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Increased risk of Parkinson's disease in individuals hospitalized with conditions related to the use of methamphetamine or other amphetamine-type drugs

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ABSTRACT

Background: Since methamphetamine and other amphetamine-type stimulants (meth/amphetamine) can damage dopaminergic neurons, researchers have long speculated that these drugs may predispose users to develop Parkinson's disease (PD), a dopamine deficiency neurological disorder.
Methods: We employed a retrospective population-based cohort study using all linked statewide California inpatient hospital episodes and death records from January 1, 1990 through December 31, 2005. Patients at least 30 years of age were followed for up to 16 years. Competing risks analysis was used to determine whether the meth/amphetamine cohort had elevated risk of developing PD (ICD-9 332.0; ICD-10 G20) in comparison to a matched population-proxy appendicitis group and a matched cocaine drug control group. Individuals admitted to hospital with meth/amphetamine-related conditions ($n = 40,472$; ICD-9 codes 304.4, 305.7, 969.7, E854.2) were matched on age, race, sex, date of index admission, and patterns of hospital admission with patients with appendicitis conditions ($n = 207,831$; ICD-9 codes 540–542) and also individuals with cocaine-use disorders ($n = 35,335$; ICD-9 codes 304.2, 305.6, 968.5).
Results: The meth/amphetamine cohort showed increased risk of PD compared to both that of the matched appendicitis group [hazard ratio (HR) = 1.76, 95% CI: 1.12–2.75, $p = 0.017$] and the matched cocaine group [HR = 2.44, 95% CI: 1.32–4.41, $p = 0.004$]. The cocaine group did not show elevated hazard of PD compared to the matched appendicitis group [HR = 1.04, 95% CI: 0.56–1.93, $p = 0.80$].
Conclusion: These data provide evidence that meth/amphetamine users have above-normal risk for developing PD.

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1. Introduction

Methamphetamine and other amphetamine-type stimulants (meth/amphetamine) comprise the second most widely used class of illicit drugs in the world (United Nations Office on Drugs and Crime, 2008). Such consumption patterns, along with serious concerns specifically about methamphetamine toxicity (Thrash et al., 2009), have had a major influence on drug policy legislation (e.g., U.S. Combat Methamphetamine Epidemic Act of 2005) (Sununu, 2005) and health service utilization in the United States (e.g., one-third of all recent publicly funded substance-abuse treatment episodes in California were due primarily to methamphetamine) (Substance Abuse and Mental Health Services Administration, 2010a,b). In addition, humans are exposed to licit amphetamine to promote wakefulness in narcoleptic patients, maintain alertness in armed forces personnel, facilitate weight reduction in the obese, and treat the symptoms of attention deficit hyperactivity disorder (ADHD) in children (Kish, 2008). Currently, the absence of powerful longitudinal studies in this area is a major critical barrier to understanding and anticipating the full, long-term impact of meth/amphetamine consumption.

It has been more than 30 years since the discovery that methamphetamine and its metabolite amphetamine can harm brain dopamine neurons in experimental animals (Fibiger and McGeer, 1971; Seiden et al., 1976; Ricaurte et al., 1984; Ryan et al., 1990). Because of the animal findings, there is concern that use of meth/amphetamine might damage dopamine neurons in humans and thereby increase the risk of developing Parkinson's disease (PD), a dopamine deficiency brain disorder (Guilarte, 2001; Caligiuri and Buitenhuys, 2005; Thrash et al., 2009).

Biochemical brain studies of young methamphetamine users (who do not show the symptoms of PD) have disclosed changes in levels of some dopamine markers (Wilson et al., 1996a; McCann

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et al., 1998). However, the findings have yet to (and may never) confirm actual structural damage to or loss of dopamine neurons, because of the likelihood that such markers are not stable measures of dopamine neuron integrity (Boileau et al., 2008).

