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# Genetic and Social Determinants of Initiation and Age at Onset of Smoking in Australian Twins

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Retrospective data on age at onset of smoking, reported by 3810 adult Australian twin pairs, were analyzed to determine the role of genetic and environmental factors in the onset of smoking. Results of nonmetric multidimensional scaling supported a two-process model in which different etiologic factors determined which individuals were at risk of becoming smokers and the age at onset of smoking in those who were at risk. Parametric model-fitting confirmed this difference. For female twins and younger male twins (aged 30 years or less), the onset of smoking was strongly influenced by genetic factors, with shared and nonshared environmental effects having a more modest impact. For older male twins, shared environmental influences on onset of smoking were very important, and the influence of genetic predisposition was slight. The age at which smoking onset occurred, however, was influenced by both genetic and nonshared environmental effects, but not by shared environmental effects, in both sexes and both cohorts.

**KEY WORDS:** Smoking initiation; age at onset; multidimensional scaling; genes; environment.

## INTRODUCTION

The many adverse effects of smoking on the health of the smoker have been extensively documented (Royal College of Physicians of London, 1962, 1971, 1977, 1983; National Health and Medical Research Council, 1962; U.S. Public Health Service, 1964; U.S. Department of Health, Education and Welfare, 1979; U.S. Department of Health and Human Services, 1980). Despite these well-publicized risks, approximately 25% of the adult population of the United States (Centers for Disease Control and Prevention, 1996) and a comparable proportion of Australians (Hill *et al.*, 1998) are smokers. The vast majority of smokers have started to smoke by the time they leave high school (Johnston *et al.*, 1987; Miller *et al.*, 1983; Centers for Disease Control and Prevention 1993; Hill *et al.*, 1994), and the proportion of smokers who take up the habit after leaving high school appears to be declining (Johnston *et al.*, 1987).. Thus, those who become smokers are, on average, starting to smoke at an increasingly early age. Early age of onset of smoking is associated with heavier smoking as an adult (U.S. Department of Health, Education and Welfare, 1979; Grant, 1998), a reduced probability of successful smoking cessation (U.S. Department of Health, Education and Welfare, 1979; Chen and Millar, 1998), and an increased risk of early mortality (U.S. Department of Health, Education and Welfare, 1979). Smoking may also function as a "gateway" habit, in which onset of smoking is associated with an increased risk of early use of alcohol and use of illicit drugs (U.S. Department of Health and Human Services, 1987; Clayton and Ritter, 1985; Kandel and Yamaguchi 1985;

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Torabi *et al.,* 1993; Lindsay and Rainey, 1997). Therefore, an understanding of the determinants of smoking onset is an important goal for prevention research.

Theories about the causes of smoking onset have mostly focused on social influences, particularly the influence of smoking by peers and by family members (U.S. Department of Health, Education and Welfare, 1979). Most such theories assume that all individuals with similar exposure histories will be equally at risk of becoming smokers. They have neglected the possibility that individuals may differ in their vulnerability to become smokers (Jones and Battjes, 1985; Hawkins *et al.,* 1986) and that differences in vulnerability may in part be under genetic control (Hannah *et al.,* 1985; Hughes, 1986; Marks *et al.,* 1989; Heath, 1990; Collins and Marks, 1991; Heath *et al.,* 1993; Heath and Martin, 1993; True *et al.,* 1997). Such genetic differences might be mediated by personality differences (Eysenck, 1973, 1980; Kozlowski 1979; Eaves *et al.,* 1989; Heath *et al.,* 1995; Gilbert and Gilbert, 1995; Arai *et. al.,* 1997), by differences in acute sensitivity to nicotine (Marks *et al.,* 1983; Perkins 1995; Pomerlau 1995), or by a variety of other heritable mediating variables. Genetic and shared environmental influences have been shown (True *et al.,* 1997), including in this sample (Heath *et al.,* 1993), to be important in the initiation of smoking behavior, with substantial additive genetic effects also observed in persistence of smoking (Heath and Martin, 1993; True *et al.,* 1997). A recent study (Lerman *et al.,* 1999) has indicated a possible association between genetic polymorphisms of a dopamine transporter (SLC6A3) and the D2 dopamine receptor (DRD2) genes and both likelihood of becoming a smoker and smoking age at onset. In this paper, we explore the relationship between the genetic influences on the initiation and age at onset of smoking, by analyzing retrospectively reported data from a sample of 3810 adult Australian twin pairs.

## METHODS

### Sample and Measures

A self-report questionnaire was mailed to all 5967 twin pairs enrolled in the Australian National Health and Medical Research Council (NH&MRC) volunteer twin registry and aged 18 years or older, between November 1980 and March 1982 (Jardine and Martin, 1984; Hannah *et al.,* 1985; Heath and Martin, 1988). Completed questionnaires were received from both members of 3810 twin pairs, giving a 64% *pairwise* response rate. For most analyses, twin pairs were subdivided into those aged 30 years or less at the time of response ("young cohort") and those pairs older than 30 years ("older cohort"). For the young cohort only, information on the harmful effects of smoking would have been widespread by the time of their adolescence (Royal College of Physicians of London, 1962; National Health and Medical Research Council, 1962; U.S. Public Health Service, 1964). The numbers of twin pairs for each sex and zygosity group are given in Table I, separately for each age cohort. Female twins and monozygotic twins were overrepresented in the sample (Lykken *et al.,* 1978; Martin and Wilson, 1982), as is commonly found in studies of volunteer twin samples. Such differences in sample size were taken into account in parametric model-fitting analyses using the method of maximum likelihood (see below). A subsample of 96 twins who responded to this mailing had previously received and returned, on average 4 months earlier, a pilot version of the same questionnaire. The latter data were used to assess the stability of responses over time.

