*Psychological Medicine*, 2007, **37**, 705–715. © 2006 Cambridge University Press
doi:10.1017/S0033291706009639 First published online 21 December 2006 Printed in the United Kingdom

# Smoking behaviour as a predictor of depression among Finnish men and women: a prospective cohort study of adult twins

TELLERVO KORHONEN[1]*, ULLA BROMS[1], JYRKI VARJONEN[2], KALLE ROMANOV[3], MARKKU KOSKENVUO[1], TARU KINNUNEN[4] AND JAAKKO KAPRIO[1,5]

[1] *Department of Public Health, University of Helsinki, Finland*; [2] *Centre of Expertise for Work Organizations, Finnish Institute of Occupational Health, Helsinki, Finland*; [3] *Research & Development Unit for Medical Education, University of Helsinki, Finland*; [4] *Department of Oral Health Policy and Epidemiology, Harvard University, Boston, MA, USA*; [5] *Department of Mental Health and Alcohol Research, National Public Health Institute, Helsinki, Finland*

## ABSTRACT

**Background.** Depression is associated with smoking, but the causality of the relationship is debated. The authors examine smoking behaviour as a predictor of depression among the Finnish adult twin population.

**Method.** Based on responses to surveys in 1975 and 1981, the authors characterized the subjects as never smokers, persistent former smokers, quitters, recurrent smokers and persistent smokers. The Beck Depression Inventory (BDI) was applied in 1990 to measure depression (BDI score >9). Although the population consisted of twins, the authors first considered the subjects as individuals. Logistic regression models were computed for 4164 men and 4934 women. In order to control for family and genetic background, conditional logistic regression analyses were conducted among twin pairs discordant for depression. Bivariate genetic modelling was used to examine genetic and environmental components of the correlation between smoking and depression.

**Results.** Among the men, persistent smoking (OR 1·42, 95% CI 1·07–1·89) and smoking in 1975 but quitting by 1981 (OR 1·68, 95% CI 1·17–2·42) was associated with a higher risk of depression, while among the women only the quitters had an elevated risk (OR 1·38, 96% CI 1·01–1·87). The gender × smoking interaction showed persistent smoking to be a stronger risk for men. When family and genetic background were controlled, smoking remained a predictor of depression. Genetic modelling among the men suggested a modest correlation ($r_g = 0{\cdot}25$) between genetic components of smoking and depression.

**Conclusions.** Smoking behaviour may be a gender-sensitive predictor of depression, the stronger association in men being partly accounted for by having underlying genes in common.

## INTRODUCTION

Smoking and depression are prevalent conditions with high public health significance (Murray & Lopez, 1997; Dani & Harris, 2005). Depression is a concept that incorporates several types of mood disorders, ranging from being mildly depressed to major depressive disorder (MDD) (Maxmen & Ward, 1986). In Finland, as elsewhere, smokers are more likely to have a history of depression or current depressive symptoms than non-smokers (Tanskanen *et al.* 1999; Haukkala *et al.* 2000; Hämäläinen *et al.*

* Address for correspondence: Dr T. Korhonen, Department of Public Health, University of Helsinki, P.O. Box 41, 00014 Helsinki, Finland.
(Email: tellervo.korhonen@helsinki.fi)

2001; Williams & Ziedonis, 2004; Dani & Harris, 2005). While this cross-sectional association is well established, the causality is being studied under various hypotheses.

First, persistent smoking may increase the risk of depression. This hypothesis has been supported by longitudinal studies in adult and adolescent populations (Wu & Anthony, 1999; Goodman & Capitman, 2000; Whitfield *et al.* 2000). Klungsøyr and colleagues (2006) showed a fourfold higher risk of depression onset among heavy smokers. Secondly, depression may increase the risk of smoking through a self-medication mechanism whereby relief from depressive symptoms motivates it (Royal College of Physicians of London, 2000; Goldstein, 2003). Pre-existing psychiatric disorders have predicted an increased risk of the onset of daily smoking and progression to nicotine dependence (Haustein *et al.* 2002; Fergusson *et al.* 2003; Murphy *et al.* 2003; Breslau *et al.* 2004; John *et al.* 2004; Repetto *et al.* 2005). Furthermore, this self-medication hypothesis is supported by studies showing that quitting smoking resulted in depression (Glassman, 1993; Stage *et al.* 1996). Thirdly, reciprocal mechanisms have also been reported (Breslau *et al.* 1998).

Fourthly, the co-morbidity may be non-causal, depression and smoking sharing a common vulnerability, that potentially includes a genetic component (Kendler *et al.* 1993*a*; Bergen & Caporaso, 1999; Williams & Ziedonis, 2004). Heritability of depression has been shown to be modest to moderate –29% for depressive symptoms (Johnson *et al.* 2002) and 37% for liability to MDD (Sullivan *et al.* 2000), for example – and for persistent smoking and smoking cessation 50–58% (Madden *et al.* 2004; Broms *et al.* 2006). However, there is conflicting evidence regarding whether depression and smoking share a genetic component (Kendler *et al.* 1993*a*; Dierker *et al.* 2002; McCaffery *et al.* 2003; Johnson *et al.* 2004).

Further, given that the prevalence of smoking is higher among men (WHO, 1997), whereas the prevalence of depression is higher among women (WHO, 2001), there is a need to explore gender differences within these associations (Perkins *et al.* 1999). Finally, because of common confounders associated with depression and smoking, the assessment of causal relations requires a design allowing the inclusion of temporal and concurrent factors contributing to the association (Fergusson *et al.* 2003).

Our primary aim was to examine smoking behaviour as a predictor of depression among the Finnish adult population, and to analyse whether the association was modified by gender. Our secondary aim was to investigate whether the association was modified by familial or genetic effects.

## METHODS

### Sample

The Finnish Twin Cohort was established to examine the genetic, environmental and psychosocial determinants of chronic diseases and health behaviours. This population-based cohort was compiled from the Central Population Registry consisting of all same-sex twin pairs born in Finland before 1958 with both co-twins alive in 1967 (13 888 pairs of known zygosity). The project was accepted by the Ethical Committee of the University of Helsinki.

The first questionnaire survey was conducted in 1975, and the second in 1981, involving all twins in the cohort who were still alive, including the non-respondents in 1975 (84% response rate, 24 053 respondents). The third questionnaire was sent in 1990 to twins born in 1930–1957, if they had responded to at least one of the previous surveys ($n = 16\,179$). This survey had a 77% response rate with 12 502 respondents, and included complete data on both depression and smoking among a total of 10 977 participants. The mean age in 1981 was 35·2 years. The zygosity of the twins was determined by means of an accurate validated questionnaire (Sarna *et al.* 1978).

