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Latent class typology of nicotine withdrawal: genetic contributions and association with failed smoking cessation and psychiatric disorders

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ABSTRACT

Background. Nicotine withdrawal is associated with failed smoking cessation and thus contributes to continuance of the habit and increases risk of smoking-related illnesses. Withdrawal is also associated with psychiatric disorders such as depression and alcoholism. However, relatively little is known about how to characterize the severity of withdrawal, including whether withdrawal subtypes exist in male smokers. If so, do these subtypes represent quantitative or qualitative differences?

Method. Smoking and withdrawal data were obtained from 4112 male–male twin pairs of the Vietnam Era Twin Registry during a 1992 administration of the Diagnostic Interview Schedule. Latent Class Analysis (LCA) was used to derive significantly different nicotine withdrawal profiles, and their association with psychiatric disorders was assessed. Genetic and environmental contributions and the correlation between these contributions were evaluated using bivariate biometrical modeling of the withdrawal phenotype and failed smoking cessation.

Results. The LCA model which best fit the data was a four-class severity continuum. Psychiatric disorders were significantly associated with more severe classes and the magnitude of the association increased as withdrawal severity increased. Genetics accounted for 31% and 51% of the variance in risk for withdrawal and failed cessation, respectively. The genetic contributions were significantly correlated ($r = 0{\cdot}37$).

Conclusions. Nicotine withdrawal classes are characterized by quantitative differences. The strong association between psychiatric disorders and withdrawal severity and the significant genetic correlation between withdrawal and cessation highlight the importance of withdrawal severity. Further refinement of the DSM definition of withdrawal to incorporate severity ratings may be warranted.

INTRODUCTION

Cigarette smoking is the single most important cause of cancer mortality in the USA, accounting for 30% of all cancer deaths (Solberg *et al.* 1998), including nearly 160 000 lung cancers annually (Fauci *et al.* 1998) and oral, pharyngeal, laryngeal, esophageal, bladder, kidney, pancreatic, and cervical cancers and other serious illness such as heart disease and emphysema. In spite of the rising anti-smoking sentiment in the USA and

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improvements in smoking cessation methods, a substantial proportion of the USA adult population continues to smoke (Landis *et al.* 1999). Among those who quit, many relapse within 1 week when withdrawal symptoms are at or near their peak (Hughes *et al.* 1990; Anonymous, 1995), and 90% who attempt to stop smoking restart within 1 year (Kottke *et al.* 1989).

Nicotine withdrawal contributes to failed smoking cessation. Characterizing how nicotine withdrawal is experienced may facilitate the development of more effective approaches to alleviating discomfort experienced during smoking cessation attempts. The impact of withdrawal on failed cessation appears to be related to both the types of symptoms experienced and their severity. In previous work (Xian *et al.* 2003), we found that 'craving' and 'depressed mood' had the strongest association with failed cessation. Depressed mood and craving have been found to be associated with the shortest time to relapse (Swan *et al.* 1996) and craving cigarettes has been reported to be the most bothersome withdrawal symptom (West *et al.* 1989). Though these studies have presented evidence that some symptoms have a greater impact on cessation, only one study has proposed symptom profiles to characterize nicotine withdrawal in women (Madden *et al.* 1997). Madden and colleagues (1997) used latent class analysis (LCA) to identify four withdrawal profiles ranging from mild to severe. Meaningful associations were found between more severe nicotine withdrawal profiles and psychiatric disorders, earlier onset of smoking, number of years smoked, heavy smoking, unsuccessful quitting and nicotine dependence. Unfortunately, the study by Madden *et al.* (1997) lacked sufficient power to estimate the genetic influence on the latent classes. LCA is a useful technique to uncover the distinct profiles or classes of withdrawal. Because the withdrawal syndrome may take many forms, LCA allows us to describe the syndrome as significantly different classes characterized by severity or qualitative differences or by some combination of the two.

After determining that classes of nicotine withdrawal exist, understanding the etiology of withdrawal can be enhanced by applying behavior genetic modeling to the latent classes. Our current study will perform the LCA analyses using a population of men and determine if genetics influence withdrawal profiles. We will expand the LCA analyses by computing bivariate genetic models of nicotine withdrawal classes and failed smoking cessation.

