Potential Occupational Risks for Neurodegenerative Diseases

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Background *Associations between occupations and neurodegenerative diseases (NDD) may be discernable in death certificate data.*
Methods *Hypotheses generated from 1982 to 1991 study were tested in data from 22 states for the years 1992–1998. Specific occupations and exposures to pesticides, solvents, oxidative stressors, magnetic fields, and welding fumes were evaluated.*
Results *About one third (26/87) of the occupations hypothesized with neurodegenerative associations had statistically significant elevated mortality odds ratios (MOR) for the same outcome. Occupations with the largest MORs were (a) for presenile dementia (PSD)—dentists, graders/sorters (non-agricultural), and clergy; (b) for Alzheimer's disease (AD)—bank tellers, clergy, aircraft mechanics, and hairdressers; (c) for Parkinson's disease (PD)—biological scientists, clergy, religious workers, and post-secondary teachers; and (d) for motor neuron disease (MND)—veterinarians, hairdressers, and graders and sorters (non-agricultural). Teachers had significantly elevated MORs for all four diseases, and hairdressers for three of the four. Non-horticultural farmers below age 65 had elevated PD (MOR = 2.23, 95% CI = 1.47–3.26), PSD (MOR = 2.22, 95% CI = 1.10–4.05), and AD (MOR = 1.76, 95% CI = 1.04–2.81). Sixty hertz magnetic fields exhibited significant exposure-response for AD and, below age 65, for PD (MOR = 1.87, 95% CI = 1.14–2.98) and MND (MOR = 1.63, 95% CI = 1.10–2.39). Welding had elevated PD mortality below age 65 (MOR = 1.77, 95% CI = 1.08–2.75).*
Conclusions *Support was observed for hypothesized excess neurodegenerative disease associated with a variety of occupations, 60 Hz magnetic fields and welding.* Am. J. Ind. Med. 48:63–77, 2005. *Published 2005 Wiley-Liss, Inc.*[†]

KEY WORDS: Alzheimer's disease; hairdresser; motor neuron disease; magnetic field; Parkinson's disease; pesticide; welding

Abbreviations: AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; BOC, Bureau of the Census; EMF, electromagnetic field; MND, motor neuron disease; MOR, mortality odds ratio; NDD, neurodegenerative disease; PD, Parkinson's disease; PMR, proportionate mortality ratios; PSD, presenile dementia.

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INTRODUCTION

Annual neurodegenerative disease (NDD) deaths in the US are projected to increase from 27,098 in 1990 to 72, and 122 by 2040, an increase of 166% [Lilienfeld and Perl, 1993]. Although genetic factors play a role in various NDD [Rocchi et al., 2003; Cordato and Chan, 2004] and are a major current focus of research, occupational and environmental factors contribute to NDD [Semchuk et al., 1992; Seidler et al., 1996; Sobel et al., 1996; Strickland et al., 1996; Davanipour et al., 1997; Liou et al., 1997; McGuire et al., 1997; Feychting et al., 1998; Gorell et al., 1998; Hock et al., 1998; Hubble et al., 1998; Johansen and Olsen, 1998; Savitz et al., 1998a; Tsui et al., 1999; Migliore and Coppede, 2002]. Mounting evidence suggests there are multiple, disparate contributing mechanisms such as oxidative damage, aberrant calcium homeostasis, metabolic compromise, amyloid precursor protein mismetabolism, and neuronal stress. The combined effects of external and internal factors appear to predispose neurons to apoptosis [Thompson, 1995; Greenamyre and Hastings, 2004]. Further studies are needed to generate, refine, and test specific hypotheses [Ying, 1996].

A study of mortality from 27 states in 1982–1991 identified occupations with elevated mortality for Alzheimer's disease (AD), Parkinson's disease (PD), motor neuron disease (MND), and presenile dementia (PSD) [Schulte et al., 1996]. These diseases were assessed individually and in combination because they share characteristics and possibly common responses to neuronal stress [Appel, 1981; Calne et al., 1992; Thompson, 1995; Ying, 1996; Masters and Beyreuther, 1998]. That hypothesis-generating study may have identified some associations by chance, as a result of information or confounding bias, or because of limitations of the proportionate mortality ratio (PMR) [Finkelstein and Liss, 1987; Stewart and Hunting, 1988]. To address these issues, a case-control study was conducted to test hypotheses from the first study in a similar population. In addition, hypothesized occupational exposure associations for solvents, magnetic fields, pesticides, and welding [Levy and Nassetta, 2003] were evaluated.

