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Environmental toxins and risk of narcolepsy among people with HLA DQB1*0602

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Abstract

One etiologic model for narcolepsy suggests that some environmental toxin selectively and irreversibly destroys hypocretin-producing cells in individuals with human leukocyte antigen (HLA) DQB1*0602. Between 2001-2005, the authors conducted a population-based case-control study in King County, Washington to examine narcolepsy risk in relation to toxins found in jobs, hobbies and other non-vocational activities. Sixty-seven cases and 95 controls were enrolled; all were between ages 18-50 and positive for HLA DQB1*0602. All were administered in-person interviews about jobs, hobbies or other non-vocational activities before age 21. All analyses were adjusted for African American race and income. Risk increased significantly for jobs involving heavy metals (odds ratio [OR]=4.7; 95% confidence interval [CI]: 1.5, 14.5) and for highest levels of exposure to woodwork (OR: 3.0; 95% CI: 1.0, 8.9), fertilizer (OR=3.1; 95% CI: 1.1, 9.1), and bug or weed killer (OR=4.5; 95% CI: 1.5, 13.4). Associations were of borderline significance for activities involving ceramics, pesticides, and painting projects. Significant dose-response relationships were evident for jobs involving metals ($p<0.03$), paints ($p<0.03$), and bug or weed killer ($p<0.02$). Additional studies are needed to replicate these findings and continue the search for specific toxins that could damage hypocretin neurons in genetically susceptible people.

Keywords

case-control; environmental exposure; epidemiology; HLA-DQ antigens; narcolepsy

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Introduction

Narcolepsy is a sleep disorder characterized by excessive daytime sleepiness, cataplexy, hypnagogic hallucinations, and sleep paralysis with an onset typically before age 21 (Yoss and Daly, 1957). It likely results from the selective loss of cells in the lateral hypothalamus that secrete neurotransmitters called hypocretins (Longstreth et al., 2007; Peyron et al., 2000; Thannickal et al., 2000). A genetic tendency for narcolepsy has been noted since the nineteenth century, and in fact, narcolepsy has one of the tightest associations with specific genetic markers. First-degree relatives are 20-40 times more likely to develop the disease than the general population (Chabas et al., 2003). However, familial clustering accounts for only 10% of patients with narcolepsy, and only 25%-31% of monozygotic twins are reported to be concordant for disease (Mignot, 1998), suggesting that environmental factors are also involved in the etiology of narcolepsy. One etiologic model for the development of narcolepsy proposes that an environmental factor selectively destroys hypocretin-producing cells in genetically susceptible individuals, defined as carriers of the human leukocyte antigen (HLA) DQB1*0602 allele (Longstreth et al., 2007; Mignot, 1998). We were particularly 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. In this group of people, we assessed the risk of narcolepsy associated with environmental toxins that may be found in jobs, hobbies, and other activities performed before age 21.

Materials and Methods

Recruitment

Recruitment methods for cases and controls are detailed elsewhere (Koepsell et al., 2009; Longstreth et al., 2009a; Ton et al., 2009). Briefly, we attempted to identify all prevalent cases of physician-diagnosed narcolepsy who were 18 years and older and residing in King County, Washington as of July 1, 2001. For controls, residents of King County without narcolepsy and within the 18-50 year-old age range were identified through random-digit dialing. 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 (Koepsell et al., 2009; Ton et al., 2009; Weinberg and Sandler, 1991). To be considered eligible for the case-control study, we required both cases and controls to carry at least one HLA DQB1*0602 allele and be within the 18-50-year-old age range. All eligible cases and controls were asked to participate in the study. Consent to participate and provide a buccal specimen was requested from each participant. Samples were assessed for the presence of HLA DQB1*0602 alleles (Gersuk and Nepom, 2009).

We identified and enrolled 425 patients into a narcolepsy registry. Of the 279 interviewed cases, 138 (49%) were positive for the HLA DQB1*0602 allele, and 67 of these were age-eligible for the study. Of 1,203 controls eligible to participate, 448 (37%) completed interviews. Of these, 95 controls carried the HLA DQB1*0602 allele and were eligible for the analyses reported here. The University of Washington's institutional review board approved the study.

