)
Ever smoked dizygotic opposite sex	4.18 (3.83-4.55)	4.43 (3.88-5.05)	4.07 (3.63-4.57)
Ever smoked dizygotic same sex	5.67 (5.22-6.17)	5.42 (4.82-6.10)	5.95 (5.29-6.70)
Ever smoked monozygotic	9.66 (8.80-10.62)	8.97 (7.84-10.30)	10.2 (8.97-11.62)
High school graduate or more, age at response	0.45 (0.43-0.48)	0.42 (0.39-0.45)	0.49 (0.45-0.52)
Age <25	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Age 25-29	1.20 (1.06-1.36)	1.30 (1.06-1.60)	1.16 (0.99-1.36)
Age 30-34	1.16 (1.03-1.30)	1.10 (0.91-1.33)	1.20 (1.03-1.39)
Age 35-39	1.49 (1.35-1.64)	1.45 (1.24-1.71)	1.52 (1.34-1.73)
Age 40-44	1.64 (1.47-1.82)	1.74 (1.46-2.06)	1.58 (1.38-1.81)
Age 45-49	1.99 (1.67-2.36)	2.33 (1.80-3.02)	1.69 (1.34-2.14)
Age 50-59	2.26 (1.89-2.71)	2.38 (1.83-3.09)	2.06 (1.57-2.69)
Age 60 +	2.36 (1.96-2.85)	2.52 (1.95-3.28)	1.72 (1.25-2.37)
Trend $P < 0.0001$			
Parents smoked	1.79 (1.69-1.90)	1.74 (1.60-1.89)	1.86 (1.71-2.02)
Male gender	1.33 (1.26-1.40)	—	—
White race	1.24 (1.16-1.33)	—	1.43 (1.31-1.57)
Close to co-twin	0.86 (0.82-0.91)	0.84 (0.77-0.91)	0.87 (0.81-0.94)
Born >1949	0.80 (0.73-0.87)	—	—

*4,519 respondents were deleted from the model due to missing values in one or more of the variables included.

race, male gender, and parental smoking increased the risk of SI by 24% to 79%, whereas having at least a high school education, being close to the co-twin, and being born after 1949 significantly reduced the risk of ever smoking by 14% to 55%. The odds of SI also increased with age at response; those ≥50 were twice as likely to have ever smoked than those <25, whether surveyed in 1992 or 2000. However, the strongest predictor of SI was whether or not the co-twin had ever smoked, although that varied by zygosity. The adjusted OR for a monozygotic twin ever smoking was 9.7 (95% CL, 8.8-10.6) if his/her co-twin had ever smoked (in comparison to having an identical twin who never smoked). For SI among dizygotic twins, the adjusted OR was 5.7 (95% CL, 5.2-6.2) if a same sex co-twin had ever smoked and 4.2 (95% CL, 3.8-4.6) if an opposite-sex co-twin ever smoked. Similar results were found by gender, although the effect of White race only appeared among females, and being born after 1949 was no longer significant when analyzed separately by gender.

Although being close to a co-twin resulted in a 14% reduction in risk of SI, the influence of the co-twin's smoking was stronger among close pairs than among distant pairs (Fig. 1A). OR's for SI if the co-twin smoked were 10.3 for close monozygotic pairs versus 7.5 for distant monozygotic, and 6.6 for close dizygotic same-sex pairs versus 4.8 for distant dizygotic same-sex pairs. Among dizygotic opposite-sex pairs, the OR's were smaller and did not differ significantly by degree of closeness (4.8 in close pairs versus 4.0 in distant pairs).

Risk Factors Associated with SP. A separate multivariate logistic regression model was used to determine the risk factors for SP, or current smoking (versus former smoking), among pairs in which both members had ever smoked. As with the SI, the co-twin's current smoking was the strongest predictor of the respondent's current smoking (Table 3), although the magnitude of the risk was lower. Among monozygotic twins, the risk of the respondent continuing to smoke was 3.5 to 4 times higher if his or her monozygotic co-twin was also a current smoker than if the monozygotic co-twin was a former smoker, and risk was increased 2.1 to 2.7 times among dizygotic like- and unlike-sex pairs. The strength of these latter effects are comparable to the increase in risk of SP when the respondent lived with a nontwin smoker. Higher alcohol consumption, depression, parental smoking, higher cigarette consumption (>1 pack/d), younger age, lower education, and non-White race also increased the risk of SP, but birth cohort did not. Findings were similar by gender.

