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# Nicotine Withdrawal Symptoms in Adolescent and Adult Twins

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We examined the variation and heritability of DSM-IV nicotine withdrawal (NW) in adult and adolescent male and female twin cigarette smokers (who reported smoking 100 or more cigarettes lifetime). Telephone diagnostic interviews were completed with 3,112 Australian adult male and female smokers (53% women; age: 24–36) and 702 Missouri adolescent male and female smokers (59% girls; age: 15–21). No gender or cohort differences emerged in rates of meeting criteria for NW (44%). Latent class analyses found that NW symptoms were best conceptualized as a severity continuum (three levels in adults and two levels in adolescents). Across all groups, increasing NW severity was associated with difficulty quitting, impairment following cessation, heavy smoking, depression, anxiety, conduct disorder and problems with alcohol use. NW was also associated with seeking smoking cessation treatment and with smoking persistence in adults. The latent class structure of NW was equally heritable across adult and adolescent smokers with additive genetic influences accounting for 49% of the variance and the remaining 51% of variance accounted for by unique environmental influences. Overall, findings suggest remarkable similarity in the pattern and heritability of NW across adult and adolescent smokers, and highlight the important role of NW in psychiatric comorbidity and the process of smoking cessation across both age groups.

**Keywords:** nicotine withdrawal, adolescents, adults, twins

The nicotine withdrawal syndrome is listed in the DSM-IV as a psychiatric disorder (American Psychiatric Association, 1994). While the course of most symptoms of nicotine withdrawal is presumed to be short and transient (American Psychiatric Association, 1994; Hughes, 2007b; Shiffman et al., 2006), even within this time frame for many individuals nicotine abstinence evokes a level of dysphoria commonly associated with clinical impairment (Hughes, 2006). A cycle of chronic nicotine dependence can be established soon after starting to smoke (DiFranza et al., 2007), which can entail numerous attempts to quit smoking (Prochaska et al., 1992), and bouts of nicotine withdrawal associated with

chronic relapse to cigarette smoking (Hughes, 2007a; Piasecki et al., 1998; Shiffman et al., 1997). There is evidence of nicotine withdrawal symptoms in both adult (Hughes, 1992) and adolescent samples of self-quitters (Prokhorov et al., 2001), and in controlled experimental studies of nicotine abstinence in adults (Gilbert et al., 1998; Gilbert et al., 2002) and adolescents (Killen et al., 2001). In clinic samples of adults seeking to quit smoking, nicotine withdrawal symptoms have been associated with relapse to smoking (Hughes, 2007a; Piasecki et al., 1998; Shiffman et al., 1997; Shiffman et al., 1976).

While recent reviews confirm the validity of particular symptoms associated with nicotine abstinence, particularly DSM-IV nicotine withdrawal symptoms (Hughes, 2007a; Hughes, 2007b; Hughes, 2007c; Shiffman et al., 2004) the predominate method of examining the symptoms of nicotine withdrawal symptoms has been to explore the factor structure or mean change in symptoms across time. While these main effects provide important information for construct validation of nicotine withdrawal symptoms, this standard approach is ‘variable-centric’ rather than ‘individual-centric’; the latter approach aims to identify subgroups of smokers that are more likely to experience particular symptoms of nicotine withdrawal. In addition, many studies to date have relied heavily on volunteer and clinical samples with few (like Breslau et al., 1992) estimates of nicotine withdrawal based on large general population samples, which can provide additional power to examine subgroups of individuals for whom particular symptoms of nicotine withdrawal co-occur.

Some previous reports that have conducted latent class or cluster modeling of nicotine withdrawal symptoms include the following: Madden et al. (1997) used latent class analysis to examine the psychometric structure of lifetime nicotine withdrawal in a survey of a cohort of adult female twins (age 32–48). Three nicotine

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withdrawal severity classes emerged with higher severity more strongly associated with more severe smoking behaviors, more psychiatric comorbidity (major depression, alcohol dependence, conduct disorder, and anxiety disorders), and increased neuroticism. Xian et al. (2005), using latent class analysis, found a similar pattern of nicotine withdrawal severity in middle-aged (age 36–55) male twins from the Vietnam Era Twin Registry. Piasecki et al. (1998; 2000) conducted cluster analyses using nicotine withdrawal reports from adults in smoking cessation clinical trials and in unaided quitters and found that specific symptom profiles, particularly those characterized by negative affect, were associated with relapse to smoking across time. Less work has reported on the clustering of nicotine withdrawal symptoms in adolescent smokers, and to our knowledge, no single study has compared the pattern of nicotine withdrawal symptoms across population-based samples of adolescents and adults.

Likewise, the heritability of nicotine withdrawal has not been compared across adult and adolescent smokers. While in adult samples, it has been shown that up to 53% of the variation in nicotine withdrawal symptoms can be accounted for by genetic factors, and significant genetic influences remain even after accounting for starting to smoke and quantity smoked (Pergadia et al., 2006b) and early social influences (Pergadia et al., 2006a), no reports to date have examined genetic influences on nicotine withdrawal in adolescent smokers. Although refining the phenotype and establishing heritability of nicotine withdrawal may help to inform the recent surge in gene-mapping projects involving smoking-related behaviors (e.g., Saccone et al., 2007a; Saccone et al., 2007b), including nicotine withdrawal (Pergadia et al., 2009).