Data collection

Trained professionals administered in-person interviews to cases and controls using a standardized exposure questionnaire. Interviews were scheduled according to availability of each subject. Questionnaires were developed using a combination of previously validated questions (Anic-Labat et al., 1999; Anonymous, 1997; Baldwin et al., 2004; Chervin and Aldrich, 1999; Douglass et al., 1994; Hublin et al., 1994; Johns, 1991; Ware and Gandek,

1998) and other questions designed for exploratory purposes. Because the onset of narcolepsy typically occurs during adolescence, questions assessing exposures specifically referred to those occurring before age 21. To determine exposure to environmental toxins commonly found in specific jobs around and outside the home, subjects were asked if they had ever held jobs which involved lawn care, garden work, painting projects, cleaning indoors as well as other odd jobs. Subjects who answered "yes" were asked whether they had engaged in such jobs infrequently, irregularly for years, or regularly for years. In addition, subjects were asked if any jobs had exposed them to toxins in general, and specifically, to heavy metals (e.g., lead, mercury, arsenic), pesticides (e.g., insecticides, herbicides, fungicides), solvents (e.g., paints, glues, gasoline) and carbon monoxide. Those who answered affirmatively were asked if they had become ill from the exposure.

In addition to jobs held before age 21, we asked subjects to recall their hobbies and other activities for the same time period. Subjects reported any involvement in activities involving leather, ceramics, house painting, oil painting, woodworking, engines or motors, wooden or plastic models, chemistry sets, and the application of fertilizer and bug or weed killer. Subjects were also asked to report the average number of hours per month or average number of times per month as well as the total number of years they had engaged in each of these activities. Information on demographic factors including age, gender, race, income and education was also obtained during the interview.

Analysis

Variables were constructed to characterize exposure in two ways: (1) dichotomously (any reported exposure vs. none), and (2) ordinally according to increasing dose. For jobs relating to lawn care, garden care, painting and cleaning, we used frequency as a measure of dose. For exposures to pesticides, heavy metals, solvents and carbon monoxide, we constructed a variable defined by no exposure, exposed but not ill, and exposed and became ill. For hobbies and other activities, cumulative hours of exposure were first calculated as continuous variables from information on frequency and duration, and then transformed into ordinal variables with three categories (none, low, and high) using the median value among exposed controls as the cutoff between low and high exposure. For activities involving fertilizer and bug or weed killer, exposure was calculated in terms of cumulative frequency of application. All dose variables contained an unexposed category that served as the reference group.

We used percentages to represent prevalence of characteristics and exposures among cases and controls. Because controls were selected according to age- and gender-specific selection probabilities, percentages were weighted by the inverse of the final selection probability to obtain accurate proportions for each characteristic. We used unconditional multivariate logistic regression to obtain estimated odds ratios (ORs) and 95% confidence intervals (CIs) adjusted for African American race and household income, and adapted to account for the sampling mechanism for controls (Weinberg and Sandler, 1991). Because household income was missing for five cases and seven controls, we multiply imputed household income using age, African American race, interview year and case status as predictors (van Buuren et al., 1999). Imputation was performed using the *mice* package in R statistical language, version 2.5 (R Development Core Team, 2006). Tests for linear trend were conducted for all dose variables by placing continuous variables of dose into the logistic models. We assessed the significance of linear trends using the Wald test. All other analyses were conducted in Stata version 9.2 (StataCorp, 2006).

As a secondary analysis to address potential disease misclassification, we restricted our analyses to 45 cases with cataplexy as determined by review of medical chart by a study neurologist, or a positive screen developed by Anic-Labat (Anic-Labat, 1999).

Results

Cases and controls did not differ significantly in regards to age and gender, as intended under the control-selection protocol (Table 1). However, cases were significantly more likely to be African American, and significantly less likely to have higher levels of household income. Given these imbalances, all regression models were adjusted for African American race and income. Cases had a mean age of onset of 13.8 (SD=6.6).

Among jobs that subjects performed around the house or in their neighborhoods before the age of 21, only painting projects suggested an association with narcolepsy in both the primary and sensitivity analyses (Table 2).