### Measures

#### *Outcome*

The Beck Depression Inventory (BDI; Beck *et al.* 1961) was applied to measure depressive symptoms in 1990. The 21-item questionnaire instructions guided the participants in describing their symptoms and attitudes as they perceived them 'right now' in terms of intensity from 0 to 3. Details of the BDI scoring procedures on the same dataset were published earlier (Varjonen *et al.* 1997).

After the exclusion of participants with missing data on the BDI, the sample comprised

https://doi.org/10.1017/S0033291706009639 Published online by Cambridge University Press

12 063 persons (5512 men, 6551 women). Owing to a 'floor-effect' within the sum score, we used the BDI as a categorical variable. We created three depression categories based on the total BDI scores: (1) 0–9 (none or minimal); (2) 10–16 (mild), and (3) 17 or more (at least moderate). For the logistic regression models we categorized the participants as a dichotomy, the 'non-affected' with a BDI score $\leqslant 9$, and the 'affected' with a score $>9$ (Beck & Beamesderfer, 1974).

*Predictor*

Current smokers comprised those who had smoked at least five packets of cigarettes over their lifetime and who were smoking regularly at the time of the study (Kaprio & Koskenvuo, 1988). This study applied multiple-time-point measurements of smoking as a predictor variable. Of the participants providing data on depression in 1990 ($n=12\,063$), 10 977 (4980 men, 5997 women) had complete data on smoking in 1975 and 1981. Six groups were formed based on 1975–1981 smoking: (1) never smokers in 1975 and 1981 ($n=5081$); (2) quitters, i.e. current smokers in 1975, former smokers in 1981 ($n=880$); (3) persistent smokers, i.e. current smokers in 1975 and 1981 ($n=2492$); (4) persistent former smokers, i.e. former smokers in 1975 and 1981 ($n=1213$); (5) recurrent smokers, i.e. former smokers in 1975, current smokers in 1981 ($n=307$); (6) others, mostly occasional smokers ($n=1004$).

The persistent never smokers were the reference category with no exposure. Other categories represented ever smokers as various risk groups, the persistent ones being the most consistently exposed. Considering the quitters and the persistent former smokers as separate categories allowed us to evaluate exposure consistency. In a secondary analysis we examined the effect of change in smoking between 1981 and 1990, the categories in 1990 being never, occasional, former and current smoker.

*Confounders*

In view of the evidence from earlier studies, we adjusted the analyses for several confounders, such as sociodemographic background, other health behaviours, and other factors correlating with depression. Most of the confounders were measured in 1981, and somatic health and social network in 1990. Among the sociodemographic variables we adjusted for gender, age, marital status (Hasin *et al.* 2005) and social class (Fryers *et al.* 2003), including education and type of work (Appelberg *et al.* 1991). Of the other health behaviours we adjusted for binge-drinking (Kaprio *et al.* 1987) and physical activity (sedentary, intermediate or active lifestyle based on the Metabolic Equivalent Task score; Kujala *et al.* 2002). Further, we adjusted for somatic health, social support (social network as a quantitative and emotional support as a qualitative component), and negative or stressful life events (Dalgard *et al.* 1995; Lillberg *et al.* 2003). A detailed description of most of these confounders is available elsewhere (Romanov *et al.* 2003).

As neuroticism is a personality trait predisposing to depression (Kendler *et al.* 1993*b*), we controlled for neuroticism assessed in 1981 using a nine-item scale based on Eysenck's personality inventory (Viken *et al.* 1994). We used life satisfaction in 1981 as a proxy for pre-existing depression, because scores on this variable correlate with the BDI ($r>0{\cdot}60$) when measured concurrently. The data on life satisfaction were based on a four-item scale categorized in three groups ['satisfied' (4–6), 'intermediate' (7–11) and 'dissatisfied' (12–20)] (Koivumaa-Honkanen *et al.* 2004).

**Assessment of selection bias**

A detailed assessment of selection bias due to mortality and morbidity, such as to hospital treatment for depression, has been reported by Romanov and colleagues (2003), indicating less prior hospitalization for depression-related causes among respondents than among non-respondents. In order to assess bias due to drop-out regarding smoking and proxy for pre-existing depression, we analysed those with data on smoking in 1975 and 1981 and on life satisfaction in 1981 who were known to have received the 1990 questionnaire ($n=13\,704$). Being a non-respondent in 1990 was predicted by smoking and life satisfaction: persistent smokers [odds ratio (OR) 1·39, 95% confidence interval (CI) 1·25–1·54], recurrent smokers (OR 1·36, 95% CI 1·07–1·73) and those with lower life satisfaction (OR 1·05, 95% CI 1·03–1·06) were more probably non-responders.

https://doi.org/10.1017/S0033291706009639 Published online by Cambridge University Press

### Statistical analyses

Although the study population consisted of twins, for the primary analyses we considered the subjects as individuals, but statistically accounted for twinship. The analyses were conducted by using the STATA statistical package, version 9 (StataCorp, College Station, TX, USA). Univariate logistic regression models tested the strength and significance of each smoking category, never smokers comprising the reference group. Because of significant smoking × gender interactions (quitters × gender, $p=0{\cdot}009$; persistent smokers × gender, $p=0{\cdot}005$), the odd ratios with 95% confidence intervals were computed for all respondents together (adjusting for age and gender), as well as for the men and women separately (with adjustment for age). The OR is a measure of association between a risk factor and disease, i.e. the ratio of the odds of disease between those with and without the risk factor (Thomas, 2004).

We used multiple logistic regression models in order to adjust for confounders. The final model was adjusted for sociodemographic background, other health behaviours, somatic disease, social network, emotional support, life events, neuroticism and life satisfaction. Because observations on twins within twin pairs may be correlated we used robust estimators of variance and the cluster option in STATA when estimating standard errors (Williams, 2000). We conducted three secondary analyses: first, we explored the dose-response relationship among the persistent smokers, then we examined the effect of change in smoking between 1981 and 1990, and thirdly, we approximated the incidence of depression in 1990.