In this article, we compare the pattern of nicotine withdrawal symptoms and heritability estimates across adolescent and adult smokers from population-based epidemiologic twin samples, and test for differential associations between nicotine withdrawal and difficulty quitting, cigarette smoking persistence, seeking cessation treatment, and impairment due to withdrawal. We also examine associations with measures of psychopathology. Our research questions include the following: (1) Do patterns of nicotine withdrawal symptoms differ across adult and adolescent male and female twins? (2) Are associations between cigarette use behaviors (e.g., difficulty quitting, smoking persistence, seeking cessation treatment) and nicotine withdrawal consistent across adult and adolescent male and female smokers? (3) Are associations between psychopathology (e.g., major depression) and nicotine withdrawal symptoms consistent across adult and adolescent male and female smokers? (4) Does heritability of nicotine withdrawal differ across these adult and adolescent twins?

## Method

### Participants

Male and female (Heath et al., 1999; Heath et al., 2002) same-sex adolescent twins were ascertained

from Missouri state birth records for three population-based studies: a study of female like-sex twin pairs born 1975–1986 (ages 12–23 at the time of first interview, mean age = 15.5): ‘MOAFTS’; and two coordinated studies of male like-sex twin pairs born 1977–1992 (aged 11–23 at the time of interview; mean age = 15.5): ‘BOYNIC’ and the ‘MARC’/Project 1. Once families were identified from birth records and traced, a parent and both twins were invited to complete a telephone diagnostic interview. Participants ( $N = 3446$  female twins and  $N = 2748$  male twins) were interviewed by telephone using a structured diagnostic assessment for DSM-IV (American Psychiatric Association, 1994) nicotine dependence, alcohol dependence, major depression, childhood conduct disorder, social anxiety, and a detailed history of consumption of alcohol and cigarettes. The interview was a modified version of the Semi-Structured Assessment on the Genetics of Alcoholism (Bucholz et al., 1994) and the smoking section was modified from the Composite International Diagnostic Interview (Cottler et al., 1991). Analyses reported here included twins aged 15–21 at the time of the telephone diagnostic interview ( $N = 1953$  female twins and  $N = 1324$  male twins) for whom we had adequate information on nicotine withdrawal in smokers (defined here as smoking 100 or more cigarettes lifetime). From this pool, 21.4% ( $N = 417$ , mean age = 17.8, standard deviation ( $SD$ ) = 1.6) of girls and 21.5% ( $N = 285$ , mean age = 18.9,  $SD = 1.7$ ) of boys reported smoking 100 or more cigarettes lifetime and a 24-hour period of quitting or cutting down on cigarettes, and were queried about the experience of nicotine withdrawal symptoms during this time. Over 90% of the boys (91.0%) and girls (92.7%) who reported smoking 100 or more cigarettes lifetime reported smoking daily for three weeks or more. Nicotine withdrawal was also assessed in some of the adolescents who smoked 20–99 cigarettes lifetime ( $N \sim 200$ ), but because this threshold of smoking was not comparable to our adult population (see below), we did not include these individuals in the analyses.

We also analyzed data from the 1989 Australian Adult Twin Cohort (Heath et al., 2001; Knopik et al., 2004; Lesov et al., 2004) — male and female twins born 1964–1971 (aged 24–36 at the time of interview; mean age = 29.9) from the population-based Australian twin panel maintained by the Australian National Health and Medical Research Council. These twins were volunteered by their parents in response to media appeals and appeals through the Australian school system in 1980–1982. From 1996–2000, participants were interviewed by telephone using a structured diagnostic assessment similar to that described above for the Missouri adolescent twins. Telephone interview data were available from a total of 6257 individual twins (3454 women and 2803 men). Of relevance to this study, twins who reported smoking 100 or more cigarettes lifetime were asked

detailed questions about nicotine withdrawal after they quit or cut down on their smoking. Approximately 47.8% ( $N = 1651$ ; mean age = 30.0,  $SD = 2.5$ ) of women and 52.1% ( $N = 1461$ ; mean age = 30.1,  $SD = 2.5$ ) of men reporting smoking and a 24-hour period of quitting or cutting down on cigarettes and thus had information on nicotine withdrawal. Approximately 94.6% of adult women and men who reported smoking 100 or more cigarette lifetime reported smoking daily for three weeks or more.

#### Measures

**Lifetime nicotine withdrawal.** Smokers were asked about problems they had after they stopped or cut down or when they were unable to smoke cigarettes. Individual DSM-IV nicotine withdrawal symptoms were considered, in addition to the binary form of DSM-IV substance dependence criteria for nicotine withdrawal: (1) Participants were queried as to whether they experienced *each* of the 8 DSM-IV nicotine withdrawal symptoms: irritable or angry, nervous, restless, trouble concentrating, decreased heart rate, increased appetite, feel down or depressed, and trouble sleeping; (2) DSM-IV substance dependence criteria for nicotine withdrawal were met if individuals endorsed 4 or more of the symptoms, or if the individual reported smoking cigarettes to relieve or avoid withdrawal symptoms.