Closeness was not a significant predictor of SP, but the respondent's risk of SP when the co-twin currently smoked was slightly (if nonsignificantly) higher among close pairs than among distant pairs (Fig. 1B). Among monozygotic twins with a co-twin who currently smoked, the adjusted OR for the respondent continuing to smoke was 3.7 among close pairs versus 2.7 among distant pairs.

Biometric Models. Table 4 shows the number of pairs available for the biometric models and Table 5 shows the best fitting models quantifying the relative contribution of genetic (h^2), shared environmental (c^2), and nonshared environmental (e^2) influences for SI and SP for all twins, and for twins stratified by twin pair closeness, by birth cohort, and by age at response. For all twins, significant gender differences in the magnitude of the genetic and environmental contributions were found for SI but not for SP (Table 5). For SI, genetic effects accounted for more than two-thirds of the variance in men (71.2%) compared with less than a third (31.6%) for women. Among women, shared environmental effects were important, accounting for 47.5% of the variance in SI compared with only 12% of the variance for men. In contrast, for SP, the results from the reduced model in which variable estimates were equated across gender (because this was not a significantly worse fit than when the estimates were independently estimated for each gender) indicated that 54.6% of the variance was accounted for by additive genetic effects, 8.6% by shared environment, and 36.8% by individual environment.

In analyses stratified by twin pair closeness (Table 5), genetic effects for SI were lower and shared environmental effects were higher among close pairs of both genders compared with distant pairs. Among close pairs, the proportion of SI variance explained by genetics was 25.7% among females and 55.3% among males, compared with 60.2% among distant pairs (of both genders). For SP, there was again no gender difference within either strata of closeness and genetic effects were unchanged between the strata (51.3%). The only difference was that shared environment accounted for a larger proportion of

the variance (18.8% versus 0%) among the close twins compared with distant twins. These results suggest a possible moderating role of twin pair closeness and therefore of environment on the expression of genetic risk for SI but not for SP.

When the results were stratified by birth cohort (Table 5), the relative contribution of genetic effects for SI was larger for males in the older birth cohort (80.3%) than for males in the younger cohort (68.4%) and there was no evidence for a significant contribution of shared environment for males in the older birth cohort, whereas small effects were found in the younger cohort (14.7%). For females, the relative contribution of genetic and environmental influences could be equated across birth cohorts, suggesting no significant differences in magnitude of variable estimates (36.6% genetic effects and 43.1% shared environmental effects). For SP, no gender difference in the magnitude of variable estimates was found in either cohort and again the proportion due to genetic effects was the same (55.9%) in each group. Very similar findings were seen when the twins were stratified according to age at response (<40, 40+).

In summary, the biometric results for SI suggest that genetic influences were strongest among males, distant pairs of both sexes, and in the older birth cohort and age group for males. There was a greater importance of shared environmental effects for women compared with men, in close compared with distant twin pairs (of both genders), and in the younger birth cohort and age group of males. For SP, little difference according to gender, closeness, birth cohort, or age at response was seen, with 51% to 57% of the variance consistently due to additive genetic effects, very little due to shared environment (8.6% overall), and 36% to 49% due to individual environmental effects.

Discussion

The prevalence of SI reported by these California twins was similar to statewide rates from the California Tobacco Survey during the same approximate time period; however, the age distributions of the two populations may have differed with fewer older females among the California twins. Our twin data indicate a slightly higher prevalence of current smoking overall (22-23%) than was found in the California Tobacco Survey (which found current smoking rates of 20.9% in 1990 and 18.1% in 1996; ref. 31). Our higher rate may be a consequence of the difference in definitions of current smoking or the difference in the composition of compliant subjects. We classified respondents as current smokers if they had smoked within the past 6 months, whereas the California Tobacco Survey classified respondents as current smokers if they reported that they currently smoked ''every day'' or ''some days.'' Thus, the twins seem to be generally representative of the state's population in their smoking habits.

