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Occupational Exposures and Movement Abnormalities among Japanese-American Men: The Honolulu-Asia Aging Study

Luenda E. Charles[a] Cecil M. Burchfiel[a] Desta Fekedulegn[a]
Michael L. Kashon[a] G. Webster Ross[c–f] Helen Petrovitch[c–f]
Wayne T. Sanderson[b]

[a]Biostatistics and Epidemiology Branch, Health Effects Laboratory Division, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, Morgantown, W. Va., [b]Department of Occupational and Environmental Health, The University of Iowa College of Public Health, Iowa City, Iowa, [c]Veterans Affairs Pacific Islands Health Care System, [d]The Pacific Health Research Institute, [e]Departments of Geriatric Medicine and Medicine, John A. Burns School of Medicine, University of Hawaii, and [f]Kuakini Medical Center and the Honolulu-Asia Aging Study, Honolulu, Hawaii, USA

Key Words
Occupational toxin exposures · Movement abnormalities · Neurological signs · Normal aging

Abstract
Objective: The authors analyzed data on 1,049 men aged 71–93 years (excluding those with prevalent Parkinson's disease and stroke) from the Honolulu Heart Program (1965–1968) and the Honolulu-Asia Aging Study (1991–1999) to determine whether occupational exposures to pesticides, solvents, metals, manganese, and mercury during middle age were associated with 14 movement abnormalities 25 years later. ***Methods:*** Analyses of variance and multivariate logistic regression were used to assess associations of interest. ***Results:*** After adjustment for age, BMI, cognitive functioning, smoking, alcohol drinking, education, and physical activity, there was a positive association between abnormal 'facial expression' and the highest exposure to metals [odds ratio (OR) = 2.62; 95% confidence interval (CI) = 1.35–5.11; trend, p = 0.02], and the highest exposure to mercury (OR = 1.91; 95% CI = 1.04–3.49; trend, p = 0.03). Age was positively associated with all movement abnormalities, and cognitive function, body mass index and physical activity were inversely associated with most movement abnormalities. ***Conclusion:*** Higher exposure to any metal, and specifically mercury, was associated with abnormal facial expression.

Introduction

Associations have been identified between occupational exposures and both the incidence (or prevalence) [1, 2] and severity [3–8] of neurological illness. Occupational exposure to mercury and manganese have been positively associated with movement abnormalities such as hand and arm tremors and mask-like facial appearance [4, 5], and exposure to pesticides and hydrocarbon solvents have been positively associated with Parkinson's disease (PD) [3, 6].

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Dr. Luenda E. Charles
National Institute for Occupational Safety and Health HELD/BEB, MS L-4050
1095 Willowdale Rd.
Morgantown, WV 26505-2888 (USA)
Tel. +1 304 285 5922, Fax +1 304 285 6112, E-Mail lcharles@cdc.gov

The objective of this study was to determine whether occupational exposures to pesticides, solvents and metals assessed prospectively are associated with the development of specific movement abnormalities associated with parkinsonism that may occur in normal aging as well. Such associations would provide evidence that the exposures may cause injury to the extrapyramidal motor system.

Methods

Study Population

The participants in this study were Japanese-American men who were participants in the Honolulu Heart Program (HHP) and the Honolulu-Asia Aging Study (HAAS). The HHP began in 1965 as a prospective cohort study of cardiovascular disease and stroke, and the HAAS was added in 1991 to investigate determinants of various health conditions in the elderly. Informed consent was obtained from the study participants and the study was approved by an institutional review committee. A detailed description of the methods of the HHP/HAAS has been previously published [9, 10].

Several exams have been conducted in the HHP and HAAS to date. Exam I took place during 1965–1968 and included 8,006 men who were between the ages of 45 and 68 years; exam II (1968–1970) included 7,498 men from the original cohort; exam III (1971–1974) included 6,860 men, and exam IV (1991–1993) included 3,845 men who were between the ages of 71 and 93 years. Participants who were diagnosed with PD (n = 61) and stroke (n = 113) prior to the first neurological exam (1991–1993) were excluded from the analysis; 2 men had both diagnoses. The neurological exams for the assessment of movement abnormalities took place during the fourth, fifth, and sixth exams. A total of 1,221 men received neurological evaluations at one or more of these exams, 426 during exam IV (1991–1993), 752 during exam V (1994–1996), and 294 during exam VI (1997–1999), and of these, 172 were excluded because of a diagnosis of PD and/or stroke. Therefore, the study sample included 1,049 men without PD or stroke.

Assessment of Occupational Exposures

Information on occupational history was collected during exams I and III. No direct exposure measurements were made. Participants were asked questions about their present and usual occupation, and the age that they started and finished working in these occupations.

Industrial hygienists from the National Institute for Occupational Safety and Health (NIOSH) assessed the potential for pesticide, metal, and solvent exposure in each reported occupation [11]. They created four levels of exposure to the agent, indicating a score of 0 for no potential of exposure, 1 for low exposure, 2 for medium exposure and 3 for potential of high exposure. The 'high' classification was assigned to those occupation/industry pairings judged to have significant exposures that were frequently well above analytically detectable concentrations and were at least occasionally near or greater than the Occupational Safety and Health Administration (OSHA)-permissible exposure limits (PELs), if a PEL existed. A 'high' score meant that the industrial hygienists were confident that the industry/occupation pairing would frequently be exposed to the agent. The 'medium' exposure classification was assigned to those occupation/industry pairings judged to involve tasks with detectable exposures to the selected agents, but which were considered to usually be below the OSHA-PELs. The 'low' exposure classification was assigned to those industry/occupation pairings judged to occasionally have undetectable exposures to the selected agents but which would rarely approach the OSHA-PEL. A '0' score indicated that workers in the industry/occupation pairing were believed to have little potential exposure to the agent. The scores not only reflected the industrial hygienists' view of the intensity of exposure, but also their confidence that jobs in these industries would mean exposure to these agents. Even though information was collected on 'present' and 'usual' jobs, 'usual' job was primarily used to determine to which industry-occupation group workers should be assigned to determine their exposure. However, if participants had none of the exposures in their usual job but had the exposures in their present job at exams I and/or III, then that information (i.e., in present job) was used in creating a measure of cumulative exposure. In addition, when exposures were present at both exams, the exposures closest to the outcome (i.e., exposures in exam III) were chosen. Exposure intensity scores (i.e., cumulative exposures) were obtained by multiplying the appropriate levels of exposure (0, 1, 2, 3) to usual or present job at exam I or III by the number of years exposed to the agent of interest. Exposure intensity scores were used as continuous variables or categorized into four levels.