MATERIALS AND METHODS

Study Population

Death certificate information for all deaths from 22 participating states in the years 1992–1998 was obtained using the National Occupational Mortality Surveillance System [Burnett et al., 1997] and included the decedent's usual occupation and kind of business or industry coded by state health departments according to the 1980 Bureau of the Census (BOC) system [U.S. Bureau of the Census, 1982]. Underlying and contributing causes of death were coded according to the International Classification of Disease (ICD), 9th Revision [Burnett et al., 1997; WHO, 1997].

A case was defined by any mention on the death certificate of: PSD (ICD:290.1), AD (ICD:331.0), PD (ICD:332.0), or MND (ICD:335.2). Controls were all decedents with no mention of neurologic disease, degenerative or otherwise, and excluding: accidental causes, malignant neoplasms of the brain (ICD 191), other senile and presenile organic psychotic conditions (ICD 290), diseases of the nervous system and sense organs (ICD 320–389), and finally, neoplasms of the lymphatic and hematopoietic tissues (ICD 200–208), due to suspect associations with solvents or electromagnetic fields (EMFs). Cases and controls lacking occupational information or with the designation housekeeper were also excluded. Socioeconomic status (SES), as constructed by Hauser and Warren [1997] based on job and industry, was classified in ten levels to permit controlling for diagnostic, health care, and other differences across occupations.

Occupation and Exposure Classification

Eighty-seven priority occupations were identified from Schulte et al. [1996] (Tables II–V) with statistically significant elevated PMRs and among the ten highest PMRs in one or more demographic subgroup for one of the four diseases. Occupations were specified as mutually exclusive subsets of BOC occupation codes; for example, the category *administrative support* did not include other categories in the list of 87 priority occupations such as *secretaries, stenographers* that otherwise would fall within the BOC *administrative support* category. Two classes of a priori hypotheses were tested: (a) that the priority occupations have higher mortality risk for the NDD previously observed to be elevated than other occupations, and (b) that occupations with solvent, pesticide, oxidative stressor, EMF, or welding fume exposures have increased risk of NDD mortality.

Exposures to solvents generally, and benzene, were assessed using a job-exposure matrix validated for cancer studies [Dosemeci et al., 1999]. Probability and intensity of exposure (both classified as: none, low, medium, and high) were used to construct composite exposure indices having ten levels: the lowest level for no exposure, the highest for jobs with *high* probability and *high* intensity of exposure.

Occupations with probable pesticide exposure, found by Schulte et al. [1996] to have increased PMRs, were evaluated in: all farming, farming occupations with likely pesticide exposure (which excluded managers), and *farmers*, *excluding horticultural*, which excluded farm workers, managers, graders, etc. These categories did not fall within the 87 priority occupations probably because of smaller PMRs or lower power for these relatively small groups. To identify occupations with exposures to oxidative stressors, chemical, and physical agents known to produce oxidative stress (such as ionizing radiation, paraquat, thallium, and solvents) were specified and the following 15 occupations identified as likely to have those exposures: radiologic technicians, dental assistants, dental laboratory technicians, dentists, pest control workers, horticultural specialty farmers, farmworkers, related agricultural workers, commercial painters, painters (artists), printmakers, hair dressers, mechanics, garage, and service station related workers.

Occupations were classified on magnetic fields using a job-exposure matrix developed for cancer epidemiology [Bowman et al., 2005]. Personal monitoring and spot measurements on power-frequency (60 Hz) magnetic fields were compiled from earlier studies by the authors and other investigators, and from publications. For 32.1% of the 502 BOC occupations, workday average magnetic field measurements were pooled to give a geometric mean exposure. For 52.7% of occupations lacking direct measurements, exposures were estimated from categories judged to have similar magnetic field sources. For example, podiatrist exposures were estimated from measurements on physicians; childcare workers in private households were estimated from other childcare workers. For 15.2% of occupations reliable exposure estimates were not possible; those subjects (numbering 5.5%) were dropped from the magnetic field analyses. Magnetic field exposures in milligauss (mG) were divided into ten equal intervals (0–0.999, 1–1.999, 2–2.999, . . . , 9–9.999 mG).

Because of reports of Parkinsonism in welders [Racette et al., 2001; Levy and Nassetta, 2003], possibly attributable to manganese exposure (from welding rods and steel alloys), BOC categories of workers using arc-welding were aggregated and evaluated for NDD. These categories were *welders and cutters*, *boilermakers*, *structural metal workers*, *millwrights*, *plumbers*, *pipefitters*, and *steamfitters*, and were selected before the data was analyzed.

