Original Paper

Neuro
epidemiology

Neuroepidemiology 2009;32:114–121
DOI: 10.1159/000177037

Received: August 2, 2008
Accepted: September 23, 2008
Published online: November 27, 2008

Active and Passive Smoking and Risk of Narcolepsy in People with HLA DQB1*0602: A Population-Based Case-Control Study

Thanh G.N. Ton[a, d] W.T. Longstreth, Jr.[a, b, d, e] Thomas Koepsell[a–c, e]

[a]Neuroepidemiology Group and Departments of [b]Epidemiology and [c]Health Services, School of Public Health and Community Medicine, and Departments of [d]Neurology and [e]Medicine, School of Medicine, University of Washington, Seattle, Wash., USA

Key Words
Case-control study · Epidemiology · HLA-DQ antigens · Narcolepsy · Smoking

Abstract
Background: We examined the risk of narcolepsy associated with active and passive smoking among genetically susceptible individuals. ***Methods:*** We conducted a population-based case-control study in King County, Wash., USA. Between 2001 and 2005, we enrolled 67 cases through physicians and public outreach, and 95 controls through random-digit dialing. Subjects were aged between 18 and 50 years and positive for HLA DQB1*0602. All subjects were administered in-person interviews about their history of active and passive smoking. ***Results:*** We observed an increased risk of narcolepsy associated with having lived with two or more household smokers (odds ratio, OR = 5.1; 95% confidence interval, CI: 1.6, 12.1); with a grandparent or a sibling who smoked (OR = 3.0; 95% CI: 1.1, 8.3); with a non-family household member who smoked (OR = 3.7; 95% CI: 1.6, 8.6); and with an unrelated smoker for 1–2 years (OR = 3.1; 95% CI: 1.0, 9.0). The risk of narcolepsy was not associated with exposure to smoke at work or with active smoking before age 21 or before age of narcolepsy onset. ***Conclusion:*** Passive smoking may be a risk factor for narcolepsy in subjects with HLA DQB1*0602. Future studies could help clarify whether passive smoking is an important etiologic component of narcolepsy among genetically susceptible individuals.

Introduction

Both cigarette smoking and environmental tobacco smoke have been assessed in relation to a variety of neurologic disorders [1–8]. Currently lacking are published reports examining associations between smoking and risk of narcolepsy, a sleep disorder characterized by excessive daytime sleepiness, and cataplexy, an episodic weakness triggered by strong emotions [9]. Results of family and twin studies implicate both genetic and environmental factors in the development of narcolepsy [10]. One etiologic model for the development of narcolepsy proposes that an autoimmune or environmental factor selectively destroys hypocretin-producing cells in the lateral hypothalamus in genetically susceptible individuals, defined as carriers of the HLA DQB1*0602 allele [9, 11]. If tobacco smoke is related to narcolepsy, we might expect passive smoking to be more influential than active smoking given that symptoms of narcolepsy usually manifest themselves in adolescence and that exposure in

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

0251–5350/09/0322–0114$26.00/0

Accessible online at:
www.karger.com/ned

Thanh G.N. Ton, PhD
Department of Neurology, Box 359775
Harborview Medical Center, 325 Ninth Avenue
Seattle, WA 98104 (USA)
Tel. +1 206 744 3654, Fax +1 206 744 8787, E-Mail thanhton@u.washington.edu

childhood to passive smoke occurs more commonly than to active smoking. We conducted a case-control study to assess the risk of narcolepsy associated with active and passive smoking among genetically susceptible individuals. To avoid selection bias associated with recruiting patients exclusively from referral or specialty clinics and to preserve the population-based nature of our study, we recruited cases and controls from the general community in King County, Wash., USA [12]. We were also interested in the etiology of narcolepsy specifically among genetically susceptible individuals, since they may be particularly sensitive to the effects of environmental precipitating factors yet to be identified. Driven by this theoretical framework, we restricted our population-based case-control study to individuals who were positive for HLA DQB1*0602.

Patients and Methods

Recruitment

Recruitment methods for cases are described in detail elsewhere [12]. Briefly, we attempted to identify all prevalent cases of physician-diagnosed narcolepsy who were 18 years and older and residing in King County as of July 1, 2001. A total of 425 cases were entered into the registry. Consent to participate and provide a buccal specimen was requested from each participant. To be considered eligible for the case-control study, we required cases to carry at least one HLA DQB1*0602 allele and be within the 18- to 50-year age range. Of the 279 cases interviewed, 138 (49%) were positive for the HLA DQB1*0602 allele, and 67 of these were also eligible regarding age for the case-control study.