To determine their age at onset of smoking, twins were asked, "Have you EVER been a smoker?" and those who answered yes to the first question were further asked, "At what age did you start smoking?" Thus, the data that we have analyzed relied upon retrospective recall and upon the subjective judgment by the respondents as to what constitutes being a smoker and what constitutes starting to smoke. In the absence of prospective data on a sample of adolescent twins, such retrospective data were all that were available for examining the question of genetic influences on onset of smoking. Reliance on retrospective data did have certain advantages: we would not expect respondents' reports to be so influenced by the legality or otherwise of smoking at the age when they first started, and we would not expect respondents who had experimented with a single cigarette during adolescence to report themselves as former smokers!

### Data Summary

Two-way contingency tables were computed for each twin group, cross-classifying the age at onset (or nonsmoking status) of the first twin by that of

Table I. Sample Sizes for Each Sex and Zygosity Group

| | Young cohort | Older cohort | Total |
|---|---|---|---|
| MZ male pairs | 274 | 293 | 567 |
| MZ female pairs | 570 | 663 | 1233 |
| DZ male pairs | 206 | 146 | 352 |
| DZ female pairs | 351 | 400 | 751 |
| Unlike-sex DZ pairs | 510 | 397 | 907 |

the cotwin. Twins were assigned as first or second members of a pair on the basis of birth order, where this information was available, or at random otherwise, except that in unlike-sex pairs, twins were reordered so that female twins were always designated first twins. From each contingency table a "similarity matrix" was derived (Heath *et al.*, 1991a): each raw cell frequency was divided by the product of the corresponding row and column marginal frequencies, to yield a similarity index, $r_{i,j} = f_{i,j}/(f_i f_j)$, where $f_{ij}$ is the observed frequency of pairs where the first twin falls into category $i$ and the second twin into category $j$, $f_i$ is the frequency of first twin in category $i$, and $f_j$ is the frequency of second twins in category $j$. High (or low) values of the similarity index imply that there are more (or fewer) twin pairs where one twin has endorsed category $i$, and the second twin category $j$, than would be expected by chance alone, and thus suggests that the two categories are proximal (or distal). These similarity matrices were used as input for nonmetric multidimensional scaling (MDS) analyses. Because of some very low cell frequencies in the observed contingency tables, data from older and younger cohorts were pooled for these analyses.

Genetic analyses focused on two variables: whether or not the respondent reported that he or she had ever been a smoker ("smoking status") and the age at onset in those who were smokers. For smoking status, two-way 2 × 2 contingency tables were computed for each twin group. Analyses of age at onset considered only those pairs (281 monozygotic and 311 dizygotic pairs of the young cohort, 296 monozygotic and 269 dizygotic pairs of the older cohort) where both twins had become smokers. Ages at onset were log-transformed, and covariance matrices, giving the variances and covariance of first and second twins, were computed separately for each twin group. Although age at onset is really a meristic variable, since the number of age categories was large, the approximation from treating it as a continuous variable would be slight.

### Multidimensional Scaling

To perform a genetic analysis of the determinants of age at onset of smoking, we needed to understand the relationship between the genetic or environmental risk factors which influence smoking status and the factors which influence age at onset. If there are differences between individuals in vulnerability to become smokers, then it is quite conceivable that the determinants of age at onset in those who are vulnerable are quite distinct from the determinants of vulnerability [we refer to this hypothesis as the "independent liability dimensions" (ILD) hypothesis] (Heath *et al.*, 1991b). Most social theories for the onset of smoking assume, in contrast, that the same risk factors (e.g., exposure to smoking by parents, sibs, or peers) are involved in each case ["single liability dimension" (SLD) hypothesis] (Heath *et al.*, 1991b). The results of the multidimensional scaling (MDS) analysis of the relationship between smoking status and age at onset were used to inform the structural equation model-fitting on each variable.

Data on twin pairs have the potential to resolve these alternative hypotheses. Under the SLD hypothesis, we would expect to find that the smoking cotwins of nonsmoking twins have a later age at onset than the smoking cotwins of smoking twins, at least insofar as the determinants of age at onset are partly influenced by genetic or shared environmental factors. Under the ILD hypothesis, however, we would not expect the age-at-onset distribution in the smoking cotwins of nonsmoking twins to differ from that observed in the smoking cotwins of smoking twins. More complex hypotheses could be formulated in which, for example, the determinants of onset at an early age are independent of the determinants of onset, but the determinants of late onset are not independent. Such hypotheses are still testable in twin data.

