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Original Contribution

Sex Differences in Attaining Cigarette Smoking and Nicotine Dependence Milestones Among Novice Smokers

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There may be sex differences in the response to nicotine, according to findings of studies in animals; however, sex differences in the natural course of cigarette smoking and nicotine dependence are documented in few studies. Prevalent ($n = 240$ girls; $n = 184$ boys) and incident ($n = 231$ girls; $n = 184$ boys) cigarette smokers from the Nicotine Dependence in Teens Study were followed up to 5 years after first puff, from age 12 to 18 years (1999–2005). We used Cox proportional hazards models to compare time to development of 3 cigarette-use (i.e., whole cigarette; 100 cigarettes lifetime; regular smoking), and 3 nicotine-dependence symptom (i.e., "really need a cigarette"; mentally addicted; physically addicted) milestones across sex. Girls were at higher risk than boys of attaining all milestones; hazard ratios (95% confidence intervals) ranged from 1.35 (1.06, 1.72) for 100 cigarettes lifetime to 1.74 (1.44, 2.10) for "really need a cigarette." Among nonregular smokers, 26% (8%; 43%) and 25% (6%; 44%) more girls than boys reported "really need a cigarette" 1 and 2 years, respectively, after first puff. Preventive interventions may need adjustment to incorporate these findings. Additional research should clarify the relative contribution of biological and social underpinnings of these sex differences.

adolescents; cigarette smoking; sex differences; tobacco use disorder

Abbreviation: ND, nicotine dependence.

Although the smoking-attributable death rate remains higher in men, the gap is narrowing and the risk of death due to smoking-related lung disease by age 45 years is now equivalent across the sexes (1). Women now bear a greater burden from cigarette smoking for coronary heart disease (2) and chronic obstructive pulmonary disease (3, 4). Furthermore, according to data from the UK Cotton Workers' Cohort Study, although smoking has a dose-response relationship with all-cause death in both sexes, women who smoked 1–14 cigarettes per day were 35% more likely to die than men who smoked the same amount (5). Several biological mechanisms have been evoked to explain sex differences in nicotine dependence (ND), cessation, and relapse (6), including neurophysiological differences between sexes (7, 8) and fluctuations in the menstrual cycle (9).

The onset of cigarette smoking typically begins with the first few puffs in adolescence (10, 11), followed by sequential attainment of predictable milestones. In the Nicotine Dependence in Teens Study, many novice adolescent smokers began to inhale shortly after first puff, experienced a variety of ND symptoms within 1 year, became daily smokers within 2 years, and experienced tobacco dependence, as outlined in *International Classification of Diseases, 10th Edition*, within 3.5 years (12). Early ND symptoms trigger escalation in smoking frequency and intensity, which, in turn, escalates ND symptoms and, in many smokers, results in attaining ND, according to *Diagnostic and Statistical Manual of Mental Disorders* or *International Classification of Diseases* criteria (13–15). A significantly faster onset of ND symptoms in teenage girls (median time between initiation of monthly smoking and ND symptoms was 21 days in girls and 183 days in boys) was reported in the Development and Assessment of Nicotine Dependence in Youths (DANDY) I Study (16). Girls were also systematically more likely to report ND symptoms over the 30-month study (16). Similar sex differences were found in a study of 25,000 current smokers 14 to 15 years old in New Zealand: Girls reported more ND symptoms on the Hooked on Nicotine Checklist and had

higher scores when stratified by lifetime cigarette consumption and at each level of current consumption prior to daily smoking (17). In contrast, there were no sex differences in latency to first symptom in DANDY II (18). Finally, Kandel et al. (19) followed adolescents 11 to 17 years old over 24 months and found no sex differences in timing of first ND symptom. However, because participants had initiated smoking in the year prior to baseline, more than 1 year may have elapsed between smoking onset and assessment of ND symptoms; thus, any sex differences at the earliest stages of smoking acquisition may have been obscured.