**Other lifetime cigarette smoking measures.** (1) Difficulty quitting smoking: more than one unsuccessful attempt to stop or cut down on smoking; (2) Smoking persistence: any smoking within the last month; (3) Smoking cessation treatment: sought treatment in the form of nicotine replacement therapy, individual or group smoking cessation counseling, or some other form of treatment to quit smoking (not measured in the girls); (4) Nicotine withdrawal-related impairment: one or more of the DSM-IV nicotine withdrawal symptoms caused difficulty at work, at home, with friends or family or interfered with life in some way; (5) Heavy smoking: smoking 20 or more cigarettes per day at peak lifetime use; (6) Heaviness of Smoking Index (HSI; Heatherton et al., 1989; Heatherton et al., 1991): scores ranging from 0–6 on, which includes average number of cigarettes smoked per day and time to first cigarette at peak lifetime use.

**Lifetime measures of psychopathology.** (1) DSM-IV major depression; (2) social anxiety (nondiagnostic) — unreasonably strong social fear, in which the individual is afraid of doing something embarrassing or humiliating, or that others would see how anxious they are; (3) DSM-IV conduct disorder: (three or more DSM-IV childhood conduct disorder symptoms (without time clustering); (4) alcohol problems (nondiagnostic) — two or more DSM-IV alcohol dependence symptoms in the girls and boys or DSM-IV alcohol dependence in the women and men; (5) DSM-IV attention deficit hyperactivity disorder (ADHD) — any subtype: inattentive, hyperactive or combined.

ADHD was available in the girls and boys through maternal reports, but not available in the adults. All of these measures are commonly correlated with smoking-related behavior (e.g., Madden et al., 1997; Xian et al., 2005; Breslau et al., 1992; Kollins et al., 2005) and represent a range of associated behaviors, from other substance-related, internalizing and externalizing disorders.

#### Statistical Approach

Prevalence rates were estimated in SAS (SAS Institute, 1999) and compared across gender and age cohorts using Stata (Stata Corp, 2003). Latent class analysis, a categorical variant of factor analysis, was performed in MPlus (version 3; Muthen et al., 2004). The maximum likelihood sandwich estimator (MLR) was used to adjust standard errors for clustering of twin data. Therefore, latent class models were fit while simultaneously accounting for the correlations between twin pairs. Additionally, cigarette smokers who were missing responses to certain withdrawal symptoms (e.g., decreased heart rate) were retained in the latent class analyses. Therefore, instead of allowing a listwise deletion to exclude any individual with a missing value for a withdrawal symptom, we used the ANALYSIS = MISSING option for missing data estimation. The Bayesian Information Criterion (BIC) was used to assess model-fit. Logistic and multinomial logistic regression analyses across gender and cohorts examined which factors predicted nicotine withdrawal class assignment in smokers. Analyses were conducted in Stata (Stata Corp, 2003), using the Huber-White Robust Variance Estimator to correct for the non-independence of measures in twins. Variables considered included: difficulty quitting, smoking persistence, seeking cessation treatment, impairment due to nicotine withdrawal, heavy smoking, HSI, major depression, social anxiety, conduct disorder, alcohol problems (dependence in the adults), and ADHD (in the adolescents only).

For heritability analyses, we used twin pairs with complete data on the latent measure of nicotine withdrawal: adult monozygotic (MZ) pairs = 416, adult dizygotic (DZ) pairs = 318, adolescent MZ pairs = 92, adolescent DZ pairs = 62. First, tetrachoric and polychoric correlations for the categorical measures were estimated using Mx (Neale et al., 2002). Second, univariate genetic models (Eaves et al., 1978; Neale et al., 2002) were fitted for the categorical measure by the method of maximum likelihood using the program Mx (Neale et al., 2002). We estimated the proportion of the total variance in nicotine withdrawal that could be explained by additive genetic factors (A), environmental influences shared by members of a twin pair (C), and nonshared environmental influences (E). When shared environmental influences were estimated at zero, or in the case were MZ pairs correlation were more than twice as high as DZ twin correlations, non-additive genetic influences (D) were estimated. Non-additive genetic effects and shared environmental

effects are confounded in twins reared together, respectively leading to DZ twin correlations less than one half the MZ correlations, and inflation of the DZ correlation to be greater than one half the MZ correlations (Martin et al., 1978). As such, non-additive genetic effects and shared environmental effects could not be included in the same models. Univariate threshold models were fitted to 2 × 2 or 3 × 3 contingency tables for the nicotine withdrawal measures. Likelihood-based 95 percent confidence intervals were computed for estimates of genetic and environmental parameters (Neale et al., 2002). The full ACE or ADE models were estimated first and compared against reduced models by likelihood-ratio chi-square, to determine the best-fitting model.