Assessment of Movement Abnormalities

A neurologist performed the motor examination section of the Unified Parkinson's Disease Rating Scale (UPDRS) [12] to participants during exams IV, V and VI. The original coding for the movement abnormalities included five levels: 0 indicated an absence of the abnormality, and 1–4 described the presence of gradually more severe abnormalities. For example, posture was originally coded as follows: 0 = normal erect; 1 = not quite erect, slightly stooped posture, could be normal for older person; 2 = moderately stooped posture, definitely abnormal; 3 = severely stooped posture with kyphosis; 4 = marked flexion with extreme abnormality of posture. Each movement abnormality variable was recoded; if a subject received a score ≥ 1 on a UPDRS item, that movement abnormality was considered present (1), otherwise it was considered absent (0).

To examine movement abnormalities in relation to exposure variables, the disorder data that was closest in time to the exposure data (i.e., closest to exams I and III) was used. Thus, if a participant had a measured value of movement abnormality at exam IV, then that value was used. Similarly, if data at exam IV were missing, then the measured value from exam V was taken if available, otherwise the value was taken from exam VI. In addition to individual movement abnormalities, movement abnormalities were placed into groups for assessment with the occupational exposures. All 14 movement abnormalities were summed and the new variable was dichotomized into 'none' versus 'any' disorders. Also, an indicator variable was created that comprised increasing numbers (six levels) of five movement abnormalities: 'facial expression', 'posture', 'gait', 'rapid alternating hand movements', and 'rigidity'. For example, level 1 of the new variable has zero, level 2 has one ('facial expression'), and level 6 has all five movement abnormalities. These propensity scores were developed in an attempt to determine the association between the exposures and multiple movement abnormalities. These specific movement abnormalities, 'facial expres-

Table 1. Prevalence of occupational exposure characteristics for study participants at exams I and III

	Pesticide		Solvent		Metal		Manganese		Mercury	
	n	%	n	%	n	%	n	%	n	%
Usual job exposure (exams I and III)										
None (0)	909	86.7	393	37.5	530	50.5	815	77.7	865	82.5
Low (1)	25	2.4	425	40.5	386	36.8	155	14.8	150	14.3
Medium (2)	3	0.3	99	9.4	59	5.6	10	0.9	34	3.24
High (3)	112	10.7	132	12.6	74	7.1	69	6.6	0	0.0
Years of exposure										
0	909	86.7	393	37.5	531	50.6	815	77.7	870	82.9
>0–15	40	3.8	117	11.2	83	7.9	44	4.2	28	2.7
16–30	72	6.9	294	28.0	219	20.9	106	10.1	72	6.9
31+	28	2.7	245	23.4	216	20.6	84	8.0	79	7.5
Intensity scores[1]										
None	909	86.7	393	37.5	531	50.6	815	77.7	870	82.9
Low	53	5.1	412	39.3	355	33.8	142	13.5	55	5.2
Medium	45	4.3	146	13.9	107	10.2	49	4.7	57	5.4
High	42	4.0	98	9.3	56	5.3	43	4.1	67	6.4

[1]Categories for exposure intensity scores (i.e., cumulative exposure) to mercury are 0, 1–25, 26–36, ≥37; categories for all other agents are 0, 1–39, 40–79, ≥80. Total sample = 1,049 men.

sion', 'posture', 'gait', 'rapid alternating hand movements', and 'rigidity', were chosen because, in the multivariate analyses, they were more likely than the others to be related to at least one occupational exposure.

Assessment of Covariates

In exam I, a physical examination was performed and self-administered questionnaires were completed by each subject. Participants were re-examined and re-interviewed at subsequent exams. Body mass index (BMI) was calculated; a physical activity index was created by multiplying estimated oxygen consumption in liters per minute required for each activity by a weighting factor and summing those values for each level of physical activity [13]. From information obtained in the questionnaires, pack-years of smoking and ounces of alcoholic beverages consumed per month were created. Participants reported the number of years of education completed. Beginning at exam IV, the Cognitive Abilities Screening Index Instrument (CASI) was used to assess cognitive function [14]. CASI score was analyzed as a continuous and as a dichotomous variable – impaired cognition (CASI ≤74), and normal cognition (CASI >74). Information on all covariates was assessed at exam IV.

Statistical Methods

All analyses were conducted using SAS version 8.02 [15]. Frequencies were obtained for all occupational exposure variables and covariates separately, and in association with each movement abnormality. Trend was assessed by using the Cochran-Armitage Trend Test and general linear models. Analysis of variance was used to obtain the mean levels of covariates by occupational exposure category. Multivariate logistic regression models were used to assess associations of interest (using the first level as the referent) as well as confounding and effect modification. Age, BMI, smoking, alcohol consumption, CASI score, education, and physical activity were assessed for potential confounding and effect modification in associations of occupational exposures with movement abnormalities.