In order to test causality and to control for family background, we utilized the fact that our population consisted of twins. Because twins share their childhood environment, an association between an explanatory factor and the outcome within such pairs would provide evidence of a causal relationship. We identified all twin pairs discordant for depression as matched cases and controls, nevertheless initially disregarding zygosity. We used the McNemar Test as an unadjusted test in order to assess the risk of being depressed given smoking, and in order to adjust for confounding variables not matched for in the design we applied conditional multiple logistic regression (Thomas, 2004).

In order to further control for genetic background, we applied the co-twin control method, comparing the risk of smoking in MZ (monozygotic) and DZ (dizygotic) twin pairs discordant for depression (Kendler *et al.* 1993*a*). These analyses did not show any smoking × gender interactions. Thus, the results were presented for men and women pooled together. Finally, we used a bivariate twin genetic model in order to explore whether the association between smoking and depression could be ascribed to underlying genetic factors in common. The greater resemblance of MZ *versus* DZ pairs in this association, as indexed by cross-twin cross-trait correlations, is formally modelled by decomposing the phenotypic correlation into correlations between genetic and environmental components of smoking and depression. The modelling was based on standard Mx scripts from the Genomeutwin Mx website (http://www.psy.vu.nl/mxbib/).

## RESULTS

### The individual data

#### *Descriptive results*

The prevalence of mild depression (BDI = 10–16) was 12·4% (9·9% in the men, 14·5% in the women), and of at least moderate depression (BDI > 16) was 4·7% (3·6% in the men, 5·6% in the women). Depressive symptoms were more prevalent among the women ($p<0{\cdot}001$), and the mean BDI scores were also significantly higher among them (mean 5·75, 95% CI 5·61–5·89, S.D. = 5·87) than among the men (mean 4·52, 95% CI 4·38–4·70, S.D. = 5·20) ($p<0{\cdot}001$). The descriptive results are given in Table 1, including the proportions of the BDI categories in each smoking group.

#### *Smoking behaviour and depression*

The results of the logistic regression analyses adjusted for age and sex suggested that the depression risk was significantly elevated among the persistent smokers (OR 1·58), the recurrent smokers (OR 1·53) and the quitters (OR 1·43) (Table 1). Among the men, the persistent smokers (OR 1·94), the recurrent smokers (OR 1·84) and the quitters (OR 1·83) showed elevated

https://doi.org/10.1017/S0033291706009639 Published online by Cambridge University Press

Table 1. *Proportions*[a] *(%) of the Beck Depression Inventory (BDI) categories by smoking status in 1975–1981 with OR (95% CI) for at least mild depression*[b] *in 1990 in each smoking category*[c]

| Smoking status | BDI | | | | | |
|---|---|---|---|---|---|---|
| All ($n=10977$) | *n* | ⩽9 | 10–16 | >16 | OR[d] | 95% CI |
| Never smokers | 5081 | 84 | 12 | 4 | 1·00 | |
| Quitters | 880 | 82 | 14 | 4 | 1·43 | 1·18–1·74 |
| Persistent smokers | 2492 | 81 | 13 | 6 | 1·58 | 1·38–1·81 |
| Persistent former smokers | 1213 | 87 | 10 | 3 | 0·97 | 0·80–1·17 |
| Recurrent smokers | 307 | 81 | 14 | 5 | 1·53 | 1·12–2·07 |
| Others[e] | 1004 | 83 | 11 | 6 | 1·28 | 1·07–1·55 |
| Men ($n=4980$) | *n* | ⩽9 | 10–16 | >16 | OR[f] | 95% CI |
| Never smokers | 1662 | 90 | 7 | 2 | 1·00 | |
| Quitters | 450 | 84 | 13 | 3 | 1·83 | 1·35–2·47 |
| Persistent smokers | 1460 | 83 | 12 | 5 | 1·94 | 1·56–2·43 |
| Persistent former smokers | 753 | 90 | 8 | 3 | 1·02 | 0·77–1·36 |
| Recurrent smokers | 179 | 84 | 13 | 4 | 1·84 | 1·19–2·85 |
| Others[e] | 476 | 87 | 9 | 4 | 1·52 | 1·11–2·09 |
| Women ($n=5997$) | *n* | ⩽9 | 10–16 | >16 | OR[f] | 95% CI |
| Never smokers | 3419 | 81 | 14 | 5 | 1·00 | |
| Quitters | 430 | 80 | 14 | 6 | 1·24 | 0·96–1·61 |
| Persistent smokers | 1032 | 77 | 16 | 7 | 1·39 | 1·16–1·66 |
| Persistent former smokers | 460 | 82 | 15 | 3 | 1·00 | 0·77–1·30 |
| Recurrent smokers | 128 | 77 | 16 | 6 | 1·38 | 0·89–2·13 |
| Others[e] | 528 | 80 | 13 | 7 | 1·20 | 0·95–1·52 |

OR, Odds ratio; CI, confidence interval.

[a] The totals may not equal 100% because of the rounding of individual percentages.

[b] BDI >9.

[c] Among the subjects with complete data in the BDI score and smoking status in 1975–1981.

[d] Adjusted for age and sex.

[e] Occasional smokers in 1975 or/and in 1990 and others.

[f] Adjusted for age.

risks, while among the women the persistent smokers had a higher risk (OR 1·39) than the never smokers.

The results of the multiple logistic regression models are given in Table 2. They remained similar after adjustment for sociodemographic confounders and changed slightly after adjustment for other confounders. Among the men, both persistent smoking (OR 1·42) and smoking in 1975 but quitting by 1981 (OR 1·68) showed a significantly higher depression risk in comparison to never smoking, while among the women it was only the quitters who had a higher risk (OR 1·38) (model III). Gender × smoking interaction ($p=0·014$) indicated that persistent smoking was a stronger risk factor for the men.

### *Secondary analyses*

We conducted several secondary analyses (not shown in the tables). First, in order to explore the dose-response relationship we classified the persistent smokers into categories: 1 = <10; 2 = 10–19; and 3 = ⩾20 cigarettes/day, coding the non-persistent smokers as 0. When we included this as a continuous variable (0, 1, 2, 3) in the model, the trend test result was OR 1·11 (95% CI 1·02–1·23) for the men, but no significant trend was evident in the women. Secondly, we examined the effect of change in smoking between 1981 and 1990. The male persistent smokers who remained smokers until 1990 had a higher depression risk (OR 1·44, 95% CI 1·07–1·93) than the never smokers, and the female former smokers or quitters in 1975–1981 who relapsed by 1990 had a higher risk (OR 1·67, 95% CI 1·11–2·52) than the never smokers.

