Occupational Mercury Exposure and Neurological Disease Prevalence

In US Dentists

BY

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THESIS

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This thesis is dedicated to my father, Thomas Wayne Anglen, who encouraged me to choose a profession that keeps me curious.

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LIST OF ABBREVIATIONS

ADA	American Dental Association
CI	Confidence Interval
Hg	Mercury
Hg^0	Elemental Mercury
HSP	Health Screening Program
LOD	Limit of Detection
MeHg	Methyl Mercury
MS	Multiple Sclerosis
NHANES	National Health and Nutrition Examination Survey
OR	Odds Ratio

SUMMARY

Using a cross-sectional approach, we carried out an epidemiologic study in US dentists characterizing the extent of occupational elemental mercury (Hg^0) exposure and its association with multiple sclerosis (MS) or tremor prevalence. The study included 13,906 dentists who attended the American Dental Association's (ADA) annual conventions in 23 years (1986–2007 and 2011–2012). Participants reported their histories of MS and tremor via questionnaire and provided urine specimens for Hg^0 analysis.

We compared the distribution of the dentists' urinary mercury (Hg^0) concentrations from 2011–2012 with that of the general population using the National Health and Nutrition Examination Survey (NHANES) 2011–2012 data. We also estimated cumulative exposure to Hg^0 based on work histories and the sample average concentrations of urinary Hg^0 for each year of the study. Logistic regression models with adjustment for age, sex, and calendar year were used to assess the association between estimates of Hg exposure and the two neurologic outcomes.

Among participating dentists, the levels of urinary Hg^0 decreased dramatically from 1976 to 2012. Yet mean urinary Hg^0 concentrations remained significantly higher among dentists (1.69 µg/L [95% confidence interval (CI)=1.58, 1.81]) than in the general population [0.66 µg/L (0.54, 0.78)] in 2011–2012. The prevalence of MS and tremor among the dentists was respectively 0.19% and 1.36%. Exposure to Hg was not associated with MS (e.g., per mean increase in cumulative Hg^0 exposure [191 µg/L]: odds ratio (OR)=.85 (95% CI, 0.39, 1.85)].

However, the risk of tremor increased significantly with cumulative Hg^0 exposure among younger dentists (<51 years): an increase in cumulative exposure of 92 µg/L corresponded to 13% higher odds of tremor (95% CI, 1.04, 1.22).

The extent of occupational Hg exposure in US dentists has decreased sharply over the last three decades and is now approaching that of the general population. The results of this study suggest that Hg exposure may be associated with tremor and although regression analyses showed no association of Hg exposure and MS, the prevalence of MS was higher than in the US general population.

I. INTRODUCTION

A. Background

Associations have not been found between exposure to Hg^0 from dental amalgam and neurological disease in the general population (Bjorkman et al., 1996; Saxe et al., 1999; Clarkson, 2002; Dodes 2001). Workers occupationally exposed to higher levels of Hg^0 (>500 µg/L urinary Hg^0), however, have been reported to experience tremors, irritability, memory deficits, blurred vision, paresthesia, nerve conduction deficits, and other signs of neurotoxicity (Albers et al., 1988; Levine et al., 1982; Miller et al., 1975). Although high exposure to Hg^0 vapor has been associated with neurological deficits, the threshold for these effects is unknown.

Dentists who currently practice face far less Hg exposure than in the past due to the development of encapsulated amalgam technology, the increasing use of composite resin restorations, and an overall heightened awareness of occupational Hg hygiene. Dentists who practiced before these changes were exposed to relatively high levels of Hg^0, with concentrations of Hg in urine (the most accurate biomarker of exposure to Hg^0 within a three-month period) averaging approximately 20 µg/L in 1980 (Naleway et al., 1985) in contrast to most recent measures of 1.98 µg/L urinary Hg^0 (unpublished ADA data). About 80% of inhaled Hg^0 vapor is absorbed by rapid diffusion through the lungs and distributed to all parts of the body via the circulatory system (Clarkson, 2002). The kidney is known to have the highest Hg^0 bioaccumulation, but the central nervous system is also of concern. When it crosses the blood-brain barrier, Hg^0 is oxidized to inorganic mercury (Hg^{2+}), which has strong affinity for thiol-containing proteins that are prevalent in the brain (Farina et al., 2013).

Multiple sclerosis is a chronic inflammatory disease of the central nervous system (McQualter et al., 2007). Immunological response factors are associated with several neurological diseases, including MS (Hemmer et al., 2002; Hirsh and Hunot, 2009; Wes et al., 2014). In rabbit and rat animal models, exposure to Hg^0 causes autoimmune disease, similar to the immune cell activity observed in MS patients (Trachtenberg, 1974; Rossert et al., 1988). Recent studies of Amazonian gold miners (Motts et al., 2014; Dorland, 2011) have shown an association between low urinary Hg^0 concentrations (median urinary Hg^0 3.7 µg/L) and both elevated cytokines and antinuclear antibodies, which are biomarkers associated respectively with immune response and autoimmune disease (Gardner et al., 2010). Furthermore, recent studies reported a positive association between Hg exposure and increased antinuclear antibodies (Somers et al., 2015), as well as Hg exposure and MS (Napier et al., 2014).

Tremor is an involuntary movement characterized by oscillatory motion that occurs at rest or during activity. The severity of tremor ranges from asymptomatic to disabling (Jankovic and Fahn, 1980; Elble, 1996). There are various classifications of tremor, including but not limited to: accentuated physiologic, parkinsonian, essential, and cerebellar tremor. In addition, these classifications have subgroups (Jankovic and Fahn, 1980; Elble, 1996). In patients with MS, tremor is characterized by demyelinating lesions in the brain that produce intention tremor, the most common type of cerebellar tremor (Elble, 2013; Elble, 1996). The prevalence of tremor in MS patients ranges from 25% to 60% (Alusi, 2001; Pittock et al., 2004; Labiano-Fontcuberta, 2012).

Occupational studies examining the association of chronic Hg^0 vapor exposure at low concentrations (<50 µg/L urinary Hg^0) with tremor have yielded varied results. Three studies found associations of low occupational exposure to Hg^0 vapor with increased risk of tremor (Verbeck et al., 1986; Langworth et al., 1992; Neghab et al., 2011), while two did not (Wastensson et al., 2006; Boogaard et al., 1996).