Risk of narcolepsy was significantly increased over two-fold for jobs exposing subjects to toxins in general (Table 3), with subjects naming a variety of exposures including chlorine, mold, cleaning products, kerosene, asbestos, fiberglass, jet fuel, mace, and fertilizer. A nearly five-fold significant increase in risk of narcolepsy was observed for jobs with exposure to heavy metals such as lead, mercury or arsenic, with a significant trend according to severity of illness from exposure.

Risk of narcolepsy was significantly increased in the highest exposure category for woodworking, applications of fertilizer, and applications of bug or weed killer (Table 4). A significant trend was only observed for cumulative applications of bug or weed killer ($p<0.02$).

When we restricted our analysis to cases with cataplexy, stronger estimates of association emerged for lawn cutting (OR=0.4; 95% CI: 0.2, 0.9), hobbies involving ceramics (OR=2.8; 95% CI; 1.1, 7.0), and for the highest exposure category to painting projects (OR=8.4; 95% CI; 1.0, 73.2). Estimates of association became non-significant for toxins, and heavy metals. Results were notably weakened only for application of fertilizer, with estimates for dichotomous exposure, cumulative exposure, and linear trend all attenuated.

Discussion

In this population-based study in which all subjects had HLA DQB1*0602, we found a nearly five-fold increase in narcolepsy risk associated with jobs containing heavy metals and with six or more applications of bug or weed killer. Risk was also elevated, but less impressively so, for job-related exposures to pesticides, toxins, and paint; for activities involving ceramics; and for the highest exposure level to activities involving wood. Results were similar when cases were restricted to those with cataplexy.

Our study is limited by possibly incomplete ascertainment of all population-based cases, small sample size and hence low statistical power to detect more subtle associations, and a multiple comparison issue arising from the exploratory nature of our aims. Because clinical sleep studies are not feasible to incorporate in the recruitment strategy for a population-based epidemiologic study, we may have sacrificed some diagnostic precision typically afforded by measures obtained in sleep laboratories. We did attempt to address disease misclassification by repeating our analyses restricted to cases with HLA DQB1*0602 who also had cataplexy. In doing so, however, we found stronger associations for certain exposures, perhaps reflecting reduced disease misclassification, but other estimates lost statistical significance, possibly due to a reduction in power. In addition, although the overall response rate of 37% among controls is typical of that documented in recent studies using similar randomized digit-dialing techniques (Bunin et al., 2007), our study is vulnerable to selection bias as a result. We attempted to control for this bias by adjusting for African-American race and annual household income, both of which were significantly associated with case-control status in our study. Also, because we relied exclusively on questionnaires to examine past exposures, our results are vulnerable to

differential recall bias, whereby cases may be more likely than controls to recall exposures. We attempted to limit our assessment of exposures to an etiologically relevant time window by specifying that subjects report exposures before age 21; however because the mean age of symptom onset reported by cases was 13.8 (SD = 6.6), our exposures may have included those occurring in a non-relevant time period for some early-onset cases. Because our study was exploratory in nature, we questioned subjects not only on a broad range of topics but also in terms of broad categories of exposure. Pesticides, for instance, encompasses an array of compounds used to deter or kill insects (insecticides), rodents (rodenticides), plants (herbicides), and fungi (fungicides) (Hatcher et al., 2008). Similarly, our findings for toxins, metals, and activities involving woodwork, ceramics and painting projects represent broad exposure categories that may each encompass a variety of constituents. Which specific factors may drive the observed associations remains to be determined.

Numerous studies have been conducted assessing certain risk factors for narcolepsy including obesity, immunologic and genetic factors, and associated diseases (Longstreth et al., 2007), but few have evaluated environmental exposures as potential risk factors for narcolepsy. Picchioni and colleagues assessed infectious agents and psychological stress as risk factors for narcolepsy (Picchioni et al., 2007). They observed an increased risk of narcolepsy from flu infections, unexplained fevers, and major change in sleep habits; the authors did not ask about exposures related to toxins. Orellano and colleagues conducted a case-control study and observed the life events in the year preceding age of onset were significantly associated with narcolepsy risk. (Orellana et al., 1994). However, neither of these two studies matched controls to cases by HLA status, a limitation that was noted in both reports.