We conducted further analyses in order to approximate the incidence of depression in 1990, applying neuroticism as a predisposing factor and poor life satisfaction as a proxy. First, we excluded the respondents with a neuroticism score >5 in 1981 (39% of subjects). Among the remaining 2724 men, the persistent smokers were at a higher risk (OR 1·57, 95% CI 1·03–2·39) than the never smokers, but among the remaining 2947 women smoking behaviour did not show elevated depression risk. We then excluded those 'dissatisfied' with their life in 1981 (13%). Of the 3637 remaining men, the persistent smokers (OR 1·77, 95% CI 1·27–2·48) and the quitters (OR 2·09, 95% CI 1·38–3·19) showed an elevated depression risk, whereas among the 4283 remaining women it was the quitters who showed a higher risk (OR 1·42, 95% CI 1·01–1·99).

## The twin data

Table 3 gives the results of the conditional logistic regression analyses of discordant pairs for depression when familial and genetic factors were controlled. First, the test for a causal relationship among all pairs showed that persistent smoking (OR 1·70) and smoking in 1975 but quitting by 1981 (OR 2·19) remained risk factors

https://doi.org/10.1017/S0033291706009639 Published online by Cambridge University Press

Table 2. *Multiple logistic regression models of smoking behaviour in 1975–1981 as a predictor of depression in 1990*

| | Model I[a] | | Model II[b] | | Model III[c] | |
|---|---|---|---|---|---|---|
| Smoking status 1975–1981 | OR | 95% CI | OR | 95% CI | OR | 95% CI |
| Men | | (*n* = 4975) | | (*n* = 4939) | | (*n* = 4164) |
| Never smokers | 1·00 | | 1·00 | | 1·00 | |
| Quitters | 1·87 | 1·38–2·53 | 1·69 | 1·23–2·30 | 1·68 | 1·17–2·42 |
| Persistent smokers | 1·88 | 1·51–2·35 | 1·53 | 1·20–1·95 | 1·42 | 1·07–1·89 |
| Persistent former smokers | 1·08 | 0·81–1·44 | 0·99 | 0·74–1·32 | 0·90 | 0·63–1·28 |
| Recurrent smokers | 1·87 | 1·21–2·89 | 1·52 | 0·97–2·37 | 1·19 | 0·68–2·10 |
| Others | 1·49 | 1·08–2·05 | 1·36 | 0·98–1·89 | 1·21 | 0·80–1·82 |
| Women | | (*n* = 5992) | | (*n* = 5935) | | (*n* = 4934) |
| Never smokers | 1·00 | | 1·00 | | 1·00 | |
| Quitters | 1·25 | 0·96–1·62 | 1·21 | 0·93–1·59 | 1·38 | 1·01–1·87 |
| Persistent smokers | 1·36 | 1·14–1·64 | 1·18 | 0·97–1·43 | 0·95 | 0·75–1·21 |
| Persistent former smokers | 1·03 | 0·80–1·34 | 1·03 | 0·79–1·33 | 0·99 | 0·72–1·36 |
| Recurrent smokers | 1·39 | 0·90–2·17 | 1·37 | 0·89–2·13 | 1·27 | 0·73–2·22 |
| Others | 1·20 | 0·95–1·52 | 1·17 | 0·93–1·48 | 1·12 | 0·84–1·50 |

OR, Odds ratio; CI, confidence interval.
[a] Model I: adjusted for sociodemographic variables (age, marital status, social class).
[b] Model II: adjusted for sociodemographic variables + health behaviours (alcohol use, physical activity).
[c] Model III: adjusted for sociodemographic + health behaviours + somatic disease, social network, emotional support, life events, neuroticism and life satisfaction.

Table 3. *Conditional multiple logistic regression models of 1975–1981 smoking behaviour among twin pairs discordant for depression*[a]

| | All pairs (*n* = 628) | | MZ pairs (*n* = 172) | | DZ pairs (*n* = 407) | |
|---|---|---|---|---|---|---|
| Smoking status | OR | 95% CI | OR | 95% CI | OR | 95% CI |
| Never smokers | 1·00 | | 1·00 | | 1·00 | |
| Quitters | 2·19 | 1·17–4·11 | 7·75 | 1·54–39·00 | 1·74 | 0·83–3·66 |
| Persistent smokers | 1·70 | 1·05–2·75 | 2·88 | 0·81–10·28 | 1·59 | 0·91–2·78 |
| Persistent former smokers | 1·10 | 0·63–1·95 | 0·56 | 0·15–2·00 | 1·31 | 0·64–2·67 |
| Recurrent smokers | 1·26 | 0·45–3·47 | 1·94 | 0·18–20·99 | 1·36 | 0·40–4·58 |
| Others | 1·42 | 0·80–2·50 | 1·78 | 0·59–5·43 | 1·28 | 0·62–2·62 |

MZ, Monozygotic; DZ, dizygotic; OR, odds ratio; CI, confidence interval.
[a] Adjusted for variables with *p* value <0·05 (somatic disease, social network, emotional support, life events, neuroticism, life satisfaction).

and secondly, among the MZ pairs persistent smokers (OR 2·88) and quitters (OR 7·75) were also at a high risk. Among the DZ pairs, all ever smokers tended to be at a higher risk, but the highest risks were faced by the persistent smokers (OR 1·59) and the quitters (OR 1·74), although the risk levels were lower than among the MZ pairs.

The correlations of liability between smoking and depression in members of the MZ and DZ twin pairs are shown in Table 4. The cross-twin, cross-trait correlations for the MZ pairs were smaller than for the DZ pairs among the women, and we therefore did no further modelling for them. The bivariate model gave a heritability estimate for smoking of 82% (95% CI 75·4–87·2) among the men, while the corresponding estimate for depression was 34% (95% CI 18·7–48·1). The correlation between genetic components was $r = 0{\cdot}25$ (95% CI 0·07–0·45) and between unshared environmental effects $r = 0{\cdot}10$ (95% CI −0·10 to 0·34), based on the best-fitting AE model ($\Delta\chi^2 = 14{\cdot}00$, $\Delta df = 12$, $p = 0{\cdot}30$, $\Delta AIC = -10{\cdot}00$).