A few studies have reported an association of low-level exposure with an increase in memory disturbance, a symptom of MS (Langworth et al., 1992; Ritchie et al., 2002; Neghab et al., 2011; Olek, 2005). To our knowledge, no study has yet evaluated MS risk among groups who have occupational exposure to Hg; however, evidence of a weak positive association between exposure to dental amalgam and MS in the general population has been reported (Bates, 2006; Aminzadeh and Etminan, 2007).

B. **Study Objectives**

The objectives of this study were to estimate the extent of occupational Hg^0 exposure in a sample of US dentists and compare with Hg^0 exposures in the US general population; estimate the prevalence of MS and tremor among dentists; and examine whether there is an association between occupational Hg^0 exposure and these neurologic outcomes in the sample.

II. METHODS

A. Sample Design

The ADA collected health information from dentists using a voluntary survey conducted during the Association's annual conference held in various cities across the United States since 1964. Data from each year's questionnaire and biological measurements of Hg^0 exposure were compiled to build a database with 34,040 observations from 1976 to 2012. This sample consisted of dentists who attended the ADA's annual conference and volunteered to participate in the health screening program (HSP).

Urinary Hg^0 testing was an additional complimentary test offered during the health-screening program. Measurements were available when the program was offered in the years 1976–1984, 1986–2007, and 2011–2012. Figure 1 describes the selection of study participants into the present study. All available urinary Hg^0 measurements (N=23,582) were used to calculate the extent of occupational Hg^0 exposure in US dentists.

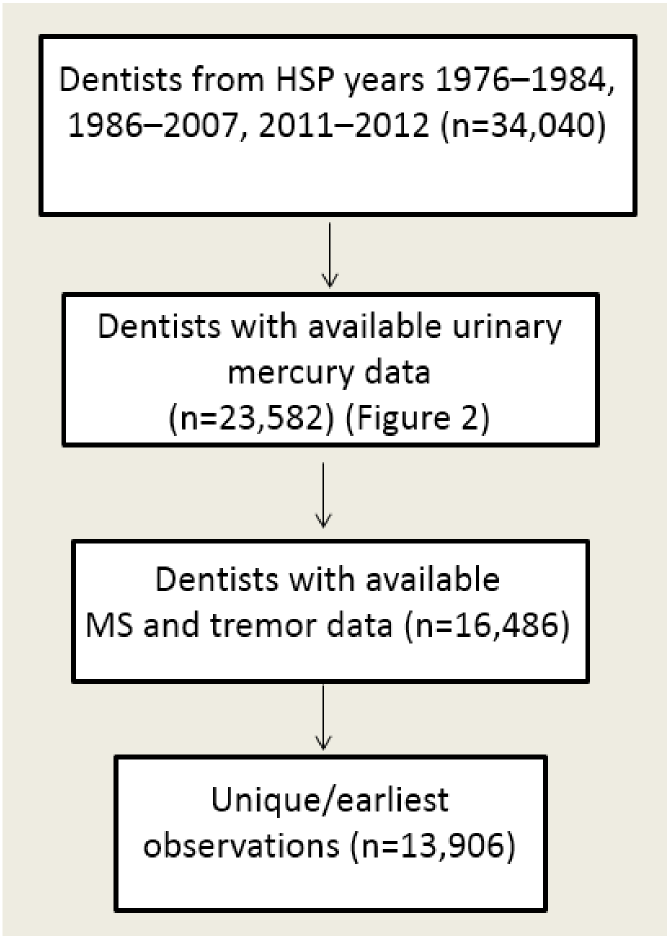


Figure 1. Diagram of study participant selection.

B. **Mercury Exposure Assessment**

Participating dentists reported in a questionnaire how often the dentist placed and removed amalgam restorations per week, if they had handled any Hg^0 spills in the last three months, and also how many years they practiced dentistry.

1. **Urinary mercury measurement**

Exposure to Hg^0 was characterized through Hg^0 assayed in spot urine samples based on a single void. All samples were held at 4º C until analysis, which was conducted at the ADA laboratory in Chicago, Illinois, using a cold vapor atomic absorption spectrophotometer with a method described elsewhere (Martin et al., 1995). The limit of detection (LOD) for urinary Hg^0 analyses was 0.2 μg/L. Urine Hg^0 concentrations below the LOD were imputed as LOD/√2 (n=272).

2. **Cumulative mercury exposure calculation**

To estimate a cumulative Hg^0 exposure for each individual dentist we used the mean urinary Hg^0 concentration of participants for each year since 1976 and applied each measure to the corresponding years the dentist practiced. We used the average of the first seven years of the survey (1976–1982) to represent the average in years prior to 1976. An adjustment was made to account for the high inter-individual variability of urinary Hg^0 based on the ratio of the individual's urinary Hg^0 level to the total average urinary Hg^0 for the year the participant was tested:

$$Hg^0 \text{ ratio} = (UHg_{individual} / average\ UHg_{year})$$

A cumulative exposure for each dentist was thus estimated using the following equation:

$$Cumulative\ Hg0\ exposure = (Hg0\ ratio) * \sum_{i=1} total\ years\ practiced\ \ (average\ urinary\ Hg0\ from\ HSP\ sample)i$$

For example, a dentist had urinary Hg^0 measured in the year 2000 and had been practicing for 20 years. Hypothetically, the dentist's urinary Hg^0 concentration in 2000 was 2.0 µg/L, while the average urinary Hg^0 for that year's HSP results was 1.0 µg/L. The ratio (2/1) would be applied to the average of each previous year that dentist worked (20 years) to calculate the cumulative dose exposed to up until that point:

$$Cumulative\ Hg\ exposure = (2/1) * \Sigma\ (average\ urinary\ Hg^0\ from\ 1980 + 1981 + 1982... + 2000)$$

C. <u>Multiple Sclerosis and Tremor Assessment</u>

Questions on MS and tremor history were only asked in surveys conducted in the years 1986–2007, 2011 and 2012. We restricted analyses of the relationships between occupational Hg exposure and the neurological outcomes to the subset of dentists who participated during these years and answered questions regarding MS and tremor (N=16,486). The question was posed: "Please indicate if you have or have ever had the following diseases or conditions. . . ."