Nonmetric multidimensional scaling provides a flexible means of exploring the relationship between smoking status and age at onset. MDS uses proximity data to estimate the coordinates in multidimensional space of a set of variables (in our application, the age at onset and nonsmoker categories) and to estimate the number of dimensions needed to represent the proximity relationships between those vari-

ables (Kruskal and Wish, 1978). Under the SLD hypothesis, we predicted that a single dimension would adequately account for the data. Under the ILD hypothesis, we predicted that a two-dimensional solution would be found, with one dimension distinguishing nonsmokers from smokers and the second dimension ranking the age-at-onset categories. We used the SAS ALSCAL procedure (SAS Institute, Inc., 1985; Young and Lewyckyj, 1980), electing the ordinal, asymmetric option, since the twin pair similarity data were neither interval nor symmetric (Heath *et al.,* 1991a; Meyer *et al.,* 1999). The "asymmetric" nature of the twin pair similarity data arises from the fact that we are not using double entry for the twin pair contingency table, i.e., there is no requirement that $C(2,1) = C(1,2)$, etc. For generality, we work with the asymmetric data: in the case of unlike-sex pairs, it cannot be avoided. To compare the goodness of fit of solutions of different dimensionality, we used a STRESS index (Kruskal and Wish, 1978) and an $R_2$ index (Young and Lewyckyj, 1980). The former may be interpreted as the "square root of the proportion of the total sum of squares of the optimally scaled data which is not accounted for by the model"; the latter, as the "proportion of variance of the optimally scaled data that is accounted for by the model" (Young and Lewyckyj, 1980). Thus, high STRESS values (by convention, values of 0.2 or greater), or low $R_2$ values, indicate a poor fit (Kruskal and Wish, 1978). Unlike-sex pairs were excluded from the MDS analyses, since otherwise we would have to assume the equivalence of age-at-onset categories across sexes (e.g. that smoking by age 12 in males is equivalent to smoking by the same age in females), which we would not generally expect to be the case.

In applying MDS to twin (or other family) data, we are using within-pair differences in response to provide information about the positions of the response categories in multidimensional space. For monozygotic twin pairs, these differences must be environmental in origin. Differences between members of a dizygotic twin pair will reflect both genetic differences arising from within-family segregation and environmental differences. It would be possible for genetic effects to act in a manner quite different from environmental effects (Heath *et al.,* 1990). We might, for example, find a single environmental liability dimension influencing both smoking status and age at onset, but independent genetic liability dimensions. For this reason, we performed MDS separately for each like-sex zygosity group.

### Model-Fitting: Smoking Status

Genetic and environmental models were fitted jointly to the five $2 \times 2$ contingency tables (for MZ male, MZ female, DZ male, DZ female, and unlike-sex pairs), separately for each age cohort, by the method of maximum likelihood (Eaves *et al.,* 1978). In model-fitting it was assumed that the observed discontinuous distribution (nonsmoker versus smoker) was determined by an underlying normally distributed latent variable (propensity to become a smoker), with a threshold on that latent distribution distinguishing smokers from nonsmokers, and that the joint distribution of twin pairs for the latent variable was bivariate normal. These are the standard assumptions implied by the estimation of tetrachoric and polychoric correlations (Pearson, 1900; Tallis, 1962; Olsson, 1979). Model-fitting by maximum likelihood made allowance for differences in sample size between twin groups. It also provided a chi-square goodness-of-fit test, a significant chi-square value indicating that a given model did not fit the observed data. The goodness of fit of different, nested models could also be compared by likelihood-ratio ("chi-square difference") chi-square.

In model-fitting, we compared the fit of three basic models: an additive genetic model, a shared environmental model, and a full model allowing for both additive genetic and shared environmental effects. All models allowed for nonshared environmental effects, which make one twin differ from his or her cotwin, since no twin groups were perfectly correlated in their smoking habits. Under the genetic model, it was assumed that the correlation between twin pairs for propensity to smoke was due entirely to the additive effects of multiple genes, so that the monozygotic twin correlations were predicted to be twice the corresponding dizygotic twin correlations. Under the shared environmental model, it was postulated that the resemblance of twin pairs for onset of smoking was due entirely to shared environmental influences (e.g., of peers, older siblings, or parents), so that the monozygotic and dizygotic twin correlations were predicted to be the same. Under the full model, both additive genetic and shared environmental effects were assumed to be important, so that the monozygotic correlation was predicted to be greater than the dizygotic correlation but less than double the dizygotic correlation (Eaves, 1977).

By computing contingency tables separately for male like-sex, female like-sex, and unlike-sex twin pairs, we were also able to test hypotheses about sex differences in the influence of genetic and environmental effects on smoking status (Jöreskog and Sörbom, 1988). We compared the fit of simple genetic, shared environmental, or full models ignoring sex differences; corresponding models which allowed for sex differences in the magnitude of genetic or environmental parameters; and models which also allowed the correlation between gene effects, or shared environmental effects, in the two sexes, to take values less than unity and which, therefore, allowed for the possibility that some of the genes or some of the environmental risk factors which were influencing onset of smoking were sex specific.

### Model-Fitting: Age at Onset

To resolve the influence of genetic and environmental effects on age at onset of smoking, we fitted the same genetic and environmental models described in the previous section to the set of five covariance matrices for log-transformed age at onset, separately for each age cohort. Model-fitting was performed by maximum likelihood using the statistical package LISREL (Jöreskog and Sörbom, 1988; Heath *et al.,* 1989). The goodness of fit of a given model was again assessed by chi-square test, and the fit of different nested models compared by likelihood-ratio chi-square test (Jöreskog, 1978). Because we were fitting models to variances and covariances, rather than correlations, differences in parameter values could arise solely as a function of sex or cohort differences in variance, even if there were no true genotype x sex or genotype x cohort interaction. We therefore fitted additional models which allowed for variance differences while constraining the ratio of genetic and environmental variance components to be constant across sexes or cohorts.