We found global risk factors for SI and SP similar to those previously reported. SI was related to educational achievement, gender, race/ethnicity, birth cohort, and age (32, 33); SP

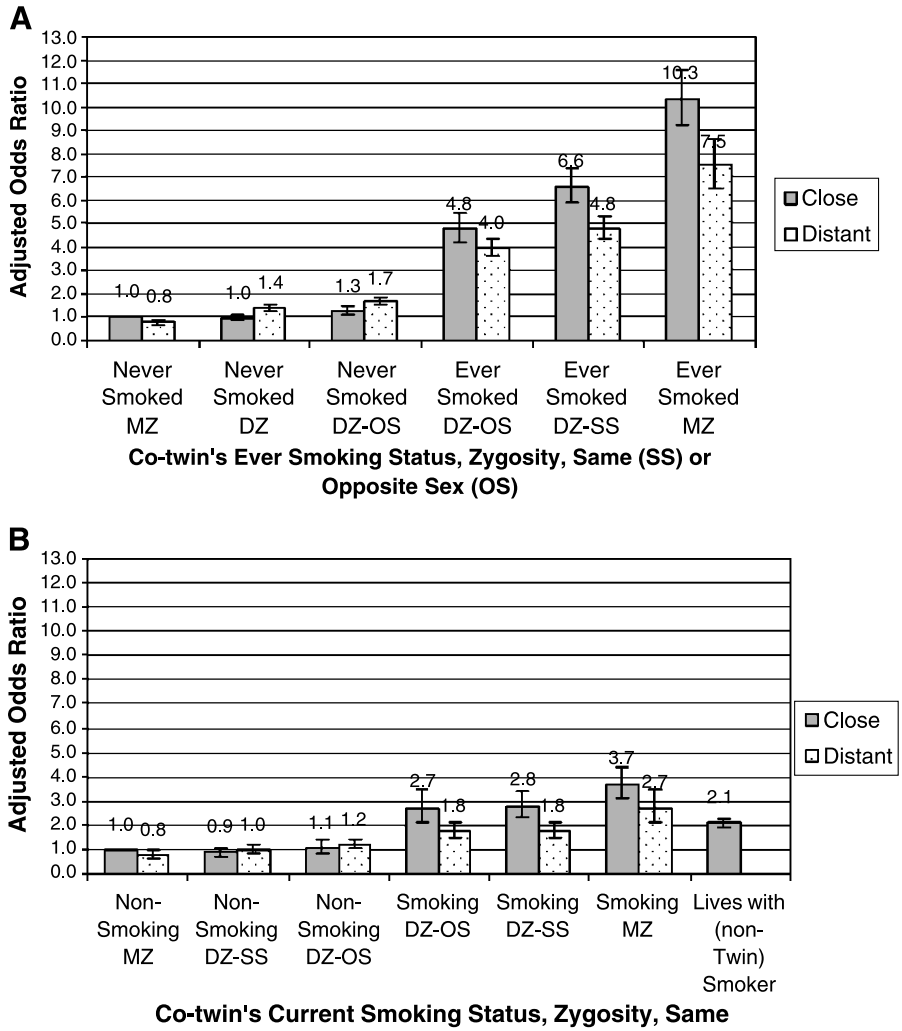

Figure 1. Adjusted ORs for SI (**A**) and for SP (**B**) by closeness between members of the pair. **A,** SI: adjusted OR for respondent ever smoking by closeness of pair and co-twin's ever smoking status (both sexes). **B,** SP: adjusted OR for SP by closeness of pair and co-twin's current smoking status (pairs in which both twins ever smoked).

Table 3. Adjusted ORs for factors associated with SP (i.e., for currently smoking twin within pairs in which both twins ever smoked): all twins and by gender