Residents of King County without narcolepsy and within the 18- to 50-year age range were identified through random-digit dialing and recruited as controls. Potential controls within households were sampled using randomized recruitment methods in which age- and gender-specific sampling fractions were applied to create a distribution of controls similar to that of the projected distribution of cases [13]. Of 1,203 controls eligible to participate, 448 (37%) completed interviews. Ninety-five controls carried at least one HLA DQB1*0602 allele and were eligible for the case-control study.

Data Collection

Trained professionals administered in-person interviews to cases and controls using a standardized exposure questionnaire. To determine history of active smoking, subjects were asked if they had ever smoked a cigarette, if they had ever smoked at least 100 cigarettes, the year of smoking initiation, duration of smoking, average number of cigarettes smoked per day, number of years smoked before age 21, and use of cigars, pipes and snuff before age 21. Passive smoking before age 21 was determined by assessing if and how long subjects had lived with persons who smoked cigarettes, including parents (father, stepfather, mother, and stepmother), other family members (grandparents and siblings) and other unrelated household members. Subjects were also asked about their exposure to cigarette smoke at work. Information on demographic factors including age, gender, race, income, and education was obtained during the interview. The University of Washington's institutional review board approved the study.

Analysis

Variables were constructed to characterize exposure to active smoking in terms of dichotomous exposure (ever/never), duration of smoking in years, average number of cigarettes per day, and cumulative smoking in pack-years. We also had information on age of smoking initiation, which enabled us to examine whether smoking initiation occurred before age of narcolepsy onset for cases and before a corresponding index date for controls. For passive smoking, we created a summary variable that described the total number of related and unrelated household smokers with whom subjects lived before age 21. Continuous variables were transformed into categorical variables for which the unexposed category served as reference group, and the median value among exposed controls served as the cutoff for the remaining exposed groups. Tests for linear trend were conducted for variables with more than two ordered categories. All p values presented are two sided.

We also restricted our analysis for passive smoking to subjects who did not report any active smoking. We attempted a similar analysis for active smoking whereby we excluded subjects exposed to passive smoking; however, because nearly all active smokers also reported exposure to passive smoking, our analysis suffered from low power, and, in many circumstances, produced statistically unstable estimates. All analyses were repeated restricting to cases with cataplexy. To assess whether age of onset (and the corresponding index date for controls) modifies the association between smoking and narcolepsy, we stratified our analyses by the median age of onset (i.e. younger than 14 years vs. 14 years and older).

Unconditional logistic regression was used to obtain estimated odds ratios (ORs) and 95% confidence intervals (CIs), adapted to account for the sampling mechanism for controls [13]. Because household income was missing for 5 cases and 7 controls, we multiply imputed household income using age, African-American race, interview year and case status as predictors [14]. All regression models were adjusted for African-American race and income. Other variables such as education and caffeine intake were assessed for their confounding effects in multivariate models. Imputation was performed using the *mice* package in R statistical language, version 2.5 [15]. All other analyses were conducted in Stata version 9.2 [16].

Results

Cases and controls did not differ significantly in regard to age and gender. However, cases were slightly more likely to have had a graduate school education than controls, were significantly more likely to be African-American, and significantly less likely to have higher levels of household income (table 1).

Table 1. Sociodemographic characteristics of cases and controls aged 18–50 years who are also positive for HLA DQB1*0602 (King County, Wash., USA, 2001–2005)