## RESULTS

Figure 1 presents the cumulative age-at-onset distributions for male and female twins from younger and older cohorts. In males, the proportion of respondents who report that they have never smoked has increased markedly, from 41.4% in the older cohort to 54.2% in the younger cohort. However, the proportion who report onset of smoking by age 18 is very similar in the two cohorts (40.8 versus 41.4%). This raises the possibility that the increased number of nonsmokers in the younger cohort may be drawn largely from those who would have been late-onset smokers in the older cohort. Results from other sources (Johnston *et al.,* 1987) suggest that these individuals from the young cohort who have not started to smoke by age 18 are not likely subsequently to become smokers. Parent–offspring or similar intergenerational data would be needed to resolve this. The young cohort males also report an earlier age at onset of smoking, on average, than the older males. In females, the proportion who have never smoked is quite similar across cohorts (61.6% in the older cohort compared to 57.2% in the younger cohort), but the age at onset is again earlier, on average, in the young cohort females. Since we have relied on retrospective reports about age at onset of smoking, it is of course possible that these findings are artefactual. The trends which we have observed, however, are consistent with findings based on contemporaneous data (U.S. Department of Health, Education and Welfare, 1979; Hill and Gray, 1982; Visalpattanasin *et al.,* 1987; Hill *et al.,* 1998). In the reliability subsample, furthermore, reports about smoking status and age at onset were very stable over time. Only a single respondent, of 96, reported that he was a nonsmoker on the first occasion but a smoker on the second occasion of testing, and this may reflect a genuine change in smoking status between the two occasions. The test–retest correlation for log-transformed age at onset was 0.98, implying that respondents at least have very stable perceptions about the age at which they started smoking.

### Multidimensional Scaling

Table II gives the raw contingency tables for age at onset of smoking, cross-classifying response of first twin by response of second twin, separately for each like-sex twin group. Even after pooling across age cohorts, absolute frequencies in some cells of the contingency tables were rather low because of the large number of age-at-onset categories used. Table III compares the stress values and $R^2$ values for one-, two-, and three-dimensional MDS solutions.

The one-dimensional solution gave a poor fit to the data in every group, all stress values being greater than 0.3 and $R^2$ values less than 0.75. In two twin groups the nonsmoker category assumed an intermediate position between the different age-at-onset categories, falling in the same position as the 16-year-old age-at-onset category in the case of dizygotic male twin pairs and falling between the 13- to 14-

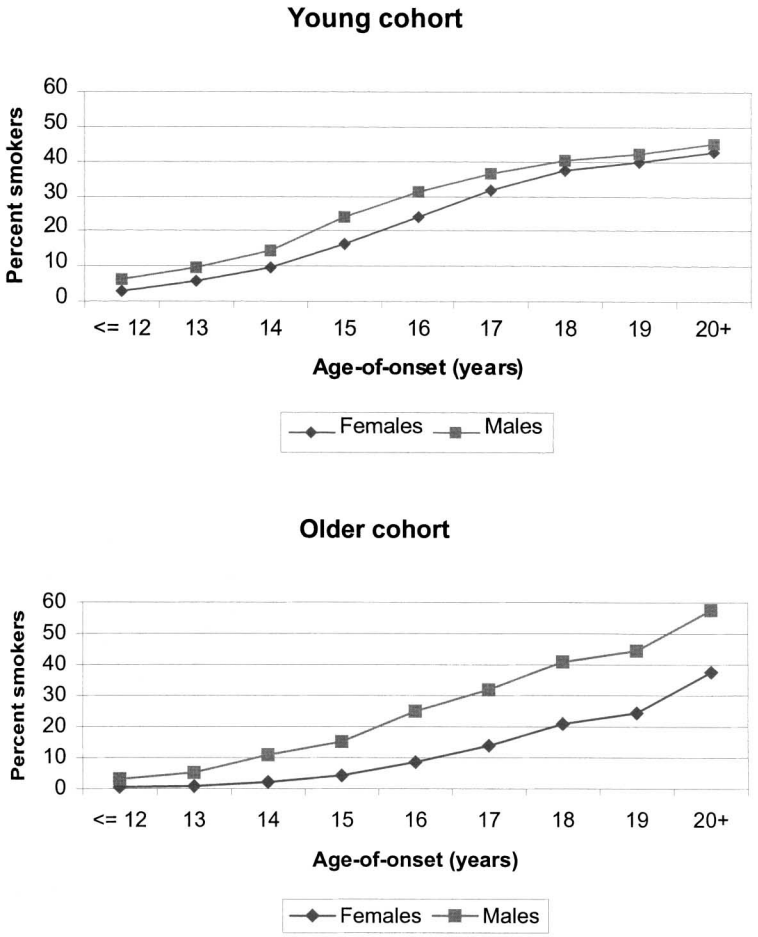


**Fig. 1.** Cumulative age-at-onset distribution for smoking, by sex and age cohort.

and the 15-year-old age-at-onset categories in the case of monozygotic female twin pairs. A one-dimensional solution was clearly inappropriate for these data.