In addition, the study was limited to the last observation for individuals who were repeatedly examined to ensure unique observations to yield a final sample size of 13,906 individual observations for studying the neurologic outcomes. However, for repeat measurements of cases, we used the earliest observation to be as close to age of diagnosis as possible and to avoid overestimating Hg exposure.

D. **Statistical Methods**

The prevalence of each neurologic outcome (i.e., number of cases/number of individuals who responded to the question) was estimated from the sample of dentists. We estimated descriptive statistics for the study population for available MS and tremor risk factors and for occupational factors related to Hg exposure, including whether or not individuals used amalgam in their practice, the number of amalgams removed and placed per week, hours worked per week, and urinary Hg^0 and cumulative Hg^0 exposure. We conducted T-tests and ANOVA to compare differences in means and Pearson chi-square tests for differences in proportions. Wilcoxon signed-rank tests were performed to compare means of non-normally distributed variables. A difference was considered to be statistically significant if $p<.05$ (two-tailed).

We used logistic regression models to estimate the association of Hg exposure with MS or tremor. Dentists who reported both MS and tremor were included in the analysis for the MS, and were both excluded and then later included in a sensitivity analysis for tremor. Age, sex, and calendar year (using a restricted cubic spline) were adjusted for in the tremor and MS models.

The only difference between models was that in the MS models we used a restricted cubic spline (knots=3) to adjust for age given the nonlinear association of age and MS as well as a priori knowledge that MS is routinely diagnosed in young adults (Ramagopalan et al., 2011). We examined, using separate models, three measures of Hg^0 exposure: the number of Hg amalgams removed and placed per week, urinary Hg^0 concentration, or cumulative Hg^0 exposure. Odds ratios (ORs) were calculated for mean unit increase in each measure of Hg^0 exposure. We first assessed dose-response relationships using quartiles of exposure, and then used continuous forms of the exposures because dose-response estimates were unstable due to small number of cases in each quartile. We also assessed associations using log-transformed urinary Hg^0 and cumulative Hg^0 exposures, however there was no statistical evidence that model fit was improved by comparing log likelihoods. We assessed effect modification for age, gender, and year by testing interaction terms of the covariate and the exposure variables using a Wald chi-square test. The only a priori interaction we noted was for age and cumulative Hg^0 (Albers et al., 1988).

We excluded dentists who were not currently using amalgam in a sensitivity analysis, by dropping retirees or those who reported not using amalgams in the last week.

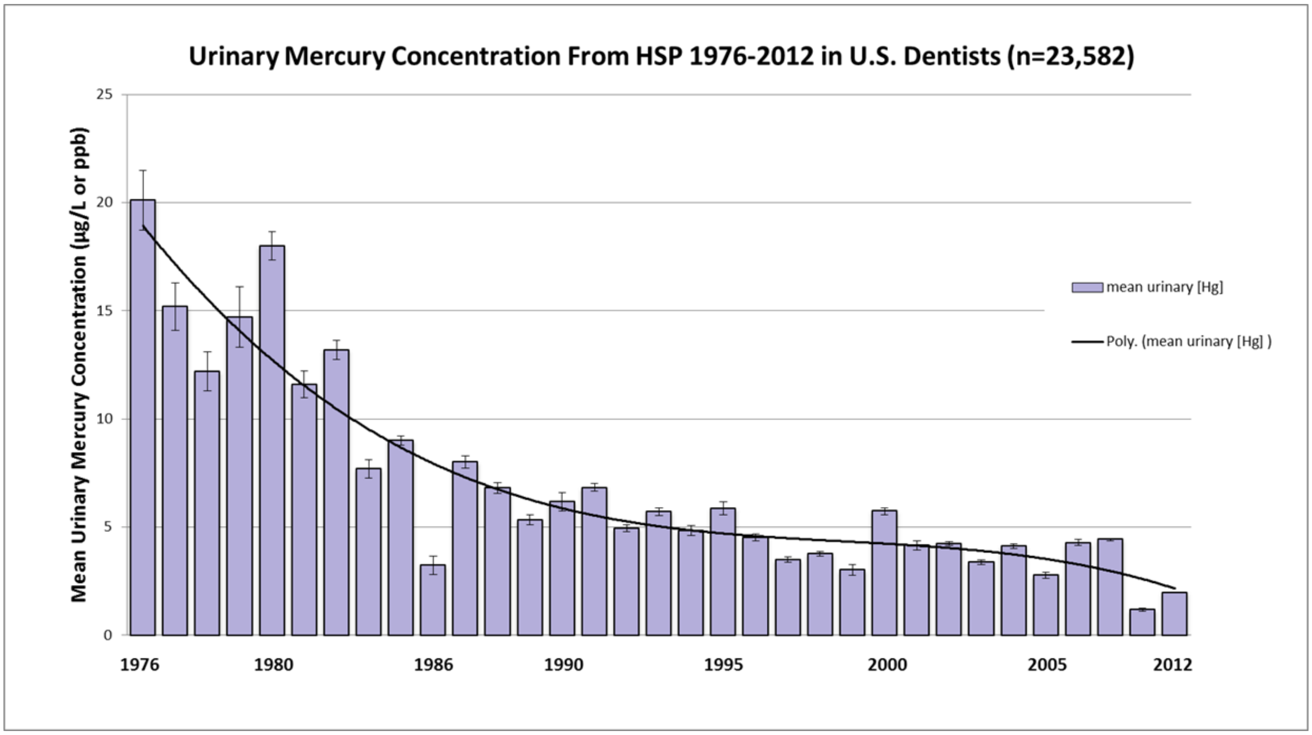
Lastly, we compared the distributions of urinary Hg^0 measurements in our sample of dentists and in the US general population. The NHANES measured urinary Hg^0 concentration of a subsample of men and women (n=2,507) in 2011–2012. The Hg^0 concentrations of 92 individuals were below the LOD, which was 0.05 ng/mL.

Measurements below the LOD were imputed by NHANES as the LOD/√2. To obtain estimates more comparable with our sample of dentists by age and income, we excluded NHANES participants younger than 25 years of age (n=976) and those from income levels <$75,000 (n=1,167). We calculated and compared distributions of urinary Hg^0 concentrations from the ADA (n=780) and resulting NHANES (n=364) samples from 2011 and 2012. We then calculated arithmetic means (with 95% CIs) categorized by age groups (<40 years, 40–59 years, and >=60 years), and stratified NHANES data by high or low seafood consumption (n=336), using the mean for seafood consumed per month for each category. The NHANES data were weighted by the survey sampling weights and design variables (US NHANES, 2015).