Because the sex-specific natural course of smoking acquisition in youth has been investigated in few studies (12–19), the extent to which girls and boys differ in the rate of attaining early cigarette smoking and ND symptom milestones is not well established. Our objectives in this study were to describe the natural course of cigarette smoking and ND symptom milestones after first puff and to explore sex differences in time to, and in the absolute risk of, milestone attainment. We hypothesized that the sex-specific response to nicotine observed in animal and human studies (6–9) would translate into sex differences in milestones in the natural course of smoking in adolescents. In this paper, sex differences encompass biological and cultural (gender) characteristics (20).

METHODS

Data were drawn from the Nicotine Dependence in Teens Study, a longitudinal investigation of 1,294 students recruited in 1999–2000 from all grade 7 classes in 10 Montreal-area secondary schools (21). Schools were selected purposively to include Francophones and Anglophones; participants of low, moderate, and high socioeconomic status; and those living in rural, suburban, and urban areas. Baseline characteristics of the sample resembled those of 13-year-old participants from the population-based, provincially representative sample of the 1999 Quebec Child and Adolescent Health and Social Survey (22). In the Nicotine Dependence in Teens Study, self-report questionnaires were administered at school every 3 months from grade 7 to grade 11, for a total of 20 cycles during the 5 years of secondary school. Parents and guardians provided informed consent and all students provided assent. The study was approved by the Ethics Research Committee of the Centre de recherche du Centre Hospitalier de l'Université de Montréal.

Study variables

First puff. Participants were asked, "Have you ever in your life smoked a cigarette, even just a puff, (drag, haul, hit)?" The response options were as follows: no; yes, 1–2 times; yes, 3–4 times; yes, 5–10 times; yes, more than 10 times. Age at first puff was recorded as the age on the date of the survey in which the participant first endorsed "yes."

Current smoking. Frequency of current smoking was assessed by having participants follow the instruction to "Check the one box that describes you best." Response options were: I have never smoked a cigarette, even just a puff; I have smoked cigarettes (even just a puff), but not at all in the past 12 months; I smoked cigarettes once or a couple of times in the past 12 months; I smoke cigarettes once or a couple of times each month; I smoke cigarettes once or a couple of times each week; I smoke cigarettes every day. Participants categorized as sporadic smokers endorsed smoking once or a couple of times in the past year. Those categorized as regular smokers reported smoking monthly, weekly, or daily.

Milestones. Age at which 3 cigarette-use milestones were attained was measured for 1) whole cigarette: age on the date of the cycle in which the participant first endorsed "yes" to "Have you ever smoked a whole cigarette (down to or close to the filter)?" (no, yes); 2) 100 cigarettes lifetime: age on the date of the cycle in which the participant first endorsed "yes" to "Have you smoked 100 or more whole cigarettes in your life? (100 cigarettes = 4 packs of 25)?" (no, yes); and 3) regular smoking: age on the date of the cycle in which the participant first endorsed any of monthly, weekly, or daily smoking.

Age at which the 3 ND symptom milestones were attained was measured for 1) really need a cigarette: age on the date of the cycle in which the participant first responded "rarely," "sometimes," or "often" to "How often have you felt like you really need a cigarette?" (never, rarely, sometimes, often); 2) feel mentally addicted to cigarettes: age on the date of the cycle in which the participant first responded "a little," "quite," or "very" to "How mentally addicted to smoking cigarettes are you?" (not at all, a little, quite, very); and 3) feel physically addicted to cigarettes: age on the date of the cycle in which the participant first responded "a little," "quite," or "very" to "How physically addicted to smoking cigarettes are you?" (not at all, a little, quite, very). The 3 ND symptoms selected often occur early in the natural course of smoking prior to monthly smoking (12), permitting investigation of sex differences in sporadic and regular smokers.Sociodemographic indicators included sex, age, primary language, and having a university-educated mother (no, yes).

