Tobacco Consumption in Swedish Twins Reared Apart and Reared Together

Kenneth S. Kendler, MD; Laura M. Thornton, PhD; Nancy L. Pedersen, PhD

Background: Prior studies of twins reared together suggest that regular tobacco use (RTU) is substantially heritable. However, strong social influences on RTU might have biased these results.

Methods: We examine the self-report lifetime history of RTU in members of 778 male-male and female-female twin pairs, raised together and apart, born from 1890 to 1958 and ascertained through the population-based Swedish Twin Registry.

Results: In men, the pattern of twin resemblance for RTU suggested both genetic and rearing-environmental effects, which, in the best-fit biometrical model, accounted for 61% and 20% of the variance in liability to RTU, respectively. For women, overall results were hard to interpret, but became clearer when divided by birth cohort. In women born before 1925, rates of RTU were low and twin resemblance was environmental in origin. In later cohorts, rates of RTU in women increased substantially, as did heritability. For women born after 1940, heritability of RTU was similar to that seen in men (63%).

Conclusions: Genetic factors play an important etiologic role in RTU. In women, the impact of genetic factors increased in more recent cohorts, suggesting that, as social restrictions on female tobacco use relaxed over time, heritable influences increased in importance.

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common in men than in women (Table 1). Age at smoking initiation (mean±SD) in the entire sample was 20.1±7.5 years and was significantly lower in men (18.5±6.1) than in women (22.4±8.8) (test for unequal variances: t1031.9=6.42; P<.0001). In the 370 complete reared-apart twin pairs, the mean±SD age at separation (2.7±3.0 years) was much younger than age at smoking initiation (19.7±7.4 years). In only 1 of these 740 separated twins (from a male DZA pair) was the reported age at smoking initiation (age 10 years) before age at separation. In reared-apart twin pairs, no association was seen between age at separation and concordance for RTU ($\chi_1^2=0.09, P=.77$).

The distribution of these pairs by sex, zygosity, and rearing is shown in Table 1. The percentage of men and women in each cohort who reported RTU is shown in Table 2. Year of birth was unrelated to the probability of RTU in men (OR, 1.00; 95% CI, 0.99-1.01; $\chi_1^2=0.23, P=.66$), but strongly related in women (OR, 1.06; 95% CI, 1.05-1.07; $\chi_1^2=139.9, P<.0001$) (Figure).

Reliability of our measure of lifetime RTU was assessed in 1160 twins who responded to the questionnaire in both 1987 and 1990. The agreement rate and
GENMOD. The P values reported are 1-tailed for these analyses because, in studies of familial resemblance, there is a compelling rationale for directional hypotheses. That is, we are, in almost all instances, interested only in excess resemblance in relatives beyond chance expectations. In this study, we begin with robust directional hypotheses of positive correlations in twins for risk to RTU and greater resemblance in MZ vs DZ and reared-together vs reared-apart twins.

We used a liability-threshold model to estimate the genetic and environmental contributions to twin resemblance. For categorical characteristics like RTU, the estimates are for the resemblance of twins in a pair for their liability to develop RTU. Liability is assumed to be continuous and normally distributed in the population, with individuals who exceed a theoretical threshold developing RTU. We also present the tetrachoric correlation, defined as the correlation in members of twin pairs for the liability to RTU. We then present parameter estimates from the best-fitting models, where a, b, c, and e equal the percentage of variance in liability due to additive genetic (A) and individual-specific environmental effects (E). However, because we have twins who were and were not reared together, we can also estimate 2 additional environment components, termed shared environment (S) and correlated environment (C), respectively. Shared environment, which might also be termed rearing environment, contributes to twin resemblance for reared-together but not reared-apart twins, and reflects the effect of being raised in the same household and community. Correlated environment refers to experiences that occur in common both with twins reared apart and twins reared together, and would include the uterine environment, the impact of contact between the twins that occurs after separation, and, because twins are identical in age, their exposure to the same social, cultural, and historical influences on tobacco use.

Therefore, in these analyses, we fit models with 4 sources of variance in liability to RTU: A, S, C, and E. As in studies of reared-together twins, E, or individual-specific environment influences, are those factors (eg, accidents, illnesses, divergent exposure to peer groups before or after leaving home) that make members of a twin pair different from one another with respect to their liability to RTU.

Models were fit directly to the contingency tables by the method of maximum likelihood using the Mx structural modeling program. Model fit is evaluated according to the principle of parsimony. Models with fewer parameters are considered preferable if they do not provide significantly worse fit. We operationalize parsimony by the Akaike information criteria (AIC) statistic (which has been recently validated), calculated as the model χ² minus 2 times the degrees of freedom (df). We then present parameter estimates from the best-fitting models, where a, b, c, and e equal the percentage of variance in liability to RTU caused by additive genetic effects and s, c, and e equal the percentage of variance in liability to RTU caused by shared, correlated, and individual-specific environmental effects, respectively.