III. RESULTS

A. **Descriptive Results**

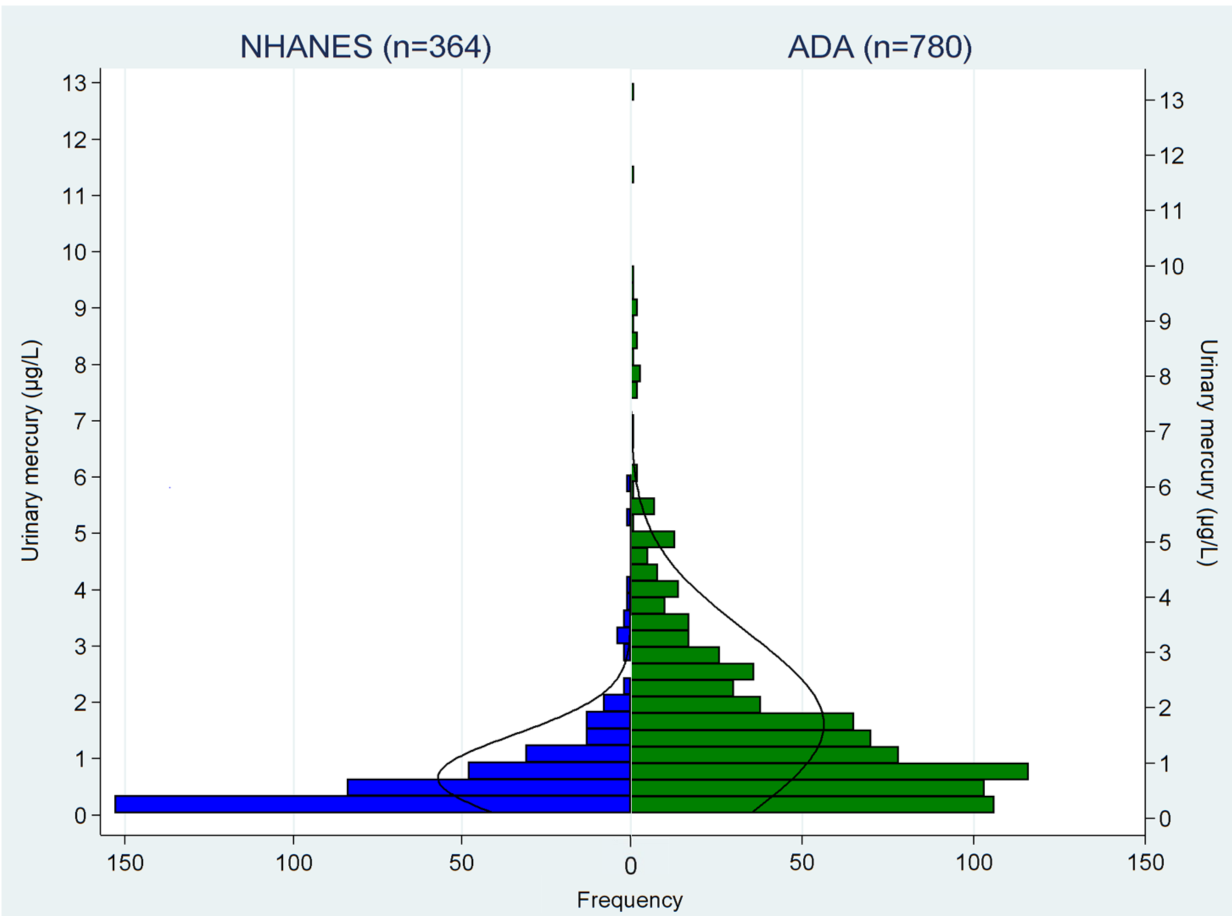
The distribution of average urinary Hg^0 concentrations for dentists by calendar year is presented in Figure 2. From an initial peak arithmetic mean of 20.1 µg/L (95% CI=14.0, 26.2) in 1976, urinary Hg^0 concentrations decreased dramatically over the subsequent 36 years. In 2012 the arithmetic mean concentration was 2.04 µg/L (95% CI=1.87, 2.22).



* Measured by the American Dental Association's Health Screening Program from 1976 to 2012