Data analyses

Because data were missing for approximately 9% of participants (Web Table 1, available at https://academic.oup.com/aje), we used a multiple imputation approach based on bootstrap expectation-maximization importance sampling (23), which incorporates longitudinal and cross-sectional data to improve the quality of the imputation. To improve performance of the imputation algorithm, some variables measured in the Nicotine Dependence in Teens Study but not used in the current analyses, including other ND symptoms (e.g., symptoms of withdrawal and self-medication, intensity of physical activity, hours of television daily, hours of computer use daily), were included in the imputation data set, and several continuous variables were log-transformed before imputation. Imputation was undertaken respecting the scale of each type of variable (i.e., continuous, ordinal, categorical), and was performed separately for each milestone using the Amelia II package (24) in R, version 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria).

Our main analysis included the 839 participants who reported cigarette smoking prior to or during the study. Participants who endorsed any response other than "no" to "Have you ever in your life smoked a cigarette, even just a puff (drag, haul, hit)?" at cohort inception were considered prevalent smokers (n = 424); the remaining were considered incident smokers (n = 415). We estimated Cox proportional hazards models to compare time to development of each milestone between boys and

girls. A separate univariate model was estimated for each milestone. We used directed acyclic graphs to represent our hypotheses about the causal associations between our variables of interest (25) and to build our models (26) (Web Figure 1).

Participants were followed from age at first puff to age at milestone attainment or, if they did not attain the milestone, up to a maximum of 5 years, after which they were censored. Follow-up for prevalent smokers was left truncated because their smoking history prior to inception was not documented. Under the assumption of proportionality of hazards, valid hazards ratios can be obtained in the presence of left truncation using a counting process specification of the Cox model (27). Prevalent smokers who reported a milestone at baseline (n = 67–209; Web Table 2) were excluded because it was not possible to assess when they had attained the milestone. To account for potentially different risks of milestone attainment between participants who initiated smoking in childhood (age <12 years, before inception) and adolescence (age ≥12 years, after inception), our Cox models were stratified to include distinct baseline hazards for prevalent and incident smokers. We verified the proportionality of hazards assumption using Schoenfeld residuals plots (28). We investigated the impact of including the prevalent smokers in the analyses by estimating the models in incident smokers only.

We conducted sensitivity analyses to account for the possible influence of frequency of smoking on ND symptom milestone occurrence. We restricted the analysis to regular smokers by using age when participants first reported monthly, weekly, or daily smoking (rather than age at first puff) in the models. These sensitivity analyses, therefore, rendered boys and girls equivalent in terms of having attained a regular smoking status. Truncation and censoring were dealt with in the same way as in the main analyses, except that prevalent and incident smokers who experienced a milestone in the same cycle in which they first reported regular smoking were excluded because the chronology of the 2 events could not be established. Participants who reported the milestone before regular smoking were also excluded. Thus, these analyses included only participants who had achieved the regular smoking milestone during follow-up.

Finally, we computed the cumulative incidence of each milestone 1 and 2 years after first puff, by sex, in 2 subgroups of incident smokers: 1) participants who remained sporadic smokers for 2 years after first puff, and 2) participants who reported regular smoking in the same cycle as first puff. This allowed us to estimate sex differences in the absolute risk of attaining each milestone, taking smoking frequency into account. Analyses were carried out with SAS, version 9.1.4 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

The analytic sample included 240 girls and 184 boys who reported smoking at cohort inception (prevalent smokers), and 231 girls and 184 boys who took their first puff on a cigarette during follow-up (incident smokers). In the cycle in which first puff was reported (or at cohort inception for prevalent smokers), lower proportions of girls than boys had university-educated mothers and had used tobacco products other than cigarettes, whereas a higher proportion of girls than boys reported that their friends smoke (Table 1). More than 30% of participants reported first puff on a cigarette before age 13 years; on average, girls reported first puff at a younger age than boys (13.5 years vs. 13.8 years, respectively).