The fit of the two-dimensional solutions was still somewhat poor (particularly in males), stress values ranging from 0.17 to 0.23 and $R^2$ values from 0.78 to 0.89. In every twin group, in the two-dimensional solution, one dimension distinguished nonsmokers from smokers, and the second dimension distinguished between smokers according to their age at onset of smoking. The ranking of the age-at-onset categories on the second dimension was exactly in accordance with prediction for the monozygotic groups, from earliest to latest age category. In the two dizygotic groups, the ordering of age-at-onset categories was only slightly different from prediction (dizygotic males, 13, 14–12–15–18–16–17–19; dizygotic females, 12, 15, 13–14, 17, 16, 18, 19). Since these differences were not consistent across sexes, they may merely be a consequence of sampling error, arising because of the low absolute frequencies of many of the cells in our original contingency tables, a problem that would have been avoided had the original sample size been even larger!

The three-dimensional solutions gave a better fit by the "stress" criterion (stress values ranging from 0.12 to 0.15) but produced little improvement in $R^2$ compared to the corresponding two-dimensional solutions. The three-dimensional solutions which were obtained also did not replicate across twin groups. We therefore provisionally accepted the two-dimensional solution, with one "smoking onset" dimension, distinguishing smokers from nonsmokers, and a second age-at-onset dimension, as the basis for subsequent analyses.

**Table II.** Observed Contingency Tables for Age at Onset of Smoking

| Twin 1 | Twin 2 | | | | | | | | Twin 1 | Twin 2 | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | I | II | III | IV | V | VI | VII | VIII | | I | II | III | IV | V | VI | VII | VIII |
| | Monozygotic male twin pairs | | | | | | | | | Monozygotic female twin pairs | | | | | | | |
| I | 11 | 5 | 2 | 1 | 3 | 0 | 1 | 2 | I | 7 | 6 | 5 | 1 | 0 | 1 | 0 | 2 |
| II | 2 | 15 | 5 | 4 | 1 | 1 | 1 | 6 | II | 4 | 18 | 4 | 2 | 2 | 1 | 5 | 5 |
| III | 2 | 8 | 6 | 7 | 4 | 4 | 3 | 5 | III | 0 | 9 | 17 | 10 | 5 | 6 | 2 | 10 |
| IV | 1 | 4 | 11 | 11 | 6 | 3 | 3 | 12 | IV | 0 | 5 | 8 | 23 | 9 | 7 | 7 | 18 |
| V | 3 | 0 | 2 | 2 | 3 | 2 | 6 | 8 | V | 0 | 2 | 4 | 15 | 24 | 7 | 9 | 11 |
| VI | 1 | 2 | 1 | 2 | 2 | 10 | 8 | 10 | VI | 0 | 0 | 2 | 5 | 10 | 22 | 15 | 27 |
| VII | 0 | 4 | 2 | 1 | 3 | 8 | 20 | 24 | VII | 0 | 2 | 2 | 5 | 12 | 17 | 49 | 57 |
| VIII | 3 | 12 | 7 | 13 | 9 | 7 | 20 | 222 | VIII | 4 | 1 | 6 | 8 | 17 | 24 | 46 | 631 |
| | Dizygotic male twin pairs | | | | | | | | | Dizygotic female twin pairs | | | | | | | |
| | 7 | 3 | 1 | 1 | 2 | 3 | 1 | 3 | | 1 | 3 | 2 | 1 | 3 | 1 | 1 | 3 |
| | 2 | 3 | 2 | 5 | 0 | 3 | 1 | 8 | | 1 | 6 | 2 | 5 | 2 | 0 | 4 | 8 |
| | 1 | 3 | 4 | 6 | 1 | 1 | 2 | 6 | | 3 | 6 | 6 | 2 | 5 | 4 | 1 | 10 |
| | 1 | 0 | 2 | 7 | 1 | 2 | 5 | 5 | | 1 | 4 | 5 | 6 | 4 | 3 | 5 | 23 |
| | 1 | 1 | 0 | 4 | 3 | 1 | 3 | 8 | | 1 | 2 | 6 | 5 | 6 | 3 | 8 | 16 |
| | 1 | 2 | 4 | 3 | 3 | 0 | 4 | 7 | | 0 | 4 | 0 | 5 | 5 | 11 | 6 | 14 |
| | 1 | 1 | 0 | 5 | 2 | 4 | 12 | 13 | | 0 | 1 | 2 | 0 | 4 | 11 | 23 | 43 |
| | 6 | 9 | 4 | 9 | 4 | 9 | 15 | 121 | | 2 | 4 | 10 | 17 | 25 | 25 | 48 | 313 |

*Note.* I, ≤ 12; II, 13–14; III,15; IV, 16; V, 17; VI, 18; VII, 19+ years age at onset; VIII, never smoked.