Results

The prevalence of occupational exposure varied widely (table 1). Jobs with solvent or any metal exposure were most common. For usual job exposure, the prevalence ranged from 13.4% for any pesticide exposure to 62.5% for any solvent exposure. For mercury exposure, no participants had 'high exposure'. Approximately 10% of men had ≥15 years of pesticide exposure compared to 51% who had the same duration of solvent exposure. Exposure intensity scores also followed the above pattern for all of the exposures.

The five movement abnormalities with the highest prevalence in this population were abnormal 'hand movements' (63.8%), 'rapid alternating hand movements' (62.1%), 'rigidity' (59.6%), abnormal 'posture' (58.6%), and abnormal 'foot agility' (57.0%) (table 2). The major-

Table 2. Prevalence of movement abnormalities by age at exam IV, 1991–1993*

Movement abnormalities	Age, years				All ages
	71–74	75–78	79–82	≥83	
Hand movements	45.9 (207)	57.5 (320)	68.8 (208)	80.6 (278)	63.8 (1,013)
Rapid alternating hand movements	39.3 (206)	56.5 (317)	68.9 (206)	81.0 (268)	62.1 (997)
Rigidity	42.5 (212)	56.5 (322)	64.8 (210)	71.8 (291)	59.6 (1,035)
Posture	33.2 (208)	51.4 (317)	64.1 (209)	81.4 (280)	58.6 (1,014)
Foot agility	36.4 (206)	56.5 (315)	55.9 (204)	74.6 (264)	57.0 (989)
Finger taps	38.9 (208)	51.4 (321)	62.0 (208)	71.5 (281)	56.6 (1,018)
Body bradykinesia	22.8 (211)	35.0 (323)	42.7 (211)	67.8 (292)	43.3 (1,037)
Gait	21.6 (213)	33.0 (318)	44.5 (209)	65.5 (287)	42.1 (1,027)
Postural stability	21.4 (210)	30.9 (311)	48.0 (204)	61.6 (268)	40.7 (993)
Facial expression	22.5 (213)	22.0 (323)	37.0 (211)	51.7 (296)	33.6 (1,043)
Speech	17.3 (214)	20.1 (324)	31.3 (211)	49.3 (296)	30.1 (1,045)
Hand tremor	25.8 (209)	24.5 (323)	29.1 (210)	34.6 (280)	28.5 (1,022)
Arising from chair	13.4 (209)	19.9 (317)	27.5 (207)	43.6 (275)	26.6 (1,008)

Prevalence in percentages; total number in parentheses.
Total sample = 1,049 men.
* One-sided trend p value <0.01 for all movement abnormalities.

ity of participants (91%) had ≥1 abnormalities with this panel of tests (data not shown). Only 2.1% of participants reported having 'tremor at rest' (not shown in table 2). Due to the small numbers in this category, 'tremor at rest' was removed from further analyses. Prevalence of all movement abnormalities increased notably with increasing age (p for trend <0.01).

Study participants ranged in age from 71 to 93 years, with a mean age of 79 years (table 3). The mean BMI was 23 (99% of the men had a BMI ≤31) and the mean years of education was 9.6 years (range 2–24 years). Among participants who provided the information, 40% were never smokers, 54% were past smokers, and 6% were current smokers; 42% had never used alcohol, 24% had consumed alcohol in the past, and 34% currently drank alcohol (data not shown).

Significant trends were observed between several covariates and the exposure intensity scores (table 3). With increasing levels of all occupational exposures, mean levels of age increased while CASI scores and years of education decreased overall. In general, mean values of BMI, and smoking and alcohol consumption were not associated with the exposures; non-smokers and non-drinkers were excluded from these analyses. An exception involved mercury exposure, where increasing levels of alcohol consumption were associated with increasing levels of exposure (p = 0.033).

Cognitive ability (CASI score), BMI, and physical activity were inversely associated with increasing prevalence of most movement abnormalities (data not shown). BMI was not associated with prevalence of 'arising from chair' and 'hand tremor', and physical activity was not associated with 'hand tremor'.

Logistic regression analyses revealed associations between exposure intensity scores to metals and one movement abnormality (table 4). There was a positive association between metal exposure in the highest category and abnormal (i.e., fixed or mask-like) 'facial expression' after full adjustment (OR = 2.62, 95% CI = 1.35–5.11, p for trend = 0.02). A significant positive association was also observed between persons in the highest level of mercury exposure and abnormal 'facial expression' (OR = 1.91, 95% CI = 1.04–3.49, p for trend = 0.03). The association between manganese exposure and abnormal 'facial expression' (OR = 1.71, 95% CI = 0.81–3.61, p for trend = 0.08) and abnormal 'posture' (OR = 1.99, 95% CI = 0.91–4.36, p for trend = 0.09) were elevated but statistical significance was borderline.

While heavy pesticide exposure more than doubled the likelihood of an abnormality in 'rapid alternating hand movements', after adjustment for age and other factors, the association was no longer significant (table 4). In contrast, there was an inverse association between heavy pesticide exposure and 'gait' after risk factor ad-

Table 3. Mean levels of participant characteristics at exam IV by exposure intensity at exams I and III