Characteristics	Weighted percentages		OR	95% CI	Test for trend p value
	cases (n = 67)	controls (n = 95)			
Age group					0.4
18–25 years	22.4	18.0	1.0	reference	
26–30 years	13.4	18.2	0.5	0.2–1.5	
31–35 years	22.4	17.7	0.8	0.3–2.2	
36–40 years	7.5	15.8	0.2	0.1–0.8	
41–45 years	16.4	17.2	0.7	0.2–1.9	
46–50 years	14.9	13.0	0.7	0.2–2.2	
Gender					
Male	29.9	41.9	1.0	reference	
Female	70.1	58.1	1.1	0.5–2.4	
Race					
White	80.6	92.1	1.0	reference	
African-American	14.9	1.4	8.2	2.1–31.1	
Asian	1.5	0.9	1.2	0.1–13.8	
Hispanic	1.5	0.5	2.5	0.2–40.2	
Other	1.5	5.1	0.3	0.0–2.6	
Annual income (imputed), USD					<0.001
<20,000	39.7	18.2	1.0	reference	
20,000–39,999	18.8	23.3	0.3	0.1–0.8	
40,000–59,999	17.6	11.7	0.5	0.2–1.6	
>60,000	23.9	46.8	0.2	0.1–0.4	
Education					0.15
High school or less	28.4	24.3	1.0	reference	
College	59.7	54.8	0.9	0.4–1.9	
Graduate school	11.9	20.9	0.4	0.1–1.2	

Results for active smoking are summarized in table 2. We did not observe any significant association between narcolepsy and active smoking exposures. Adjustment for coffee consumption before age 21 and education did not appreciably change estimates (data not shown) and were not included in the final models.

In contrast to active smoking, we observed several significant associations between risk of narcolepsy and passive smoking (table 3). Although risk of narcolepsy was not associated with parental smoking, it was three- to fourfold higher if other family members or non-family members were smokers. Among those who had at least two smokers in the household, we observed a fivefold increase in narcolepsy risk compared to those who did not live with any smokers. Compared to those who had never lived with a household smoker, risk of narcolepsy was significantly elevated threefold for those who lived with an unrelated household smoker for 1–2 years. Exposure to tobacco smoke at work was not significantly associated with narcolepsy risk.

A subgroup analysis in which passive smoking was assessed among never smokers of 100 cigarettes resulted in even stronger measures of association than in the original unrestricted analysis, some of which remained statistically significant: having lived with a non-family smoking household member was associated with an almost ninefold increased risk of narcolepsy and having lived with an unrelated smoker for ≥ 3 years increased the risk of narcolepsy by more than eightfold (table 3).

When we reanalyzed our data by further restricting cases to those with cataplexy (data not shown), associations were essentially unchanged for active smoking. For certain aspects of passive smoking that were already statistically significant in the original analysis, measures of association remained significant. For instance after restricting cases to those with cataplexy, risk of narcolepsy associated with having lived with a related household smoker member other than a parent increased slightly to 3.2 (95% CI: 1.1, 8.3), and the association with having lived with an unrelated smoker increased to 4.4 (95% CI: 1.6, 8.67).

Table 2. Active smoking and narcolepsy among 18- to 50-year-old subjects who are also positive for HLA DQB1*0602 (King County, Wash., USA, 2001–2005)

Lifetime exposure	Weighted percentages		OR[a]	95% CI	Test for trend p value
	cases (n = 67)	controls (n = 95)			
Ever smoked a cigarette					
No	23.8	31.5	1.0	reference	
Yes	76.2	68.5	1.2	0.5–2.8	
Ever smoked ≥100 cigarettes					
No	60.3	58.8	1.0	reference	
Yes	39.7	41.2	0.9	0.4–1.9	
Duration of smoking					0.3
Never smoked ≥100 cigarettes	60.3	58.8	1.0	reference	
1–8 years	20.6	21.3	1.2	0.4–3.1	
≥9 years	19.1	19.9	0.7	0.2–1.7	
Cigarettes per day					0.6
Never smoked ≥100 cigarettes	60.3	58.8	1.0	reference	
<20	31.8	32.5	1.0	0.4–2.2	
≥20	7.9	8.7	0.6	0.2–2.4	
Total pack-years					0.5
Never smoked ≥100 cigarettes	60.3	58.8	1.0	reference	
1–9 pack-years	27.0	28.7	1.0	0.4–2.4	
≥10 pack-years	12.7	12.5	0.6	0.2–2.0	
Smoked before age 21					
No	40.7	45.6	1.0	reference	
Yes	59.3	54.4	1.2	0.6–2.5	
Duration smoked before age 21					0.4
Did not smoke any cigarette	40.7	45.6	1.0	reference	
1–2 years	20.3	27.4	0.9	0.4–2.4	
≥3 years	39.0	26.9	1.5	0.6–3.4	
Smoked cigars before age 21					
No	85.7	82.6	1.0	reference	
Yes	14.3	17.4	1.2	0.4–4.0	
Smoked pipes before age 21					
No	95.2	93.5	1.0	reference	
Yes	4.8	6.5	1.0	0.1–7.4	
Used snuff before age 21					
No	90.5	86.4	1.0	reference	
Yes	9.5	13.6	1.0	0.3–3.3	
Smoked before age at onset					
Never smoked a cigarette	23.8	31.5	1.0	reference	
1st cigarette before age at onset	27.0	26.7	1.0	0.4–2.7	
1st cigarette after age at onset	49.2	40.8	1.4	0.6–3.4	
Smoked regularly before age at onset					
Never smoked ≥100 cigarettes	60.3	58.8	1.0	reference	
Regularly before age at onset	11.1	9.6	1.0	0.3–3.7	
Regularly after age at onset	28.6	31.6	0.8	0.4–1.9	