A possible difference in the probability of RTU across birth cohorts can be approached in 2 ways. To remove the effect of birth cohort (which should contribute to the estimate for C), the impact of year of birth (Ag for age) on liability to RTU can be added to the model. To evaluate the hypothesis that the sources of twin resemblance for RTU change over cohorts requires that we first fit a relaxed model in which the parameters (eg, A, S, C, E) are estimated separately in each age cohort and then fit a constrained model to the same data in which the parameter estimates are set equal across the cohorts. We can then compare the fit of the relaxed vs constrained model, both by a χ² difference test and by the AIC.

We used logistic regression to predict risk for RTU from year of birth and to test whether, in reared-apart twins, pair concordance vs discordance for RTU is predicted by age at separation.

### Table 2. Percentage of Twins Who Reported Regular Tobacco Use and Parameter Estimates of Full Model by Birth Cohort for Men and Women*

<table>
<thead>
<tr>
<th>Birth Years</th>
<th>No. of Pairs</th>
<th>Regular Tobacco Use, %</th>
<th>Parameter Estimates of Full Model†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1890-1909</td>
<td>17</td>
<td>61</td>
<td>(b^2) 0.53 (s^2) 0.45 (c^2) 0.00 (e^2) 0.02</td>
</tr>
<tr>
<td>1910-1924</td>
<td>130</td>
<td>65</td>
<td>(b^2) 0.58 (s^2) 0.00 (c^2) 0.08 (e^2) 0.34</td>
</tr>
<tr>
<td>1925-1939</td>
<td>106</td>
<td>66</td>
<td>(b^2) 0.51 (s^2) 0.31 (c^2) 0.00 (e^2) 0.17</td>
</tr>
<tr>
<td>1940-1958</td>
<td>65</td>
<td>72</td>
<td>(b^2) 0.64 (s^2) 0.00 (c^2) 0.09 (e^2) 0.27</td>
</tr>
</tbody>
</table>

*\(a^2\) indicates additive genetic effects; \(s^2\), shared (rearing) environment; \(c^2\), correlated environment; and \(e^2\), unique (individual-specific) environment.

† Ellipses indicate that the value could not be estimated because of small sample size.

κ coefficients were 95% and +0.87 (95% CI, 0.84-0.91), respectively.

**TWIN RESEMBLANCE FOR RTU**

Twin resemblance for RTU was substantial in the 55 pairs of MZA male twins (OR, 8.3; 95% CI, 2.1-33.1; \(P=0.01\); \(r^2=0.66\)) (Table 1). In addition, the pattern of twin resemblance in the male-male pairs suggested both a genetic effect (MZA>DZA and MZT>DZT) and an effect of shared rearing environment (MZA>DZA and DZT>DZA). Examining the difference in the ORs, the test for genetic effects in the reared-apart twins (MZA vs DZA) was significant (χ²=4.0, \(P=0.02\)) and the test in reared-together twins was nearly significant (MZT vs DZT) (χ²=2.4, \(P=0.06\)). The test for shared environment was not significant in MZ pairs (MZT vs MZA) (χ²=0.5, \(P=0.25\)) but was in DZ pairs (DZT vs DZA) (χ²=3.0, \(P=0.04\)).

Twin resemblance for RTU was also evident in the 56 pairs of MZA female twins (OR, 3.8; 95% CI, 1.0-14.2; \(P=0.03\); \(r^2=0.45\)). However, a readily interpretable pattern of results was not seen in all the female-female...
pairs. The DZA correlation for RTU exceeded the MZA correlation, while the MZT correlation was modestly greater than the DZT correlation. One of these 4 comparisons of ORs was significant (MZT vs MZA twins: $\chi^2 = 3.2, P = .04$).

**STANDARD MODEL FITTING**

As outlined in Table 3, we began by fitting a full model containing A, S, C, and E. For men, the full model (model 1) fit well ($\chi^2 = 0.6, P = .46$). We next, in turn, set the parameters C, S, and A to 0 in models 2, 3, and 4, respectively. Of these 3 models, model 2 fit as well as the full model, with 1 less parameter, and therefore had the best AIC. Then, we tried to further simplify model 2 by setting the parameters S and A to 0 in models 5 and 6, respectively; neither improved the AIC value. In particular, the SE model fit quite poorly and could be strongly rejected against the ASE model ($\chi^2 = 23.0, P < .0001$), providing evidence for the importance of genetic effects on RTU in Swedish men. The parameter estimates and 95% CIs for the best-fitting model, model 2, are seen in Table 4. These results suggest that in Swedish men, approximately 60% of the variance in liability to RTU is genetic, while shared rearing environment and individual-specific environment each account for approximately 20% of the variance.