Participant characteristic	Intensity[a]	Pesticide		Solvent		Metal		Manganese		Mercury		Overall
		n	mean ± SD	n	mean ± SD	n	mean ± SD	n	mean ± SD	n	mean ± SD	mean ± SD
Age, years	None	907	79.2 ± 5.1	391	79.4 ± 5.1	529	79.5 ± 5.1	813	79.3 ± 5.1	867	79.4 ± 5.2	79.3 ± 5.1
	Low	52	78.0 ± 3.8	411	79.0 ± 5.2	354	78.5 ± 5.0	141	78.5 ± 5.2	55	77.5 ± 4.5	
	Medium	45	80.4 ± 5.2	146	79.7 ± 5.1	107	80.8 ± 5.3	49	81.3 ± 5.6	57	77.4 ± 4.1	
	High	42	83.5 ± 5.7	98	80.1 ± 5.1	56	80.3 ± 5.2	43	79.7 ± 4.9	67	81.3 ± 5.2	
	p_{trend}		<0.0001		<0.0001		<0.0001		<0.0001		0.0049	
BMI, kg/m^2	None	865	23.2 ± 3.3	374	23.0 ± 3.1	505	23.1 ± 3.1	776	23.1 ± 3.3	823	23.2 ± 3.3	23.2 ± 3.2
	Low	51	24.2 ± 3.5	392	23.5 ± 3.3	337	23.4 ± 3.5	132	23.7 ± 3.0	53	23.8 ± 3.4	
	Medium	40	23.2 ± 2.9	138	23.4 ± 3.6	100	23.1 ± 3.2	45	23.2 ± 3.2	57	23.5 ± 3.1	
	High	38	23.0 ± 2.9	90	22.8 ± 2.9	52	23.5 ± 2.9	41	23.5 ± 3.0	61	23.1 ± 3.2	
	p_{trend}		0.7514		0.0559		0.6936		0.7760		0.6735	
Physical activity	None	806	30.5 ± 4.6	348	30.1 ± 4.3	472	30.1 ± 4.2	719	30.3 ± 4.4	770	30.4 ± 4.7	30.6 ± 4.7
	Low	48	32.1 ± 6.2	367	31.0 ± 5.2	314	31.0 ± 5.1	130	31.5 ± 6.2	50	31.0 ± 4.6	
	Medium	37	29.6 ± 4.4	132	30.4 ± 4.7	95	30.9 ± 5.5	44	31.1 ± 5.3	52	31.6 ± 5.4	
	High	39	31.2 ± 4.5	83	31.5 ± 4.5	49	32.6 ± 4.9	37	32.5 ± 4.5	58	31.7 ± 4.9	
	p_{trend}		0.9710		0.0012		<0.0001		0.0008		0.0186	
CASI score	None	906	75.9 ± 19.3	391	76.3 ± 19.3	529	75.6 ± 19.5	812	75.3 ± 19.6	865	75.3 ± 19.8	75.6 ± 19.4
	Low	52	78.6 ± 13.1	410	75.6 ± 19.1	352	76.6 ± 17.9	140	79.2 ± 17.0	55	78.8 ± 18.2	
	Medium	44	70.1 ± 22.5	145	74.2 ± 20.4	107	72.5 ± 23.2	49	70.9 ± 20.9	57	79.8 ± 10.8	
	High	42	71.2 ± 22.6	98	74.2 ± 19.9	56	74.1 ± 18.7	43	74.4 ± 20.2	67	73.2 ± 19.9	
	p_{trend}		<0.0001		<0.0001		<0.0001		0.0008		0.0443	
Education years	None	907	9.8 ± 3.1	391	10.6 ± 3.4	529	10.2 ± 3.2	813	9.8 ± 3.1	867	9.7 ± 3.1	9.6 ± 3.1
	Low	52	8.8 ± 2.8	411	9.2 ± 2.8	354	9.3 ± 3.0	141	9.5 ± 3.1	55	9.7 ± 3.1	
	Medium	45	7.8 ± 3.4	146	9.2 ± 2.7	107	8.8 ± 3.1	49	8.6 ± 3.1	57	9.2 ± 2.7	
	High	42	9.6 ± 3.6	98	8.3 ± 2.4	56	8.4 ± 2.2	43	8.7 ± 2.3	67	9.0 ± 3.9	
	p_{trend}		0.0137		<0.0001		<0.0001		0.0004		0.1430	
Pack-years of smoking[b]	None	472	42.4 ± 36.0	186	40.7 ± 32.9	259	42.9 ± 35.3	415	43.2 ± 36.1	443	43.5 ± 35.5	42.4 ± 35.2
	Low	20	44.8 ± 29.9	228	44.0 ± 37.1	205	40.7 ± 34.1	75	42.1 ± 33.7	33	41.5 ± 37.1	
	Medium	20	48.0 ± 31.4	76	46.6 ± 35.9	44	54.8 ± 42.4	26	39.7 ± 31.9	34	35.1 ± 29.6	
	High	23	34.8 ± 24.7	45	34.4 ± 32.8	27	30.4 ± 23.8	19	30.3 ± 22.4	25	34.4 ± 34.2	
	p_{trend}		0.7110		0.2741		0.3665		0.1279		0.1017	
Alcohol consumption[c] g/month	None	453	10.06 ± 15.77	181	10.80 ± 20.08	248	10.11 ± 16.50	386	9.98 ± 16.10	409	9.55 ± 13.95	10.02 ± 15.22
	Low	20	9.09 ± 10.23	198	8.99 ± 9.92	172	8.59 ± 10.20	72	9.63 ± 10.55	26	10.24 ± 11.05	
	Medium	18	10.23 ± 8.79	74	8.85 ± 9.84	58	13.05 ± 20.61	31	7.70 ± 9.55	38	10.98 ± 13.22	
	High	20	10.00 ± 11.33	58	12.59 ± 17.93	33	11.44 ± 15.71	22	15.16 ± 18.11	38	13.98 ± 27.74	
	p_{trend}		0.5911		0.8712		0.6624		0.5221		0.0333	

[a] Categories for exposure intensity scores (i.e., cumulative exposure) to mercury are 0, 1–25, 26–36, ≥ 37; categories for all other agents are 0, 1–39, 40–79, ≥ 80.