Significant and enduring dopamine toxicity caused by meth/amphetamine might only become clinically evident in susceptible users who have advanced to middle or older age—a time characterized by some age-related loss of dopamine neurons—and, as a result, longitudinal cohort designs offer a rigorous way to test this possibility. Given the high cost and common obstacles (e.g., participant loss to follow-up) associated with long-term longitudinal studies of illicit drug users, especially in regards to the estimation of low-incidence (but quite debilitating) conditions such as PD, a large-scale record-linkage approach may be one of the only feasible and effective designs available to assess the potential link between meth/amphetamine use and incidence of PD. In a previous epidemiological investigation of a small sample of older hospitalized meth/amphetamine users (≥50 years old) in California, we introduced a record-linkage approach which provided preliminary data suggesting that use of meth/amphetamine, sufficient to warrant a hospital diagnosis, might be associated with developing PD (Callaghan et al., 2010). Our present study adds significantly to this preliminary work by including: (1) a much larger and age-diversified group of meth/amphetamine users from California; (2) a sufficiently sized cocaine drug-control cohort; (3) a longer follow-up time (up to 16 years); and (4) the use of a more sophisticated statistical technique (i.e., competing risks analysis), along with the addition of death-record information, to account for potential differences in mortality across cohort groups. Here, we assess the risk of developing Parkinson's disease among meth/amphetamine users in comparison to that of population-proxy and stimulant-drug controls.

2. Materials and methods

2.1. Data sources

2.1.1. California Patient Discharge Database (PDD) and Vital Statistics Database (VSD): 1990–2005. The current study utilized California Office of Statewide Health Planning and Development (OSHPD) inpatient hospital admission data from January 01, 1990 until December 31, 2005 from the Patient Discharge Database (PDD). The dataset consists of a record containing demographic information and diagnoses (up to 25) for each inpatient discharged from a California licensed hospital. Licensed hospitals include general acute care, acute psychiatric care, chemical dependency recovery, and psychiatric health facilities. Death records from the California Vital Statistics Database (VSD; which captures all death records for the state) were linked to the PDD inpatient data. The probabilistic matching algorithm linking California inpatient records to state death records has a linkage sensitivity and specificity of 0.9524 and 0.9998, respectively, and positive and negative predictive values of 0.994 and 0.998 (Zingmond et al., 2004).

2.2. Measurement of outcome

The primary outcome variable in the study was time to: (1) subsequent inpatient admission with a diagnosis, in any position in the diagnostic record, of Parkinson's disease [ICD-9 code: 332.0 (Parkinson's disease, Paralysis Agitans)]; or (2) death with an underlying cause of death listed on the death certificate as ICD-9 code 332.0 or ICD-10 code G20 (Parkinson's disease).

2.3. Patient group assignment

2.3.1. Appendicitis cohort assignment. Individuals at least 30 years old were included in the appendicitis group if they had: (1) a diagnosis of an appendicitis-related condition (ICD-9 codes 540–542), which indicated their index admission; (2) no prior or concurrent indication (in relation to their index appendicitis admission) of Parkinson's disease (ICD-9 332.0) or parkinsonism [ICD-9 332.1 (secondary parkinsonism); 333.0 (other degenerative diseases of the basal ganglia), 333.1 (essential and other specified forms of tremor)]; (3) no indication, at any time, of any ICD-9 alcohol- or drug-use diagnoses [303 (alcohol dependence), 305.0 (alcohol abuse), 980.0 (alcohol poisoning); 304.4 (amphetamine and other psychostimulant dependence), 305.7 (amphetamine or related acting sympathomimetic abuse), 969.7 (psychostimulant poisoning) and E854.2 (accidental/unintentional psychostimulant poisoning); 304.2 (cocaine dependence), 305.6 (cocaine abuse), 968.5 (cocaine poisoning); 304.0 (opioid dependence), 304.7 (combination of opioid dependence with any other drug), 305.5 (opioid abuse), 965.0 (poisoning by opioids and related narcotics); 304.3 (cannabis dependence), 305.2 (cannabis abuse), 969.6 (poisoning by hallucinogens, such as cannabis); other drug abuse or dependence conditions (ICD-9 304.1, 304.5–304.9, 305.3, 305.4, 305.9)]; and (4) given that HIV can facilitate the development of parkinsonism (Tse et al., 2004), no indication of HIV [ICD-9 042 (human immunodeficiency virus) or V08 (asymptomatic human immunodeficiency virus)] in their diagnostic records prior to or concurrent with their PD diagnosis, if any.