Figure 2. Arithmetic mean urinary Hg^0 concentrations (µg/L) in US dentists

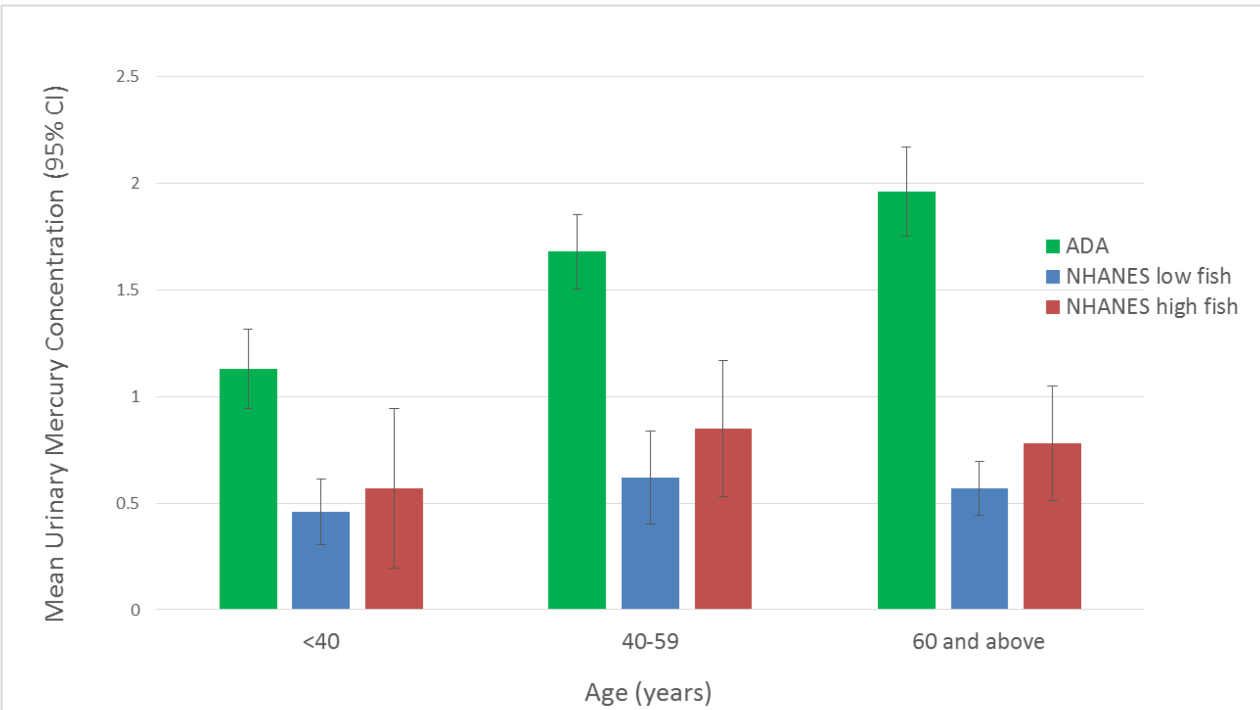
Figure 3 compares the distribution of urinary Hg^0 among NHANES and ADA samples in years 2011 and 2012. Even though the mean concentration of urinary Hg^0 had fallen substantially, it was still significantly higher among dentists [1.69 µg/L (95% CI=1.58, 1.81)] than among the NHANES population [0.66 µg/L (95%CI=.54, 0.78)]. The range of urinary Hg^0 was 0.4 µg/L–6.02 µg/L in NHANES, whereas it was 0.1 µg/L–13.1 µg/L in the ADA sample.



* NHANES 2011–2012 cycle from individuals over 25 years of age with income >$75,000 and dentists who participated in ADA health screenings in 2011 and 2012.

Figure 3. Urinary Hg^0 (µg/L) distributions from dentists and NHANES in 2011–2012.

Arithmetic mean urinary Hg^0 concentrations of dentists and NHANES were also examined by age (Figure 4). Dentists were found to have significantly higher urinary Hg^0 concentrations in every age group**.** The concentrations of Hg were found to increase with age among dentists.



* ADA dentists (n=780) and NHANES 2011–2012 (n=336) (excluding those <25 years of age with annual family income <$75,000 and missing fish consumption information).

Figure 4. Arithmetic mean urinary [Hg^0] of dentists and NHANES in 2011–2012 by age group.

Table I describes covariates of interest in terms of Hg^0 exposure. Those with high cumulative Hg^0 exposure were older than 50 years and male. However, differences in sex may be explained by age distributions, where we found that the proportion of females in the younger age category was much higher than in the older age category [(24.6% versus 8.0% (not shown in table)]. Table II provides detailed descriptive statistics for the dentist sample from 1986 through 2012 stratified by outcome status. Those experiencing tremor were more likely to be older, male, had placed and removed a lower mean number of amalgam restorations per week, and had higher mean cumulative exposures of Hg^0 than non-cases. Smoking was weakly (p=.07) associated with an increased risk of MS. In addition, among the 23 cases of MS, nine indicated experiencing tremor [39.1% (not shown in tables)].

TABLE I

DESCRIPTIVE STATISTICS FOR COVARIATES OF INTEREST BY HG EXPOSURE

	Amalgams placed and removed per week (N=8,566[a])			Urinary Hg^0 (µg/L) (N=7,632)			Cumulative Hg^0 (µg/L) (N=6,480)		
	N	**Mean (SD)**	***P* value**	**N**	**Mean (SD)**	***P* value**	**N**	**Mean (SD)**	***P* value**
Age, years									
< 40	1965	21 (14)		1697	4.6 (6.4)		1552	51.9 (107.1)	
40–49	2188	21 (14)	<.01	2038	4.4 (5.1)	0.17	1760	118.7 (165.8)	<.01
50–59	2242	18 (14)		2137	4.7 (6.9)		1806	217.0 (354.8)	
>59	2171	17 (14)		1760	4.8 (6.7)		1362	368.8 (522.3)	
Sex									
Female	1527	17 (14)	<.01	1091	3.3 (4.3)	<.01	918	63.3 (148.4)	<.01
Male	7039	20 (14)		6541	4.9 (6.5)		5562	202.4 (357.9)	
Hours worked/week									
<30	931	14 (12)		685	3.5 (4.0)		588	196.1 (303.5)	
30–39	3187	20 (13)	<.01	2761	4.4 (6.2)	<.01	2410	179.4 (322.9)	0.08
>40	1663	19 (14)		1467	4.9 (6.0)		1312	161.4 (362.4)	
Missing	2785	20 (14)		2719	5.0 (6.9)		2170	195.5 (352.3)	
Tobacco use									
Yes	355	21 (14)		344	5.3 (8.7)		303	187.1 (272.8)	
No	5560	19 (14)	0.01	5013	4.9 (6.9)	0.33	4275	186.6 (351.8)	0.98
Missing	2651	19 (14)		2275	3.9 (4.0)		1902	173.1(321.0)	
Amalgam use									
Yes	7752	21 (13)		6976	4.8 (6.3)		6032	184.0 (328.8)	
No	621	0 (0)	<.01	286	2.5 (2.9)	<.01	196	133.5 (345.1)	0.03
Missing	193	0 (0)		370	4.1 (8.2)		252	188.8 (535.8)	
Amalgams in mouth									
$\leq$ 10	3775	20 (14)		3145	4.4 (5.4)		2584	175.9 (306.8)	
> 10	375	22 (14)	<.01	407	5.3 (5.5)	<.01	352	238.6 (337.2)	<0.01
Missing	4416	19 (14)		4080	4.7 (7.0)		3544	182.0 (361.7)	