Deficient in the literature is an understanding of how environmental toxins may contribute to narcolepsy risk. Solvents, pesticides and heavy metals such as mercury, lead, and arsenic are widely known to be neurotoxic (Firestone and Longstreth, 1994; Graham Doyle G et al., 2003). One possible mechanism is that toxins can directly injure the brain. Pesticides may be of particular interest because almost 40% of all pesticides used in the United States contain organophosphorous (OP) compounds (Feldman, 1999), and because OP compounds inhibit cholinesterase resulting in excess acetylcholine, a neurotransmitter used in the circuitry for regulation of sleep, wakefulness, and arousal (Nieuwenhuys et al., 2008). Possibly, OP compounds affect acetylcholine-rich areas of the midbrain, disturbing the sleep-wake cycle involved in narcolepsy. In humans, exposure to OP compounds has been associated with difficulty in maintaining alertness, lethargy, drowsiness, sleep problems and other narcoleptic-like symptoms (Metcalf and Holmes, 1969), and many OP compounds have been shown to increase rapid eye movement sleep by inhibiting acetylcholinesterase (Duffy et al., 1979; Metcalf and Holmes, 1969). Hypersensitivity to acetylcholine has also been implicated in the pathophysiology of narcolepsy (Kilduff et al., 1986; Mignot, 2000; Nishino and Mignot, 1997). Another plausible mechanism involves excitotoxicity, a process by which neurons are damaged or killed as a result of activation of excitatory amino acids (Hauser and Beal, 2008). In the case of narcolepsy, glutamate-induced excitotoxity may play a role in selectively damaging hypocretin neurons. Katsuki and colleagues demonstrated that hypocretin neurons were selectively and irreversibly damaged by N-methyl-D-aspartate (NMDA), an excitotoxin that mimics the neurotransmitter glutamate (Katsuki and Akaike, 2004). Hypocretin neurons contain both functional and non-functional NMDA receptors, and their electrical activity appears to be influenced by excitatory glutaminergic input (Katsuki and Akaike, 2004). Therefore, any exogenous or endogenous compound with the potential to elicit glutamate-related toxicity should be explored as a potential risk factor. Finally, given the mounting evidence of an immunologic basis for narcolepsy (Black, 2005; Carlander et al., 1993; Cvetkovic-Lopes et al., 2010; Hallmayer et al., 2009; Mignot et al., 1995; Nepom, 1993), it is also possible that an environmental factor can trigger an autoimmune response leading to the selective destruction of hypocretins in the lateral hypothalamus. Such a mechanism for

narcolepsy has been recently speculated for exposure to streptococcal infections (Koepsell et al., 2010; Longstreth et al., 2009b) and second hand smoke (Ton et al., 2009).

Our findings for narcolepsy provide etiologic clues that warrant not only replication by future studies but also attempts to identify the specific environmental toxins that may plausibly increase the risk of narcolepsy among genetically susceptible individuals.

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The University of Washington's institutional review board approved the study.

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Table 1

Sociodemographic Characteristics of Cases and Controls Ages 18-50 Who Were Also Positive for HLA DQB1*0602

	Percentages*				
Characteristic	**Cases (N=67)**	**Controls (N=95)**	**OR**	**95% CI**	**Linear Trend *P*-value**
Age group (years)					(matched)
18-25	22.4	18.0	1.0	Reference	
26-30	13.4	18.2	0.5	0.2, 1.5	
31-35	22.4	17.7	0.8	0.3, 2.2	
36-40	7.5	15.8	0.2	0.1, 0.8	
41-45	16.4	17.2	0.7	0.2, 1.9	
46-50	14.9	13.0	0.7	0.2, 2.2	
Gender					
Male	29.9	41.9	1.0	Reference	(matched)
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 (after imputation)					<0.001
Under $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	

* Percentages were weighted by the inverse of the final selection probability

Table 2

Risk of Narcolepsy Associated With Jobs Performed by Subjects Around the House or in Their Neighborhoods Before the Age of 21