The results in women (Table 3) were different. The full model (model 1) did not fit well ($\chi^2 = 8.4, P = .004$). Model 2 (which dropped C) produced a large deterioration in fit, indicating that correlated environmental effects were important. Both model 3 (which dropped S) and model 4 (which dropped A) produced an improvement in the AIC over model 1, although model 3 was modestly superior. Attempts at simplifying model 3 by dropping C (model 5) or A (model 6) did not result in further AIC improvement. As seen in Table 4, the best-fit model, model 3, suggested that 63% of the variance in liability to RTU in Swedish women was because of the correlated environment, while genetic and individual-specific environmental factors were responsible for 15% and 22% of the variance, respectively.

The discrepancy between the results in men and women was perplexing. Given the strong relationship between year of birth and RTU in women, we refit the data to a model containing year of birth. As outlined in Table 3, the best-fit model (model 4) included year of birth, as well as A, C, and E. The parameter estimates for this best-fit model (Table 4) did not change for $a^2$ or for $e^2$, but the estimate for $c^2$ declined from 63% to 43%, while 20% of the variance was now ascribed to Ag. We also fit this model to the results for male twins. The best-fit model was identical to that obtained in our previous analyses.

**GENE BY COHORT INTERACTION MODELS**

Including year of birth accounts for main effects of age on RTU and for interactions between age and genetic effects were important. Both model 3 (which dropped S) and model 4 (which dropped A) produced an improvement in the AIC over model 1, although model 3 was modestly superior. Attempts at simplifying model 3 by dropping C (model 5) or A (model 6) did not result in further AIC improvement. As seen in Table 4, the best-fit model, model 3, suggested that 63% of the variance in liability to RTU in Swedish women was because of the correlated environment, while genetic and individual-specific environmental factors were responsible for 15% and 22% of the variance, respectively.

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**Table 3. Model-Fitting Results for Lifetime Regular Tobacco Use in Male and Female Swedish Twins Reared Together and Apart**

<table>
<thead>
<tr>
<th>Model</th>
<th>df</th>
<th>$\chi^2$</th>
<th>$P$</th>
<th>AIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. ASCE</td>
<td>1</td>
<td>0.6</td>
<td>.46</td>
<td>1.4</td>
</tr>
<tr>
<td>2. ASE</td>
<td>2</td>
<td>0.6</td>
<td>.76</td>
<td>3.4†</td>
</tr>
<tr>
<td>3. ACE</td>
<td>2</td>
<td>2.4</td>
<td>.31</td>
<td>1.4</td>
</tr>
<tr>
<td>4. SCE</td>
<td>2</td>
<td>5.4</td>
<td>.07</td>
<td>1.4</td>
</tr>
<tr>
<td>5. AE</td>
<td>3</td>
<td>7.2</td>
<td>.07</td>
<td>1.2</td>
</tr>
<tr>
<td>6. SE</td>
<td>3</td>
<td>23.6</td>
<td>&lt;.001</td>
<td>17.6</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. ASCE</td>
<td>1</td>
<td>8.4</td>
<td>.003</td>
<td>6.4</td>
</tr>
<tr>
<td>2. ASE</td>
<td>2</td>
<td>81.9</td>
<td>&lt;.001</td>
<td>77.9</td>
</tr>
<tr>
<td>3. ACE</td>
<td>2</td>
<td>8.4</td>
<td>.02</td>
<td>4.4†</td>
</tr>
<tr>
<td>4. SCE</td>
<td>2</td>
<td>9.8</td>
<td>.01</td>
<td>5.8</td>
</tr>
<tr>
<td>5. AE</td>
<td>3</td>
<td>81.9</td>
<td>&lt;.001</td>
<td>75.9</td>
</tr>
<tr>
<td>6. CE</td>
<td>3</td>
<td>11.1</td>
<td>.01</td>
<td>5.1</td>
</tr>
</tbody>
</table>

†Best-fit model by AIC.26
‡Age included as main effect on regular tobacco use in model.

*df indicates degrees of freedom; AIC, Akaike information criterion; A, additive genetic effects; S, shared (rearing) environment; C, correlated environment; E, unique (individual-specific) environment; and Ag, effects of age.

The prevalence and estimated heritability of regular tobacco use in 3 historical birth cohorts of Swedish male and female twins reared together and reared apart.