[a] Adjusted for income (multiply imputed) and African-American race.

We observed no effect modification of the association between passive smoking and narcolepsy when we stratified our analyses according to the median age of onset. The risk of narcolepsy associated with having lived with one household smoker was not different for those whose age at onset was <14 years (OR = 0.9; 95% CI: 0.2, 3.2) and those ≥14 years (OR = 1.3; 95% CI: 0.4, 4.3). Likewise, the risk of narcolepsy related to having lived with two or more

Table 3. Passive smoking and narcolepsy among 18- to 50-year-old subjects who are also positive for HLA DQB1*0602 (King County, Wash., USA, 2001–2005)

Exposure before age 21	Weighted percentages		Overall			Among all non-smokers[b]		
	cases (n = 67)	controls (n = 95)	OR[a]	95% CI	test for trend p value	OR[a]	95% CI	test for trend p value
Total number of smokers in household[c]					0.007			0.13
None	29.2	29.3	1.0	reference		1.0	reference	
1 smoker	41.5	60.3	1.1	0.5–2.6		1.8	0.8–3.8	
≥2 smokers	29.2	10.4	5.1	1.6–12.1		3.9	0.8–18.9	
Either parent a smoker								
Neither	37.9	36.0	1.0	reference		1.0	reference	
At least one	62.1	64.0	1.2	0.6–2.5		1.0	0.4–2.6	
Lived with smoking family members other than parents, such as grandparents and siblings								
No	77.6	87.7	1.0	reference		1.0	reference	
Yes	22.4	12.3	3.0	1.1–8.3		5.3	0.9–32.3	
Lived with smoking non-family members								
No	68.7	84.3	1.0	reference		1.0	reference	
Yes	31.3	15.7	3.7	1.6–8.6		8.9	1.7–47.4	
Duration lived with smoking non-family members					0.01			0.03
None	70.2	84.3	1.0	reference		1.0	reference	
1–2 years	14.9	9.6	3.1	1.0–9.0		6.3	0.6–64.5	
≥3 years	14.9	6.1	3.5	0.1–12.0		8.6	0.8–91.0	
Exposed to smoke at work								
No	69.2	64.7	1.0	reference		1.0	reference	
Yes	30.9	35.3	0.9	0.4–2.0		0.7	0.3–2.1	
Duration exposed to smoke at work					0.8			0.6
Not exposed	65.7	64.7	1.0	reference		1.0	reference	
1–4 years	14.9	13.1	0.9	0.3–2.5		0.8	0.2–3.2	
≥5 years	19.4	22.2	0.9	0.3–2.4		0.7	0.2–2.6	
Active and passive smoking								
Neither	16.4	19.3	1.0	reference				
Active only	8.2	9.7	0.6	0.1–3.0				
Passive only	42.6	40.6	1.8	0.7–5.2				
Both	32.8	30.4	1.7	0.5–5.0				

[a] Adjusted for income (multiply imputed) and African-American race. [b] Never smoked >100 cigarettes.

household smokers was similar for those with age at onset <14 years (OR = 4.5; 95% CI: 0.8, 24.1) and those ≥14 years (OR = 4.9; 95% CI: 1.1, 21.8) (data not shown).

Discussion

Among genetically susceptible individuals, we found no association between narcolepsy and active smoking. On the other hand, we observed significant associations between narcolepsy and passive smoking before age 21, i.e. having lived with related and unrelated household members who smoked. Exposure to tobacco smoke in the workplace was not significantly associated with narcolepsy risk.