[b] Pack-years of smoking include only current and former smokers.

[c] Alcohol consumption includes only current and former drinkers. Mean values of grams were divided by 100 for convenience.

justment, p for trend = 0.04. There was no association of exposure to solvents and movement abnormalities and there was no evidence of effect modification between the main exposures and the seven covariates presented in table 3 for any of the movement abnormalities.

No trend was observed between the occupational exposures and an indicator variable that comprised increasing numbers of these five movement abnormalities: 'rapid alternating hand movements', 'rigidity', 'posture', 'gait', and 'facial expression'. This analysis was repeated with 'body bradykinesia' replacing 'facial expression'; there was no change in the results. As the number of movement abnormalities increased, (a) the proportion of persons with low CASI scores (<74) increased ($p < 0.001$), (b) the proportion of relatively younger persons (71–78 years) decreased ($p < 0.001$), and (c) the proportion of persons who were less physically active (physical activity score 24–29.0) increased ($p < 0.001$) (data not shown).

Table 4. Association between occupational exposure intensity[a] and selected movement abnormalities, unadjusted and adjusted odds ratios and 95% CI and p values from logistic regression models

	n	Unadjusted		Age adjusted		Risk factor adjusted[b]		
		OR	95% CI	OR	95% CI	OR	95% CI	p_{trend}
Pesticides								
Rapid alternating hand movements								
None	868	1.00		1.00		1.00		0.35
Low	51	0.76	0.43–1.34	0.81	0.45–1.46	1.00	0.53–1.93	
Medium	44	1.09	0.58–2.04	0.93	0.48–1.80	0.87	0.40–1.91	
High	37	2.26	1.02–4.99	1.45	0.63–3.34	1.97	0.80–4.87	
Posture								
None	884	1.00		1.00		1.00		0.46
Low	50	0.72	0.41–1.27	0.77	0.42–1.40	0.82	0.43–1.59	
Medium	44	2.44	1.19–0.99	2.25	1.06–4.77	1.55	0.68–3.55	
High	39	0.93	0.49–1.77	0.45	0.22–0.93	0.59	0.27–1.27	
Gait								
None	895	1.00		1.00		1.00		0.04
Low	50	0.62	0.34–1.15	0.66	0.35–1.27	1.01	0.51–2.02	
Medium	45	0.97	0.53–1.78	0.79	0.41–1.51	0.73	0.33–1.60	
High	40	0.71	0.37–1.38	0.35	0.17–0.71	0.40	0.18–0.90	
Facial expression								
None	908	1.00		1.00		1.00		0.22
Low	50	0.56	0.28–1.11	0.63	0.32–1.27	0.80	0.37–1.74	
Medium	45	1.58	0.87–2.89	1.42	0.76–2.67	1.25	0.57–2.71	
High	42	1.10	0.58–2.10	0.67	0.34–1.32	0.62	0.28–1.39	
Solvents								
Rapid alternating hand movements								
None	372	1.00		1.00		1.00		0.77
Low	395	1.03	0.77–1.38	1.08	0.80–1.47	1.20	0.85–1.70	
Medium	138	1.03	0.69–1.55	0.99	0.65–1.51	0.97	0.61–1.53	
High	95	1.02	0.64–1.63	0.92	0.56–1.49	0.98	0.56–1.69	
Posture								
None	379	1.00		1.00		1.00		0.84
Low	400	1.16	0.87–1.54	1.25	0.92–1.69	1.21	0.86–1.70	
Medium	141	1.07	0.73–1.59	1.05	0.69–1.59	0.89	0.56–1.41	
High	97	1.25	0.79–1.98	1.12	0.69–1.82	1.18	0.68–2.06	
Gait								
None	384	1.00		1.00		1.00		0.28
Low	405	0.92	0.70–1.23	0.96	0.71–1.30	1.03	0.73–1.46	
Medium	144	0.95	0.65–1.40	0.91	0.60–1.37	0.93	0.58–1.48	
High	97	1.46	0.93–2.28	1.35	0.84–2.17	1.50	0.86–2.59	
Facial expression								
None	392	1.00		1.00		1.00		0.19
Low	409	1.11	0.83–1.49	1.18	0.87–1.60	1.32	0.91–1.92	
Medium	146	1.05	0.70–1.57	1.02	0.67–1.56	1.18	0.72–1.93	
High	98	1.35	0.86–2.14	1.29	0.80–2.07	1.57	0.89–2.79	
Metals								
Rapid alternating hand movements								
None	504	1.00		1.00		1.00		0.23
Low	340	0.93	0.70–1.24	1.04	0.77–1.40	1.18	0.85–1.65	
Medium	101	0.89	0.58–1.38	0.74	0.47–1.18	0.79	0.47–1.32	
High	55	0.81	0.46–1.43	0.70	0.39–1.28	0.66	0.33–1.29	
Posture								
None	512	1.00		1.00		1.00		0.28
Low	344	1.04	0.79–1.38	1.23	0.92–1.66	1.17	0.84–1.62	
Medium	105	1.03	0.67–1.57	0.84	0.53–1.34	0.78	0.47–1.31	
High	56	1.85	1.01–3.40	1.75	0.92–3.33	2.02	0.99–4.12	