**Results**

Table 1 shows the prevalence rates for DSM-IV nicotine withdrawal measures for female and male adult (Women and Men) and adolescent (Girls and Boys) cigarette smokers. Overall, no gender or cohort difference emerged in rates of meeting criteria for nicotine withdrawal using the DSM-IV substance dependence criteria, or in reports of concentration problems, or decreased heart rate. Age effects: the adults reported significantly higher rates of withdrawal-related restlessness compared to adolescent smokers, while adolescent smokers reported significantly greater levels of withdrawal-related nervousness compared to adult smokers. Gender effects: female smokers were more likely to report withdrawal-related depressed

mood compared to male smokers. Age by gender effects: adolescent girls reported significantly higher levels of withdrawal-related irritability compared to all other groups. Rates of irritability were elevated across the entire age-range of adolescent girls (15–21) ranging from 52.3% in 19-year-old girls up to 67.4% in 16-year-old girls. Adolescent boys were significantly less likely to report increased appetite compared to all other groups and to report higher rates of sleep problems compared to adult female smokers.

The best-fitting latent class solutions for the eight DSM-IV nicotine withdrawal symptoms are depicted in Figure 1, along with standard error bars for the probability of item endorsement within each class. The BIC indices for each group are included below (with the best-fitting solution in bold type):

- Women: 1) 14,705 (1 class), 13,132 (2 classes), 13,031 (3 classes), 13,069 (4 classes)
- Men: 1) 12,720 (1 class), 11,672 (2 classes), 11,563 (3 classes), and 11,598 (4 classes)
- Girls: 1) 3,923 (1 class), 3,668 (2 classes), and 3,688 (3 classes)
- Boys: 1) 2,688 (1 class), 2,359 (2 classes), and 2,367 (3 classes).

Analyses indicated the best-fitting solution for women and men were three-class solutions, while the best-fitting solutions for girls and boys were two-class solutions. Models could be constrained across adult women and men ( $\chi^2_{26} = 38.0$ ;  $p > .05$ ; see Figure 1a), but could not be constrained across girls (Figure 1b)

**Table 1**

Age and Prevalence Estimates of DSM-IV Nicotine Withdrawal among Australian Adult and Missouri Adolescent Cigarette Smokers#

	Australian Women (N = 1651)	Australian Men (N = 1461)	Missouri Girls (N = 417)	Missouri Boys (N = 285)
Mean age (SD)	30.0 (2.5)	30.1 (2.5)	17.8 (1.6)	18.9 (1.7)
DSM-IV NW <sup>a</sup>	44.2	43	49.6	43.2
Irritability <sup>a</sup>	47.4	45	56.2	43.4
Restlessness <sup>b</sup>	57.2	60.2	46.7	39.9
Concentration problems	27.6	27.9	26.7	30.3
Depressed mood <sup>c</sup>	27	18.7	24.2	17.1
Increased appetite <sup>d</sup>	54.9	57	51.8	31.7
Sleep problems <sup>e</sup>	17	19.3	19.6	24.6
Nervousness <sup>f</sup>	17.1	15.9	31.3	30.3
Decreased heart rate	13	15.3	15.1	19

Note: <sup>a</sup>Cigarette smokers: Those who smoked 100 or more cigarettes lifetime.

SD: Standard deviation.

<sup>a</sup>DSM-IV Nicotine Withdrawal (NW; substance dependence criterion): 4 or more NW symptoms within 24-hour after nicotine reduction, or smoking to relieve symptoms.

<sup>b</sup>Wald  $\chi^2 = 17.0$ ,  $p < .001$ ; higher in girls compared to all other groups.

<sup>c</sup>Wald  $\chi^2 = 43.7$ ,  $p < .001$ ; higher in adult compared to adolescent smokers.

<sup>d</sup>Wald  $\chi^2 = 30.1$ ,  $p < .001$ ; higher in female compared to male smokers.

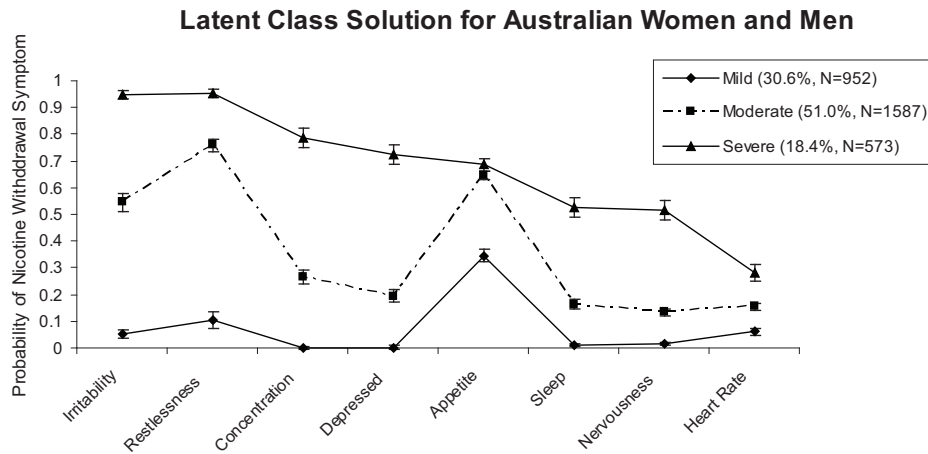
<sup>e</sup>Wald  $\chi^2 = 54.8$ ,  $p < .001$ ; lower in boys compared to all other groups.

<sup>f</sup>Wald  $\chi^2 = 8.9$ ,  $p < .05$ ; higher in adolescent male compared to adult female smokers.