Several limitations relating to the general design of our study are notable. First, because we were interested in the etiology of narcolepsy specifically among genetically susceptible individuals, and because sleep studies would not be feasible to incorporate in the recruitment strategy for a population-based study, we only required that cases within the specified age range have a physician diagnosis of narcolepsy and be positive for HLA DQB1*0602. In the pursuit of our hypothesis and to preserve the population-based nature of our study, we may have sacrificed some diagnostic precision typically afforded by sleep studies. We did, however, attempt to address disease misclassification by repeating our analyses restricted to cases with HLA DQB1*0602 who also had cataplexy. Second, because our study was small, we were unable to detect more

subtle associations that may provide a greater understanding about the etiology of narcolepsy. Third, although we attempted to identify all cases of narcolepsy in King County using multiple methods [12], we may not have been able to capture all existing cases in the community.

Specific to these analyses are a number of other limitations that may have influenced our results. First, although the overall response rate of 37% among controls is typical of that documented in recent studies using similar randomized digit-dialing techniques [17], this low response rate represents a substantial potential for selection bias when examining smoking history as the primary exposure because, in general, non-respondents are more likely than respondents to be current smokers [18]. If a similar association between passive smoking and participation exists among controls, selection bias may account for part or all of the observed significant associations between passive smoking and narcolepsy. Second, because we relied on questionnaires to examine past exposures of active and passive smoking, our results are vulnerable to differential recall bias, whereby cases would be more likely to recall and report having lived with a smoker than controls. In this particular study where a popular hypothesis linking passive smoking and narcolepsy was lacking, differential recall of passive smoking between cases and controls may be less problematic than in other studies, for example of lung cancer, where passive smoking is highly suspected to be an important risk factor [19].

Non-differential exposure misclassification is another potential source of error. Because we had no information on precisely when exposure to passive smoke may have occurred in relation to age of narcolepsy onset, our ascertainment of passive smoking before age 21 is likely to include exposure during an etiologically irrelevant time window. Exposure misclassification may also stem from imprecise measurement of passive smoke exposure, which was based on the number of household members who smoked. Ultimately, exposure to passive smoking also depends on other variables such as number of cigarettes smoked in a particular location, size of the room, the ventilation system of the building [20], none of which was known in this study but might be worth investigating in future studies. An attenuation of estimates resulting from these sources of non-differential misclassification, however, would make the argument for passive smoking even more compelling.

Finally, although we attempted to control for confounding, our results may still be distorted by unmeasured or residual confounding. Studies from the US and United Kingdom suggest that adults exposed to secondhand smoke generally have less healthy lifestyles [21, 22] or that secondhand smoke exposure is associated with correlates of lifestyle that influence health outcomes [23].

One possible explanation for the positive finding for passive smoking and null results for active smoking could relate to the nature of the disease itself. Narcolepsy typically starts during adolescence [11]. Cases in this study had a median age at onset of 14 years. A national survey reported only 8.4% of middle-school students and 6.7% of high-school students reported smoking their first cigarette before the age of 11 [24]. In contrast, a far higher proportion of infants, children and youth are potentially exposed to secondhand smoke than to cigarette smoke from active use. In phases I and II of the NHANES III (1988–1994), 84.7% of children aged 4–11 years had a serum cotinine level indicative of nicotine metabolism presumably from exposure to passive smoke [25, 26]. In contrast to active cigarette smoking, exposure to passive smoking may be considered more etiologically relevant to narcolepsy due to the timing of exposure in relation to disease onset. The explanation for the lack of association for exposure to secondhand smoke in the workplace may follow a similar argument in which employment before age 21 precludes ages defined by infancy and childhood when cigarette smoking has not been initiated, but when exposure to passive smoking can be highly prevalent.

Whether different etiologies exist for those who develop narcolepsy earlier than for those in whom disease onset occurs later remains speculative. Evidence of a modifying effect of age at onset on the association between passive smoking and narcolepsy could suggest disparate etiologies for those who develop the disease at a younger age than those in whom onset occurs much later. However, we did not observe any such effect modification in our data.