Selected variables	All twins*	Males	Females
	Adjusted OR (95% CL)	Adjusted OR (95% CL)	Adjusted OR (95% CL)
Co-twin's current smoking status and zygosity			
Not smoking monozygotic	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Not smoking dizygotic same sex	1.02 (0.87-1.20)	1.00 (0.81-1.25)	1.04 (0.82-1.33)
Not smoking dizygotic opposite sex	1.26 (1.06-1.50)	0.98 (0.76-1.25)	1.62 (1.25-2.07)
Smoking dizygotic opposite sex	2.12 (1.81-2.48)	2.14 (1.69-2.71)	2.19 (1.76-2.72)
Smoking dizygotic same sex	2.30 (1.98-2.67)	1.96 (1.60-2.40)	2.74 (2.20-3.40)
Smoking monozygotic	3.48 (2.97-4.08)	3.08 (2.45-3.85)	3.98 (3.17-5.01)
Age at response			
<25	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
25-29	0.61 (0.45-0.84)	0.62 (0.37-1.03)	0.62 (0.42-0.92)
30-34	0.43 (0.32-0.57)	0.45 (0.28-0.74)	0.42 (0.29-0.60)
35-39	0.33 (0.26-0.42)	0.36 (0.23-0.54)	0.31 (0.23-0.43)
40-44	0.27 (0.21-0.35)	0.26 (0.17-0.40)	0.27 (0.20-0.38)
45-49	0.23 (0.18-0.31)	0.22 (0.14-0.34)	0.25 (0.17-0.36)
50-59	0.14 (0.10-0.18)	0.12 (0.08-0.19)	0.18 (0.12-0.28)
60+	0.08 (0.06-0.12)	0.08 (0.05-0.12)	0.09 (0.05-0.16)
Lives with a smoker	2.10 (1.90-2.33)	2.23 (1.94-2.57)	1.98 (1.72-2.29)
Alcohol consumption			
None per 2 weeks	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
1-9 drinks/2 weeks	1.08 (0.96-1.22)	1.01 (0.84-1.21)	1.15 (0.98-1.35)
10-19 drinks/2 weeks	1.22 (1.05-1.43)	1.13 (0.90-1.40)	1.32 (1.06-1.65)
20+ drinks/2 weeks	1.90 (1.67-2.16)	1.72 (1.45-2.04)	2.12 (1.72-2.61)
High school graduate or more	0.63 (0.57-0.69)	0.64 (0.55-0.73)	0.63 (0.55-0.72)
Frequency of depression			
None	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Some days	1.34 (1.19-1.51)	1.36 (1.16-1.59)	1.35 (1.11-1.64)
For weeks/always	2.05 (1.72-2.45)	1.89 (1.44-2.47)	2.20 (1.71-2.82)
White race	0.78 (0.68-0.90)	0.81 (0.67-0.98)	0.76 (0.63-0.93)
Smoked 20+ cigarettes/d	1.26 (1.13-1.41)	1.21 (1.05-1.40)	1.30 (1.10-1.54)
Parents smoked	1.25 (1.09-1.43)	1.34 (1.12-1.61)	1.16 (0.95-1.41)
Started smoking <21	0.73 (0.66-0.82)	0.76 (0.65-0.89)	0.71 (0.61-0.83)

*4,520 respondents were deleted from the model due to missing values in one or more of the variables included.

was associated with depression and alcohol use (22-26, 34, 35). Although our study had limitations in the measurement of smoking phenotypes, the definitions of SI and SP were similar to those used elsewhere (7, 10). Unlike other studies, which have used only like-sex pairs, our study also included unlike-sex pairs, which allows us to directly test the heterogeneity of genetic and environmental effects across sex. With 4,593 to 6,231 pairs in each subgroup, our sample size is much larger than any of the other twin cohorts, and we minimized nonresponse bias by obtaining proxy characterizations of nonrespondent twins.

The strongest determinant of SI and SP was the co-twin's smoking behavior. Although this effect was more influential among monozygotic twins than among dizygotic twins, to attribute the larger association in monozygotic twins solely to genetic factors would be erroneous. The equal environment assumption, i.e., that unmeasured shared environmental factors are the same between monozygotic and dizygotic like-sex pairs has been challenged (29), especially with regard to smoking behavior, for which peer influences are especially powerful (27). We attempted to assess the effects of the environment by stratifying our twin pairs in several ways.

Table 4. Number of pairs included in calculations for biometric models

Phenotype	Zygosity and gender of pair					
	Monozygotic male	Monozygotic female	Dizygotic male	Dizygotic female	Dizygotic male-female	Total
SI						
All pairs	4,783	5,835	5,559	6,231	9,951	32,359
Close pairs	2,739	4,621	2,014	4,018	3,225	16,617
Distant pairs	2,044	1,214	3,545	2,213	6,726	15,742
Born <1950	1,472	890	1,895	1,048	2,720	8,025
Born >1949	3,311	4,945	3,664	5,183	7,231	24,334
Age <40 at response	2,537	4,006	2,735	3,990	5,477	18,745
Age 40+ at response	2,246	1,829	2,824	2,241	4,474	13,359
SP						
All pairs	1,535	1,457	1,742	1,448	2,443	8,625
Close pairs	834	1,128	597	908	810	4,277
Distant pairs	701	329	1,145	540	1,633	4,348
Born <1950	635	286	747	329	882	2,879
Born >1949	900	1,171	995	1,119	1,561	5,746
Age <40 at response	650	925	705	809	1,112	4,201
Age 40+ at response	885	532	1,037	639	1,331	4,424