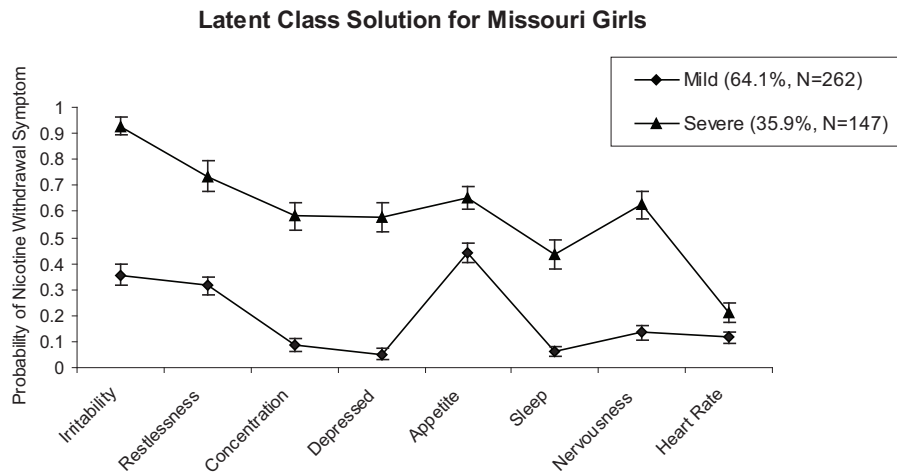
<sup>g</sup>Wald  $\chi^2 = 68.0$ ,  $p < .001$ ; higher in adolescent compared to adult smokers.

Prevalence rates in women and men previously reported in Pergadia et al. (2006b) are here for comparison purposes.

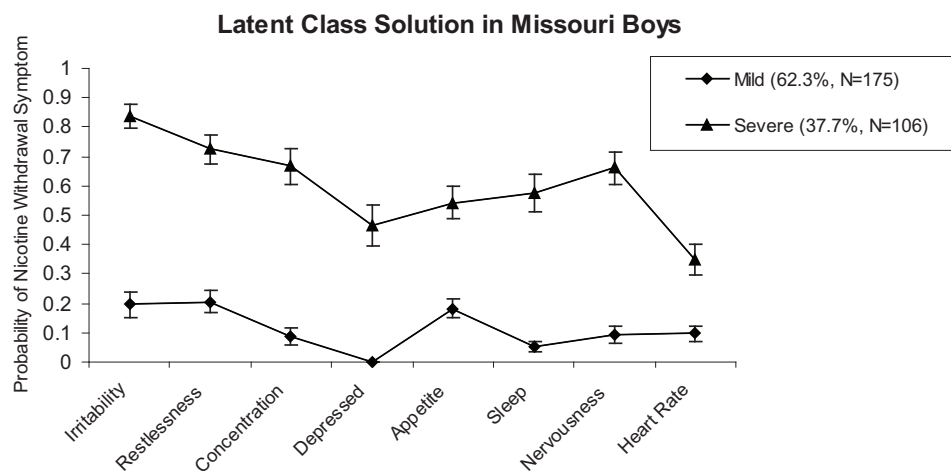
a.



b.



c.



**Figure 1**

Latent class solutions for DSM-IV nicotine withdrawal symptoms.

and boys (Figure 1c;  $\chi^2_{17} = 38.6$ ;  $p < .05$ ). Girls in the mild class reported significantly higher rates of withdrawal-related depressed mood and increased appetite compared to boys in the mild class (4.2% vs. 0% and 45.0% vs. 18.3%, respectively). The pattern that emerged across all the groups was consistent with a severity continuum for nicotine withdrawal, where the probability of an individual endorsing each nicotine withdrawal symptom was significantly higher with each respective class. Evidence for this included, with a single exception, the lack of overlap of standard error bars (i.e., no lines that overlapped or cross-over). The only borderline exception to this case was in the adults, where the endorsement probability for withdrawal-related increased appetite for the moderate class overlapped that for the severe class. This moderate class in the adults was characterized by elevated endorsement probabilities for irritability, restlessness and increased appetite. There were no significant age differences across latent classes in the adults ( $p = .80$ ), girls ( $p = .26$ ) or boys ( $p = .17$ ), suggesting that increases in nicotine withdrawal severity are not accounted for by age. The prevalence of each class is ample; in the adolescents, over 35% of the smokers fall into the severe class, and in the adults 51% fall into the moderate class and 18% into the severe class. This suggests that over a third of smokers are at increased risk of experiencing all of the DSM-IV nicotine withdrawal symptoms upon nicotine reduction.

The results of multinomial logistic and logistic regression analyses predicting latent classes indicative of severity of nicotine withdrawal from other measures of smoking behavior and psychopathology, in the adult and adolescent cohorts respectively, are depicted in Tables 2 and 3. Every variable that we considered was significantly associated with increased risk for severe nicotine withdrawal, with the exceptions of smoking persistence and ADHD in the adolescent cohort. Severe nicotine withdrawal was most highly associated with HSI levels (adults: OR = 3.5–127.5; adolescents: OR = 2.5–18.3), impairment (adults: OR = 13.5–74.6; adolescents: OR = 7.7), difficulty quitting (adults: OR = 4.4–11.8; adolescents: OR=3.8–5.3), and seeking treatment for smoking cessation (adults: OR = 4.5–11.0; boys: 4.3). The relationship between difficulty quitting and severe nicotine withdrawal was significantly stronger in the boys (OR = 5.3) compared to the girls (OR = 3.8). In adjusted multivariate models, all significant univariate predictors remained except for heavy smoking, conduct disorder, and alcohol problems in the adolescents. However, in the adults, smoking persistence only remained associated with moderate nicotine withdrawal and not severe, while major depression only remained associated with increased risk for severe nicotine withdrawal.