We have recently reported on a method to create weights for the severity of nicotine withdrawal (Xian *et al.* 2003). This produced a nicotine severity score that accounted for both the number of withdrawal symptoms and the weight of each withdrawal item. Our analyses found that genetic influences accounted for 54% and 29·7% of the variance in risk for failed smoking cessation and nicotine withdrawal, respectively. The correlation between genetic influences was significant ($r = 0{\cdot}31$, 95% CI 0·17–0·45). We also found that the magnitude of the association between failed cessation and nicotine withdrawal varies by symptom.

Our analyses using weights assumed a quantitative characterization of nicotine withdrawal by summing the weighted symptoms and ignoring the structure of the symptom profile. We believe further research using LCA will determine if the withdrawal syndrome differs by severity or by quality while taking into account the structure of the relationship among withdrawal symptoms.

In the present study of 4112 male–male twins from the Vietnam Era Twin (VET) Registry, we utilize LCA to accomplish several objectives. First, we sought to determine if classes of nicotine withdrawal were best characterized by a severity continuum or by qualitatively distinct symptom profiles. Secondly, we used the LCA results to estimate the association between classes of nicotine withdrawal and psychiatric disorders that have been found to increase risk of failed cessation. Thirdly, we used the LCA results to estimate the association between nicotine withdrawal classes and failed cessation. Finally, we sought to measure the magnitude of genetic influences on the latent class profiles and, if a significant genetic influence is present, the degree to which these same genetic factors are common to the risk for failed cessation.

METHOD

Subjects

The VET Registry is a nationally distributed sample consisting of male-male twin pairs in which both twins served in the military during

the Vietnam Era (1965–1975). A complete description of the registry's construction (Eisen *et al*. 1987; Henderson *et al*. 1990) and method of determining zygosity have been previously reported (Eisen *et al*. 1989).

In 1992, twins were invited to participate in a study to collect data on psychiatric disorders, using a computerized telephone version of the Diagnostic Interview Schedule, Version III Revised (DIS-3R; Robins *et al*. 1988). The DIS-3R is a structured interview used to derive psychiatric diagnoses according to the criteria of DSM-III-R (APA, 1987). Interviewing was performed by experienced staff from the Institute for Survey Research (ISR), Temple University, Philadelphia, PA, USA, who were trained in the telephone administration of the DIS-3R by one of the investigators (M.J.L.). Data collection and interviewing quality were monitored by an ISR study director trained by the developers of the DIS at Washington University, St Louis, MO. Before interviewing, twins were sent a letter that explained the purpose of the study and informed them that they would be contacted by a telephone interviewer. The interview was administered only after obtaining the respondent's verbal informed consent. This method of obtaining informed consent received Institutional Review Board approval.

To be eligible for interview in 1992, twins must have had a Department of Defense military record, and identifying and locating information had to be available. Of 10 300 eligible individuals (5150 pairs) from the VET Registry, 8169 (79·3%) were successfully interviewed. The pairwise response rate was 66·1% (3372 pairs). The mean age of respondents was 44·6 years (S.D. $\pm$2·8, range 36–55 years); 90·4% were non-Hispanic white, 4·9% African American, 2·7% Hispanic, 1·3% Native American/Alaskan Native, and 0·7% 'other'; 33·3% were high-school graduates and 38·6% college graduates; 92·6% were employed full-time and 1·8% part-time. For the present paper, pertinent data were available for 4112 twins who were made up of 876 monozygotic (MZ) pairs, 465 MZ singletons, 690 dizygotic (DZ) pairs and 515 DZ singletons.

Cigarette-smoking measures

The 1992 interview included the nicotine dependence section of the DIS-3R from which lifetime regular smokers, past-year failed quitters, successful quitters and symptoms of nicotine withdrawal were obtained. Lifetime regular smoking was defined as having smoked daily for at least one month or more. Among lifetime regular smokers, a quit attempt was defined as ever trying to quit or cut down on smoking or using tobacco. Quit attempts could have occurred at any time prior to interview. Among respondents, 7% of smokers reported never trying to quit. Failed smoking cessation was defined as having ever made a quit attempt and reporting smoking within 12 months preceding the interview. Successful smoking cessation was defined as having made a quit attempt and reporting no smoking for at least 12 months preceding the interview. The time-frame of abstinence over one year is a commonly used criterion for defining successful quitting in studies of smoking cessation (Senore *et al*. 1998; Zhu *et al*. 2000). We have previously reported that alternative definitions of smoking cessation do not result in differences in the association between withdrawal and failed cessation (Xian *et al*. 2003). Specifically, we found no differences in the association with the following definitions:

(1) Any smoking in the month prior to interview was considered failed cessation, and no smoking for at least 1 month prior to interview was defined as successful quitting.