2.3.2. Meth/amphetamine cohort assignment. Individuals at least 30 years old were assigned to the meth/amphetamine group only if they had the following characteristics: (1) an ICD-9 diagnosis, in any diagnostic position, of 304.4 (amphetamine and other psychostimulant dependence), 305.7 (amphetamine or related acting sympathomimetic abuse), 969.7 (psychostimulant poisoning) or E854.2 (accidental/unintentional psychostimulant poisoning), with the earliest ICD-9 meth/amphetamine diagnosis indicating the index admission; (2) no prior or concurrent indication (in relation to their index admission) of PD or parkinsonism (as defined previously using ICD-9 codes); (3) no indication, at any time, of any alcohol or drug use other than meth/amphetamine (using the ICD-9 codes previously outlined); and (4) no indications of HIV (as listed above).

Even though the ICD-9 coding framework does not distinguish between methamphetamine and other amphetamine-type stimulants, it is likely that the ICD-9 amphetamine-related codes serve as reasonable proxies for methamphetamine-related conditions in our study of California hospital admission records. From 1992 to 2005, there were 514,625 primary amphetamine-related inpatient and outpatient treatment admissions to publicly funded substance abuse treatment programs in California, and methamphetamine accounted for 97.8% of all of these primary amphetamine-related episodes (Substance Abuse and Mental Health Services Administration, 2010b). Also, in California, Arizona, and Nevada, U.S. methamphetamine-precursor legislation, which was designed to reduce the manufacture and supply of methamphetamine, was associated with statistically significant reductions in inpatient hospital admissions with the same ICD-9 amphetamine-related codes as used in our study (Cunningham and Liu, 2003). Consistent with these observations, we previously reported much higher blood and brain levels of methamphetamine than those of its metabolite amphetamine in an autopsied brain study of recreational drug users from California (Wilson et al., 1996a). Based on these lines of evidence, we argue that it is reasonable to expect that the bulk of the admissions in our study are specific to methamphetamine; however, in order to account for the full range of methamphetamine and other amphetamine-type stimulant conditions captured in the ICD-9 classification system, we use the term "meth/amphetamine" throughout the paper.

2.3.3. Cocaine cohort assignment. Patients at least 30 years old were assigned to the cocaine group only if they had the following characteristics: (1) an ICD-9 diagnosis, in any diagnostic position, of 304.2 (cocaine dependence), 305.6 (cocaine abuse), or 968.5 (cocaine poisoning), with the earliest ICD-9 cocaine diagnosis indicating the index admission; (2) no prior or concurrent indication (in relation to their index admission) of PD or parkinsonism (as listed above); (3) no indication, at any time, of ICD-9 indication of any alcohol or drug use other than cocaine (using the ICD-9 codes previously outlined); and (4) no indications of HIV (as listed above).

2.4. Analytic plan

2.4.1. Propensity-score matching of case and control subjects. To account for possible confounding across variables captured in the medical records, we used a greedy nearest-neighbor propensity-score matching approach (Austin, 2009) to match case and control cohorts on the following variables: age, race, sex, date of index admission and total number of an individual's inpatient admissions which occurred after the index episode until the PD outcome (or the end of the study). To ensure that this method produced matched samples, balance between the variables in all of the propensity-score matched cohorts was assessed using standardized differences (Austin and Mamdani, 2006).

2.4.2. Competing risks analyses. We used a competing risks analysis (Pintilie, 2006) with a robust variance estimator (Austin, 2008) to compare the hazard of developing PD across matched groups, while accounting for the higher rate of mortality in the drug cohorts (Singleton et al., 2009; Degenhardt et al., 2011). All competing risks analyses were computed using the "crrSC package" for the R statistical software program (Zhou and Latouche, 2011).

3. Results

A description of the baseline and matched features of all eligible individuals assigned to the appendicitis ($n = 207,831$), meth/amphetamine ($n = 40,472$), and cocaine ($n = 35,335$) groups can be found in Tables 1–3. Approximately 96% of individuals in the unmatched meth/amphetamine group ($n = 40,472$) received a

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Table 1
Comparison of characteristics of individuals at least 30 years of age in the unmatched and matched appendicitis and methamphetamine groups.