Finally, polychoric twin-pair correlations for the three level latent class nicotine withdrawal solution among adults were the following: MZ:  $r = 0.52$  (95%

**Table 2**

Associations With Nicotine Withdrawal (NW) Severity in Australian Adult Female and Male Smokers ( $N = 3112$ ): Unadjusted and Adjusted (All Variables in Model Simultaneously) Odds Ratios (and 95% CI) are Reported With the Mild Class as the Reference Group

	Unadjusted		Adjusted	
	Moderate	Severe	Moderate	Severe
Difficulty quitting	4.4(3.7–5.3)	11.8(9.2–15.2)	2.4(2.0–3.0)	4.0(2.9–5.4)
Smoking persistence	2.0(1.7–2.3)	2.2(1.7–2.8)	1.3(1.03–1.5)	.93(.69–1.3)
Cessation treatment	4.5(3.5–5.8)	11.0(8.3–14.6)	2.0(1.5–2.7)	2.9(2.0–4.2)
NW-related impairment	13.5(8.6–21.0)	74.6(46.9–118.5)	8.7(5.3–14.2)	36.0(21.5–60.3)
Heavy smoking <sup>a</sup>	3.2(2.6–3.8)	6.1(4.9–7.7)	1.1(.89–1.5)	1.1(.76–1.5)
HSI <sup>b</sup>				
1	3.5(2.8–4.3)	6.6(4.2–10.4)	2.7(2.1–3.4)	4.4(2.7–7.2)
2	6.3(4.8–8.3)	13.5(8.3–22.0)	4.0(2.9–5.4)	7.0(4.0–12.3)
3	7.9(6.0–10.3)	27.4(17.2–43.5)	4.5(3.2–6.2)	11.5(6.7–19.7)
4	9.7(6.7–14.1)	53.5(31.6–90.5)	5.3(3.3–8.3)	18.6(9.7–35.6)
5	5.6(3.4–9.4)	48.7(26.3–90.0)	2.7(1.4–5.0)	14.4(6.3–33.1)
6	16.2(5.6–46.9)	127.5(41.7–389.8)	8.0(2.5–25.5)	37.3(9.8–141.9)
DSM-IV depression	1.5(1.2–1.7)	3.8(3.0–4.7)	1.2(.95–1.4)	2.3(1.7–3.1)
Social anxiety	1.5(1.3–1.8)	2.5(2.0–3.1)	1.3(1.04–1.6)	1.6(1.2–2.1)
DSM-IV conduct disorder				
Women	2.2(1.2–3.9)	4.0(2.1–7.6)	1.4(.76–2.5)	1.3(.55–3.0)
Men	1.0(.76–1.4)	1.9(1.3–2.7)	—	.88(.56–1.4)
DSM-IV alcohol dependence	1.6(1.3–1.9)	2.3(1.9–3.0)	1.2(.99–1.5)	1.4(1.01–1.8)

Note: Estimates were equated across gender unless noted.

<sup>a</sup>Heavy smoking: Smoking 20 or more cigarettes per day at peak lifetime use.

<sup>b</sup>HSI: Heaviness of Smoking Index (Heatherton et al., 1989; Heatherton et al., 1991) with values 0–6 (0 as the comparison group).



**Table 3**

Associations with Nicotine Withdrawal (NW) Severity in Missouri Adolescent Female and Male Smokers ( $N = 702$ ): Unadjusted and Adjusted (All Variables in Model Simultaneously) Odds Ratios (and 95% CI) are Reported With the Mild Class the Reference Group

	Unadjusted severe	Adjusted severe
Difficulty quitting		
Girls	3.8 (2.4–6.0)	3.3 (1.9–5.6)
Boys	5.3 (3.0–9.3)	3.0 (1.5–5.9)
Smoking persistence	1.8 (.95–3.3)	—
Cessation treatment (boys only)	4.3 (2.3–8.1)	2.4 (1.1–5.2)
NW-related impairment	7.7 (5.0–12.0)	4.5 (2.8–7.4)
Heavy smoking <sup>a</sup>	3.2 (2.3–4.5)	1.1 (.69–1.8)
HSI <sup>b</sup>		
1	2.5 (1.3–4.7)	1.6 (.81–3.3)
2	4.4 (2.4–8.1)	3.0 (1.5–6.1)
3	6.1 (3.4–11.1)	4.1 (2.1–7.9)
4	14.2 (7.6–26.5)	6.5 (3.1–13.8)
5	18.3 (7.5–44.7)	8.8 (2.8–28.2)
6	12.0 (3.9–36.7)	6.4 (1.6–24.9)
DSM-IV depression	2.7 (1.9–3.9)	1.6 (1.02–2.4)
Social anxiety	1.9 (1.4–2.6)	1.5 (1.01–2.2)
DSM-IV conduct disorder	2.6 (1.8–3.9)	1.3 (.80–2.1)
≥ 2 DSM-IV alcohol problems	1.7 (1.3–2.4)	1.4 (.92–2.0)
DSM-IV ADHD	1.1 (.62–1.9)	—

Note: Estimates were equated across gender unless noted.