Table 5. Proportion (% and 95% confidence intervals) of phenotypic variance explained by genetic (h^2), shared environmental (c^2), and nonshared environmental (e^2) influences on SI and SP for the best-fitting univariate models for all twins and stratified by co-twin closeness, by birth cohort, and by age group (California Twin Program)

Twin groups	h^2 (95% confidence intervals)	c^2 (95% confidence intervals)	e^2 (95% confidence intervals)
All twins SI			
Females	31.6 (24.2-39.1)	47.5 (41.1-53.7)	20.9 (18.8-23.1)
Males	71.2 (66.7-75.4)	12.0 (8.7-15.7)	16.7 (15.0-18.7)
All twins SP			
Females = males	54.6 (43.6-65.5)	8.6 (0-17.1)	36.8 (32.9-40.9)
By closeness SI			
Close twin pairs			
Females	25.7 (17.0-35.0)	55.7 (47.4-63.2)	18.6 (16.4-21.0)
Males	55.3 (46.4-63.0)	31.1 (24.2-39.2)	13.5 (11.5-15.9)
Distant twin pairs			
Females = males	60.2 (52.3-67.9)	14.1 (8.4-19.8)	25.7 (22.7-28.9)
By closeness SP			
Close twin pairs			
Females = males	*51.3 (45.5-56.9)*	18.8 (13.1-24.7)	29.9 (26.4-33.5)
Distant twin pairs			
Females = males	*51.3 (45.5-56.9)*	—	48.7 (43.1-54.5)
By birth cohort SI			
Older cohort (born <1950)			
Females	*36.6 (30.0-43.4)*	*43.1 (37.0-48.8)*	*20.4 (18.4-22.4)*
Males	80.3 (76.5-83.7)	—	19.7 (16.3-23.5)
Younger cohort (born >1949)			
Females	*36.6 (30.0-43.4)*	*43.1 (37.0-48.8)*	*20.4 (18.4-22.4)*
Males	68.4 (62.2-73.8)	14.7 (10.4-19.8)	16.9 (14.7-19.3)
By birth cohort SP			
Older cohort (born <1950)			
Females = males	*55.9 (51.0-60.6)*	—	44.1 (39.5-49.0)
Younger cohort (born >1949)			
Females	*55.9 (51.0-60.6)*	8.3 (1.8-14.8)	35.8 (30.8-41.1)
Males	*55.9 (51.0-60.6)*	—	44.1 (39.5-49.0)
By age group SI			
Older age group (40+ y)			
Females*	32.8 (19.2-46.2)	41.6 (30.4-52.4)	25.6 (21.5-30.1)
Males	78.5 (72.6-83.0)	3.7 (0.7-8.4)	17.8 (15.2-20.7)
Younger age group (<40 y)			
Females	33.2 (24.2-42.7)	48.0 (39.6-55.8)	18.8 (16.4-21.3)
Males	65.9 (58.7-72.1)	16.5 (11.5-22.4)	17.6 (15.0-20.5)
By age group SP			
Older age group (40+ y)			
Females = Males	*57.4 (52.9-61.7)*	—	*42.6 (38.3-47.1)*
Younger age group (<40 y)			
Females†	*57.4 (52.9-61.7)*	10.1 (3.2-16.8)	32.5 (27.1-38.4)
Males	*57.4 (52.9-61.7)*	—	*42.6 (38.3-47.1)*

NOTE: Within phenotype, italicized estimates could be equated across closeness or birth cohort.
*For female twins, either h^2 or c^2, but not both together, could be equated across age groups.
†Either h^2 or c^2, but not both, could be dropped from the model without significant deterioration of model fit.