**Table III.** Results of Nonmetric Multidimensional Scaling

| | One dimension | | Two dimensions | | Three dimensions | |
|---|---|---|---|---|---|---|
| Twin group | Stress | $R^2$ | Stress | $R^2$ | Stress | $R^2$ |
| MZ male pairs | 0.32 | 0.72 | 0.22 | 0.81 | 0.12 | 0.93 |
| MZ female pairs | 0.39 | 0.64 | 0.17 | 0.89 | 0.12 | 0.93 |
| DZ male pairs | 0.47 | 0.46 | 0.23 | 0.78 | 0.16 | 0.87 |
| DZ female pairs | 0.32 | 0.74 | 0.19 | 0.87 | 0.15 | 0.90 |

## Determinants of Smoking Status

Table IV gives the 2 × 2 contingency tables for the lifetime smoking status of first twin (smoker versus nonsmoker) cross-classified by that of the cotwin, or the smoking status of the female twin cross-classified by that of the male twin, in the case of unlike-sex twin pairs. Since we were interested in the determinants of onset of smoking, both current and ex-smokers were classified as smokers. Tetrachoric correlations estimated from these tables are given in Table V. Monozygotic twin correlations for smoking status were rather higher in the younger cohort than in the older, implying that the overall importance of familial influences (both genetic and shared environmental effects) on smoking onset has increased: In the older male like-sex twin pairs, monozygotic and dizygotic twin correlations were almost-identical, indicating that genetic influences on smoking status were unimportant in this age cohort. In the younger male twin pairs, and both older and younger female like-sex pairs, the dizygotic twin correlation was less than the monozygotic twin correlation but greater than one-half the monozygotic twin correlation, implying that both genetic effects and shared environmental effects were influencing smoking status.

Table VI summarizes the results of fitting genetic and environmental models to the observed contingency tables. In both age cohorts, all purely environ-

**Table IV.** Twin Contingency Tables for Smoking Status

| | | Twin 2/male twin | | | |
|---|---|---|---|---|---|
| | | Young cohort | | Older cohort | |
| | Twin 1/female twin | Smoker | Nonsmoker | Smoker | Nonsmoker |
| MZ male pairs | Smoker | 89 | 31 | 119 | 36 |
| | Nonsmoker | 26 | 128 | 45 | 93 |
| MZ female pairs | Smoker | 192 | 51 | 177 | 77 |
| | Nonsmoker | 45 | 282 | 61 | 348 |
| DZ male pairs | Smoker | 57 | 31 | 68 | 19 |
| | Nonsmoker | 33 | 85 | 23 | 36 |
| DZ female pairs | Smoker | 105 | 48 | 88 | 68 |
| | Nonsmoker | 58 | 140 | 74 | 170 |
| Unlike-sex pairs | Smoker | 149 | 77 | 113 | 36 |
| | Nonsmoker | 115 | 169 | 150 | 98 |

**Table V.** Maximum-Likelihood Estimates of Twin Tetrachoric Correlations for Smoking Status ($p$) and Their Standard Errors (SE)

| | Young cohort | | Older cohort | |
|---|---|---|---|---|
| | $p$ | SE | $p$ | SE |
| MZ male pairs | 0.79 | 0.05 | 0.64 | 0.06 |
| MZ female pairs | 0.86 | 0.03 | 0.77 | 0.03 |
| DZ male pairs | 0.55 | 0.09 | 0.59 | 0.10 |
| DZ female pairs | 0.58 | 0.06 | 0.40 | 0.07 |
| DZ unlike-sex pairs | 0.39 | 0.06 | 0.26 | 0.08 |

mental models were rejected by chisquare goodness-of-fit test. In the young cohort, a simple genetic model, which did not allow for sex differences, gave an adequate fit to the data. No more complex model gave a significant improvement in fit for the young cohort, but the most general model, allowing for sex differences in genetic and shared environmental parameters and a correlation between gene effects less than unity, gave an improvement in fit that was just short of significance (($\chi^2_4 = 9.09$, $p = 0.06$). Under this model, 48% (in males) and 56% (in females) of the variance in liability to start smoking was attributable to the additive effects of genes, and 31 and 29%, respectively, to shared environmental effects, with the remaining 21 and 15% of the variance attributable to nonshared environmental effects.

In the older cohort, all models which ignored sex differences were rejected by chi-square goodness-of-fit test. The simplest model which gave an adequate fit to the data was a full model allowing for sex differences in the magnitude of genetic and shared and nonshared environmental influences. Under this model, in females, 74% of the variance in liability to start smoking was due to additive genetic effects, and 3% to shared environmental effects. In males, however, shared environmental effects accounted for 53% of the variance in liability to start smoking, and genetic effects were unimportant, accounting for no more than 11% of the variance.

### Determinants of Age-at-Onset of Smoking

As the multidimensional scaling analysis indicated the independence of the liability to smoke and the age at which a person begins to smoke, structural equation model-fitting of age at onset considered only those twin pairs where both twins had become smokers. Table VII gives the twin covariance matrices for log-transformed age at onset of smoking. Monozygotic twin correlations were consistently higher than the corresponding dizygotic correlations in both sexes and both cohorts. Once again, when genetic and environmental models were fitted to these data, all shared environmental models were reject, as were models ignoring sex differences in genetic and environmental effects (Table VIII). In each