There were no violations of the proportional hazards assumption in any of the Cox models (Table 2). Between 67 and 209

Table 1. Sociodemographic Characteristics[a] of the Analytic Sample, by Sex, Nicotine Dependence in Teens Study, 1999–2005

Sociodemographic Characteristic	Girls, % (n = 471)	Boys, % (n = 368)
Age, years[b]	13.5 (1.1)	13.8 (1.3)[c]
Primary language is French	36.3	34.0
Born in Canada	93.6	95.4
Single-parent family	15.1	11.4
Mother is university educated	28.0	36.7[c]
Use tobacco products other than cigarettes	30.4	38.6[d]
Drinks alcohol	66.0	69.8
Parent(s) smoke	45.7	40.8
Siblings(s) smoke	26.1	22.6
Friends smoke	80.5	71.5[c]

[a] Characteristics were assessed for prevalent smokers at inception and for incident smokers in the cycle in which first puff was reported.
[b] Values are expressed as mean (standard deviation).
[c] $P \leq 0.01$ for t test (age) and χ^2 tests otherwise.
[d] $P < 0.05$ for t test (age) and χ^2 tests otherwise.

Table 2. Hazard Ratios for the Association Between Sex and Each of 6 Cigarette-Use and Nicotine-Dependence Symptom Milestones[a], Nicotine Dependence in Teens Study, 1999–2005

Milestone	All Smokers (n = 630–772)[b,c]		Incident Smokers (n = 415)[b]	
	HR[d]	95% CI[e]	HR[d]	95% CI[e]
Whole cigarettes	1.49	1.21, 1.84	1.33	1.04, 1.71
100 cigarettes lifetime	1.35	1.06, 1.72	1.28	0.92, 1.77
Regular (at least monthly) smoking	1.57	1.30, 1.90	1.40	1.07, 1.82
Feel like you really need a cigarette	1.74	1.44, 2.10	1.79	1.38, 2.31
Feel mentally addicted	1.58	1.28, 1.95	1.51	1.16, 1.97
Feel physically addicted	1.65	1.31, 2.09	1.52	1.09, 2.13

Abbreviations: CI, confidence interval; HR, hazard ratio.
[a] Models are univariate and stratified to include distinct baseline hazards for prevalent and incident smokers.
[b] Includes participants at risk of attaining the milestone at baseline (i.e., the cycle in which participants reported first puff).
[c] Number of all smokers varies because prevalent smokers who reported the milestone of interest at inception were eliminated from the analyses.
[d] Boys were the reference group for all estimates.
[e] Wald robust confidence intervals. Multiple imputation was used to impute missing values.

Table 3. Hazard Ratios for the Association Between Sex and Nicotine-Dependence Symptom Milestones Among Regular Smokers[a], Nicotine Dependence in Teens Study, 1999–2005

Milestone	No.[b]	All Smokers		No.[b]	Incident Smokers	
		HR[c]	95% CI[d]		HR[c]	95% CI[d]
Feel like you really need a cigarette	90–114	1.69	0.81, 3.49	44–55	2.07	0.58, 7.38
Feel mentally addicted	155–170	1.66	0.88, 3.12	74–88	1.79	0.68, 4.71
Feel physically addicted	188–208	1.63	1.02, 2.62	95–103	2.21	0.94, 5.23

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] The regular smoking milestone was attained the first time a participant reported smoking monthly, weekly, or daily. These analyses include only participants who had achieved the regular smoking milestone during follow-up and after first puff. Smokers who reported the milestone before or at the time of regular smoking milestone were excluded. Models are univariate and stratified to include distinct baseline hazards for prevalent and incident smokers.

[b] Numbers vary because of multiple imputation.

[c] Boys were the reference group for all estimates.

[d] Wald robust confidence intervals. Multiple imputation was used to impute missing values.

prevalent smokers were excluded from these analyses because they reported attaining the milestone of interest at cohort inception. Girls were consistently at higher risk of attaining all milestones after first puff, with hazard ratios ranging from 1.35 for the 100-cigarette lifetime milestone to 1.74 for "really need a cigarette." Results from the models restricted to incident smokers were similar (Table 2).