(2) Any smoking in the month prior to interview was considered failed cessation, and successful quitting was defined as no smoking for at least 12 months prior to interview, with removal of subjects who smoked between 11 and 2 months prior to interview.

All subjects who attempted to stop smoking were asked a series of questions to determine if they experienced nicotine withdrawal within 24–48 hours after a quit attempt at any time in their life. The DIS-3R captures the following seven symptoms of nicotine withdrawal according to the DSM-III-R criteria (APA, 1987): 'craving for nicotine', 'anger/irritability', 'anxiety/nervousness', 'restlessness', 'trouble concentrating', 'decreased heart rate' and 'increased appetite or weight gain'. The DIS-3R also queries the following five nicotine withdrawal symptoms specific to the DIS: 'headache', 'drowsy', 'nausea', 'hands shake' and 'depressed'.

Data analysis: latent class analyses

LCA (McCutcheon, 1987) is a statistical model-fitting method that can be used to investigate an observed association among a set of categorical items or variables. It is based on the assumption that the frequencies with which different symptom profiles occur can be explained by the existence of a small number of mutually exclusive classes (M) with each class having a distinctive profile of item endorsement probabilities that is constant for all members of that particular class. A critical implication of this assumption is that, under an M-class solution, the conditional probabilities of endorsing a set of items are statistically independent within a given latent class. While factor analysis assumes continuously distributed latent variables, LCA may be understood as a categorical form of factor analysis. For a given latent class model, the parameter estimates are class membership probabilities, which may be thought of as prevalence, and symptom endorsement probabilities (SEPs), that reflect the likelihood that a symptom is endorsed by an individual, given membership in that class. The Bayesian Information Criterion (BIC) was used as an index of goodness-of-fit (Schwartz, 1978; Li & Nyholt, 2001). The null hypothesis is a 1-class solution: that is, all individuals belong to the same latent class. The BIC allows rejection of the null hypothesis by comparing models with two or more parameters to the 1-class solution. The null hypothesis is rejected if models with more parameters provide a better fit than the 1-class solution. More complex models may be compared to each other by examining the BIC value. The best-fitting model may be selected by the smallest BIC value and the difference in BIC values.

The Latent Class Analysis Program (LCAP; Neuman *et al*. 1999) was used to fit latent class models to the nine DSM-III-R nicotine withdrawal symptoms using the method of maximum likelihood. Latent class models consist of class membership probabilities and item endorsement probabilities. Class membership is based on an individual's symptom profile (i.e. pattern of symptom endorsement). Individuals with the same symptom pattern are assigned to the same class. Item endorsement probabilities, which are similar to factor loadings in factor analysis, reflect the likelihood that an item is endorsed given membership of that class.

As described in detail in the Results section below, the best-fitting LCA model was a four-class solution. Following resolution of a latent class solution we computed separate logistic regressions to obtain the unadjusted odds ratios to evaluate the association of the independent nicotine withdrawal classes with failed smoking cessation, smoking behaviors and psychiatric disorders. Using the four-class solution, we created three dummy variables for the ordinal four-level nicotine withdrawal variable (four latent classes) with class 1 as a common reference. *Post hoc* tests were used to test if odds ratios were significantly different for class 2 *versus* class 1 as compared with class 3 *versus* class 1 as compared with class 4 *versus* class 1. Analyses used STATA software to adjust for the non-independence of twin pair data (StataCorp, 1997) by computation of the Huber–White robust variance estimator.