DESCRIPTIVE STATISTICS FOR COVARIATES OF INTEREST BY HG EXPOSURE

	Amalgams placed and removed per week (N=8,566[a])			**Urinary Hg^0 (μg/L) (N=7,632)**			**Cumulative Hg^0 (μg/L) (N=6,480)**		
	N	**Mean (SD)**	***P* value**	**N**	**Mean (SD)**	***P* value**	**N**	**Mean (SD)**	***P* value**
Self-reported diagnosis of MS									
Yes	14	17 (12)	0.47	14	3.9 (2.7)		10	112.6 (189.9)	0.51
No	8552	19 (14)		7618	4.6 (6.3)	0.64	6470	182.8 (339.9)	
Self-reported diagnosis of tremors									
Yes	96	14 (12)		111	5.6 (13.4)		84	243.5 (388.7)	
No	8433	19 (14)	<.01	7492	4.6 (6.1)	0.09	6375	181.0 (337.2)	0.09
Missing	37	17 (14)		29	4.8 (3.9)		21	450.2 (659.6)	

[a] N=number of participants who answered the question

TABLE II

DESCRIPTIVE STATISTICS[a] FOR COVARIATES OF INTEREST BY OUTCOME STATUS

	Multiple Sclerosis (23 / 12,550)			Tremor (170 / 12,543)		
	Yes	**No**	***P* value**	**Yes**	**No**	***P* value**
Total (prevalence)	23 (0.2%)	12,527 (99.8%)	--	170 (1.4%)	12.373 (98.6%)	--
Sex						
Male	20 (88%)	10, 226 (83%)	0.62	150 (89%)	10,085 (83%)	0.03
Female	3 (12%)	2,076 (17%)		18 (11%)	2,064 (17%)	
Amalgam use						
Yes	20 (95%)	10,995 (94%)	0.75	142 (92%)	10,858 (93%)	0.52
No	1 (5%)	764 (6%)		12 (8%)	755 (7%)	
Tobacco use [b]						
Yes	3 (17%)	556 (6%)	0.07	9 (8%)	549 (6%)	0.36
No	15 (83%)	8,310 (94%)		98 (92%)	8,236 (94%)	
Age (years)						
Mean (SD)	48.1 (13.6)	49.5 (12.1)	0.61	53.9 (11.5)	49.4 (12.1)	<.001
Amalgams removed & placed per week [c]						
Mean (SD)	16.6 (14.6)	19.3 (13.9)	0.59	14.5 (11.8)	19.3 (13.9)	<.001
Urinary Hg^0 (µg/L) [d]						
Mean (SD)	3.9 (2.7)	4.7 (6.4)	0.87	5.5 (12.8)	4.6 (6.2)	0.99

DESCRIPTIVE STATISTICS[a] FOR COVARIATES OF INTEREST BY OUTCOME STATUS

	Multiple Sclerosis (23 / 12,550)			Tremor (170 / 12,543)		
	Yes	**No**	***P* value**	**Yes**	**No**	***P* value**
Cumulative Hg^0 (µg/L) [e] Mean (SD)	112.6 (189.9)	182.8 (339.9)	0.21	257.6 (394.2)	182.0 (338.8)	0.001
Hours worked/week Mean (SD) [f]	34.3 (12.8)	34.5 (8.3)	0.93	34.2 (7.9)	34.5 (8.3)	0.87

[a] Number of participants for each characteristic may not equal the overall total number of participants because of missing data. See below.
[b] Question was asked for survey years 1986–1995 and 2006–2012 (n=MS: 18 / 9,322; tremor: 107 / 8,892)
[c] Question was asked for survey years 1990–1991, 1993–2012 (n=MS: 14/ 8,912; tremor: 112 / 8,906)
[d] N= MS: 14 / 7,935; Tremor 122 / 7,928
[e] N= MS: 10 / 6,733; Tremor: 95 / 6,732
[f] Question asked 1986–1988, 1995–2012; (MS: 11 / 7,883; tremor: 87 / 7,868)

B. **Regression Analyses**

Results from logistic regression modeling for MS are presented in Table III and for tremor in Table IV. The OR corresponding to the mean increase for each Hg^0 exposure variable is presented for ease of interpretation; however, the unit increases were modeled continuously and results are presented in Tables V and VI. None of the measures of exposure were associated with an increased risk of prevalent MS. Higher numbers of amalgams placed and removed per week was highly (p=.001) associated with a decreased risk of prevalent tremor [for each additional amalgam placed/removed, OR=.97, 95% CI (0.96, 0.99)].

Urinary Hg^0 was associated, at borderline significance, with an increased risk for prevalent tremor [per mean (4.7 µg/L) increase, OR=1.10; 95% CI (1.00, 1.21)]. The association between cumulative Hg^0 exposure and tremor prevalence varied significantly by age (p-value=.05). To further explore the interaction, we categorized participants into two groups of equal sample size based on their age, 50 years of age or younger and older than 50 years. Among the youngest age group, higher cumulative Hg^0 exposure was significantly associated with prevalent tremor risk, the mean exposure (92 µg/L) corresponding to an OR of 1.13 (95% CI: 1.04, 1.22). By contrast, there was little evidence for an association among the older dentists [OR=1.02 (0.86, 1.21)].

TABLE III

ADJUSTED[a] ASSOCIATION OF MS WITH OCCUPATIONAL HG EXPOSURE MEASURED BY AMALGAMS REMOVED AND PLACED PER WEEK, URINARY HG^0 (μG/L), AND CUMULATIVE HG^0 EXPOSURE (μG/L).

Exposure	**Cases / N**	**OR for mean unit increase (95% CI)[b]**	**p-value**
Amalgams rem/placed per week	14 / 8,566	0.70 (0.33, 1.50)	0.36
Urinary Hg^0 (μg/L)	14 / 7,632	0.80 (0.43, 1.49)	0.48
Cumulative Hg^0 exposure (μg/L)	10 / 6,446	0.85 (0.40, 1.84)	0.69

[a] Adjusted for age, sex, and calendar year.

[b] Means: amalgams removed and placed per week =19.1 amalgams, urinary Hg^0=4.7 μg/L, cumulative Hg^0=191 μg/L

TABLE IV

ADJUSTED[A] ASSOCIATION OF TREMOR AND OCCUPATIONAL HG EXPOSURE MEASURED BY AMALGAMS REMOVED AND PLACED PER WEEK, URINARY HG^0 (µG/L) AND CUMULATIVE HG^0 EXPOSURE (µG/L).