## DISCUSSION

The aim was to investigate whether smoking behaviour predicted depression, and whether gender or genetic vulnerability modified the

https://doi.org/10.1017/S0033291706009639 Published online by Cambridge University Press

Table 4. *The tetrachoric correlations (95% CI)*[a] *of liability between smoking behaviour*[b] *and depression*[c] *in members of the monozygotic and dizygotic twin pairs*

| | Twin 1 | | Twin 2 | |
|---|---|---|---|---|
| Men | Smoking | Depression | Smoking | Depression |
| Twin 1 | | | | |
| Smoking | — | **0·19 (0·10–0·28)** | **0·79 (0·75–0·82)** | **−0·04 (−0·13 to 0·05)** |
| Depression | *0·20 (0·14–0·26)* | — | **0·20 (0·11–0·29)** | **0·51 (0·44–0·57)** |
| Twin 2 | | | | |
| Smoking | *0·50 (0·45–0·55)* | *0·19 (0·13–0·25)* | — | **0·13 (0·04–0·22)** |
| Depression | *0·19 (0·13–0·25)* | *0·19 (0·13–0·25)* | *0·22 (0·16–0·28)* | — |
| | Twin 1 | | Twin 2 | |
| Women | Smoking | Depression | Smoking | Depression |
| Twin 1 | | | | |
| Smoking | — | **−0·01 (−0·09 to 0·07)** | **0·80 (0·77–0·83)** | **−0·13 (−0·20 to −0·06)** |
| Depression | *0·12 (0·06–0·18)* | — | **−0·08 (−0·16 to 0·00)** | **0·54 (0·48–0·59)** |
| Twin 2 | | | | |
| Smoking | *0·74 (0·71–0·77)* | *−0·05 (−0·11 to 0·01)* | — | **0·22 (0·15–0·29)** |
| Depression | *0·08 (0·02–0·14)* | *0·21 (0·15–0·26)* | *0·04 (−0·02–0·10)* | — |

[a] Correlations in the monozygotic (MZ) twins are above the diagonal (in bold); those for the dizygotic (DZ) twins are below the diagonal (in italics).
[b] Smoking status 1975–1981: 0 = never smokers + persistent former smokers; 1 = persistent smokers + recurrent smokers + quitters.
[c] Depression 1990: 0 = no depression 1 = at least mild depression (BDI > 9).

association. Smoking behaviour did seem to be a predictor, and more strongly among the men: when the sociodemographic variables were adjusted the persistent smokers, the recurrent smokers and the quitters showed an increased risk, whereas among the women it was only the persistent smokers who had an elevated risk. When other confounders were adjusted, the male persistent smokers and quitters remained at a higher risk, while among the women the risk was significant only for the quitters. Controlling for 1981–1990 change in smoking increased the depression risk among the persistent male and recurrent female smokers, while approximating the incidence of depression strengthened the role of smoking behaviour among the men. When family background was controlled for by using discordant twin pairs, ever smoking remained a predictor of depression, thus providing evidence of a causal relationship. However, controlling for genetic background tended to produce a higher risk among the MZ pairs. Finally, the bivariate model suggested that the co-morbidity was partly accounted for by the underlying genes in common among the men.

## Persistent smoking predicted depression

Persistent smoking seemed to predict depression. The risk estimates among the persistent smokers, adjusted for age, marital status and social class were significant for both sexes, although when other confounders were adjusted, the risk remained significant only among the men. The recent support for this causal relationship comes from a Norwegian study (Klungsøyr *et al*. 2006), which reported a fourfold higher risk of depression onset for heavy smokers when other plausible explanations were controlled for. Klungsøyr and co-workers found a stronger influence of smoking on depression than we did, which may be partly due to the differences in the measures used. The Composite International Diagnostic Interview used in the Norwegian study has good reliability and validity, but limited use in general population samples (Andrews & Peters, 1998), whereas the BDI we used is a well recognized measure with good properties for screening depression cases in the population (Lasa *et al*. 2000). The Norwegian study demonstrated a dose-response relationship between smoking and depression.

https://doi.org/10.1017/S0033291706009639 Published online by Cambridge University Press

Although our study focused on the effects of consistency in smoking through follow-up, we also found some evidence of a dose-response relationship among the men.

### Quitting smoking predicted depression

It was not only the persistent smokers but also those who had quit before the outcome assessment who showed an elevated depression risk. This result emphasises the risk of ever smoking, and is supported by the results of another population study in which both current and former smokers had a higher depression risk than never smokers (John *et al*. 2004). The fact that our data did not show an elevated risk for the persistent former smokers suggests that during considerably longer time of abstinence the risk may decrease to the level of never smokers. The elevated depression risk among the quitters raises the question of whether these persons had pre-existing 'depressiveness', which they had masked by tobacco use, and which could have emerged after they had stopped smoking (Stage *et al*. 1996). We conducted *post hoc* analyses to explain this result by comparing the mean scores for life satisfaction and neuroticism among the quitters with the scores of those in the other smoking categories. The quitters differed from the others in having better life satisfaction than the persistent smokers, but had higher neuroticism scores than the never and the persistent former smokers. Higher neuroticism may partly explain the pre-existing depression vulnerability among the quitters.

### Gender modification

Gender seemed to modify the association between smoking and depression. Another study based on the same twin cohort reported a gender-specific relationship between smoking and psychiatric morbidity that was significant only among the men (Koivumaa-Honkanen, 1998). However, another Finnish study reported a stronger cross-sectional association among women (Haukkala *et al*. 2000). One explanation for the discrepancy may be that we had a longitudinal design and adjusted for several predictors of depression. We also included those ever smokers in several categories. When we adjusted only for age, both the male and the female persistent smokers showed an elevated depression risk, but when we included all significant confounders, the risk for women was elevated only among the quitters. Thus, it seems that depression among women may be more influenced by these other factors. Further, in a secondary analysis on the change in smoking from 1981 to 1990, it was only the men who had continued smoking and only the women who had started to smoke again who had a higher depression risk. This suggests that the association between smoking behaviour and depression may be more stable for men than for women.

In general, assessment of whether these associations are different in men than in women may partly be confounded by the different prevalence of smoking and depression. One explanation for the observed difference is that smoking may not be motivated by the same factors in both genders: for example, nicotine reinforcement may control smoking to a greater degree among men (Perkins *et al*. 1999). In relation to smoking cessation, women may face more other stressors, such as negative affectivity and depression (Gritz *et al*. 1996). While our finding that men's mental health was more vulnerable among the persistent smokers was surprising, it may be meaningful. Although the prevalence of depression is lower among men, the condition may have more serious consequences: suicide attempts (Blair-West *et al*. 1999) have been associated with persistent smoking (Breslau *et al*. 2005).