Univariate genetic model-fitting

The genetic modeling approach holds that additive genetic effects (denoted 'A'), shared family environmental (denoted 'C'), and unique environmental effects (denoted 'E') account for the variance in a trait such as nicotine withdrawal. Additive genetic influences are correlated 100% between members of an MZ twin pair and 50% between members of a DZ twin pair. Shared environmental influences are the effects from events experienced equally by twins reared in the same family environment and are assumed to contribute to similarity equally in MZ and DZ twin pairs. Finally, unique environmental influences, which include measurement error, are non-shared experiences that contribute to differences within MZ and DZ twin pairs. Univariate genetic models were fit to the raw data for both the four-class nicotine withdrawal and the failed smoking cessation phenotype. Univariate models estimated the proportion of phenotypic variance due to additive genetic (annotated A), shared family environmental (annotated C) and unique environmental factors (annotated E) that contributed to the ordinal, four-level nicotine withdrawal phenotype. The best-fitting, most parsimonious model, was determined by the difference between -2 log-likelihood values of the reduced as compared

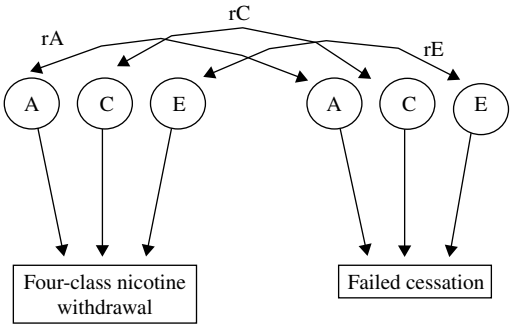

FIG. 1. Path diagram of full general bivariate model for ordinal four-level nicotine withdrawal phenotype and failed smoking cessation.

with the full model. If a model could be reduced without a significant decrease in goodness of fit, it was selected as best fitting the data.

Bivariate genetic model-fitting

We fit a general bivariate model to the data as shown in Fig. 1. Bivariate analyses compared the fit of the full model (ACE) to that of reduced models, which removed one or more genetic (A) or environmental C or E) parameters that could contribute to the risk of the four-class nicotine withdrawal phenotype and to the risk of failed smoking cessation phenotype. The best-fitting bivariate model is selected based on -2 log-likelihood value. The most parsimonious model is chosen as best fitting if the difference in -2 loglikelihood values between a reduced model and the full model does not produce a significant decrease in goodness of fit. MX software (Neale, 1991) was used for genetic modeling.

RESULTS

Latent class model-fitting results are shown in Table 1. The best-fitting model was a four-class solution. This model could be selected by determining the BIC with the greatest reduction in value from the 1-class solution (ΔBIC = $-6203{\cdot}00$). The endorsement probabilities for nicotine withdrawal symptoms are shown in Fig. 2, which clearly shows that classes differ by severity. There is no evidence for qualitative differences for the latent class solution. Class 1 is the least severe and is characterized by craving and increase in appetite or weight gain and by very low endorsement of anger and irritability, anxiety, restless and decreased heart rate. Class 2

Table 1. *Model-fitting results from latent class analyses of nicotine withdrawal data in 4112 members of the Vietnam Era Twin Registry*

Model	-2 loglikelihood	BIC*	ΔBIC
One-class	47268·30	47368·16	0
Two-class	41853·14	42061·18	$-5306{\cdot}98$
Three-class	40923·76	41239·92	$-6128{\cdot}24$
Four-class	**40740·77**	**41165·17**	**$-6203{\cdot}00$**
Five-class	40651·52	41184·10	$-6184{\cdot}06$
Six-class	40604·97	41245·74	$-6122{\cdot}42$
Seven-class	40569·57	41318·53	$-6049{\cdot}63$

* BIC, Bayesian Information Criterion.
Bold represents best-fitting model.

has higher SEPs for craving and increase in appetite or weight gain (craving SEP = 0·858; appetite or weight gain SEP = 0·619). Class 2 is distinguished from class 1 by the larger SEP values for the symptoms of anger and irritability, anxiety and restlessness (SEP = 0·454, 0·522 and 0·645, respectively). Class 3 and the most severe class 4 are similar in terms of SEPs which are more severe than class 1 or 2 for symptoms of craving (class 3: SEP = 0·994; class 4: SEP = 0·946), anger (class 3: SEP = 0·836; class 4: SEP = 0·946), anxiety (class 3: SEP = 0·869; class 4: SEP = 0·935), restlessness (class 3: SEP = 0·992; class 4: SEP = 0·898) and trouble concentrating (class 3: SEP = 0·697; class 4: SEP = 0·765). Classes 3 and 4 are similar to class 2 for the symptom of increased appetite. Class 4 is distinguished from Class 3 by larger SEP values for the symptoms of headache, drowsiness, nausea and depression (SEP = 0·371, 0·292, 0·287 and 0·658, respectively). The number of subjects in classes 1, 2, 3 and 4 was 1026 (24·9%), 1830 (44·5%), 752 (18·3%) and 504 (12·3%), respectively.