	Appendicitis	Methamphetamine	$\chi^2/F/d$	p
Unmatched				
Sample size	$n = 207,831$	$n = 40,472$		
Age, years[a]	47.11 (14.10)	39.48 (8.08)	99.93	< 0.001
Race			2823	< 0.001
Black	3.6% ($n = 7476$)	4.7% ($n = 1904$)		
White	61.2% ($n = 127,240$)	73.1% ($n = 29,578$)		
Hispanic	22.8% ($n = 47,394$)	16.5% ($n = 6691$)		
Other	12.4% ($n = 25,683$)	5.7% ($n = 2292$)		
Sex (females)	45.6% ($n = 94,840$)	45.7% ($n = 18,488$)	0.03	0.86
Mean years from index admission until study end[e]	7.00 (4.49)	6.16 (4.38)	34.72	< 0.001
Average no. visits[b]	0.62 (1.89)	0.91 (2.43)	54.43	< 0.0001
Matched				
Sample size[c]	$n = 40,358$	$n = 40,358$		
Age, years	39.09 (8.59)	39.48 (8.08)	4.7[d]	
Race				
Black	4.1% ($n = 1672$)	4.7% ($n = 1892$)	2.7[d]	
White	74.2% ($n = 29,955$)	73.1% ($n = 29,940$)	2.6[d]	
Hispanic	16.3% ($n = 6593$)	16.6% ($n = 6687$)	0.6[d]	
Other	5.3% ($n = 2138$)	5.7% ($n = 2289$)	1.6[d]	
Sex (females)	44.4% ($n = 17,929$)	45.7% ($n = 18,426$)	2.5[d]	
Mean years from index admission until study end[e]	6.12 (4.38)	6.15 (4.38)	0.7[d]	
Average no. visits[b]	0.68 (2.63)	0.88 (2.15)	8.1[d]	
Number of incident PD cases	29	51		
Median age (years), incident PD cases	63.8 (range 35–92)	57.2 (range 33–88)		0.015[f]
No. of deaths[g]	1510	3391		

[a] Numbers in parentheses represent the standard deviation unless otherwise noted.
[b] Number of inpatient admissions (subsequent to index admission) during the study period.
[c] We used a 1:1 case-to-control propensity-score match on age, sex, race, number of hospital admissions, and date of index admission.
[d] This parameter is the standardized difference (d), which accounts for group differences after matching; a value greater than 10 represents a meaningful difference between groups (Austin and Mamdani, 2006).
[e] Average time (years) from index admission until the last day in the study period (December 31, 2005).
[f] Given that the age distributions were not normally distributed, a Mann–Whitney–Wilcoxon test was used to compare ages across the matched groups.
[g] Number of deaths occurring between index admission and first hospital indication of PD or study end (December 31, 2005).

Table 2
Comparison of characteristics of individuals at least 30 years of age in the unmatched and matched methamphetamine and cocaine groups.

	Methamphetamine	Cocaine	$\chi^2/F/d$	p
Unmatched				
Sample size	$n = 40,472$	$n = 35,335$		
Age, years[a]	39.48 (8.08)	40.74 (8.74)	19.80	<0.0001
Race			23,781	<0.0001
Black	4.7% ($n = 1904$)	54.1% ($n = 19,119$)		
White	73.1% ($n = 29,578$)	29.3% ($n = 10,345$)		
Hispanic	16.5% ($n = 6691$)	12.5% ($n = 4427$)		
Other	5.7% ($n = 2292$)	4.1% ($n = 1435$)		
Sex (females)	45.7% ($n = 18,488$)	40.0% ($n = 14,132$)	248.85	<0.0001
Mean years from index admission until study end[e]	6.16 (4.38)	8.10 (4.58)	58.31	<0.0001
Average no. visits[b]	0.91 (2.43)	1.21 (2.97)	14.70	<0.0001
Matched				
Sample size[c]	$n = 17,696$	$n = 17,696$		
Age, years	40.19 (8.87)	40.17 (8.52)	0.2[d]	
Race				
Black	10.8% ($n = 1904$)	10.8% ($n = 1919$)	0.3[d]	
White	58.6% ($n = 10,368$)	58.3% ($n = 10,314$)	0.6[d]	
Hispanic	23.1% ($n = 4079$)	23.3% ($n = 4118$)	0.5[d]	
Other	7.6% ($n = 1345$)	7.6% ($n = 1345$)	0[d]	
Sex (females)	38.1% ($n = 6750$)	37.6% ($n = 6653$)	1.1[d]	
Mean years from index admission until study end[e]	7.68 (4.46)	7.71 (4.63)	0.6[d]	
Average no. visits[b]	1.00 (2.40)	1.00 (2.64)	0.1[d]	
Number of incident PD cases	36	15		
Median age (years), incident PD cases	58.1 (range = 34–88)	60.4 (range = 33–87)		0.69[f]
No. of deaths[g]	1824	1663		