With respect to SI (but not with respect to SP), we found striking differences in the influence of common environment by gender, with a much larger effect among females. This may indicate that females are more influenced by friends, family, and societal influences than are males. We also stratified our analyses on a measure of closeness between pair members. In both genders, the proportion of variance due to environmental effects was increased among close pairs; however, the apparent genetic effect among males was still twice as high as among females. There was no gender difference in the variable estimates among distant pairs, indicating that the underlying genetic propensity to smoke may be no different by sex. The results were also stratified on birth cohort. In those born more recently (i.e., after 1949), growing up at a time when smoking was less accepted by society, the apparent genetic influence on SI was reduced among males compared with the cohort born before 1950, but no difference was seen for females, among whom the role of genes was less influential. The differences in the proportion of variance for SI attributable to genetics by gender, closeness, and birth cohort indicate an important role of environment (e.g., societal norms, peers, etc.), and suggest that the expression of a genetic liability for SI, especially among males, is amenable to modification.

The influence of environment seems less profound for SP. The apparent genetic predisposition to continue smoking was relatively unaffected by the birth cohort, closeness between pair members, or gender. This indicates that, despite the decline in SI in recent years, the factors associated with SP have not changed over time and may be more dependent on a genetic predisposition.

Two recent meta-analyses of data from multiple studies done in different countries have been completed (7, 10). Both found differences in the role of additive genetic and environmental effects by gender. In contrast with our results, Li et al. (7) found that genetic factors accounted for a larger proportion of the variance in SI among females (55%) than males (37%), whereas shared environment was more important for males (49%) than for females (24%). This meta-analysis combined data from 17 smaller cohorts primarily from Australia, Finland, and the U.S., ranging in sample size from ~300 to ~3,000 pairs in each sex and zygosity-specific group. Heritability estimates from the individual cohorts also varied considerably from 11% to 64% among males, and from 32% to 78% among females. The study by Madden et al. (10), based on some of the same cohorts (from Australia and Finland) as well as on Swedish twins, found that the genetic influence for

lifetime smoking (i.e., SI) was consistent across cultures and age groups, and was lower (as we found), for females (46%) than males (57%), with a more important environmental role for females.

These differences may be due to different definitions of smoking phenotypes. Definitions of the SI phenotype varied among the cohorts, with the Finnish and Swedish twins categorized as ever-smokers if they responded affirmatively to the question ''Do you smoke or have you at some time smoked regularly, in other words daily or almost daily?'' whereas the Australian twins were simply asked ''Have you ever been a smoker?'' Our definition was based on having smoked at least 100 cigarettes (i.e., five packs) in their lifetime.

The comparison of previous results for SP is more complex, especially due to differing definitions of the phenotype. Li et al. (7) combined studies with multiple definitions of SP including current tobacco use, quantity of cigarettes smoked/d, and nicotine dependence as measured by the DSM-III-R criteria. In the study of Madden et al. (10), the Scandinavian twins were considered to have SP if they answered ''Yes'' to the question ''Do you still smoke regularly?'', whereas the Australian twins were assumed to be persistent smokers if there was no age given for quitting among those who ever smoked. We defined SP as still smoking within the last 6 months among those who had indicated that they had smoked at least 100 cigarettes.

Our finding of little difference across strata in the proportion of variance for SP due to genetic effects (54.6%; 95% CL, 43.6-65.5) is consistent with results from Madden et. al. (10) who attributed 52% (95% CL, 47-56%) of variance in SP to genetic effects. Just as they found no difference in this result across age groups and cultures, we found essentially no difference according to birth cohort, age at response, or closeness between pair members. Li et. al. (7) found that genetic effects accounted for 59 $\pm$ 2% of the variance for SP in men and 46 $\pm$ 12% in women.

Our finding that heritability of SP did not vary by gender seems inconsistent with the previous studies which showed that the phenotype of nicotine dependence has more biological characteristics among men and more psychosocial characteristics among women (28, 36), and that nicotine replacement therapy is more effective among men than among women (37). However, other studies (38) have not replicated this finding, and gender differences have not been found in the effectiveness of bupropion for smoking cessation (39, 40). These observations both relate to the phenotype of nicotine dependence, which is correlated with SP (41), but which was not measured directly in this study.

Because women are typically less successful than men in quitting smoking regardless of the strategy used, it is important to identify ways to improve existing smoking cessation treatments for women. If SI is more environmentally determined among women (that is, more related to societal factors), and quitting is more difficult for them, it becomes especially important to develop smoking prevention programs aimed specifically at women. Additional research is needed to identify behavioral interventions that can help women overcome the cultural aspects of their smoking behavior, including concern about bodyweight gain, variability in mood, and withdrawal symptoms over the menstrual cycle, social networks, and social/environmental cues to smoke (36).

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