Table 4 (continued)

	n	Unadjusted		Age adjusted		Risk factor adjusted[b]		
		OR	95% CI	OR	95% CI	OR	95% CI	p_{trend}
Gait								
None	520	1.00		1.00		1.00		0.22
Low	348	0.81	0.62–1.07	0.91	0.68–1.22	0.95	0.68–1.34	
Medium	106	1.19	0.78–1.81	1.01	0.65–1.58	1.07	0.64–1.79	
High	56	1.43	0.82–2.49	1.32	0.73–2.36	1.81	0.93–3.55	
Facial expression								
None	530	1.00		1.00		1.00		0.02
Low	352	0.96	0.72–1.27	1.07	0.79–1.45	1.26	0.88–1.80	
Medium	107	1.22	0.79–1.88	1.07	0.68–1.68	1.13	0.66–1.94	
High	56	1.65	0.95–2.88	1.57	0.88–2.80	2.62	1.35–5.11	
Manganese								
Rapid alternating hand movements								
None	774	1.00		1.00		1.00		0.54
Low	137	0.85	0.58–1.22	0.92	0.62–1.35	1.09	0.71–1.67	
Medium	47	1.29	0.68–2.41	1.01	0.52–1.98	0.92	0.44–1.92	
High	42	0.89	0.47–1.67	0.83	0.43–1.60	0.78	0.37–1.65	
Posture								
None	790	1.00		1.00		1.00		0.09
Low	136	0.89	0.62–1.29	1.01	0.68–1.49	1.12	0.73–1.72	
Medium	48	1.60	0.85–2.98	1.25	0.64–2.47	1.42	0.67–3.02	
High	43	1.67	0.86–3.26	1.64	0.82–3.31	1.99	0.91–4.36	
Gait								
None	800	1.00		1.00		1.00		0.38
Low	138	0.83	0.57–1.20	0.89	0.60–1.33	1.06	0.68–1.65	
Medium	49	1.55	0.87–2.76	1.20	0.65–2.23	1.29	0.63–2.62	
High	43	0.98	0.53–1.83	0.92	0.48–1.78	1.31	0.62–2.79	
Facial expression								
None	813	1.00		1.00		1.00		0.08
Low	140	0.88	0.60–1.30	0.96	0.64–1.43	1.26	0.79–1.99	
Medium	49	1.37	0.76–2.47	1.11	0.60–2.05	1.24	0.61–2.55	
High	43	1.18	0.62–2.26	1.15	0.60–2.21	1.71	0.81–3.61	
Mercury								
Rapid alternating hand movements								
None	826	1.00		1.00		1.00		0.27
Low	51	1.02	0.57–1.83	1.29	0.70–2.36	1.23	0.65–2.32	
Medium	57	0.77	0.45–1.33	0.95	0.54–1.66	1.01	0.55–1.86	
High	66	0.99	0.59–1.66	0.76	0.44–1.31	0.66	0.36–1.21	
Posture								
None	840	1.00		1.00		1.00		0.13
Low	53	1.54	0.85–2.79	2.16	1.17–4.01	2.09	1.09–4.01	
Medium	57	0.61	0.36–1.05	0.77	0.44–1.36	0.89	0.48–1.66	
High	67	1.84	1.06–3.18	1.46	0.81–2.63	1.64	0.85–3.14	
Gait								
None	853	1.00		1.00		1.00		0.04
Low	53	1.00	0.57–1.75	1.35	0.74–2.43	1.60	0.84–3.05	
Medium	57	0.76	0.43–1.33	0.99	0.55–1.77	1.07	0.56–2.04	
High	67	1.73	1.05–2.85	1.40	0.82–2.39	1.72	0.93–3.16	
Facial expression								
None	867	1.00		1.00		1.00		0.03
Low	54	0.92	0.51–1.67	1.16	0.63–2.14	1.61	0.82–3.16	
Medium	57	0.79	0.43–1.42	0.99	0.54–1.82	1.05	0.52–2.09	
High	67	1.63	0.99–2.69	1.37	0.82–2.32	1.91	1.04–3.49	

[a] Categories for exposure intensity scores (i.e., cumulative exposure) to mercury are 0, 1–25, 26–36, ≥37; categories for all other agents are 0, 1–39, 40–79, ≥80.

[b] Results adjusted for age, BMI, physical activity, CASI score, education, smoking, and alcohol consumption.

p value for trend is obtained from using the continuous form of the exposure variable in the risk-factor-adjusted logistic model.

Discussion

Our findings were based on men who were free of PD and stroke. We found that exposures to both metal and mercury were positively and independently associated with fixed 'facial expression'. The literature supports the association between exposure to metals and certain movement abnormalities. We also observed very strong associations for age and CASI score with all movement abnormalities. The results regarding age and movement abnormalities are consistent with the results of previous studies [16, 17].

A few studies have investigated the effects of occupational exposure, mostly manganese and mercury exposures, on movement abnormalities. A study conducted in Brazil investigated the health effects of the fungicide Maneb (a pesticide that contains manganese) in 50 male rural workers [18]. There was a significantly higher prevalence of several neurological symptoms in the exposed group (e.g., plastic rigidity with cogwheel phenomenon, bradykinesia) compared to the unexposed group. In another study, 5 patients who experienced chronic manganese intoxication for 10 years showed significant gradual deterioration in neurologic features, the most prominent of which were gait, rigidity, and speed of foot tapping [19]. Case reports of persons exposed to manganese intoxication showed associations with several neurological symptoms including paraplegia, slowness and difficulty in speech, shaking of the arms and legs, and mask-like facial appearance [5]. Occupational exposure to mercury compounds was associated with hand and arm tremors [4, 8, 20, 21]. The biologic mechanisms involved in the neurotoxicity of mercury include increase of intracellular Ca^{2+} with disturbance of neurotransmitter function, oxidative stress, and inhibition of protein synthesis [22].

The literature provides ample evidence that movement abnormalities that occur with PD are caused by selective degeneration of dopaminergic neurons of the substantia nigra, oxidative damage, and mitochondrial impairment [23, 24]. The lipophilic pesticide rotenone has been shown to cause degeneration of the dopaminergic neurons in substantia nigra in rats [25]. The rotenone-treated animals developed motor and postural deficits characteristic of PD, such as hypokinesia, unsteady movement, hunched posture, rigidity, and rest tremor. Manganese is known to increase the oxidation rate of dopamine [26].