[a] Numbers in parentheses represent the standard deviation unless otherwise noted.
[b] Number of inpatient admissions (subsequent to index admission) during the study period.
[c] We used a 1:1 case-to-control propensity-score match on age, sex, race, number of hospital admissions, and date of index admission.
[d] This parameter is the standardized difference (d), which accounts for group differences after matching; a value greater than 10 represents a meaningful difference between groups (Austin and Mamdani, 2006).
[e] Average time (years) from index admission until the last day in the study period (December 31, 2005).
[f] Given that the age distributions were not normally distributed, a Mann–Whitney–Wilcoxon test was used to compare ages across the matched groups.
[g] Number of deaths occurring between index admission and first hospital indication of PD or study end (December 31, 2005).

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Table 3
Comparison of characteristics of individuals at least 30 years of age in the unmatched and matched appendicitis and cocaine groups.

	Appendicitis	Cocaine	$\chi^2/F/d$	p
Unmatched				
Sample size	$n = 207,831$	$n = 35,335$		
Age, years[a]	47.11 (14.10)	40.74 (8.74)	73.82	<0.0001
Race			79,262	<0.0001
Black	3.6% ($n = 7476$)	54.1% ($n = 19,119$)		
White	61.2% ($n = 127,240$)	29.3% ($n = 10,345$)		
Hispanic	22.8% ($n = 47,394$)	12.5% ($n = 4427$)		
Other	12.4% ($n = 25,683$)	4.1% ($n = 1435$)		
Sex (females)	45.6% ($n = 94,840$)	40.0% ($n = 14,132$)	388.29	<0.0001
Mean years from index admission until study end[e]	7.0 (4.49)	8.1 (4.58)	42.25	<0.0001
Average no. visits[b]	0.62 (1.89)	1.21 (2.97)	70.57	<0.0001
Matched				
Sample size[c]	$n = 23,281$	$n = 23,281$		
Age, years	41.31 (10.38)	41.39 (9.37)	0.8[d]	
Race				
Black	30.4% ($n = 7077$)	30.5% ($n = 7105$)	0.3[d]	
White	46.3% ($n = 10,779$)	44.3% ($n = 10,325$)	3.9[d]	
Hispanic	17.7% ($n = 4111$)	19.0% ($n = 4421$)	3.4[d]	
Other	5.6% ($n = 1314$)	6.1% ($n = 1430$)	2.1[d]	
Sex (females)	40.0% ($n = 9320$)	38.6% ($n = 8987$)	2.9[d]	
Mean years from index admission until study end[e]	7.84 (4.62)	7.76 (4.65)	1.6[d]	
Average no. visits[b]	0.92 (3.21)	0.97 (2.27)	1.9[d]	
Number of incident PD cases	21	20		
Median age (years), incident PD cases	76.5 (range 62–93)	63.9 (range 34–88)		0.12[f]
No. of deaths[g]	1396	2395		

[a] Numbers in parentheses represent the standard deviation unless otherwise noted.
[b] Number of inpatient admissions (subsequent to index admission) during the study period.
[c] We used a 1:1 case-to-control propensity-score match on age, sex, race, number of hospital admissions, and date of index admission.
[d] This parameter is the standardized difference (d), which accounts for group differences after matching; a value greater than 10 represents a meaningful difference between groups (Austin and Mamdani, 2006).
[e] Average time (years) from index admission until the last day in the study period (December 31, 2005).
[f] Given that the age distributions were not normally distributed, a Mann–Whitney–Wilcoxon test was used to compare ages across the matched groups.
[g] Number of deaths occurring between index admission and first hospital indication of PD or study end (December 31, 2005).

single ICD-9 code representing a diagnosis of meth/amphetamine dependence or meth/amphetamine abuse at their index admission.

The unmatched appendicitis group in our study ($n = 207,831$; 468 events; 1,369,705 person-years of follow-up) manifested a PD incidence within standard age strata similar to corresponding rates found in a systematic review of relevant worldwide studies (Twelves et al., 2003).