	Among 67 cases with and without cataplexy, and 95 controls					Among 45 cases with cataplexy†, and 95 controls		
	Percentages*							
Exposure	**Cases**	**Controls**	**OR**	**95% CI**	***P*-value‡**	**OR**	**95% CI**	**P-value‡**
CUT LAWN								
Any exposure	59.7	75.2	0.6	0.3, 1.3	0.2	0.4	0.2, 0.9	0.03
Frequency of exposure					0.5			0.3
None	40.9	24.8	1.0	Reference		1.0	Reference	
Infrequently	12.1	19.5	0.3	0.1, 0.9		0.2	0.5, 0.6	
Irregularly for years	15.2	9.6	2.1	0.7, 6.3		0.7	0.2, 2.8	
Regularly for years	31.8	46.1	0.6	0.2, 1.3		0.5	0.2, 1.3	
OTHER LAWN CARE								
Any exposure	62.7	71.7	0.8	0.4, 1.8	0.6	0.7	0.3, 1.7	0.4
Frequency of exposure					0.7			0.9
None	38.5	28.3	1.0	Reference		1.0	Reference	
Infrequently	15.4	12.2	1.0	0.4, 3.1		0.4	0.1, 1.7	
Irregularly for years	13.9	26.0	0.5	0.2, 1.3		0.4	0.1, 1.4	
Regularly for years	32.3	33.5	1.0	0.4, 2.5		1.1	0.4, 3.0	
GARDEN WORK								
Any exposure	70.1	68.9	1.3	0.6, 2.8	0.4	1.2	0.5, 2.6	0.7
Frequency of exposure					0.9			0.8
None	30.3	31.1	1.0	Reference		1.0	Reference	
Infrequently	21.2	11.9	2.4	0.8, 6.5		2.3	0.7,7.2	
Irregularly for years	13.6	23.7	0.8	0.3, 2.3		0.6	0.2, 2.1	
Regularly for years	34.9	33.3	1.2	0.5, 2.8		1.1	0.4, 2.9	
PAINTING PROJECTS								
Any exposure	61.2	56.9	1.7	0.9, 3.5	0.13	1.7	0.8, 3.8	0.2
Frequency of exposure					0.031			0.031
None	40.0	43.1	1.0	Reference		1.0	Reference	

	Among 67 cases with and without cataplexy, and 95 controls					Among 45 cases with cataplexy†, and 95 controls		
	Percentages*							
Exposure	**Cases**	**Controls**	**OR**	**95% CI**	***P*-value‡**	**OR**	**95% CI**	**P-value‡**
Infrequently	32.2	42.9	1.2	0.5, 2.6		1.0	0.4, 2.6	
Irregularly for years	21.5	11.6	2.4	0.9, 6.7		2.6	0.8, 8.3	
Regularly for years	6.2	2.4	5.2	0.8, 35.0		8.4	1.0, 73.2	
ODD JOBS								
Any exposure	58.2	54.9	1.1	0.5, 2.2	0.9	1.2	0.5, 2.7	0.7
Frequency of exposure					0.8			0.3
None	41.8	45.8	1.0	Reference		1.0	Reference	
Infrequently	4.5	4.6	0.7	0.1, 2.1		0.3	0.03, 2.7	
Irregularly for years	14.9	8.9	1.9	0.6, 6.0		1.4	0.3, 5.6	
Regularly for years	38.8	40.7	1.0	0.5, 2.2		1.4	0.6, 3.4	
CLEANING INDOORS								
Any exposure	98.5	95.8	1.5	0.1, 19.1	0.8	0.8	0.05, 12.3	0.9
Frequency					0.5			0.6
None	1.5	4.2	1.0	Reference		1.0	Reference	
Infrequently	4.5	5.6	0.9	0.5, 17.7		0.6	0.02, 13.5	
Irregularly for years	22.4	13.7	3.6	0.3, 53.3		1.5	0.08, 25.4	
Regularly for years	71.6	76.4	1.2	0.9, 15.7		0.7	0.05, 11.2	

*Percentages were weighted by the inverse of the final selection probability

†Cataplexy defined as present after medical chart review, or by a positive screen developed by Anic-Labat and colleagues.