The results of sensitivity analyses, using age at first report of regular smoking as time zero, are listed in Table 3. The sample sizes for these analyses were smaller than in the main analyses because 40%–44% of boys and 28%–30% of girls remained sporadic smokers throughout the study. In addition, depending on the milestone, we also excluded participants who reported regular smoking and attaining the milestone of interest in the same cycle, because the temporality of the 2 events could not be established. The findings were similar to those of the primary analyses: Girls were consistently at higher risk than boys of attaining all milestones. "Feel physically addicted" was, however, the only milestone that was statistically significant (odds ratio = 1.63, 95% confidence interval: 1.02, 2.62). Restricting the sample to incident smokers did not change the results substantially (Table 3).

Table 4 shows the absolute risk, by sex, of attaining each milestone within 1 or 2 years of first puff. In the subset of incident smokers who remained sporadic smokers (30%–33% of participants at 1 year and 25%–28% at 2 years), the proportion that attained each milestone increased over time and was consistently higher among girls than boys in both the 1- and 2-year analyses. The risk of attaining each milestone was higher for girls than boys by 2–26 percentage points in the year after first puff and by 6–25 percentage point in the 2 years after first puff. However, only the risk difference for "really need a cigarette" was statistically significant across sexes (after 1 year: 26%, 95% confidence interval: 0.08, 0.43; after 2 years: 25%, 95% confidence interval: 0.06, 0.44).

The absolute risk of smoking a whole cigarette or developing ND symptoms was substantially higher in the subset of participants who reported regular smoking in the same cycle as first puff (Table 5). In the year after first puff, the proportion that attained the milestones ranged from 58% to 93% in girls and 86% to 100% of boys. In the 2 years after first puff, these proportions were 83% to 100% in girls and 89% to 100% in boys. Only 1 risk difference was statistically significantly different: A lower proportion of girls than boys (78% vs. 95%, respectively) reported "feel mentally addicted" in the year after first puff. Indeed, male sex was systematically associated with higher absolute risks 1 year after first puff, although the only statistically significant result was that corresponding to the "feel mentally addicted" milestone (absolute risk = −0.17, 95% confidence interval: −0.34, −0.01. However, these differences were no longer apparent at the 2-year mark.

DISCUSSION

In this longitudinal study of sex differences in the natural course of smoking and ND symptoms, girls were at higher risk than boys for attaining all smoking and ND symptom milestones, including smoking a whole cigarette, smoking 100 cigarettes lifetime, regular smoking, "really need a cigarette," "feel mentally addicted," and "feel physically addicted." To assess whether smoking frequency explained the sex differences observed in ND symptom milestones, we conducted sensitivity analyses restricted to regular smokers and observed similar findings, with 1 exception: The subgroup of boys who attained regular smoking in the same cycle as first puff had higher absolute risks of developing ND symptom milestones than girls at 1 year. However, this sex difference was not apparent after 2 years, suggesting a transient phenomenon likely explained by the greater proportion of boys who reported daily smoking at first puff in that subgroup. Overall, although the results suggest sex influences in attaining ND symptoms irrespective of smoking frequency, future research will need to formally test the hypothesis by estimating mediation models that decompose the association into direct and indirect effects (i.e., through the contribution of smoking intensity or frequency). However, this will require additional methodological work because current mediation models in Cox proportional hazards models do not easily allow for inclusion of time-varying mediators such as smoking frequency (29) and, in addition, have restrictive rare-event assumptions that are not met in our data (30, 31).

According to findings from animal models and human laboratory studies, the response to nicotine may be sex specific,

Table 4. Absolute Risk[a] of Attaining Each Cigarette-Use or Nicotine-Dependence Symptom Milestone Within 1 or 2 Years After First Puff, by Sex, in Incident Smokers Who Remained Sporadic Smokers, Nicotine Dependence in Teens Study, 1999–2005