**Table VI.** Results of Fitting Genetic and Environmental Models to Smoking Initiation Data

| | | Goodness-of-fit test | | | | | Likelihood-ratio test against full model | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Young cohort | | Older cohort | | | Young cohort | | Older cohort | |
| Model | df | $\chi^2$ | $p$ | $\chi^2$ | $p$ | df | $\chi^2$ | $p$ | $\chi^2$ | $p$ |
| Genetic | 12 | 20.67 | 0.06 | 25.99 | <0.01 | 4 | 9.15 | 0.06 | 9.49 | 0.05 |
| Genetic[a] | 11 | 18.89 | 0.06 | 23.28 | 0.02 | 3 | 7.39 | 0.06 | 6.78 | 0.08 |
| Genetic[b] | 10 | 18.65 | 0.04 | 21.71 | 0.02 | 2 | 7.17 | 0.02 | 5.28 | 0.07 |
| Shared environment | 12 | 74.94 | <0.001 | 65.59 | <0.001 | 4 | 65.59 | <0.001 | 49.55 | <0.001 |
| Shared environment[a] | 11 | 68.47 | <0.001 | 64.57 | 0.001 | 3 | 57.31 | <0.001 | 47.71 | <0.001 |
| Shared environment[b] | 10 | 40.29 | <0.001 | 43.37 | <0.001 | 2 | 28.04 | <0.001 | 26.32 | <0.001 |
| Full | 11 | 18.38 | 0.07 | 25.91 | 0.007 | 3 | 6.76 | 0.08 | 9.42 | 0.02 |
| Full[a] | 9 | 14.14 | 0.12 | 16.72 | 0.05 | 1 | 2.51 | 0.11 | 0.01 | 0.98 |
| Full[b] | 8 | 11.58 | 0.17 | 16.72 | 0.03 | — | — | — | — | — |

[a] Model allows for sex differences in magnitude of genetic or environmental effects.
[b] Model allows for a correlation of less than unity between genetic or shared environmental effects in the two sexes.

**Table VII.** Covariance Matrices for Log-Transformed Age at Onset of Smoking[a]

| | Young cohort | | Older cohort | |
|---|---|---|---|---|
| | ($N$ = 192) | | ($N$ = 174) | |
| MZ female pairs | 0.3304 | *0.6592* | 0.4570 | *0.5282* |
| | 0.1839 | 0.2355 | 0.2330 | 0.4257 |
| | ($N$ = 88) | | ($N$ = 119) | |
| MZ male pairs | 0.3043 | *0.5600* | 0.4014 | *0.4442* |
| | 0.2197 | 0.5060 | 0.1874 | 0.4436 |
| | ($N$ = 104) | | ($N$ = 86) | |
| DZ female pairs | 0.2913 | *0.3072* | 0.3700 | *0.1587* |
| | 0.0843 | 0.2582 | 0.0627 | 0.4227 |
| | ($N$ = 57) | | ($N$ = 68) | |
| DZ male pairs | 0.4363 | *0.3090* | 0.6988 | *0.3020* |
| | 0.1429 | 0.4905 | 0.1988 | 0.6202 |
| | ($N$ = 148) | | ($N$ = 111) | |
| Unlike-sex pairs | | | | |
| Female twin | 0.2563 | *0.3294* | 0.3682 | *0.2103* |
| Male twin | 0.1133 | 0.4614 | 0.1076 | 0.7107 |

[a] Variances and covariances have been multiplied by 10. Correlation is given as the upper triangular element in each matrix, in italics.

**Table VIII.** Results of Fitting Models to Covariance Matrices for Log Age at Onset of Smoking

| | | Goodness-of-fit test | | | |
|---|---|---|---|---|---|
| | | Young cohort | | Older cohort | |
| Model | df | $\chi^2$ | $p$ | $\chi^2$ | $p$ |
| Genetic | 13 | 58.61 | <0.001 | 29.36 | 0.006 |
| Genetic[a] | 11 | 19.60 | 0.051 | 16.07 | 0.139 |
| Genetic[b] | 10 | 19.44 | 0.035 | 28.70 | <0.001 |
| Shared environment | 13 | 88.42 | <0.001 | 50.45 | <0.001 |
| Shared environment[a] | 11 | 45.64 | <0.001 | 36.41 | <0.001 |
| Shared environment[b] | 10 | 41.41 | <0.001 | 30.51 | 0.001 |
| Full | 12 | 58.61 | <0.001 | 29.36 | 0.003 |
| Full[a] | 9 | 19.54 | 0.02 | 15.74 | 0.07 |
| Full[b] | 8 | 19.43 | 0.01 | 15.48 | 0.05 |

[a] Model allows for sex differences in magnitude of genetic or environmental effects.
[b] Model allows for a correlation of less than unity between genetic or shared environmental effects in the two sexes.

cohort, a model allowing for sex-dependent genetic and nonshared environmental effects, with no shared environmental effects, and a correlation of unity between the gene effects in the two sexes, gave an adequate fit to the data, and no other model gave a significantly better fit. However, these differences appear to be a consequence of overall differences in variance between males and females. When we fitted a model under which the heritability of age at onset was the same in both sexes, but which allowed for differences in total variance, this gave a good fit to the data (young cohort, $\chi^2_{12} = 20.40$, $p = 0.06$; older cohort, $\chi^2_{12} = 16.33$, $p = 0.18$) and a fit that was not significantly worse than the fit of the simple sex-dependent genetic effects model by likeli-