The association between several occupational and environmental agents and PD is well documented. A French case-control study, after adjustment for confounders, reported a positive association between PD and occupational exposure to pesticides (OR = 2.2, 95% CI = 1.1–4.3) [3]. Their results, however, did not show a clear exposure-response relationship. Pezzoli et al. [6] reported that the intensity of occupational exposure to hydrocarbon solvents was directly proportional to the severity of PD symptoms. They identified nine blue-collar occupations that experienced a preponderance of hydrocarbon exposure, including 'farmers'. In a case-control study [27], investigators found an increased risk for PD with occupational exposure to some metals, and a protective relationship with exposure to mercury. Persons who were exposed to manganese for more than 20 years had an elevated risk for PD (OR = 10.61, 95% CI = 1.06–105.83), and this was also true for exposure to copper (OR = 2.49, 95% CI = 1.06–5.89).

There are a few limitations of this study. Information on short part-time jobs, non-occupational sources of exposures to these specific compounds, and biological markers of the exposures of interests were not included in our assessment of exposure. Misclassification of environmental exposures is likely to have resulted in non-differential bias, producing weaker associations. We based our exposure estimates on reported usual or last job held. Therefore, this may not have accurately reflected all the jobs that the participants held over their exposure history. Although the intensity values of exposure (0, 1, 2, 3) failed to take into account the variability in use of personal protective equipment, local exhaust ventilation, etc., we do not believe that this failure seriously biased our exposure classification. First, the workers were all assessed during the same time period and would have had roughly the same access to personal protective equipment and other engineering controls regardless of job type or industry. Second, the industrial hygienists from NIOSH assigned intensity levels based not only on the job titles, but also on the industry and their knowledge of the specific job duties. Even so, some inter-worker exposure variability would still be present, but it is often not feasible, in occupational epidemiological studies, to capture and analyze individual exposures.

This study has several strengths. The information for this study was collected prospectively, removing any possibility of recall bias. The sample size is large, thus allowing for adequate power even after stratification. A unique approach was implemented in the design of the study by excluding PD and stroke cases, thereby removing the confounding effects of these medical conditions on the associations with movement abnormalities. Several potential effect modifiers and confounders were available for as-

sessment in this study. Assessment of the movement abnormalities was carried out using the UPDRS, a validated, diagnostic instrument for diagnosis of PD, by an experienced neurologist. Industrial hygienists utilized their professional expertise to assign levels of likely exposure to all reported usual jobs. This study used the best possible method for assessing chronic exposure in an occupational epidemiologic study and it is likely that this process contributed to a reduction in exposure misclassification bias [28].

Movement abnormalities eventually result in decreased independence in activities of daily living and increased mortality [16, 29, 30]. In a study of disability as related to movement abnormalities, 48% of persons who reported tremors had difficulty with household tasks and 18% had difficulty dressing themselves [29]. In a population of elderly persons in East Boston, Massachusetts, who were 65 years of age or older, the prevalence of parkinsonian signs were 14.9% for people 64–74 years of age, 29.5% for those 75–84 years of age, and 52.4% for those 85 and older [16]. After adjustment for age and sex, the overall risk of death among people with parkinsonism was twice that among people without. Another cohort study demonstrated that the severity of gait disorders and the rate of progression were related to increased mortality [30]. Movement abnormalities might be expected to have caused the men in our study to have some difficulties with activities of daily living. Whether these abnormalities are associated with increased mortality is worthy of future study.

Studies investigating risk factors for movement abnormalities are important because these outcomes are becoming more of a public health problem as the population ages. The number of elderly persons (≥ 65 years) living in the US in 2000 was 35 million, and this number has been predicted to grow dramatically over the next few decades [31]. Knickman and Snell [31] surmise that the most important challenge related to aging populations may be that of keeping seniors disability-free. Identifying and reducing exposures in the environment and workplace has significant implications for influencing overall health and promoting healthy aging. By investigating occupational risk factors that could increase movement abnormalities, this study plays a role in potentially reducing disability in old age.

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References

1 Calvert GM, Plate DK, Das R, Rosales R, Shafey O, Thomsen C, Male D, Beckman J, Arvizu E, Lackovic M: Acute occupational pesticide-related illness in the US, 1998–1999: surveillance findings from the SENSOR-Pesticides Program. Am J Ind Med 2004;45:14–23.

2 Petrovitch H, Ross GW, Abbott RD, Sanderson WT, Sharp DS, Tanner CM, Masaki KH, Blanchette PL, Popper JS, Foley DJ, Launer LJ, White LR: Plantation work and risk of Parkinson's disease in a population-based longitudinal study. Arch Neurol 2002;59:1787–1792.

3 Baldi I, Cantagrel A, Lebailly P, Tison F, Dubroca B, Chrysostome V, Dartigues JF, Brochard P: Association between Parkinson's Disease and exposure to pesticides in southwestern France. Neuroepidemiology 2003;22:305–310.

4 Frumkin H, Letz R, Williams PL, Gerr F, Pierce M, Sanders A, Elon L, Manning CC, Woods JS, Hertzberg VS, Mueller P, Taylor BB: Health effects of long-term mercury exposure among chloralkali plant workers. Am J Ind Med 2001;39:1–18.

5 Lee JW: Manganese intoxication. Arch Neurol 2000;57:597–599.

6 Pezzoli G, Canesi M, Antonini A, Righini A, Perbellini L, Barichella M, Mariani CB, Tenconi F, Tesei S, Zecchinelli A, Leenders KL: Hydrocarbon exposure and Parkinson's disease. Neurology 2000;55:667–673.