Analysis

Mortality odds ratios (MOR) were calculated with unconditional logistic regression using EPICURE [Preston et al., 1993]. The analysis controlled for age (<45, 45–48,49–54 . . . ,85+), race (white, black), gender, region (northeast, midwest, south, west), and SES by means of a stratification procedure, which in EPICURE, includes all interactions of the stratifying variables. Exposure terms were introduced as sums in a log-linear model. For investigating priority occupations, two models were specified each presenting about half of the priority categories as indicator terms. For investigating gender- and race-specific effects, four subsets of the priority occupations showing overall excesses were further classified on gender and race and evaluated separately in models in which each of the three other subsets of occupations showing excesses were represented by single indicator variables (to allow manageable model specifications). Solvents, oxidative stressors, and EMF were evaluated in models with no other exposure terms except for assessment of an EMF-solvent interaction. Because strata with lower levels of solvent generally showed deficits in NDD mortality, suggesting some uncontrolled confounding, a term for any solvent exposure was included in models along with a continuous (ten level) solvent exposure index.

Some analyses tested whether exposure associations depended on age by adding a term equal to exposure when the age at death was less than 65; otherwise that term was 0.0. For outcomes like dementias or PD whose mortality odds increase dramatically with age, the same attributable excess that is statistically significant at lower ages could become non-significant at older ages due to the higher background rate.

RESULTS

Demographic Risk Factors

Out of 2,614,346 deaths during 1992 to 1998 in 22 participating states, 112,805 deaths (4.3%) were caused or contributed to by NDD, including 47,783 with Alzheimer's and 33,678 from PD (Table I). Within race groups, numbers of deaths for dementias (PSD, AD) were comparable by gender but men experienced considerably more cases of PD and MND than women. Deaths excluded from controls (other neurological diseases, accidental deaths, and lymphopoietic or CNS cancer) comprised 3.1% of all deaths. Compared with other deaths and without regard to occupation, MOR for PSD, AD, and PD all increased strongly with age while MND was relatively constant, declining above age 65 (Table II). The high MORs for PSD in older ages probably reflects PSD as a contributing cause of death. There was variation with geographic region, the northeast having somewhat lower age- and SES-adjusted MORs particularly for PSD (Table II). All four NDD MORs increased with SES, particularly PD and MND. MORs for PSD and AD decreased from the lowest to second lowest SES levels, followed by a consistent upward trend with higher SES except at the highest level. These demographic determinants are identified as possibly important confounders of occupation.

Associations With Occupational Groups

In 7 years of observation beyond the previous study [Schulte et al., 1996], almost half (n = 38) of 87 priority occupations exhibited at least one significant NDD-association, 26 of them for the same outcomes elevated originally (Table III; associations with prior evidence of excess mortality are presented in bold face). Some occupations exhibited elevated NDD mortality across three or four disease categories: clergy, hairdressers, secretaries, and teachers (primary/secondary). Among 18 occupational groups previously showing excess PSD mortality, six had

TABLE I. Numbers of Deaths 1992–1998 With an Underlying or Contributing Cause From Any of Four Classes of Neurodegenerative Diseases From 22 Reporting States in the US, by Race and Gender

	White men	White women	Non-white men	Non-white women	Total
Presenile dementia	12,431	13,279	752	912	27,374
Alzheimers disease	22,444	22,238	1,363	1,738	47,783
Parkinson's disease	22,796	9,609	849	424	33,678
Motor neuron disease	3,851	2,152	203	141	6,347
Total cases[a]	61,522	47,278	3,167	3,215	115,182
Total unique individuals	60,035	46,469	3,126	3,175	112,805
Total deaths	1,479,921	803,110	203,862	127,453	2,614,346

Excludes those without usual occupation on death certificate other than housekeeper.
[a]Some deaths had more than one of these neurological causes coded on death certificate as underlying or contributing causes of death.