3.1. Parkinson's disease outcome

In the matched competing risks results presented below, all but one incident PD case (which occurred within the meth/amphetamine cohort) was identified by ICD-9 code 332.0 (Parkinson's disease) in the inpatient medical records.

3.1.1. Parkinson's disease risk: meth/amphetamine vs. appendicitis cohorts. In the meth/amphetamine-appendicitis competing risks analyses using a 1:1 matched sample, the meth/amphetamine cohort had a significantly greater risk of a PD outcome (measured as an inpatient admission with a diagnosis of PD or an underlying cause of death listed as PD) than the appendicitis group [hazard ratio (HR) = 1.76, 95% CI: 1.12, 2.76, $p = 0.014$] (see Table 4).

3.1.2. Parkinson's disease risk: meth/amphetamine vs. cocaine cohorts. In the meth/amphetamine-cocaine competing risks analyses using a 1:1 matched sample, the meth/amphetamine group had a greater hazard of a PD outcome than the cocaine group (HR = 2.41, 95% CI: 1.32, 4.41, $p = 0.0042$).

3.1.3. Parkinson's disease risk: cocaine vs. appendicitis cohorts. In a 1:1 cocaine-appendicitis matched sample, the cocaine group was not more likely to develop PD than the appendicitis cohort (HR = 1.04, 95% CI: 0.56, 1.93, $p = 0.80$).

4. Discussion

Our epidemiological data showing, in hospitalized meth/amphetamine users, increased risk of subsequent diagnosis of PD in hospitalization or death records provides support to the long-hypothesized notion, based on animal data, that meth/amphetamine exposure might lead to enduring damage of brain dopamine neurons in humans. We found that meth/amphetamine users had a 76% increased risk of developing PD in comparison to a matched population-proxy control group. Based on our findings, this means that if we followed 10,000 meth/amphetamine users (at least 30 years of age) and 10,000 people of similar age, race, and sex from a California population-based sample for 10 years, we would expect approximately 21 cases of PD in the methamphetamine group and approximately 12 in the population group. The current work significantly extends an earlier preliminary study (Callaghan et al., 2010) by including a longer follow-up time (16 years vs. 10 years), a much younger and larger sample of subjects (~40,000 meth/amphetamine users vs. 1800 meth/amphetamine users), as well as linked mortality information and a statistical approach (competing risks analysis) which accounted for the elevated mortality rates in our stimulant drug cohorts.

The meth/amphetamine group also had a higher risk of PD than a group of users of cocaine, a stimulant drug like methamphetamine. Individuals with cocaine diagnoses were selected as a "drug control" group because both cocaine and methamphetamine users can be expected to experience similar health effects associated with an illicit drug lifestyle; and both are dopaminergic stimulants but with a different primary mechanism of action (cocaine: monoamine neurotransmitter transporter blockade; methamphetamine: monoamine neurotransmitter release and transporter blockade) (Ross and Kelder, 1979; Kish, 2008). Although human

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Table 4
Competing risks models estimating hazard of subsequent indication of Parkinson's disease (ICD-9: 332.0; ICD-10: G20) across matched cohort groups.

Matched groups	Hazard ratio (HR)	Sig.[a]	95% CI[b] of HR	
			Lower	Upper
Methamphetamine (appendicitis)[c]	1.76	$p = 0.014$	1.12	2.76
Methamphetamine (cocaine)[c]	2.41	$p = 0.004$	1.32	4.41
Cocaine (appendicitis)[c]	1.04	$p = 0.80$	0.56	1.93

[a] Statistical significance, *p* value.
[b] 95% Confidence Interval.
[c] Reference category in parentheses.

postmortem brain findings are somewhat conflicting on the question of brain dopamine marker changes in cocaine users (Wilson et al., 1996b; Staley et al., 1997; Little et al., 2009), the lack of increased risk in the cocaine group in comparison to our population-proxy appendicitis cohort is consistent with animal findings showing lack of dopamine neuron toxicity following exposure to this stimulant (Ryan et al., 1988; Wilson and Kish, 1996).