Exposure	Cases / N	OR for mean unit increase (95% CI)[b]	p-value
Amalgams rem/placed per week	97 / 8,545	0.61 (0.45, 0.83)	0.001
Urinary Hg^0(µg/L)	112 / 7,610	1.10 (1.00, 1.21)	0.06
Mean Cumulative Hg^0 exposure (µg/L)			
Age 23–50 years	34 / 3,473	1.13 (1.04, 1.22)	0.002
Age 51 and above	53 / 2,994	1.02 (0.86, 1.21)	0.80

[a] Adjusted for age, sex, and calendar year

[b] Means: amalgams removed and placed per week =19.1 amalgams, urinary Hg^0=4.7 µg/L, mean cumulative exposure by age group: Ages <=50= 92 µg/L and ages >50 years= 302 µg/L

TABLE V

ADJUSTED[A] ASSOCIATION OF MS WITH OCCUPATIONAL HG EXPOSURE MEASURED BY AMALGAMS REMOVED AND PLACED PER WEEK, URINARY HG^0 (µG/L) AND CUMULATIVE HG^0 EXPOSURE (µG/L).

Exposure	**Cases / N**	**OR for unit increase (95% CI)**	**p-value**
Amalgams rem/placed per week	14 / 8,566	0.98 (0.94, 1.02)	0.36
Urinary Hg^0 (µg/L)	14 / 7,632	0.95 (0.83, 1.09)	0.48
Cumulative Hg^0 exposure (µg/L)	10 / 6,446	1.00 (1.00, 1.00)	0.69

[a] Adjusted for age, sex and calendar year

TABLE VI

ADJUSTED[A] ASSOCIATION OF TREMOR AND OCCUPATIONAL HG EXPOSURE MEASURED BY AMALGAMS REMOVED AND PLACED PER WEEK, URINARY HG^0 (µG/L) AND CUMULATIVE HG^0 EXPOSURE (µG/L).

Exposure	**Cases / N**	**OR for unit increase (95% CI)**	**p-value**
Amalgams rem/placed per week	97 / 8,545	0.97 (0.96, 0.99)	0.001
Urinary Hg^0 (µg/L)	112 / 7,610	1.02 (1.00, 1.04)	0.07
Cumulative Hg^0exposure (µg/L)			
Age 23–50 years	34 / 3,473	1.00 (1.00, 1.00)	0.002
Age 51 and above	53 / 2,994	1.00 (1.00, 1.00)	0.796

[a] Adjusted for age, sex, and calendar year

IV. DISCUSSION

A. Summary of Results

Occupational Hg^0 exposure in US dentists has declined substantially over the past 36 years. These remarkable reductions in exposure reflect heightened Hg^0 hygiene awareness, the development of pre-capsulated amalgam material, as well as the increased use of composite resin for dental restorations. Current urinary Hg^0 levels are slightly higher than the general population reported in NHANES, particularly among older dentists.

Our findings for cumulative Hg^0 exposure and tremor varied by age. The probability of tremor increased with cumulative Hg^0 exposure in younger dentists (<50 years of age) but not in older dentists (≥ 50 years of age), although prevalence of tremor was higher in the older age group. This interaction was different from the age-cumulative Hg^0 interaction found by Albers et al. (1988).

Because cumulative Hg^0 exposure is the product of the total years practiced and one urinary Hg^0 measurement, two dentists of different ages with the same cumulative Hg^0 exposure have different durations and doses of Hg^0. A younger dentist who has the same cumulative Hg^0 exposure as an older dentist will have had a higher dose of Hg^0 over a shorter period of time, thus the occurrence of adverse events like tremor might be likely among younger dentists. Alternatively, the probability of tremor could be unrelated to the Hg^0 dose, but rather related to the duration of working with vibrational tools like dental handpieces (Szymańska, 2001).

However, in our study, hours worked per week did not vary dramatically by age group. Dentists of age 23–40 years worked for a mean 36.3 (SD=7.8, n=1,902) hours per week, while dentists of age 41–50 years worked on average 35.4 (SD=7.9, n=2,182), dentists aged 51–59 years worked for a mean of 34.6 (SD=7.4, n=2,390) hours per week, and dentists of age 60 or greater years worked 31.5 (SD=9.5, n=1,878) hours per week.

Duration of practice was also examined as an additional covariate in all models. The only model that it significantly improved (p=.04) was urinary Hg^0 exposure with the outcome of tremor. When duration was included in the model, the urinary Hg^0 exposure estimate changed [OR=1.10 (1.00, 1.21) to OR=1.00 (0.85, 1.17)], suggesting that duration rather than the current urinary Hg^0 exposure is more important. Duration of practice was not found to be significant or change estimates of cumulative Hg^0 exposure, which suggests that cumulative Hg^0 exposure may be a more appropriate measure of exposure for chronic disease outcomes.

We did not observe an increased risk of MS with any of the measures of occupational Hg^0 exposure examined in this study. Regression analyses may have had limited power due to the small number of cases (n=23) in our sample. However, the prevalence of MS in our sample was higher than the prevalence reported in the US population. The most recent MS prevalence study from The Centers for Disease Control and Prevention estimated the prevalence of MS in three large geographic areas in the northern, middle, and southern United States (Williamson et al., 2010).

They estimated prevalence ranging from 47.2 per 100,000 in Texas, 86.3 per 100,000 in Missouri, and 109.5 per 100,000 population in the Ohio area. In 2009, The National Society for Multiple Sclerosis reported 400,000 prevalent cases of MS in the United States, or 130 per 100,000 (National Society for Multiple Sclerosis, 2009). The prevalence of MS in our sample is substantially higher at 183 per 100,000. We would expect MS would be even lower than the reported figures given that MS is more common in women and our study was 83. 4% male (TABLE II).

B. **Strengths and Limitations**

This is the largest study to date describing Hg^0 exposure among practicing dentists. The study is fairly homogeneous with respect to education—all participants were dentists—thus we would expect less confounding by socioeconomic status in the study population than in samples from the general population.

The main limitation of our study is the manner in which the data were collected. As mentioned previously, the survey data were collected from participants in the HSP in years ranging from 1986 to 2012, held during the ADA's annual conference. The voluntary nature of this survey could bias our findings in either direction. For example, dentists who had neurological illness or had been using amalgam more frequently than usual may have been more interested in participating. On the other hand, dentists with MS or severe tremor might have been less likely to visit the annual session, or no longer practiced dentistry.