Milestone	1 Year After First Puff (n = 125–138)[b]				2 Years After First Puff (n = 104–116)[b]			
	AR	95% CI	RD	95% CI	AR	95% CI	RD	95% CI
Whole cigarette			0.04	−0.14, 0.21			0.09	−0.12, 0.29
F	0.30	0.17, 0.43			0.46	0.32, 0.60		
M	0.26	0.14, 0.37			0.37	0.23, 0.51		
100 cigarettes lifetime			0.07	−0.10, 0.24			0.13	−0.12, 0.37
F	0.25	0.12, 0.38			0.41	0.18, 0.64		
M	0.18	0.06, 0.30			0.28	0.14, 0.43		
Feel like you really need a cigarette			0.26	0.08, 0.43			0.25	0.06, 0.44
F	0.54	0.41, 0.68			0.76	0.64, 0.87		
M	0.28	0.16, 0.41			0.51	0.36, 0.65		
Feel mentally addicted			0.09	−0.09, 0.36			0.10	−0.09, 0.29
F	0.33	0.19, 0.46			0.45	0.30, 0.59		
M	0.24	0.13, 0.36			0.34	0.20, 0.49		
Feel physically addicted			0.03	−0.13, 0.17			0.06	−0.12, 0.25
F	0.15	0.03, 0.26			0.30	0.15, 0.46		
M	0.12	0.03, 0.22			0.24	0.12, 0.36		

Abbreviations: AR, absolute risk; CI, confidence interval; F, female; M, male; RD, risk difference.
[a] Cumulative incidence (proportion) of participants who attained each milestone within 1 or 2 years of first puff.
[b] Sample sizes vary due to multiple imputation.

and women may be more susceptible to ND than men, although the underlying biological mechanisms are not fully elucidated (7). Estradiol and progesterone, hormones associated with the menstrual cycle, may be associated with craving and reward from smoking (9, 32), which aligns with the finding that estradiol and progesterone interact with dopamine release in rodent models (7, 33, 34). Dopamine controls the reward pathway and, thus, is a major contributor to the development of addiction (35). However, this is complicated by the age-dependent process of sex differentiation of the brain that is not complete until the end of adolescence. This process affects the brain regions responsible for reward processing and behavior (6, 9). As a result, dopamine receptor levels in boys and girls differ during adolescence (36, 37). This, paired with the findings that nicotine affects reward-related regions of the brain more strongly during adolescence than adulthood (6), may result in observed sex differences in smoking and ND during adolescence (38).

Notably, the risk differences were 31% and 24% in sporadic smokers over 1 and 2 years, respectively, in reports of "really need a cigarette." This echoes cross-sectional findings among 1,425 current smokers, in which adolescent girls had higher emotional dependence scores reflecting the need to smoke to deal with negative affect (i.e., when stressed, sad, depressed, angry, nervous) or to relax (39). Similarly, despite equivalent cigarette consumption, girls in a cross-sectional study of 1,195 German adolescent ever-smokers had higher scores than boys on the Autonomy Over Tobacco Scale, which tapped psychological dependence (i.e., using smoking for stress reduction and relief from boredom) and cue-induced craving (40).

Whether and how sex differences in smoking should be incorporated into interventions are controversial. Some authors call for inclusion of gender-related factors in tobacco reduction and cessation interventions (41), whereas others suggest that gender or sex are merely superficial indicators of individual differences and that interventions should focus on underlying processes such as reasons for smoking, individual reactions to nicotine, and cultural sanctions and roles (42). There is ample evidence that the tobacco industry has successfully used gender-targeted marketing and tobacco product development to increase sales (43), but the evidence that sex-specific tobacco control interventions are effective is scarce (41, 44) and usually restricted to adults (45). One exception may be the Not on Tobacco program, a psychosocial cessation intervention offered separately to boys and girls (46). However, before our findings can inform intervention, increased understanding of the relative contributions of biology and the social aspects of gender to these differences is needed.

Limitations

We limited our analyses to 3 early ND symptoms; thus, our findings are uninformative regarding later ND symptom milestones (i.e., withdrawal, tolerance, *International Classification of Diseases*–defined tobacco dependence). Our analyses included incident and prevalent smokers whose follow-up was left truncated. Because their exclusion would have biased the results (47), we retained prevalent smokers except those who reported a milestone at baseline. This exclusion could have resulted in selection bias.