<sup>a</sup>Heavy smoking: Smoking 20 or more cigarettes per day at peak lifetime use.

<sup>b</sup>HSI: Heaviness of Smoking Index (Heatherton et al., 1989; Heatherton et al., 1991) with values 0–6 (0 as the comparison group).

Confidence Interval (CI): 0.43–0.61), DZ:  $r = 0.13$  (95% CI:  $-0.003$ – $0.27$ ); tetrachoric twin-pair correlations for the two class solution among adolescents were: MZ:  $r = 0.48$  (95% Confidence interval (CI): 0.18–0.71), DZ:  $r = 0.15$  (95% CI:  $-0.26$ – $0.52$ ). In each case, the MZ correlation was more than twice that of the DZ twin-pair correlation, suggest important additive (A) and non-additive (D) genetic influences, with minimal influences of shared family environment. The results of structural equation modeling for the latent class measure of nicotine withdrawal, which tested ADE models against sub-models, found the most parsimonious model to be an AE model, in which estimates could be constrained across the cohorts and gender. In this best fitting genetic model of nicotine withdrawal, in both the adolescent and adult smokers, A was estimated at: 49% (95% CI: 40%–57%) and E at 51% (95% CI: 43%–60%).

## Discussion

Our findings highlight the similarity of the prevalence, pattern and heritability of nicotine withdrawal across adolescents, adults and gender, in addition to comparable associations with difficulty quitting, smoking persistence and withdrawal-related impairment and psychopathology.

In terms of prevalence rates of nicotine withdrawal symptoms, our study is mostly consistent with others,

which found similar rates across gender (Breslau et al., 1992) and age (CDC, 1994). In our analyses, however, there was evidence of heterogeneity for a few specific items. Adult smokers were more likely to report restlessness and less likely nervousness compared to the adolescent smokers; female smokers had higher rates of depressed mood associated with nicotine abstinence compared to male smokers; and among the adolescent smokers, girls reported more irritability and hunger and boys more sleep-related problems. The finding of higher rates of depressed mood in female versus male adolescent smokers extends the findings that we previously reported in the adult sample (Pergadia et al., 2006b). Despite the increased probability of heavy smoking in adults, particularly men, (women: 33%, men: 47%) compared with adolescents (girls: 31%, boys: 29%), only one withdrawal symptom — restlessness — was elevated in the adult smokers over their adolescent counterparts, suggesting that many nicotine withdrawal symptoms emerge during nicotine abstinence simply after becoming a smoker (defined here as smoking 100 or more cigarettes lifetime). While it has been suggested that nicotine withdrawal symptoms in adolescents may reflect mood fluctuations associated with adolescence and not necessarily nicotine withdrawal (Prokhorov et al., 2005), our findings show that adolescent reports of withdrawal are highly consistent with adult reports, with the exception of higher levels of nervousness in girls and

boys, irritability in girls and sleep problems in boys. This difference in nicotine withdrawal-related nervousness found in this study may not simply reflect an age difference, but may indicate a possible cultural difference in the way different populations of smokers perceive or define 'nervousness' within the context of nicotine withdrawal as assessed by the CIDI (Cottler et al., 1991). In other words, the Australian interpretation of 'nervousness' may simply be different. While the prevalence rates of other DSM-IV nicotine withdrawal items closely approximated previous reports of nicotine withdrawal symptoms in US samples of adult (Breslau et al., 1992) and adult male veteran (Xian et al., 2003) smokers, the rate of nervousness reported in our adult Australian sample of smokers appeared strikingly lower than these previous reports. For instance, Breslau et al. (1992) reported a rate of nervousness of 50%, and Xian et al. (2003), 53%, closer to the 31% reported in our adolescent samples and much higher than the 17% reported by our adult Australian smokers. In subsidiary analyses examining the prevalence of nicotine withdrawal symptoms in the mothers of our US adolescent boy sample (BOYNIC), who reported smoking 100 or more cigarettes lifetime ( $N = 809$ ), we found a rate of nervousness of 47%. This rate was within the range of nervousness reported by Breslau et al. (1992) and Xian et al. (2003). Future studies will explore the cross-cultural difference in reports of nicotine withdrawal symptoms, including data obtained from US and Australian smokers. Modification of the assessment of nicotine withdrawal-related nervousness to include both 'nervous' and 'anxious' may lead to higher endorsement rates, as our current assessment only included nervousness. It may be the case that 'nervousness' in a sample of Australian smokers may be perceived as situation specific or may reflect outcome-related anticipatory anxiety (e.g., nervous about not being able to quit smoking).