### Modification by common vulnerability

The influence of genetic factors on covariation between smoking and depression has been investigated in few studies (Kendler *et al*. 1993*a*; Lerman *et al*. 1998; Dierker *et al*. 2002; McCaffery *et al*. 2003; Audrain-McGovern *et al*. 2004; Johnson *et al*. 2004). Kendler and co-workers (1993*a*) found that co-morbidity of smoking and MDD among women largely arose from familial factors, while Dierker and colleagues (2002) concluded that MDD did not demonstrate shared vulnerability with smoking, although milder depression did. McCaffery and colleagues (2004) suggested that non-shared environmental factors accounted for the majority of covariation between liability to depression and smoking among men, and finally, Johnson and co-workers (2004) found familial

https://doi.org/10.1017/S0033291706009639 Published online by Cambridge University Press

liability to the co-morbidity of MDD and heavy smoking.

So far, no similar investigations have been conducted in Finland. When we controlled for family background by using discordant twins, smoking behaviour remained a predictor of depression, and thus, this analysis gave preliminary support for a causal relationship. Furthermore, the fact that the risk tended to be higher among the MZ than the DZ pairs also suggested some genetic vulnerability. However, this method used only twins who were discordant for depression. In order to enhance power we applied Mx models in which we expected the greater similarity in the MZ twins than in the DZ twins to support the hypothesis that genetic transmission was a component of importance, under the assumption that MZ and DZ share their trait-relevant environmental experiences to the same extent (Boomsma *et al*. 2002). However, given the correlations of liability between smoking and depression in the MZ and DZ twin pairs, we fitted the bivariate model only to the men, with a modest correlation between genetic components. The strength and nature of genetic and environmental influences on smoking and depression seem to be sensitive to the various phenotypes and study design used in each analysis.

### The alternative hypothesis

It would be ideal if a single longitudinal study could test the 'smoking-to-depression', the 'depression-to-smoking', the 'reciprocal', and the 'common vulnerability' hypotheses. The population-based Finnish Twin Cohort includes data on smoking in 1975, 1981 and 1990, allowing the long-term examination of smoking behaviour. Because depression was investigated only in 1990, this design was valid for testing the hypothesis of whether smoking predicts depression. Further, as these data consist of twins, the hypothesis of common vulnerability could be tested.

While not directly testing the 'depression-to-smoking' hypothesis, we controlled our analyses for life satisfaction and neuroticism. Further, we conducted additional *post hoc* analyses by using poor life satisfaction in 1981 as a proxy for pre-existing depressiveness. Because this adult cohort did not provide optimal data for investigating smoking initiation we used current smoking in 1990 as an outcome. The adjusted ORs of poor life satisfaction did not significantly predict smoking (men, OR 1·27, 95% CI 0·96–1·68; women, OR 1·19, 95% CI 0·90–1·57). Thus, poor life satisfaction as a proxy for pre-existing depressiveness did not provide evidence of alternative causality.

### Methodological issues

This study has several methodological strengths. First, we controlled for numerous confounders. Secondly, because our study was prospective our measures were not confounded by recall bias. Thirdly, this population-based cohort followed up through 15 years provides reliable data on the effects of long-term smoking behaviour on depression. Fourthly, we tested the smoking-to-depression causality by using discordant twin pairs as matched cases and controls.

A potential weakness regarding the predictor is the question of whether we should have accounted for change in smoking between 1981 and 1990. We did so in a secondary analysis and found a significant depression risk among the male persistent smokers and among the women quitting, but relapsing by 1990. However, because smoking in 1990 may have been confounded by concurrent depression, these results should be interpreted with caution.

A further concern is whether drop-out caused any bias. In order to estimate this we used the 1981 data on smoking and life satisfaction to explain participation in 1990. As expected, ever smoking and poor life satisfaction modestly predicted non-participation in 1990. Thus, the results could be underestimated with regard to both the risk factor and the outcome.

The way in which depression was ascertained by means of a questionnaire at a single time-point may be a limitation. Optimally we would have conducted psychiatric interviews and assessments at multiple time-points to capture true incident cases during the follow-up. The episodic and sometimes chronic nature of depression makes incident case definition difficult. However, because life satisfaction and depression correlated strongly, we controlled for pre-existing depressiveness by excluding those dissatisfied at baseline. On the other hand, the BDI is a well recognized measure of depression with good properties for screening cases in the

population (Lasa *et al*. 2000). We used the cut-off BDI >9 for the 'affected', including participants with varying degrees of severity (Varjonen *et al*. 1997). It is possible that including mild depressive symptoms may have diluted the risk effects of smoking. Finally, the assessment of depression in 1990 probably underestimated its incidence during the follow-up period as episodes that were fully resolved prior to 1990 were missed. This is unlikely to bias the relative risk estimates, however.

## Conclusions

This study supported the hypothesis that smoking behaviour predicts depression. Moreover, smoking as a predictor seems to be modified by gender: when we adjusted for other predictors of depression we found that persistent smoking increased the risk only among the men. The increased risk among both male and female quitters provides a challenge for further research. The co-morbidity among men may partly be accounted for by common genetic vulnerability to smoking and depression.

## ACKNOWLEDGMENTS

This study was supported in part by the Academy of Finland (grant no. 107681), the Paavo Nurmi, the Juho Vainio Foundations (TK), the Centre of Excellence in Complex Disease Genetics and GenomEUtwin (FP5 QLG2-CT-2002-01254) (J.K.). The authors thank Karri Silventoinen and Esko Levälahti for their help with the Mx modelling.

## DECLARATION OF INTEREST

None.

## REFERENCES

**Andrews, G. & Peters, L.** (1998). The psychometric properties of the Composite International Diagnostic Interview. *Social Psychiatry and Psychiatric Epidemiology* **33**, 80–88.

**Appelberg, K., Romanov, K., Honkasalo, M. L. & Koskenvuo, M.** (1991). Interpersonal conflicts at work and psychosocial characteristics of employees. *Social Science & Medicine* **32**, 1051–1056.

**Audrain-McGovern, J., Lerman, C., Wileyto, E. P., Rodriguez, D. & Shields, P. G.** (2004). Interacting effects of genetic predisposition and depression on adolescent smoking progression. *American Journal of Psychiatry* **161**, 1224–1230.