Curiously, while associations related to certain passive smoking exposures were strong, we observed a lack of association between narcolepsy risk and having at least one parent who smoked while subjects were 21 years or younger. If a biological mechanism exists to explain the observed association between passive smoking and narcolepsy, this null finding may be due to increased awareness among smoking parents of the adverse health effects of secondhand smoke in the home [27], or to implementations of in-home smoking bans among smoking parents [28], or possibly to an underlying distribution of socioeconomic factors from residual confounding. Alterna-

tively, although the observed associations represent intriguing possibilities in the etiology of narcolepsy, our findings could simply be due to chance.

Possibly, passive smoking represents an environmental insult occurring during an etiologically relevant time period and initiating the destruction of hypocretin-producing cells in genetically susceptible individuals. In contrast to active smoking, exposure to environmental tobacco smoke is likely to occur during critical periods of brain development that precede the potential onset of narcolepsy. Environmental tobacco smoke contains over 4,000 chemical components as well as contaminants such as pesticides, many of which are implicated in neuronal cell death and in the underlying pathology of neurodegenerative diseases. Environmental tobacco smoke is also associated with serious bacterial infections [29]. Neurologic disorders with a hypothesized autoimmune etiology have been known to result from streptococcal infections [30]. In the case of narcolepsy, exposure to passive smoke may increase the likelihood of streptococcal infections due to immunosuppression [31–33], which in turn could trigger an autoimmune response leading to the selective destruction of hypocretins in the lateral hypothalamus of people with HLA DQB1*0602.

Few population-based studies have been conducted in the field of narcolepsy because of the many challenges that exist for studying such a disease [11, 12]. Despite numerous limitations, our efforts represent an attempt to incorporate HLA typing into a population-based study designed to explore etiologic factors implicated in the gene-environment hypothesis. Given that nicotine and other tobacco smoke constituents are potent neurotoxicants, our results represent preliminary suggestions of a possible role for passive smoking in the development of narcolepsy among genetically susceptible individuals. Replication of these findings is needed.

Acknowledgments

This study would not have been possible without help on patient identification and recruitment from the many sleep medicine specialists in King County, and without help on HLA genotyping from Dr. Gerald Nepom at the Benaroya Research Institute at Virginia Mason, Seattle, Wash., USA. The authors also gratefully acknowledge the assistance of Dr. Sarah Velde and Ms. Audrey Hendrickson in conducting this research.

References

1 Fratiglioni L, Wang HX: Smoking and Parkinson's and Alzheimer's disease: review of the epidemiological studies. Behav Brain Res 2000;113:117–120.
2 Hernan MA, Takkouche B, Caamano-Isorna F, Gestal-Otero JJ: A meta-analysis of coffee drinking, cigarette smoking, and the risk of Parkinson's disease. Ann Neurol 2002;52:276–284.
3 Letenneur L, Larrieu S, Barberger-Gateau P: Alcohol and tobacco consumption as risk factors of dementia: a review of epidemiological studies. Biomed Pharmacother 2004;58:95–99.
4 Nelson LM, Longstreth WT Jr, McGuire V: Cigarette smoking and risk of amyotrophic lateral sclerosis: a population-based case-control study. Neuroepidemiology 1998;17:7.
5 Phillips LE, Longstreth WT Jr, Koepsell T, Custer BS, Kukull WA, van Belle G: Active and passive cigarette smoking and risk of intracranial meningioma. Neuroepidemiology 2005;24:117–122.
6 Norman MA, Holly EA, Preston-Martin S: Childhood brain tumors and exposure to tobacco smoke. Cancer Epidemiol Biomarkers Prev 1996;5:85–91.
7 Hankey GJ: Smoking and risk of stroke. J Cardiovasc Risk 1999;6:207–211.
8 Mikaeloff Y, Caridade G, Tardieu M, Suissa S: Parental smoking at home and the risk of childhood-onset multiple sclerosis in children. Brain 2007;130:2589–2595.
9 Dauvilliers Y, Arnulf I, Mignot E: Narcolepsy with cataplexy. Lancet 2007;369:499–511.
10 Chabas D, Taheri S, Renier C, Mignot E: The genetics of narcolepsy. Annu Rev Genomics Hum Genet 2003;4:459–483.
11 Longstreth WT Jr, Koepsell TD, Ton TG, Hendrickson AF, van Belle G: The epidemiology of narcolepsy. Sleep 2007;30:13–26.
12 Longstreth WT Jr, Ton TG, Koepsell TD, Gersuk VH, Hendrickson AF, Velde S: Prevalence of narcolepsy in King County, Washington. Sleep Med 2008, in press.
13 Weinberg CR, Sandler DP: Randomized recruitment in case-control studies. Am J Epidemiol 1991;134:421–432.
14 van Buuren S, Boshuizen HC, Knook DL: Multiple imputation of missing blood pressure covariates in survival analysis. Stat Med 1999;18:681–694.
15 R Development Core Team: A Language and Environment for Statistical Computing. Vienna, R Foundation for Statistical Computing, 2006.
16 Stata: Stata Statistical Software: Release 9. College Station, Stata, 2005.
17 Bunin GR, Spector LG, Olshan AF, Robison LL, Roesler M, Grufferman S, Shu XO, Ross JA: Secular trends in response rates for controls selected by random digit dialing in childhood cancer studies: a report from the Children's Oncology Group. Am J Epidemiol 2007;166:109–116.
18 Shahar E, Folsom AR, Jackson R: The effect of nonresponse on prevalence estimates for a referent population: insights from a population-based cohort study. Atherosclerosis Risk in Communities (ARIC) Study Investigators. Ann Epidemiol 1996;6:498–506.
19 Morabia A: Active and passive smoking in breast cancer. Epidemiology 2002;13:744–745.