7 Menegon A, Board PG, Blackburn AC, Mellick GD, Le Couteur DG: Parkinson's disease, pesticides, and glutathione transferase polymorphisms. Lancet 1998;352:1344–1346.

8 Langworth S, Almkvist O, Soderman E, Wikstrom BO: Effects of occupational exposure to mercury vapour on the central nervous system. Br J Ind Med 1992;49:545–555.

9 Kagan A, Harris BR, Winkelstein W, Johnson KG, Kato H, Syme SL, Rhoads GG, Gay ML, Nichaman MZ, Hamilton HB, Tillotson J: Epidemiologic studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii and California: demographic, physical, dietary and biochemical characteristics. J Chronic Dis 1974;27:345–364.

10 Worth RM, Kagan A: Ascertainment of men of Japanese ancestry in Hawaii through World War II selective service registration. J Chronic Dis 1970;23:389–397.
11 Abbott RD, Ross GW, White LR, Sanderson WT, Burchfiel CM, Kashon M, Sharp DS, Masaki KH, Curb JD, Petrovitch H: Environmental, life-style, and physical precursors of clinical Parkinson's disease: recent findings from the Honolulu-Asia Aging Study. J Neurol 2003; 250(suppl 3):111/30–111/39.
12 Fahn S, Elton RL: Members of the UPDRS Development Committee: unified Parkinson's disease rating scale; in Fahn S, Marsden CD, Calne DB, Goldstein M (eds): Recent Developments in Parkinson's Disease. Florham Park, Macmillan, 1987, vol 2, pp 153–164.
13 Burchfiel CM, Sharp DS, Curb JD, Rodriguez BL, Hwang LJ, Marcus EB, Yano K: Physical activity and incidence of diabetes: the Honolulu Heart Program. Am J Epidemiol 1995; 141:360–368.
14 Teng EL, Hasegawa K, Homma A, Imai Y, Larson E, Graves A, Sugimoto K, Yamaguchi T, Sasaki H, Chiu D, White LR: The Cognitive Abilities Screening Instrument (CASI): a practical test for cross-cultural epidemiologic studies of dementia. Int J Psychogeriatr 1994;6: 45–58.
15 SAS Institute: SAS User's Guide: Statistics, Version 8.2. Cary, SAS Institute, 1999–2001.
16 Bennett DA, Beckett LA, Murray AM, Shannon KM, Goetz CG, Pilgrim DM, Evans DA: Prevalence of parkinsonian signs and associated mortality in a community population of older people. N Engl J Med 1996;334:71–76.
17 Kaye JA, Oken BS, Howieson DB, Howieson J, Holm LA, Dennison K: Neurologic evaluation of the optimally healthy oldest old. Arch Neurol 1994;51:1205–1211.
18 Ferraz HB, Bertolucci PH, Pereira JS, Lima JGC, Andrade LAF: Chronic exposure to the fungicide maneb may produce symptoms and signs of CNS manganese intoxication. Neurology 1988;38:550–553.
19 Huang CC, Chu NS, Lu CS, Chen RS, Calne DB: Long-term progression in chronic manganism: ten years of follow-up. Neurology 1998;50:698–700.
20 Taylor JR: Neurotoxicity of certain environmental substances. Clin Lab Med 1984;4:489–497.
21 Fawer RF, De Ribaupierre Y, Guillemin MP, Berode M, Lob M: Measurement of hand tremor induced by industrial exposure to metallic mercury. Br J Ind Med 1983;40:204–208.
22 Sanfeliu C, Sebastia J, Cristofol R, Rodriguez-Farre E: Neurotoxicity of organomercurial compounds. Neurotox Res 2003;5:283–305.
23 Baba M, Nakajo S, Tu PH, Tomita T, Nakaya K, Lee VM, Trojanowski JQ, Iwatsubo T: Aggregation of alpha-synuclein in Lewy bodies of sporadic Parkinson's disease and dementia with Lewy bodies. Am J Pathol 1998;152:879–884.
24 Dexter DT, Carter CJ, Wells FR, Javoy-Agid F, Agid Y, Lees A, Jenner P, Marsden CD: Basal lipid peroxidation in substantia nigra is increased in Parkinson's disease. J Neurochem 1989;52:381–389.
25 Betarbet R, Sherer TB, MacKenzie G, Garcia-Osuna M, Panov AV, Greenamyre JT: Chronic systemic pesticide exposure reproduces features of Parkinson's disease. Nat Neurosci 2000;3:1301–1306.
26 Florence TM, Stauber JL: Manganese catalysis of dopamine oxidation. Sci Total Environ 1989;78:233–240.
27 Gorell JM, Johnson CC, Rybicki BA, Peterson EL, Kortsha GX, Brown GG, Richardson RJ: Occupational exposures to metals as risk factors for Parkinson's disease. Neurology 1997; 48:650–658.
28 Teschke K, Olshan AF, Daniels JL, De Roos AJ, Parks CG, Schulz M, Vaughn TL, Kromhout H: Occupational exposure assessment in case-control studies: opportunities for improvement. Occup Environ Med 2002;59: 575–594.
29 Louis ED, Marder K, Cote L, Wilder D, Tang MX, Lantigua R, Gurland B, Mayeux R: Prevalence of a history of shaking in persons 65 years of age and older: diagnostic and functional correlates. Mov Disord 1996;11:63–69.
30 Wilson RS, Schneider JA, Beckett LA, Evans DA, Bennett DA: Progression of gait disorder and rigidity and risk of death in older persons. Neurology 2002;58:1815–1819.
31 Knickman JR, Snell EK: The 2030 problem: caring for aging baby boomers. Health Serv Res 2002;37:849–884.