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The major strength of this study is the inclusion of both reared-together and reared-apart MZ and DZ twins. This combination of twin and adoption designs is especially powerful at resolving the genetic and environmental sources of individual differences. Furthermore, this sample of twins is the largest systematically ascertained sample of reared-apart and reared-together twins currently available.

Three limitations are noteworthy. First, age at separation was variable, although more than two thirds were separated by their second birthday. We showed no correlation, among the separated twin pairs, between age at separation and similarity for RTU; only 1 twin began tobacco use before separation from his co-twin. Second, although, to our knowledge, ours is the largest available systematic sample of twins reared together and apart, our sample size was still only moderate, as indicated by the CIs for the parameter estimates. Third, we relied solely on self-report measures of tobacco use; however, such measures have been found to be relatively reliable and valid and had good test-retest reliability in our sample.

RTU IN MEN

As would be expected if genetic factors were of etiologic importance in RTU, MZA male twins were highly correlated in their liability to RTU (OR, 8.3; 95% CI, 2.1-33.1; r = +0.66). Furthermore, the correlation in risk to RTU was higher in MZA than in DZA twins and higher in MZT than in DZT twins. Model fitting estimated the heritability of liability to RTU in male Swedish twins to be 0.61, quite close to the 0.56 estimate from our recent review of 14 studies of twins reared together.6

In addition, the correlation in liability to RTU was apparently influenced by rearing status, being higher in MZT than MZA twins and higher in DZT than DZA twins. This pattern suggests that being reared in the same family influences risk for RTU. This impression was supported by the model fitting, which estimated that 20% of the variance in liability to RTU in Swedish male twins resulted from shared rearing environment, similar to the 24% estimated from our recent review.6

RTU IN WOMEN

As would be predicted if genetic factors influenced risk for RTU, female MZA twins were significantly correlated in their liability to RTU (OR, 3.8; 95% CI, 1.0-14.2; r = 0.45). However, the similarity in risk was higher in DZA than MZA twins and only slightly greater in MZT than DZT pairs. Modeling suggested that most twin resemblance was because of correlated environment and age, with genes playing only a modest role.

When women were examined by birth cohort, a large secular change was observed in rates of RTU. Given the widely different social context of smoking for women in

Table 4. Parameter Estimates From Best-Fitting Model for Lifetime Regular Tobacco Use in Male and Female Swedish Twins Rared Together and Apart

<table>
<thead>
<tr>
<th>Sex</th>
<th>No. Parameters</th>
<th>Parameters</th>
<th>s²</th>
<th>c²</th>
<th>e²</th>
<th>Ag²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>2</td>
<td>ASE</td>
<td>0.61 (0.36-0.86)</td>
<td>0.20 (0.00-0.45)</td>
<td></td>
<td>0.19 (0.02-0.36)</td>
</tr>
<tr>
<td>Women</td>
<td>3</td>
<td>ACE</td>
<td>0.15 (0.0-0.34)</td>
<td></td>
<td>0.63 (0.48-0.77)</td>
<td>0.22 (0.11-0.33)</td>
</tr>
<tr>
<td>Women‡</td>
<td>4</td>
<td>ACE†Ag</td>
<td>0.15 (0.0-0.34)</td>
<td></td>
<td>0.45 (0.26-0.59)</td>
<td>0.22 (0.11-0.33)</td>
</tr>
</tbody>
</table>

*CI indicates confidence interval; A, additive genetic effects; S, shared (rearing) environment; C, correlated environment; E, unique (individual-specific) environment; and Ag, effect of age.
†Ellipses indicate that the value could not be estimated because of small sample size.
‡Age included as main effect on regular tobacco use in model.
Sweden over this period, the pattern of genetic and environmental risk factors for RTU might also have changed over time. Analyzing 3 age cohorts separately revealed a dramatic increase in heritability over this historical period, from 0 in those born before 1924 to levels comparable with that seen in men for those born after 1940. This gene-by-cohort interaction with increasing heritability in twins from more recent cohorts has been described for other behavioral and health-related traits: age at intercourse in Australian twins, \(^{31}\) alcohol consumption in Finnish twins, \(^{32}\) and educational level in Norwegian \(^{33}\) and Swedish twins. \(^{34}\) However, P. Madden, PhD (written communication, November 1999), did not find this pattern for smoking initiation in Australian, Swedish, and Finnish twins, although none of these samples included twins born before 1920. Also, we found no evidence for changes in heritability of alcohol abuse in Swedish men born from 1902 to 1949. \(^{35}\)