Our latent class analysis results were consistent with findings of Madden et al. (1997) in an older cohort of female twins and Xian et al. (2005) in middle-aged male veteran twins. Like them, we found that nicotine withdrawal symptoms were best described as being arrayed on a severity continuum: three levels in adult smokers (no significant differences across men and women) and two levels in adolescent smokers (girls and boys differing only with respect to higher rates of depression and appetite). Similarly, we found that difficulty quitting, nicotine dependence (as defined by the HSI), impairment due to withdrawal symptoms, heavy smoking, depression, social anxiety, conduct disorder, and alcohol dependence were associated with increasing levels of nicotine withdrawal severity. To our knowledge, this is the first study to replicate this pattern of nicotine withdrawal, associated smoking measures and comorbidity in both adult and adolescent cohorts, in addition to examining age and gender differences. While previous studies have

found ADHD to be associated with early stages of smoking, such as regular smoking (e.g., Kollins et al., 2005), in this study we found no association with nicotine withdrawal — a later stage of smoking-related behavior. Additionally, we found that seeking smoking cessation treatment was associated with more severe nicotine withdrawal. The only difference in terms of patterns of nicotine withdrawal observed across the adults versus adolescents was a moderate class that emerged in the adults that was not observed in the adolescents. This moderate class was mostly comprised of individuals who reported high level of irritability, restlessness and increased appetite. This class was substantial in the adults (51%). Interestingly, only this moderate class retained a significant association with smoking persistence in the multivariate multinomial logistic regression model, after controlling for other measures of smoking behavior and psychopathology.

Findings on the degree to which smoking persistence is associated with nicotine withdrawal severity are mixed. While Breslau et al. (1992) and Madden et al. (1997) found no association, Xian et al. (2005), did. Our findings are mixed as well. We found no association between nicotine withdrawal severity and smoking persistence in the adolescent smokers, possibly due to little variance in those samples (91% of the girls and 93% of the boys were persistent smokers — most likely because they are earlier in their smoking careers). On the other hand, in the adults, smoking persistence was associated with more severe nicotine withdrawal. However, once other factors were taken into account the significant association remained only for the moderate class. This suggests that the association between smoking persistence and nicotine withdrawal severity is accounted for by other smoking behavior and psychopathology for the most severe class, while this is not the case for the moderate class. This relationship between smoking persistence and moderate nicotine withdrawal was maintained even when we expanded our criteria of smoking persistence from any smoking within the last month to any within the last year, as was used by Breslau et al. (1992). Our study may have included additional covariation between nicotine withdrawal smoking persistence compared to Breslau et al. (1992), wherein nicotine withdrawal symptoms were only assessed among those with at least one unsuccessful quit attempt. Change in societal views on smoking could in part account for the differential effects of withdrawal on persistence between our samples here and the older cohort described in Madden et al. (1997). Future studies should explore this particular group of adult smokers highlighted here who report specifically high levels of irritability, restlessness and increased appetite during nicotine abstinence, in terms of increased risk for persisting in the smoking habit.

Finally, we found significant additive genetic, 49%, and unique environmental influences, 51%, contributing

to variation in nicotine withdrawal equally in both adolescent and adult smokers. This is the first report, to our knowledge, to provide estimates of heritability of nicotine withdrawal in adolescents, in addition to examining comparable influences in adults. The heritability estimate obtained for the latent class structure of nicotine withdrawal of 49% is virtually identical to the estimate associated with meeting criteria for the DSM-IV NW syndrome previously reported (47%; Pergadia et al., 2006b). Thus, the phenotypic and genetic structure of nicotine withdrawal — whether binary as defined in DSM (American Psychiatric Association, 1994) or multi-level from latent classes — is quite consistent across the adolescent and adult samples of smokers.

There are limitations to our findings. While our analyses included adolescents aged 15–21 years and young adults aged 24–36 years, they did not include individuals aged 22 to 23 years. However, given the similarity of findings across the cohorts, we might expect a similar pattern of results, and we saw no age differences across our latent class solutions. In addition, seeking smoking cessation treatment was highly associated with nicotine withdrawal severity in both the adults and in the adolescent boys, but that information was not gathered from the girls at the time of their initial interview. In future work, we can examine this association with information provided through follow-up assessments of this cohort. Our assessments of nicotine withdrawal were retrospective in nature. While the degree to which recall of nicotine withdrawal symptoms reflect symptoms of nicotine withdrawal experiences in real-time is an ongoing area of study, previous psychometric studies of self-reported symptoms found high test-retest (Hughes et al., 1984; Tate et al., 1993) and moderate inter-rater reliability of nicotine withdrawal symptoms (Hughes et al., 1986). Retrospective reports of lifetime smoking history, more generally, show high agreement with real-time reports with agreements rates up to .74 after 14 years (Kenkel et al., 2003).

Overall, our findings suggest remarkable similarity in the pattern and heritability of nicotine withdrawal across young adult and adolescent smokers and across culture. More severe nicotine withdrawal was associated with all aspects of smoking cessation considered in the adults: difficulty quitting, persistent smoking, impairment following quitting, and seeking smoking cessation treatment, in addition to difficulty quitting and impairment in girls and boys, and seeking cessation treatment in the boys. Taken together, our results suggest that nicotine withdrawal plays an important role in psychiatric comorbidity and the process of smoking cessation in adult and adolescent smokers.

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