**Table IX.** Variance Components from Best-Fitting Models for Smoking Status and Age at Onset of Smoking

| | Additive genetic effects | Shared environment effects | Nonshared environment effects |
|---|---|---|---|
| Smoking status | | | |
| Young males | 0.48 | 0.31 | 0.21 |
| Young females | 0.56 | 0.29 | 0.15 |
| Older males | 0.11 | 0.53 | 0.36 |
| Older females | 0.74 | 0.03 | 0.23 |
| Age at onset of smoking | | | |
| Young cohort | 0.62 | — | 0.38 |
| Older cohort | 0.51 | — | 0.49 |

hood-ratio chi-square test (young cohort, $\chi^2_1 = 0.37$, $p > 0.05$; older cohort, $\chi^2_1 = 0.26$, $p > 0.61$). The heritability of age at onset of smoking did differ as a function of cohort, additive genetic effects accounting for 62% of the variance in age at onset in the younger cohort but for only 51% of the variance in the older cohort. This difference was significant: when we compared the fit of a model which assumed constant heritability but differences in variance as a function of sex and cohort ($\chi^2_{25} = 41.37$, $p = 0.021$), it was significantly worse, by likelihood-ratio chi-square test, than that of the model allowing for cohort differences in heritability ($\chi^2_1 = 4.64$, $p = 0.03$). Proportions of variance attributed to additive genetic, shared environment, and nonshared environment effects by the best-fitting models for smoking status and age at onset of smoking are summarized in Table IX.

## DISCUSSION

Both the multidimensional scaling results and the model-fitting results indicate that what determines who is at risk of becoming a smoker is rather different from what determines the age at which those who are at risk will begin to smoke. From the MDS analyses we found that separate smoking onset and age-at-onset dimensions were needed to explain the observed pattern of twin concordances for smoking status and age at onset. Model-fitting analyses revealed that shared environmental influences were important in determining whether or not smoking onset would eventually occur (except in females from the older cohort) but did not influence the age at which smoking onset occurred in those who were at risk. Genetic influences on age at onset were found in both sexes and both cohorts, but very little genetic influence on risk of becoming a smoker was found in the older male cohort.

From the model-fitting analyses presented here it appears that genetic differences account for a substantial proportion of the variance in liability to become a smoker in all groups except the older male twins. This extends the previous report of genetic influences on smoking status in that sample (Hannah *et al.*, 1985), which did not consider the possibility of genotype × cohort interaction. Meyer *et al.* (unpublished) likewise found significant heritability of smoking onset, in a U.S. twin sample. It is unlikely that those twins in our study whose use of cigarettes was limited to occasional or one-time experimental use would report themselves as former smokers. Thus this genetic influence may be partly a reflection of genetic differences in acute sensitivity to nicotine (Marks *et al.*, 1983; Perkins, 1995; Pomerlau, 1995), with genetically sensitive individuals never progressing beyond the stage of experimentation. Alternatively, the genetic effects may be mediated by personality differences which have been hypothesized to influence smoking (Eysenck, 1973, 1980; Kozlowski, 1979; Eaves *et al.*, 1989; Heath *et al.*, 1995; Gilbert and Gilbert, 1995; Arai *et al.*, 1997) and which have been shown to be moderately heritable in many genetic studies, including a study of this same sample (Martin and Jardine, 1986; Eaves *et al.*, 1989), or by other heritable traits. We have no *a priori* explanation for the anomalous finding in the older male cohort, except to note a similar anomaly for alcohol consumption patterns in this same group. Jardine and Martin (1984) reported moderate heritability of alcohol consumption patterns in female twin pairs and young male twin pairs but, again, not in the older male cohort; and subsequent analysis has suggested that this difference related mainly to the

determinants of whether or not alcohol use occurred, rather than of level of consumption in those who were regular drinkers (Heath *et al.,* 1991b).

We found strong shared environmental influences on liability to become a smoker in all groups except the older female cohort. In the U.S. twin sample, too, shared environmental influences were found to be important. Such shared environmental effects could include the influence of parents, shared friends, shared schooling, or a variety of other features of shared family background and shared upbringing. We have argued elsewhere, in the context of a discussion of the absence of shared environmental effects on age at onset of female teenage alcohol use, that this may reflect the greater "deviance" of this behavior in females, and it is certainly the case that smoking would have been more deviant in the older female cohort. However, the U.S. analyses have found evidence for shared environmental influences on onset of smoking by older females (Meyer *et al.,* unpublished), so the finding in the older female cohort must be considered an unexplained anomaly.

Our finding of significant genetic influences on age at onset of smoking may be contrasted with the failure of Eaves and Eysenck (1980) to find any significant genetic effects on age at onset. Sample sizes were much larger in the Australian study, however, and Eaves and Eysenck remark that their findings may be a consequence of the smaller numbers of twin pairs, and consequent low statistical power, of the London study. More unexpected was the lack of evidence for shared environmental effects on age at onset. This implies that while such shared features of family background as parental or sibling smoking habits may influence whether or not an individual is at risk of becoming a smoker, they do not influence whether onset of smoking occurs at an early or late age. If smoking by peers is influencing age at onset of smoking, then our data imply that such effects do not involve simply the passive receipt of peer influences, but rather an active searching-out of behaviorally similar individuals as peers, and that MZ twin pairs, being more highly concordant in their personalities and other behaviors, are selecting more similar friends (with more similar habits) than are DZ twin pairs.

It must be emphasized that our analyses have relied upon retrospective data about age at onset of smoking, reported by adults who may be current or former smokers. While the retest data from the reliability subsample indicate that respondents have very stable beliefs about when they started smoking, they do not indicate whether or not such beliefs have any validity. It is thus important that the findings which we have reported be tested in prospective studies, as can be achieved with considerable power using studies of adolescent twin pairs (Eaves *et al.,* 1986; Hewitt *et al.,* 1988).

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