**Beck, A. T. & Beamesderfer, A.** (1974). Assessment of depression: the depression inventory. *Modern Problems of Pharmacopsychiatry* **7**, 151–169.

**Beck, A. T., Ward, C. H., Mendelson, M., Mock, J. & Erbaugh, H.** (1961). An inventory for measuring depression. *Archives of General Psychiatry* **4**, 561–571.

**Bergen, A. W. & Caporaso, N.** (1999). Cigarette smoking. *Journal of the National Cancer Institute* **91**, 1365–1375.

**Blair-West, G. W., Cantor, C. H., Mellsop, G. W. & Eyeson-Annan, M. L.** (1999). Lifetime suicide risk in major depression: sex and age determinants. *Journal of Affective Disorders* **55**, 171–178.

**Boomsma, D., Busjahn, A. & Peltonen, L.** (2002). Classical twin studies and beyond. *Nature Reviews Genetics* **3**, 872–882.

**Breslau, N., Novak, S. P. & Kessler, R. C.** (2004). Psychiatric disorders and stages of smoking. *Biological Psychiatry* **55**, 69–76.

**Breslau, N., Peterson, E., Schultz, L. R., Chilcoat, H. D. & Andreski, P.** (1998). Major depression and stages of smoking: a longitudinal investigation. *Archives of General Psychiatry* **55**, 161–166.

**Breslau, N., Schultz, L. R., Johnson, E. O., Peterson, E. L. & Davis, G. C.** (2005). Smoking and the risk of suicidal behavior: a prospective study of a community sample. *Archives of General Psychiatry* **62**, 328–334.

**Broms, U., Silventoinen, K., Madden, P. A. F., Heath, A. C. & Kaprio, J.** (2006). Genetic architecture of smoking behaviour: a study of Finnish twins. *Twin Research and Human Genetics* **9**, 64–72.

**Dalgard, O. S., Bjork, S. & Tambs, K.** (1995). Social support, negative life events and mental health. *British Journal of Psychiatry* **166**, 29–34.

**Dani, J. A. & Harris, R. A.** (2005). Nicotine addiction and comorbidity with alcohol abuse and mental illness. *Nature Neuroscience* **8**, 1465–1470.

**Dierker, L. C., Avenevoli, S., Stolar, M. & Merikangas, K. R.** (2002). Smoking and depression: an examination of mechanisms of comorbidity. *American Journal of Psychiatry* **159**, 947–953.

**Fergusson, D. M., Goodwin, R. D. & Horwood, L. J.** (2003). Major depression and cigarette smoking: results of a 21-year longitudinal study. *Psychological Medicine* **33**, 1357–1367.

**Fryers, T., Melzer, D. & Jenkins, R.** (2003). Social inequalities and the common mental disorders: a systematic review of the evidence. *Social Psychiatry and Psychiatric Epidemiology* **38**, 229–237.

**Glassman, A. H.** (1993). Cigarette smoking: implications for psychiatric illness. *American Journal of Psychiatry* **150**, 546–553.

**Goldstein, M. G.** (2003). Pharmacotherapy for smoking cessation. In *The Tobacco Dependence Treatment Handbook* (ed. D. B. Abrams, R. Niaura, R. A. Brown, K. M. Emmons, M. G. Goldstein and P. M. Monti), pp. 230–248. Guilford Press: New York.

**Goodman, E. & Capitman, J.** (2000). Depressive symptoms and cigarette smoking among teens. *Pediatrics* **106**, 748–755.

**Gritz, E. R., Nielsen, I. R. & Brooks, L. A.** (1996). Smoking cessation and gender: the influence of physiological, psychological and behavioral factors. *Journal of the American Medical Women's Association* **51**, 35–42.

**Hämäläinen, J., Kaprio, J., Isometsä, E., Heikkinen, M., Poikolainen, K., Lindeman, S. & Aro, H.** (2001). Cigarette smoking, alcohol intoxication and major depressive episode in a representative population sample. *Journal of Epidemiology and Community Health* **55**, 573–576.

**Hasin, D. S., Goodwin, R. D., Stinson, F. S. & Grant, B. F.** (2005). Epidemiology of major depressive disorder: results from the National Epidemiologic Survey on Alcoholism and Related Conditions. *Archives of General Psychiatry* **62**, 1097–1106.

**Haukkala, A., Uutela, A., Vartiainen, E., McAlister, A. & Knekt, P.** (2000). Depression and smoking cessation: the role of motivation and self-efficacy. *Addictive Behaviors* **25**, 311–316.

**Haustein, K. O., Haffner, S. & Woodcock, B. G.** (2002). A review of the pharmacological and psychopharmacological aspects of smoking and smoking cessation in psychiatric patients. *International Journal of Clinical Pharmacology and Therapeutics* **40**, 404–418.

**John, U., Meyer, C., Rumpf, H. J. & Hapke, U.** (2004). Depressive disorders are related to nicotine dependence in the population but

do not necessarily hamper smoking cessation. *Journal of Clinical Psychiatry* **65**, 169–176.

**Johnson, E. O., Rhee, S. H., Chase, G. A. & Breslau, N.** (2004). Comorbidity of depression with levels of smoking: an exploration of the shared familial risk hypothesis. *Nicotine & Tobacco Research* **6**, 1029–1038.

**Johnson, W., McGue, M., Gaist, D., Vaupel, J. W. & Christensen, K.** (2002). Frequency and heritability of depression symptomatology in the second half of life: evidence from Danish twins over 45. *Psychological Medicine* **32**, 1175–1185.

**Kaprio, J. & Koskenvuo, M.** (1988). A prospective study of psychological and socioeconomic characteristics, health behavior and morbidity in cigarette smokers prior to quitting compared to persistent smokers and non-smokers. *Journal of Clinical Epidemiology* **41**, 139–150.

**Kaprio, J., Koskenvuo, M., Langinvainio, H., Romanov, K., Sarna, S. & Rose, R. J.** (1987). Genetic influences on use and abuse of alcohol: a study of 5638 adult Finnish twin brothers. *Alcoholism, Clinical and Experimental Research* **11**, 349–356.

**Kendler, K. S., Kessler, R. C., Neale, M. C., Heath, A. C. & Eaves, L. J.** (1993*b*). The prediction of major depression in women: toward an integrated etiologic model. *American Journal of Psychiatry* **150**, 1139–1148.