Results of univariate logistic regression analyses are shown in Table 2, in which nicotine withdrawal class 1 is compared with withdrawal classes 2, 3 and 4. All of the associations between nicotine withdrawal classes and each smoking variable are significant. Consistent with each nicotine withdrawal class representing a level of nicotine withdrawal severity, the magnitude of association increases from class 2 through class 4. *Post hoc* comparisons between odds ratios found, with the exception of failed cessation and wanting to quit, that the odds ratios for all smoking variables by class were significantly different from one another ($p < 0{\cdot}05$).

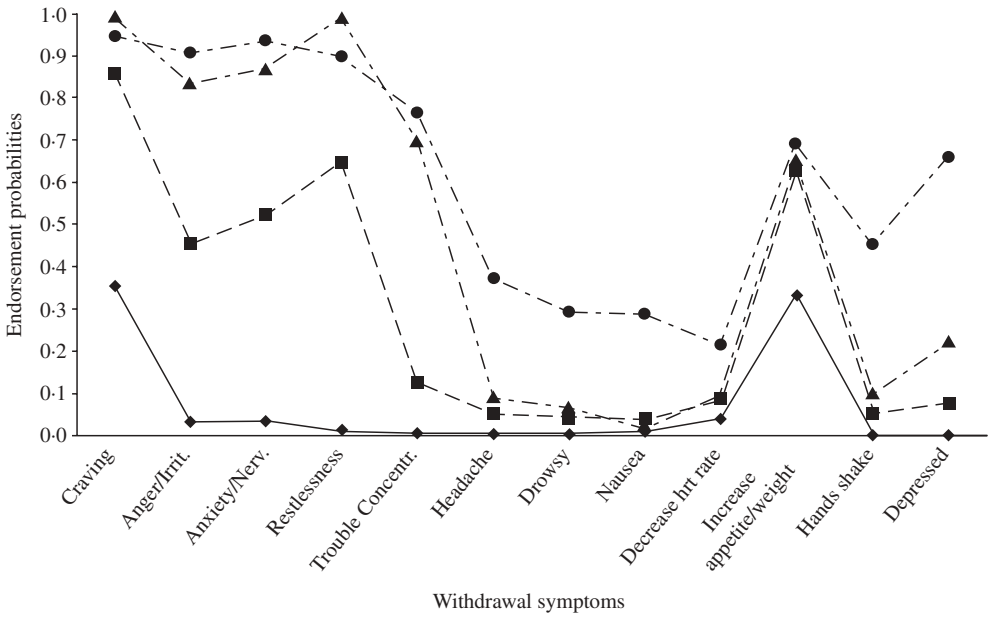

FIG. 2. Nicotine withdrawal symptom endorsement probabilities under best-fitting four-class solution. —◆—, Class 1; – –■– –, class 2; - –●- –, class 3; - –▲- –, class 4.

Associations between psychiatric disorders and nicotine withdrawal classes were all significant ($p<0{\cdot}05$) with the following exceptions: dysthymia and mania were significantly associated only with class 4, and panic disorder and generalized anxiety disorder were significantly associated only with classes 3 and 4. As observed for smoking behaviors, the magnitude of the association between psychiatric disorders and nicotine withdrawal increased with class severity. This increase was confirmed by *post hoc* tests which revealed that odds ratios were significantly different from one another ($p<0{\cdot}05$) for alcohol dependence, illicit drug dependence, major depression, generalized anxiety disorder and post-traumatic stress disorder.

We computed the mean number of cigarettes smoked during subjects' heaviest smoking period. Subjects in nicotine withdrawal classes 4, 3, 2 and 1 smoked a mean of 35·8 (S.D. = 19·9), 32·7 (S.D. = 14·2), 29·9 (S.D. = 15·4) and 24·7 (S.D. = 16·4) cigarettes per day, respectively. The amount smoked was significantly different across classes ($F=71{\cdot}16$, 3 df, $p<0{\cdot}001$) and the mean smoked was significantly different between each class (class 4 > class 3 > class 2 > class 1; $p<0{\cdot}05$).