The most plausible explanation for our finding is that a reduction in the social restrictions on smoking in women in Sweden as the 20th century progressed permitted genetic factors influencing the risk for RTU to increasingly express themselves. This interpretation is consistent with the findings of educational attainment for women in the Swedish Adoption/Twin Study of Aging. \(^{36}\)

**COMPARISON WITH OTHER STUDIES OF TOBACCO USE IN REARED-APART TWINS**

We are aware of 4 prior studies of RTU in reared-apart twins. Fisher \(^{13}\) reported that the concordance rate for “smoking habit” in 27 MZ twins reared apart, ascertainment through the Maudsley Psychiatric Hospital, was 85%. In 12 pairs of systematically ascertainment MZ twins from Denmark who were reared apart (Raaschou-Nielsen \(^{14}\)), the concordance rate for smoking was 75%. In the largest previous sample of MZA twins (42 pairs), ascertainment mostly through a television appeal in England, \(^{15}\) the concordance rate for smoking was 77%. In a systematic study of Finnish reared-apart twins, \(^{16}\) which included both MZ and DZ pairs, probandwise concordance for lifetime cigarette smoking was similar in MZ (29 pairs) (67%) and DZ twins (88 pairs) (68%). In our sample of 111 MZ twin pairs reared apart, we found the probandwise concordance rate for lifetime RTU to be 81%, similar to that reported in previous samples. Concordance rates in our 259 pairs of DZA twins (68%) was identical to that found in the Finnish sample. \(^{16}\)

**LEVEL OF TOBACCO CONSUMPTION AMONG REGULAR USERS**

Substance use is likely a 2-stage phenomenon. One set of risk factors influences initiation. Another, possibly correlated set of factors affects the risk for high levels of use or misuse given initiation. We found this pattern with regular smoking and nicotine dependence in female-female Virginia twin pairs. \(^{36}\) Although we had no direct measures of nicotine dependence in this Swedish sample, we could examine average tobacco intake—a rough proxy for levels of dependence. \(^{36}\) Twin correlations for amount of tobacco consumed were significant in male and female MZA (+0.36 [P = .05] and +0.83 [P = .01], respectively) and MZT pairs (+0.62 [P < .001] and +0.76 [P < .001], respectively) but not in male and female DZA (+0.27 and +0.01, respectively) and DZT pairs (+0.24 and +0.20, respectively). In accordance with our prior findings, \(^{36}\) these results suggest that genetic factors not only play an important etiologic role in the initiation of RTU, but also affect the subsequent level of consumption among regular users.

**IMPLICATIONS FOR RESEARCH**

Twin studies have played an increasingly central role in attempts to clarify the role of genetic and environmental risk factors in the etiology of psychiatric and substance use disorders. \(^{33}\) However, a key assumption in such studies is that MZ and DZ twins are equally correlated in their exposure to etiologically relevant environmental risk factors. This “equal environment assumption” has been empirically supported for psychiatric conditions by most, \(^{11,12,37-39}\) but not all investigations. \(^{40,41}\) Regular tobacco use is likely to be a particularly problematic trait for standard twin studies because of the strong peer group influences on risk for smoking initiation. \(^{33}\) Furthermore, in childhood and adolescence, MZ twins spend more time together and share peer groups more closely than do DZ twins. \(^{10,11}\) Studies of reared-together twins may, therefore, produce estimates of heritability that are inflated because MZ twins are more highly correlated than DZ twins for peer-group influences on RTU. In a study of Virginia reared-together twins, the extent of social contact in adolescence predicted twin resemblance only for smoking initiation among the 8 psychiatrically relevant traits examined. \(^{11}\) In the reared-apart twins from Swedish Adoption/Twin Study of Aging, Pedersen et al \(^{42}\) found a small but significant relationship between degree of contact and twin similarity for alcohol consumption.

It is, therefore, of particular interest that in these twins reared together and apart, the estimated heritabilities of RTU for all men and for women born after 1940 were very similar to those found in prior studies of twins reared together. Similarly, at least in men, we also replicated the evidence from studies of twins reared together that rearing environment significantly contributes to twin resemblance for RTU. Our ability, in this combined twin-adoption design, to replicate closely the results from studies of twins reared together suggests that this traditional twin design, when applied to psychiatric and substance use-related phenotypes, is likely to provide relatively accurate answers and not to be substantially biased.

Finally, the results presented here further strengthen the evidence that genetic factors in humans play an important role in influencing the vulnerability to RTU as well as to quantity of tobacco consumed among regular users. These findings, therefore, should provide further impetus to efforts to identify the specific loci and alleles that influence these vulnerabilities (eg, Sabol et al \(^{43}\) and Straub et al \(^{44}\)).

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