Our study used individuals hospitalized with appendicitis-related conditions as a population-proxy control group. This particular group was chosen because: (1) appendicitis is a relatively frequent reason for inpatient admission and, as a result, yields a sample sufficiently large to provide precise matches for the target cohorts; (2) it has a relatively well-described clinical course (Sauerland et al., 2004); (3) by choosing an inpatient control condition, potential biases of method variance can be limited, as prior research has shown that selection of an external control group outside of medical data systems (which have been used to identify the target cohort) can introduce bias into the estimation of hazard ratios (Card et al., 2006); (4) appendicitis is not related to socioeconomic status (Poikolainen et al., 1985), nor does it appear to be related to PD or drug use disorders; and (5) prior epidemiological studies have successfully used individuals with appendicitis-related conditions as a basis for hospital-based population-proxy control groups (Mueller et al., 1990; Lin et al., 2008a,b; Callaghan and Khizar, 2010). In our study, the unmatched and matched appendicitis cohorts had a PD incidence within standard age strata similar to corresponding rates found in a systematic review of relevant worldwide studies (Twelves et al., 2003).

Compared to patients in the appendicitis group, meth/amphetamine users may have had lower rates of healthcare insurance resulting in reduced access to medical care, a pattern which would lead to underestimation of the actual risk of PD in our meth/amphetamine cohort. On the other hand, meth/amphetamine users, because of ongoing medical problems, may have been more likely to gain admission to hospitals and to have potential for receiving neurological assessment. This issue was addressed in our study by matching the subjects with respect to number of hospital admissions during the study period and by incorporating a cocaine drug control group which could be expected to have similar patterns of hospital utilization and health-insurance status as meth/amphetamine users. Also, recent systematic reviews have shown that current smokers have nearly a threefold reduction in risk of developing PD in comparison to individuals who have never smoked (Allam et al., 2004; Ritz, 2007). Thus, given that methamphetamine users have a much higher prevalence of tobacco use than individuals in the general population (90% vs. 20%), (Weinberger and Sofuoglu, 2009) the hazard ratio in our meth/amphetamine-appendicitis analysis would likely underestimate the actual risk. Matching the meth/amphetamine cohort with the cocaine group, in which the prevalence of current smokers is likely to be similarly high (Kalman et al., 2005; Weinberger and Sofuoglu, 2009), addressed this potential bias.

In case-registry studies, there is a generic concern regarding the use of administrative diagnostic codes to identify outcome conditions. In relation to the PD outcome, prior research has shown that the ICD-9 code 332.0 (Parkinson's disease) in administrative data files has a positive predictive value of 0.76–0.79 in relation to: (1) a working diagnosis of PD ascertained by medical-chart review (Szumski and Cheng, 2009); or (2) combination of both self-reported PD diagnosis and pharmacy claim files indicating receipt of PD-related medications (Noyes et al., 2007). To our knowledge, even though there is no evidence to suggest the possibility of differential ascertainment bias of ICD-defined PD events across case and control cohorts in the administrative data we used for the study, it is possible that such bias may have affected our results. In addition, even though our study relied primarily on ICD-9 codes from inpatient medical settings to capture incident PD events, a majority of PD patients (~70%) are admitted to inpatient hospital within 6 years of their initial diagnosis (Guttman et al., 2003).

Our investigation cannot provide information on age of initiation, frequency, dose, or duration of drug use. Nevertheless, it is reasonable to assume that the drug users in our study were, for the most part, "moderate to heavy" stimulant users having clinically significant problems as indicated by a formal hospital diagnosis of a meth/amphetamine-use disorder. In this regard, 96% of individuals in our meth/amphetamine cohort had received an inpatient diagnosis indicative of either meth/amphetamine abuse or dependence at their index admission. Here we emphasize that the clinical relevance of our findings might be limited to high dose meth/amphetamine users.

The findings of our epidemiological study might seem to be "at variance" with the apparent absence of any "epidemic" of PD in methamphetamine users that is obvious to the public or to caregivers. This could be explained in part by the relatively low incidence of both conditions in the population and also by the likelihood that prior meth/amphetamine use (e.g., as a young adult) would not typically be considered by treating physicians as a possible cause of PD in the late middle-aged patient. Our findings are consistent with a hypothetical scenario in which Parkinsonian symptoms develop in only a susceptible subgroup of chronic, perhaps high dose, meth/amphetamine users only when they reach middle or older age and have suffered an age-related loss of dopamine neurons. While our study does raise the question of whether licit amphetamines might also increase the risk of Parkinson's disease, it is important to emphasize that our findings might not at all relate to those individuals who take much lower doses of amphetamine drugs for therapeutic purposes (e.g., for ADHD).

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