The most parsimonious solution for univariate model-fitting results allowed for additive genetic and unique environmental influences (AE model), and the AE model was not significantly worse-fitting than the full (ACE) model (difference in −2 loglikelihood = 0, approximates χ^2, 1 df, $p>0{\cdot}10$). A model that did not allow for additive genetic influences (CE) produced a significantly worse fit and was rejected (difference in −2 loglikelihood = 11·39, approximates χ^2, 1 df, $p<0{\cdot}05$). Under the full model, additive genetic effects accounted for 31·3% (95% CI 15·4–37·7%) of the variance in the four-class nicotine withdrawal phenotype. Family environmental influences accounted for 0·0% (95% CI 0–13·0%), and unique environmental influences accounted for the remaining 68·7% (95% CI 62·3–68·7%) of variance.

Bivariate model-fitting results are shown in Table 3. Models that constrained additive genetic correlation to 1·0 or to 0·0 produced significantly worse fits to the data as compared with the full model (difference in −2 loglikelihood = 26·19, approximates χ^2, 1 df, $p<0{\cdot}05$ and difference in −2 loglikelihood = 53·14, approximates χ^2, 1 df, $p<0{\cdot}05$). Constraining the unique environmental correlation to zero

Table 2. *Association* [*odds ratio* (*95% confidence interval*)] *between smoking behaviors, DSM-III-R psychiatric disorders and nicotine withdrawal classes among 4112 members of the Vietnam Era Twin Registry*

	Withdrawal		
	Class 2 *v.* 1	Class 3 *v.* 1	Class 4 *v.* 1
Smoking behaviors			
Failed cessation	**2·16 (1·84–2·53)** A*	**2·37 (1·94–2·89)** A	**3·15 (2·51–3·96)** B
Wanted to quit	**2·91 (2·23–3·79)** A	**5·15 (3·32–8·01)** B	**6·97 (3·82–12·69)** B
Unable to quit or cut down	**2·10 (1·77–2·51)** A	**2·55 (2·07–3·14)** B	**3·43 (2·73–4·31)** C
Cut down ⩾1 time	**2·39 (2·04–2·80)** A	**4·17 (3·35–5·18)** B	**6·09 (4·61–8·04)** C
Hard to quit	**3·69 (2·71–5·03)** A	**9·60 (5·14–17·93)** B	**11·83 (5·17–27·07)** B
Nicotine dependence	**4·55 (3·86–5·37)** A	**27·77 (19·53–39·49)** B	**43·83 (26·15–73·48)** B
Psychiatric disorders			
Alcohol dependence	**1·52 (1·29–1·79)** A	**2·12 (1·73–2·58)** B	**2·82 (2·52–3·52)** C
Illicit drug dependence†	**1·97 (1·48–2·63)** A	**2·67 (1·93–3·69)** B	**4·36 (3·14–6·06)** C
Major depression	**1·45 (1·06–1·97)** A	**2·67 (1·91–3·72)** B	**5·70 (4·09–7·93)** C
Dysthymia	0·95 (0·56–1·59) A	1·13 (0·61–2·08) A	**3·44 (2·04–5·80)** B
Mania	1·69 (0·54–5·24) A	2·05 (0·58–7·30) A	**5·16 (1·61–16·52)** B
Panic disorder	1·83 (0·82–4·07) A	**2·59 (1·09–6·15)** A	**8·62 (3·92–18·94)** B
Generalized anxiety disorder	1·31 (0·71–2·42) A	**2·31 (1·21–4·42)** B	**4·57 (2·46–8·49)** C
Post-traumatic stress disorder	**1·74 (1·29–2·35)** A	**2·59 (1·86–3·61)** B	**5·23 (3·76–7·26)** C
Antisocial personality disorder	**1·81 (1·14–2·88)** A	**1·75 (1·01–3·01)** A	**3·16 (1·83–5·40)** B

Bold indicates significant odds ratio.
* Odds ratios that do not share letters (A, B, C) are significantly different: $p<0·05$.
† Lifetime dependence on any combination of the following: cannabis, amphetamines, cocaine, sedatives, hallucinogens.

produced a significantly worse fit to the data as compared with the full model (difference in -2 loglikelihood = 11·12, approximates χ^2, 1 df, $p<0·05$). Fixing the shared environmental correlation to zero produced the most parsimonious solution without a significant decrease in goodness of fit (difference in -2 loglikelihood = 0·0, approximates χ^2, 3 df, $p>0·10$). The best-fitting model allowed for correlated additive genetic influences to the four-class nicotine withdrawal phenotype and failed cessation. This model also allowed for a correlated unique environmental contribution to both phenotypes.