**Kendler, K. S., Neale, M. C., MacLean, C. J., Heath, A. C., Eaves, L. J. & Kessler, R. C.** (1993*a*). Smoking and major depression. A causal analysis. *Archives of General Psychiatry* **50**, 36–43.

**Klungsøyr, O., Nygard, J. F., Sorensen, T. & Sandanger, I.** (2006). Cigarette smoking and incidence of first depressive episode: an 11-year, population-based follow-up study. *American Journal of Epidemiology* **163**, 421–432.

**Koivumaa-Honkanen, H.** (1998). *Life satisfaction as a health predictor* (dissertation). Kuopio University Publications D. Medical Sciences 143. Kuopio, Finland.

**Koivumaa-Honkanen, H., Kaprio, J., Honkanen, R., Viinamäki, H. & Koskenvuo, M.** (2004). Life satisfaction and depression in a 15-year follow-up of healthy adults. *Social Psychiatry and Psychiatric Epidemiology* **39**, 994–999.

**Kujala, U. M., Kaprio, J. & Koskenvuo, M.** (2002). Modifiable risk factors as predictors of all-cause mortality: the roles of genetics and childhood environment. *American Journal of Epidemiology* **156**, 985–993.

**Lasa, L., Ayuso-Mateos, J. L., Vazquez-Barquero, J. L., Diez-Manrique, F. J. & Dowrick, C. F.** (2000). The use of the Beck Depression Inventory to screen for depression in the general population: a preliminary analysis. *Journal of Affective Disorders* **57**, 261–265.

**Lerman, C., Caporaso, N., Main, D., Audrain, J., Boyd, N. R., Bowman, E. D. & Shields, P. G.** (1998). Depression and self-medication with nicotine: the modifying influence of the dopamine D4 receptor gene. *Health Psychology* **17**, 56–62.

**Lillberg, K., Verkasalo, P. K., Kaprio, J., Teppo, L., Helenius, H. & Koskenvuo, M.** (2003). Stressful life events and risk of breast cancer in 10808 women: a cohort study. *American Journal of Epidemiology* **157**, 415–423.

**Madden, A. F., Pedersen, N. L., Kaprio, J., Koskenvuo, M. J. & Martin, N. G.** (2004). The epidemiology and genetics of smoking initiation and persistence: crosscultural comparisons of twin study results. *Twin Research* **7**, 82–97.

**Maxmen, J. S. & Ward, N. G.** (1986). *Essential Psychopathology and its Treatment*. W. W. Norton: New York.

**McCaffery, J. M., Niaura, R., Swan, G. E. & Carmelli, D.** (2003). A study of depressive symptoms and smoking behavior in adult male twins from the NHLBI twin study. *Nicotine & Tobacco Research* **5**, 77–83.

**Murphy, J. M., Horton, N. J., Monson, R. R., Laird, N. M., Sobol, A. M. & Leighton, A. H.** (2003). Cigarette smoking in relation to depression: historical trends from the Stirling County Study. *American Journal of Psychiatry* **160**, 1663–1669.

**Murray, C. J. & Lopez, A. D.** (1997). Alternative projections of mortality and disability by cause 1990–2020: Global Burden Disease Study. *Lancet* **349**, 1498–1504.

**Perkins, K. A., Donny, E. & Caggiula, A. R.** (1999). Sex differences in nicotine effects and self-administration: review of human and animal evidence. *Nicotine & Tobacco Research* **1**, 301–315.

**Repetto, P. B., Calwell, C. H. & Zimmerman, M. A.** (2005). A longitudinal study of the relationship between depressive symptoms and cigarette use among African American adolescents. *Health Psychology* **24**, 209–219.

**Romanov, K., Varjonen, J., Kaprio, J. & Koskenvuo, M.** (2003). Life events and depressiveness – the effect of adjustment for psychosocial factors, somatic health and genetic liability. *Acta Psychiatrica Scandinavica* **107**, 25–33.

**Royal College of Physicians of London** (2000). *Nicotine Addiction in Britain*. Royal College of Physicians of London: London.

**Sarna, S., Kaprio, J., Sistonen, P. & Koskenvuo, M.** (1978). Diagnosis of twin zygosity by mailed questionnaire. *Human Heredity* **28**, 241–254.

**Stage, K. B., Glassman, A. H. & Covey, L. S.** (1996). Depression after smoking cessation: case reports. *Journal of Clinical Psychiatry* **57**, 467–469.

**Sullivan, P. F., Neale, M. C. & Kendler, K. S.** (2000). Genetic epidemiology of major depression: review and meta-analysis. *American Journal of Psychiatry* **157**, 1552–1562.

**Tanskanen, A., Viinamäki, H., Koivumaa-Honkanen, H. T., Hintikka, J., Jääskeläinen, J. & Lehtonen, J.** (1999). Smoking and depression among psychiatric patients. *Nordic Journal of Psychiatry* **53**, 45–48.

**Thomas, D. C.** (2004). *Statistical Methods in Genetic Epidemiology*. Oxford University Press: New York.

**Varjonen, J., Romanov, K., Kaprio, J., Heikkilä, K. & Koskenvuo, M.** (1997). Self-rated depression in 12 063 middle-aged adults. *Nordic Journal of Psychiatry* **51**, 331–338.

**Viken, R. J., Rose, R. J., Kaprio, J. & Koskenvuo, M.** (1994). A developmental genetic analysis of adult personality: extraversion and neuroticism from 18 to 59 years of age. *Journal of Personality and Social Psychology* **66**, 722–730.

**Whitfield, J. B., Pang, D., Bucholz, K. K., Madden, P. A. F., Heath, A. C., Statham, D. J. & Martin, N. G.** (2000). Monoamine oxidase: associations with alcohol dependence, smoking and other measures of psychopathology. *Psychological Medicine* **30**, 443–454.

**WHO** (2001). *The World Health Report 2001 – Mental Health*. World Health Organisation: Geneva.

**WHO** (1997). *Tobacco or Health: A Global Status Report*. World Health Organisation: Geneva.

**Williams, J. M. & Ziedonis, D.** (2004). Addressing tobacco among individuals with a mental illness or an addiction. *Addictive Behaviors* **29**, 1067–1083.

**Williams, R. L.** (2000). A note on robust variance estimation for cluster-correlated data. *Biometrics* **56**, 645–646.

**Wu, L. T. & Anthony, J. C.** (1999). Tobacco smoking and depressed mood in late childhood and early adolescence. *American Journal of Public Health* **89**, 1837–1840.