TABLE II. Risk Factors for Neurodegenerative Disease (as Mortality Odds Ratios) in Study Population Without Regard to Exposure History

	Presenile dementia	Alzheimer's disease	Parkinson's disease	Motor neuron disease
Number of deaths	27,374	47,783	33,678	6,347
Baseline prevalence at death[a]	0.0008	0.0017	0.0020	0.0028
		MOR[b]		
Race, non-white	0.68	0.69	0.43	0.40
Gender, women	1.49	1.42	0.65	1.23
Age, <45	0.04	0.03	0.03	0.52
45–54	0.21	0.19	0.25	0.90
55–64[c]	1.00	1.00	1.00	1.00
65–69	2.95	2.81	2.67	0.96
70–74	5.84	5.47	5.57	0.74
75–79	12.15	10.52	9.40	0.59
80–84	18.99	16.17	11.95	0.37
85+	25.69	19.14	9.95	0.14
Region[d], Northeast 1	1.00	1.00	1.00	1.00
Midwest 2	1.33	1.10	1.10	1.21
South 3	1.24	1.20	0.91	1.01
West 4	1.51	1.20	1.10	1.18
SES level[e], low 0–9.9	1.00	1.00	1.00	1.00
10–19.9	0.83	0.93	1.14	1.08
20–29.9	0.84	0.95	1.16	1.14
30–39.9	0.92	1.08	1.37	1.56
40–49.9	0.95	1.08	1.42	1.88
50–59.9	1.14	1.20	1.82	2.30
60–69.9	1.05	1.25	1.76	2.22
70–79.9	1.27	1.44	2.20	2.74
High 80–89.9	1.26	1.15	2.66	2.48

[a]Baseline odds (prevalence if rare disease) for reference: white men, aged: 55–64, Region 1 (NE), SES Group 1 (low); excluding from controls other causes of death associated with solvents, EMF, or with NDD, such as injuries.
[b]Based on single logistic regression model for each disease outcome as underlying or a contributing cause of death.
[c]Reference age category; two strata combined for stability.
[d]Region 1—Northeast (Maine, New Hampshire, New Jersey, Rhode Island, Vermont), reference category; Region 2—Midwest (Indiana, Kansas, Ohio, Wisconsin); Region 3—South (Georgia, Kentucky, North Carolina, Oklahoma, South Carolina, West Virginia); Region 4—West (Colorado, Hawaii, Idaho, Nevada, New Mexico, Utah, Washington).
[e]SES—Hauser–Warren Occupational Socioeconomic Index.

TABLE III. Mortality Odds Ratios for Neurodegenerative Diseases in Occupational Groups (46 of 87) Previously Found to Have Statistically Significant Elevated PMRs for One or More Neurological Outcomes