Under the best-fitting model, we found that genetics accounted for 31·0% (95% CI 24·3–32·7%) of the variance in risk for the withdrawal phenotype and 50·6% (95% CI 42·8–57·5%) of the variance in failed cessation. The correlation between these genetic influences was 0·37 (95% CI 0·23–0·50). For this model, the unique environment explained 69·0% (95% CI 63·1–75·7%) of the variance in withdrawal and 49·4% (95% CI 42·1–57·2) of the variance in failed cessation. The correlation between these unique environmental influences was 0·15 (95% CI 0·06–0·24).

DISCUSSION

In a sample of 4112 middle-aged male twin pairs, we found that the best model for nicotine withdrawal consisted of four subtypes characterized by increasing severity. There was no evidence for qualitative differences among the

Table 3. *Bivariate model-fitting results for four-class nicotine withdrawal and failed smoking cessation for 4112 male–male twin pairs from the Vietnam Era Twin Registry*

Bivariate model*		Correlation			Fit of model: parsimony		
Four-class nicotine withdrawal	Failed cessation	Genetic correlation	Shared environmental correlation	Unique environmental correlation	Δ df	−2 loglikelihood	Δ −2 loglikelihood
ACE	ACE	0·37	0·05	0·15	—	16069·832	—
ACE	ACE	**a**	0·05	0·31	1	16096·018	26·19
ACE	ACE	b	0·05	0·00	1	16122·971	53·14
ACE	ACE	0·37	**a**	0·15	1	16069·832	0·00
ACE	ACE	0·37	b	0·15	1	16069·832	0·00
ACE	ACE	0·52	0·05	**a**	1	16080·952	11·12
AE	**AE**	**0·37**	**a**	**0·15**	**3**	**16069·832**	**0·00**
AE	AE	a	a	0·31	4	16096·018	26·17
AE	E	b	a	0·00	4	16122·971	53·14
AE	AE	0·52	a	a	4	16080·952	11·12

Best-fitting model in bold type.
* A indicates additive genetic factors, C indicates shared environmental factors, E indicates unique environmental factors.
a, correlation fixed to zero; b, correlation fixed to 1.

four classes. This result in men is similar to that found by Madden and colleagues' (1997) analyses of 571 middle-aged women (mean age 39 years) from an Australian twin register. Both studies found a four-class severity continuum best described the classes of nicotine withdrawal; both found that 'craving' was the most commonly endorsed symptom and both found high symptom endorsement of irritability and restlessness to be characteristic of the two most severe withdrawal classes. Thus the withdrawal phenotype may be refined by the addition of a severity component.

We found that amount smoked, failed cessation, wanting and being unable to quit, attempting to cut down more than once, finding it hard to quit and nicotine dependence were all significantly associated with severity of withdrawal class. The magnitude of this association increased with more severe withdrawal classes and for most variables this was confirmed by significantly larger odds ratios. These results are consistent with the concept that continuance of smoking may relate to the severity of nicotine dependence and withdrawal symptoms experienced. Evidence from animal studies suggests that nicotine withdrawal results in significant decreases in brain reward function, which is a potential explanation for the physiological basis of smoking relapse (Epping-Jordan *et al.* 1998). In studies with humans, withdrawal symptoms have been identified as a predictor of relapse from smoking cessation (Swan *et al.* 1996; Shiffman *et al.* 1997).

The most severe withdrawal class, compared with the least severe withdrawal class, was significantly associated with alcohol and illicit drug dependence, major depression, dysthymia, mania, panic disorder, generalized anxiety disorder, post traumatic stress disorder and antisocial personality disorder. A decrease in the magnitude of the association between withdrawal and psychiatric disorders was observed when comparing class 3 with class 1 and when comparing class 2 with class 1. Again, these results are quite consistent with Madden and colleagues' LCA findings in a female sample (Madden *et al.* 1997). The fact that the magnitude of the association between having a lifetime diagnosis of a psychiatric disorder increases with latent class severity is consistent with numerous studies of withdrawal and mental illness which have demonstrated that subjects with a history of psychiatric disorders experience more severe nicotine withdrawal (Breslau *et al.* 1992; Bergen & Caporaso, 1999).