‡p-value from Wald test in multivariate model adjusted for African American race and household income; for ordinal variables with ≥2 categories, Wald test of continuous variable constitutes test for linear trend

Table 3

Risk of Narcolepsy Associated With Jobs Where Subjects Reported Exposure to Toxins Before the Age of 21

	Among 67 cases with and without cataplexy, and 95 controls					Among 45 cases with cataplexy†, and 95 controls		
	Percentages*							
Exposure	**Cases**	**Controls**	**OR**	**95% CI**	***P*-value‡**	**OR**	**95% CI**	**P-value‡**
TOXINS								
Any exposure	23.8	12.7	2.6	1.0, 6.9	0.053	2.0	0.6, 6.5	0.3
HEAVY METALS								
Any exposure	17.7	7.9	4.7	1.5, 14.5	0.006	3.1	0.9, 11.4	0.09
Severity of illness					0.027		0.2	
Not exposed	82.3	89.8	1.0	Reference		1.0	Reference	
Not ill	16.1	9.2	3.4	1.1, 10.3		2.0	0.6, 7.5	
Ill	1.6	1.0	3.7	0.2, 69.4		5.6	0.2, 132.7	
PESTICIDES								
Any exposure	24.6	21.1	2.1	0.9, 5.2	0.092	2.2	0.8, 6.7	0.15
Severity of Illness					0.2			0.3
Not exposed	76.6	77.9	1.0	Reference		1.0	Reference	
Not ill	21.9	22.1	1.6	0.7, 4.0		1.7	0.6, 5.0	
Ill	1.6	0.0	Inf	n/a		Inf	n/a	
SOLVENTS								
Any exposure	40.3	40.4	1.1	0.6, 2.4	0.7	1.1	0.5, 2.4	0.9
Severity of Illness					0.8			0.8
Not exposed	59.7	59.6	1.0	Reference		1.0	Reference	
Not ill	34.3	33.6	1.2	0.5, 2.5		1.0	0.4, 2.4	
Ill	6.0	6.8	1.0	0.2, 5.1		1.3	0.2, 7.8	
CARBON MONOXIDE								
Any exposure	11.9	7.5	2.1	0.6, 7.0	0.2	1.9	0.5, 7.8	0.4
Severity of Illness								0.064
Not exposed	88.1	92.5	1.0	Reference		1.0	Reference	
Not ill	4.5	7.5	0.5	0.1, 2.5		0.5	0.8, 3.0	

	Among 67 cases with and without cataplexy, and 95 controls					Among 45 cases with cataplexy†, and 95 controls		
	Percentages*							
Exposure	**Cases**	**Controls**	**OR**	**95% CI**	***P*-value‡**	**OR**	**95% CI**	**P-value‡**
Ill	7.4	0.0	Inf	n/a		Inf	n/a	

*Percentages were weighted by the inverse of the final selection probability

†Cataplexy defined as present after medical chart review, or by a positive screen developed by Anic-Labat and colleagues.

‡p-value from Wald test in multivariate model adjusted for African American race and household income; for ordinal variables with ≥2 categories, Wald test of continuous variable constitutes test for linear trend

Table 4

Risk of Narcolepsy Associated With Hobbies and Other Non-Vocational Activities That Subjects Performed Before the Age of 21

	Among 67 cases with and without cataplexy, and 95 controls					Among 45 cases with cataplexy†, and 95 controls		
	Percentages*							
Exposure	**Cases**	**Controls**	**OR**	**95% CI**	***P*-value‡**	**OR**	**95% CI**	**P-value‡**
LEATHER WORK								
Any exposure	14.9	7.9	1.3	0.4, 4.1	0.6	1.5	0.5, 5.3	0.4
Cumulative hours					0.6			0.9
None	85.1	92.1	1.0	Reference		1.0	Reference	
1-479	11.9	3.1	3.7	0.9, 14.4		4.5	1.0, 20.0	
480+	3.0	4.8	0.2	0.02, 1.2		0.3	0.04, 2.0	
CERAMICS								
Any exposure	23.9	14.7	2.0	0.9, 4.7	0.11	2.8	1.1, 7.0	0.034
Cumulative hours					0.11			0.030
None	76.1	85.3	1.0	Reference		1.0	Reference	
1-239	10.5	7.2	1.7	0.5, 5.8		2.1	0.5, 8.5	
240+	13.4	7.5	2.3	0.7, 6.8		3.3	1.0, 20.8	
HOUSE PAINTING								
Any exposure	13.4	15.7	1.0	0.3, 3.1	1.0	1.3	0.4, 4.5	0.7
Cumulative hours					1.0			0.8
None	86.6	84.3	1.0	Reference		1.0	Reference	
1-83	6.0	5.0	1.0	0.2, 5.4		1.6	0.3, 8.8	
84+	7.4	10.7	1.0	0.2, 4.2		1.0	0.2, 5.9	
OIL PAINTING								
Any exposure	10.5	7.2	1.3	0.3, 4.8	0.7	1.2	0.3, 4.9	0.8
Cumulative hours					0.8			0.9
None	89.6	92.8	1.0	Reference		1.0	Reference	
1-119	4.5	1.5	1.8	0.3, 12.5		2.5	0.4, 17.1	
120+	5.9	5.7	1.0	0.2, 5.3		0.5	0.06, 3.9	
WOODWORKING								