20 Assessment of exposure to secondhand smoke. The health consequences of involuntary exposure to tobacco smoke: a report of the Surgeon General. Atlanta, US Department of Health and Human Services, Centers for Disease Control and Prevention, Coordinating Center for Health Promotion, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2006, chapt 3, pp 83–126.
21 Matanoski G, Kanchanaraksa S, Lantry D, Chang Y: Characteristics of nonsmoking women in NHANES I and NHANES I epidemiologic follow-up study with exposure to spouses who smoke. Am J Epidemiol 1995; 142:149–157.
22 Thornton A, Lee P, Fry J: Differences between smokers, ex-smokers, passive smokers and non-smokers. J Clin Epidemiol 1994;47: 1143–1162.
23 Kawachi I, Colditz GA: Invited commentary: confounding, measurement error, and publication bias in studies of passive smoking. Am J Epidemiol 1996;144:909–915.
24 Youth tobacco surveillance – United States, 1998–1999. MMWR CDC Surveill Summ 2000;49:1–94.
25 Prevalence of exposure to secondhand smoke. The health consequences of involuntary exposure to tobacco smoke: a report of the Surgeon General. Atlanta, US Department of Health and Human Services, Centers for Disease Control and Prevention, Coordinating Center for Health Promotion, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2006, chapt 4, pp 127–164.
26 Mannino DM, Moorman JE, Kingsley B, Rose D, Repace J: Health effects related to environmental tobacco smoke exposure in children in the United States: data from the Third National Health and Nutrition Examination Survey. Arch Pediatr Adolesc Med 2001;155:36–41.
27 State-specific prevalence of smoke-free home rules – United States, 1992–2003. MMWR Morb Mortal Wkly Rep 2007;56: 501–504.
28 Eriksen W, Bruusgaard D: Smoking behaviour in young families. Do parents take practical measures to prevent passive smoking by the children? Scand J Prim Health Care 1995; 13:275–280.
29 Kum-Nji P, Meloy L, Herrod HG: Environmental tobacco smoke exposure: prevalence and mechanisms of causation of infections in children. Pediatrics 2006;117:1745–1754.
30 Snider LA, Swedo SE: Post-streptococcal autoimmune disorders of the central nervous system. Curr Opin Neurol 2003;16:359–365.
31 Wang L, Joad JP, Abel K, Spinner A, Smiley-Jewell S, Liu H, Pinkerton KE: Effects of environmental tobacco smoke on the developing immune system of infant monkeys. J Allergy Clin Immunol 2007;120:445–451.
32 Avanzini MA, Ricci A, Scaramuzza C, Semino L, Pagella F, Castellazzi AM, Marconi M, Klersy C, Pistorio A, Boner AL, Marseglia GL: Deficiency of INFgamma producing cells in adenoids of children exposed to passive smoke. Int J Immunopathol Pharmacol 2006;19:609–616.
33 Ricci A, Avanzini MA, Scaramuzza C, Castellazzi AM, Marconi M, Marseglia GL: Toll-like receptor 2-positive and Toll-like receptor 4-positive cells in adenoids of children exposed to passive smoking. J Allergy Clin Immunol 2005;115:631–632.