Table 5. Absolute Risk[a] of Attaining Each Cigarette-Use or Nicotine-Dependence Symptom Milestone Within 1 or 2 Years After First Puff, by Sex, in Incident Smokers Who Attained the Regular Smoking Milestone in the Same Cycle as First Puff, Nicotine Dependence in Teens Study, 1999–2005

Milestone	1 Year After First Puff ($n = 59$)				2 Years After First Puff ($n = 54$)			
	AR	95% CI	RD	95% CI	AR	95% CI	RD	95% CI
Whole cigarette			−0.04	−0.16, 0.09			−0.02	−0.14, 0.10
F	0.93	0.84, 1.00			0.95	0.87, 1.00		
M	0.97	0.88, 1.00			0.97	0.88, 1.00		
100 cigarettes lifetime			−0.20	−0.46, 0.07			−0.06	−0.27, 0.14
F	0.58	0.40, 0.76			0.83	0.68, 0.98		
M	0.78	0.60, 0.96			0.89	0.75, 1.00		
Feel like you really need a cigarette			−0.05	−0.12, 0.02			0.00	
F	0.95	0.88, 1.00			1.00	0.87, 1.00		
M	1.00	0.81, 1.00			1.00	0.81, 1.00		
Feel mentally addicted			−0.17	−0.34, −0.01			−0.03	−0.17, 0.10
F	0.78	0.64, 0.91			0.92	0.82, 1.00		
M	0.95	0.86, 1.00			0.95	0.74, 1.00		
Feel physically addicted			−0.13	−0.34, 0.08			−0.02	−0.17, 0.21
F	0.73	0.58. 0.87			0.88	0.75, 1.00		
M	0.86	0.71, 1.00			0.86	0.63, 0.96		

Abbreviations: AR, absolute risk; CI, confidence interval; F, female; M, male; RD, risk difference.
[a] Cumulative incidence (proportion) of participants who attained each milestone within 1 or 2 years of first puff.

We could not distinguish sex (i.e., the impact of biology on physiological processes, genetics, and body structures) and gender (i.e., the social meaning of being a girl or a boy (48)). If our results are attributable to biology, then our modeling was appropriate because biology and ND symptom milestones cannot share a common cause. If gender is influential, then the association observed could be confounded if the processes involved in acquiring a gender identity and in achieving ND symptom milestones share a common cause (e.g., societal influences that shape a female identity that is more attuned to report feelings could explain the results). This distinction may need investigation before the notions of gender and sex are incorporated into tobacco control intervention, although sex and gender may be inseparable constructs that interact and the resulting effects may be difficult to disentangle (49).

Adolescent girls are more likely to smoke mentholated cigarettes (50), which are hypothesized to engender higher ND than nonmentholated cigarettes because of greater nicotine exposure (51). Although we did not measure cigarette preferences, findings of a Canadian study indicate 30% of adolescents may smoke mentholated cigarettes (52). Sex differences in use of mentholated cigarettes might contribute to sex differences in milestones.

Finally, because data were collected every 3 months, we could not measure the acute effects of nicotine that might have contributed to the sex differences observed. For example, use of nicotine to alleviate negative affect due to withdrawal is postulated as 1 mechanism underlying ND (53). Female smokers report greater diminution in negative affect by smoking after tobacco abstinence (54, 55) than do male smokers, and they have more difficulty quitting (56). In contrast, according to the findings of several studies in rats, acute administration of nicotine may have greater anxiety-relieving effects in adolescent male rats than in adolescent female or adult male and female rats (7, 57), possibly influenced by sex hormones (58) and/or immature functioning of nicotinic acetylcholine receptors during adolescence (59). More research is needed to investigate whether acute sex-specific responses to nicotine during adolescence translate into sex differences in smoking or ND.

Conclusion

Adolescent girls are at higher risk than boys of becoming regular smokers and developing ND symptoms. Increased understanding of the relative contributions of biology and gender-related social aspects to sex differences in smoking is needed before this finding can inform intervention. However, our data highlight that boys and girls can develop ND symptoms soon after first puff and that early intervention is needed to prevent first puff and progression in smoking after first puff.

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