Under the full univariate model we found that genes accounted for 31% and unique environmental influences accounted for 69% of the variance in the four-class nicotine withdrawal phenotype. The best bivariate model of nicotine withdrawal and failed cessation allowed for genetic (31%) and unique environmental (69%) variance in risk for nicotine withdrawal and for

genetic (37%) and unique environmental (49%) variance in risk for failed cessation. The genetic influences to these two disorders were significantly correlated ($r = 0{\cdot}37$). As expected, these modeling results are similar to those obtained when we conducted a bivariate analysis between failed cessation and a nicotine withdrawal phenotype that accounted for severity and number of symptoms (Xian *et al.* 2003). In this previous work we found that genetics explained 30% and 54% of the variance in withdrawal and failed cessation, respectively. Our previous work also found a genetic correlation of 0·31 between the phenotypes. Our estimate of 51% for the genetic contribution to failed cessation is less than the range of 58–74% reported for the genetic influence to smoking persistence (Heath & Madden, 1995; True *et al.* 1997), and it is less than Li and colleagues' (2003) meta-analyses which found a 59% genetic influence to persistence. Lastly, our estimate is much less than the 70% genetic variance due to the transition to nicotine dependence (Sullivan & Kendler, 1999). The smaller magnitude in variance owing to genetics may be partly due to our controlling, by design, for all familial factors that partly overlap with the risk of smoking initiation (True *et al.* 1997). In addition, as described by Heath and Madden (1995), the genetic estimates for smoking persistence are at the low end when twin pairs in whom one twin never smoked are excluded from analyses, as has been done in the present research. However, our findings are within the confidence intervals reported in a multicultural study which found that the genetic variance specific to persistent smoking in men aged 36–46 years of age was 42% (95% CI 24–51%) (Madden *et al.* 1999).

Our results should be interpreted in the light of potential limitations. Because the VET Registry is all male, we cannot generalize the genetic model-fitting results to females for whom there is evidence of varying genetic effects associated with smoking (Li *et al.* 2003). Minorities are under-represented among respondents, therefore these results should be applied with caution to non-whites. The retrospective nature of data collection might have introduced recall bias. These results do not necessarily generalize to all smokers from the Registry, because we selected only twin pairs where both smoked and both attempted to quit. Finally, nicotine withdrawal is limited to symptoms experienced after attempting to quit smoking cigarettes. Results may differ for other forms of tobacco consumption.

There are a number of strengths to consider. First, our LCA results are consistent with Madden and colleagues' (1997) findings from a female cohort. Secondly, data were collected from a non-clinical sample assembled without prior knowledge of respondents' lifetime smoking status. We used standardized data collection methods and structured interviews to derive nicotine withdrawal symptoms according to DSM-III-R criteria. Lastly, the large sample size and the national distribution of participants enhances generalizability.

CONCLUSIONS

In this sample of middle-aged men, nicotine withdrawal classes represented a severity continuum. More severe classes as compared with less severe classes were more strongly associated with nicotine dependence, difficulty quitting and failed cessation, and a greater magnitude of association with psychiatric disorders. In addition, the genetic contributions to the classes of nicotine withdrawal and failed cessation were correlated.

The similarities in results among the present study, Madden and colleagues' (1997) LCA in women, and our previously published factor analytic approach to nicotine withdrawal (Xian *et al.* 2003) provide a strong basis for considering a refinement of the DSM diagnoses for withdrawal that would include severity. Adding a severity dimension might help determine the level of risk for co-morbid psychiatric disorder and difficulty in quitting among patients experiencing withdrawal. Finally, the utility of phenotyping is well demonstrated in these collective works. Finding similar genetic influences across varying phenotypes of withdrawal and across populations allows us to conclude that genetics account for approximately one-third of the risk in withdrawal and that these additive genetic effects are correlated with those that contribute to failed cessation.

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DECLARATION OF INTEREST

None.

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