1. **Selection bias**

The likelihood of tremor may not increase in the older age group because the majority of dentists who attend the conference are currently working (93.7%), and thus this study is most likely to be biased by the exclusion of dentists who are not healthy enough to work. This selection bias may be stronger for older than for younger dentists (Checkoway et al., 2004). We also observed a strong protective association of the number of amalgams placed and removed per week on the prevalence of tremor. This observation is also most likely indicative of a selection bias in that dentists with tremor might reduce their hours in more physically demanding tasks such as performing restorations.

2. **Exposure misclassification**

A serious limitation in our study was that it lacked detailed information on other possible sources of Hg exposure, such as seafood consumption and amalgams in one's mouth. Thus, we may be overestimating the amount of Hg^0 exposure attributable to occupation. As observed in individuals with high-income status, it is expected that dentists consume more fish than the general population (Tyrrell et al., 2013). A recent study among dentists found that methyl mercury (MeHg) exposure via fish consumption contributes to urinary Hg^0 measurements more than previously thought (Sherman et al., 2013). In our sample, information was available for the number of seafood meals per week during 1987 and 1988. Urinary Hg^0 and seafood consumption were not correlated [r=.03 (p= .3)]; however, our overall sample spans

1986 to 2012 so these results may not reflect characteristics of the overall sample. Furthermore, seafood availability and consumption has increased in the last 20 years (Kearney, 2010).

Some studies have shown the number of amalgam restorations in participants' mouths contributes to urinary Hg^0 concentrations and is correlated with the Hg content of brain tissue at autopsy (Kingman, 1998; Dye, 2005; Bates, 2006). In our sample, urinary Hg^0 varied between those with high versus low amalgams in the mouth [>10 or ≤10 amalgams (Sherman, 2013)] ($p<.01$) as seen in Table I; however, the magnitude of these differences was small and standard deviations were relatively large [5.3 µg/L (±5.5) versus 4.4 µg/L (±5.4)].

Furthermore, because the cumulative Hg^0 calculation was partly based on dentists' urinary Hg^0 measurement, if they were currently not practicing dentistry or using amalgams in their practice, their cumulative Hg^0 exposure would be underestimated. To address this issue, we conducted a sensitivity analysis by excluding retirees and those who did not use amalgam in their practice. We did not observe a difference in estimates as compared to our overall analysis, which we expected because 93.7% of dentists in our sample were currently working.

Although we lack complete information on seafood consumption and amalgam restorations among participants, our data support urinary Hg^0 concentrations that vary mainly by occupational exposure, as Table I highlights those who use amalgam have higher concentrations of urinary Hg^0 [4.8 µg/L (±6.3) versus 2.5 µg/L (±2.9)].

3. **Potential unmeasured confounding**

Fish consumption could also confound the association of Hg^0 exposure and tremor. Studies involving fish consumption and the nervous system have found both harmful and protective effects conditional upon the amount of MeHg and omega-3 fatty acids in the fish consumed (Pottala et al., 2014; Bäärnhielm et al., 2014). Furthermore, without proper adjustment, fatty acids in fish can mask the harmful effects of MeHg on the nervous system (Choi et al., 2014). Some studies have found associations of high MeHg exposure from fish consumption and decreased performance on psychomotor tests, which are considered preclinical indicators for some types of tremor (Dolbec et al., 1999; Lebel et al., 1998; Roels et al., 1989). If fish consumption were positively associated with Hg^0 exposure, it could protect against or cause tremor, depending on the type of fish consumed, biasing our estimates in either direction. Information on tobacco use was limited and missing for a large percentage (31%) of the study participants. However, smoking is not likely to be a confounder in this study. While smoking is a risk factor for MS and is both positively associated as well as inversely related to different types of tremor (Salzer et al., 2012; Louis et al., 2008; Hernan et al., 2002), only a trace amount of Hg is present in cigarettes and does not contribute substantially to the body burden of Hg (Chiba and Masironi, 1992). Furthermore, smoking is not common among dentists. As seen in Table I, mean Hg^0 measurements do not vary by tobacco use (p=.3).

4. **Outcome misclassification**

The quality of the diagnostic information also limited our study. Misclassification of outcomes must be considered because they were self-reported, and furthermore, self-diagnosis is possible because participants are healthcare professionals. However, self-diagnosis of MS is unlikely, considering MS is diagnosed by a neurologist using MRI, a spinal tap, and electro-diagnostic tests (Mayo Clinic Staff, 2014). Thus, more specific information on the subtype of MS (Relapsing-remitting MS, secondary-progressive MS, primary-progressive MS and progressive-relapsing MS) could be important. The prevalence of MS in our sample is only slightly higher at 191 per 100,000, therefore misclassification of MS is unlikely.

Self-diagnosis of tremor could be a more realistic limitation. The diagnosis of tremor requires a physical and neurological exam, but due to the nature of the condition, healthcare professionals may be more prone to self-diagnose.

More specific information regarding the type of tremor could have been useful. As mentioned before, pathologic tremor may be classified as accentuated physiologic, parkinsonian, essential, and cerebellar tremor; within these classifications many subgroups exist (Jankovic and Fahn, 1980; Elble, 1996). Additional tests may be useful, including an electromyogram and blood and urine tests to detect drug interaction, chronic alcoholism, or another condition that may cause tremor (NIH, 2012). Unfortunately, we could not conduct analyses of these subgroups because our analysis was based on self-reported disease and conditions.

V. CONCLUSIONS

Occupational Hg^0 exposure in US dentists has dramatically declined over the past few decades and is now slightly higher on average than Hg^0 exposure in the general population. The ADA's health screening survey from years 1986 to 2012 has allowed us to calculate the prevalence of MS and tremor and to assess whether these neurological diseases are related to occupational Hg^0 exposure.

Although this study has a large sample size that spans more than two decades, the study has limitations. However, we believe our finding of an association between Hg^0 exposure and tremor is of particular concern because it appears to be among young dentists.

An association was not found between Hg exposure and MS; however, the prevalence of MS was almost twice as high in our sample as the MS prevalence in the northern-most measured latitude in the general population. More studies of tremor as well as MS to among dentists are needed to confirm these findings. Future studies should include retired dentists with better characterization of exposures, potential confounders, and neurologic outcomes.

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