	Among 67 cases with and without cataplexy, and 95 controls					Among 45 cases with cataplexy†, and 95 controls		
	Percentages*							
Exposure	**Cases**	**Controls**	**OR**	**95% CI**	***P*-value‡**	**OR**	**95% CI**	**P-value‡**
Any exposure	23.4	16.0	1.6	0.6, 3.9	0.3	1.5	0.6, 4.2	0.4
Cumulative hours					0.07			0.2
None	77.6	84.5	1.0	Reference		1.0	Reference	
1-119	6.0	6.3	0.7	0.2, 3.4		1.0	0.2, 5.2	
120+	16.4	9.2	3.0	1.0, 8.9		2.5	0.7, 8.7	
ENGINES OR MOTORS								
Any exposure	13.4	15.9	0.9	0.3, 2.4	0.8	0.8	0.2, 2.5	0.7
Cumulative hours					0.9			0.5
None	86.6	84.1	1.0	Reference		1.0	Reference	
1-179	4.5	6.6	0.8	0.2, 3.4		1.3	0.3, 6.1	
180+	8.9	9.3	1.0	0.3, 3.6		0.5	0.1, 2.4	
WOODEN OR PLASTIC MODELS								
Any exposure	14.9	23.0	0.7	0.3, 1.8	0.5	0.5	0.2, 1.5	0.2
Cumulative hours					0.7			0.4
None	85.1	77.0	1.0	Reference		1.0	Reference	
1-155	6.0	9.6	0.4	0.1, 1.8		0.2	0.03, 1.1	
156+	8.9	13.4	1.0	0.3, 3.3		1.0	0.2, 3.8	
CHEMISTRY SETS								
Any exposure	31.4	23.2	1.5	0.6, 3.4	0.4	1.3	0.5, 3.3	0.6
Cumulative hours					0.2			0.6
None	68.7	76.8	1.0	Reference		1.0	Reference	
1-119	10.5	12.7	1.0	0.3, 3.4		1.2	0.3, 4.5	
120+	20.9	10.5	1.9	0.7, 5.1		1.3	0.4, 4.0	
APPLICATION OF FERTILIZER								
Any exposure	26.9	19.7	1.8	0.7, 4.6	0.2	1.4	0.4, 3.9	0.6
Cumulative times					0.08			0.4
No	73.1	80.3	1.0	Reference		1.0	Reference	
1-3	4.5	9.7	0.4	0.1, 2.3		0.6	0.1, 3.6	

	Among 67 cases with and without cataplexy, and 95 controls					Among 45 cases with cataplexy†, and 95 controls		
	Percentages*							
Exposure	**Cases**	**Controls**	**OR**	**95% CI**	***P*-value‡**	**OR**	**95% CI**	**P-value‡**
4+	22.4	10.0	3.1	1.1, 9.1		1.9	0.6, 5.6	
APPLICATION OF BUG OR WEED KILLER								
Any exposure	23.9	14.2	2.1	0.8, 5.4	0.12	1.6	0.5, 4.9	0.4
Cumulative times					0.02			0.026
None	76.1	85.8	1.0	Reference		1.0	Reference	
1-5	3.0	7.6	0.3	0.04, 1.9		--	--	
6+	20.9	6.6	4.5	1.5, 13.4		4.0	1.2, 13.8	

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†Cataplexy defined as present after medical chart review, or by a positive screen developed by Anic-Labat and colleagues.

‡p-value from Wald test in multivariate model adjusted for African American race and household income; for ordinal variables with ≥2 categories, Wald test of continuous variable constitutes test for linear trend