	Presenile dementia			Alzheimer's disease			Parkinson's disease			Motor neuron disease		
	MOR	95% CI	P	MOR	95% CI	P	MOR	95% CI	P	MOR	95% CI	P
Administrative support	**1.03**	**0.94–1.13**	**0.47**	1.09	1.02–1.17	0.011	1.16	1.08–1.26	<0.001	0.93	0.79–1.10	0.43
Aircraft mechanics	0.74	0.43–1.18	0.24	**1.35**	**1.02–1.74**	**0.03**	0.97	0.70–1.31	>0.5	1.41	0.78–2.35	0.22
Athletes, dancers	0.93	0.46–1.66	>0.5	1.46	0.96–2.10	0.06	1.26	0.76–1.97	0.33	**1.41**	**0.50–3.07**	**0.45**
Bank tellers	1.73	1.36–2.17	<0.001	**1.40**	**1.14–1.70**	**0.001**	1.21	0.89–1.62	0.20	1.29	0.66–2.27	0.41
Biological, medical scientists	1.21	0.62–2.14	>0.5	0.81	0.44–1.36	0.46	**2.04**	**1.37–2.92**	**<0.001**	1.71	0.67–3.53	0.20
Broadcast-equip operators	1.30	0.46–2.85	>0.5	**1.72**	**0.91–2.94**	**0.07**	1.07	0.46–2.10	>0.5	0.58	0.03–2.57	>0.5
Bus drivers	1.00	0.77–1.29	>0.5	**1.08**	**0.89–1.30**	**0.40**	1.17	0.97–1.41	0.10	1.61	1.09–2.28	0.011
Chemists, chemical engineers	1.16	0.91–1.45	0.21	**1.13**	**0.95–1.34**	**0.17**	1.08	0.91–1.28	0.35	0.97	0.64–1.42	>0.5
Clergy	**1.41**	**1.19–1.65**	**<0.001**	**1.38**	**1.21–1.55**	**<0.001**	**1.79**	**1.58–2.02**	**<0.001**	1.31	0.93–1.79	0.11
Communication equipment	1.05	0.90–1.22	>0.5	1.15	1.02–1.29	0.017	1.06	0.89–1.26	>0.5	**1.42**	**0.96–2.02**	**0.069**
Dental assistants	**1.22**	**0.74–1.91**	**0.41**	1.80	1.30–2.43	<0.001	**1.26**	**0.71–2.10**	**0.40**	3.18	1.36–6.63	0.004
Dental laboratory	0.84	0.30–1.82	>0.5	**1.62**	**0.95–2.56**	**0.055**	1.34	0.71–2.27	0.33	2.18	0.67–5.16	0.13
Dentists	**1.69**	**1.08–2.80**	**0.03**	1.26	0.88–1.86	0.23	1.12	0.77–1.59	>0.5	**1.39**	**0.58–3.36**	**0.47**
Designers	1.17	0.94–1.43	0.14	**1.12**	**0.73–1.22**	**0.20**	0.85	0.67–1.07	0.19	0.71	0.41–1.13	0.18
Excavating, grading operators	0.41	0.07–1.29	0.21	1.01	0.48–1.84	>0.5	0.70	0.28–1.43	0.39	**2.41**	**0.74–5.63**	**0.081**
Extruding	0.76	0.19–1.99	>0.5	0.84	0.33–1.72	>0.5	**1.60**	**0.82–2.77**	**0.13**	1.07	0.06–4.78	>0.5
Financial records processing	1.06	0.95–1.18	0.30	1.09	1.00–1.18	0.058	1.22	1.09–1.36	<0.001	**1.10**	**0.86–1.39**	**0.45**
Food counter and fountain and related	1.25	0.49–2.58	>0.5	1.26	0.65–2.20	0.45	**0.65**	**0.16–1.71**	**0.46**	3.38	1.04–7.96	0.016
Furnace, kiln, excluding food	1.23	0.89–1.65	0.19	1.25	0.98–1.56	0.067	**0.86**	**0.64–1.13**	**0.30**	1.10	0.50–2.07	>0.5
Graders and sorters, excluding agriculture	**1.59**	**1.14–2.15**	**0.004**	1.00	0.73–1.34	>0.5	0.96	0.61–1.43	>0.5	**2.20**	**1.00–4.13**	**0.028**
Hairdressers and cosmetologists	**1.23**	**1.06–1.42**	**0.006**	**1.23**	**1.10–1.40**	**<0.001**	1.08	0.91–1.28	0.37	**1.38**	**1.00–1.87**	**0.046**
Health-diagnostic practitioners (nec)	0.87	0.39–1.65	>0.5	1.19	0.71–1.85	0.48	0.57	0.26–1.07	0.11	**1.24**	**0.38–2.93**	**>0.5**
Horticultural specialists	**0.85**	**0.30–1.86**	**>0.5**	1.48	0.84–2.39	0.14	1.65	0.92–2.71	0.066	0.00	0.00–1.31	>0.5

(*Continued*)

TABLE III. (*Continued*)

	Presenile dementia			Alzheimer's disease			Parkinson's disease			Motor neuron disease		
	MOR	95% CI	P	MOR	95% CI	P	MOR	95% CI	P	MOR	95% CI	P
Information clerks	1.13	0.92–1.38	0.22	1.22	1.04–1.41	0.011	1.10	0.88–1.35	0.4	**1.28**	**0.86–1.82**	**0.21**
Lawyers and judges	1.55	1.12–2.24	0.013	**1.30**	**1.00–1.73**	**0.061**	1.09	0.82–1.44	>0.5	1.22	0.63–2.38	>0.5
Librarians, archivists	0.95	0.74–1.22	>0.5	1.06	0.86–1.29	>0.5	**1.01**	**0.76–1.33**	>**0.5**	**1.45**	**0.85–2.39**	**0.15**
Material recording, scheduling, clerks (nec)	1.18	1.03–1.35	0.014	1.13	1.02–1.25	0.018	**1.17**	**1.05–1.30**	**0.004**	1.28	1.00–1.60	0.043
Mechanics and repair	1.12	1.03–1.22	0.008	**1.07**	**1.00–1.14**	**0.045**	0.97	0.90–1.04	0.35	1.11	0.94–1.29	0.21
Misc. electrical equipment repair	1.51	0.82–2.52	0.14	1.51	0.97–2.25	0.053	1.00	0.57–1.61	>0.5	**1.09**	**0.27–2.87**	>**0.5**
Painters, sculptors	0.95	0.73–1.22	>0.5	**1.24**	**1.03–1.47**	**0.019**	1.23	1.00–1.51	0.047	**1.18**	**0.78–1.71**	**0.41**
Pest control	2.96	1.34–5.59	0.003	0.59	0.15–1.54	0.36	**1.19**	**0.47–2.43**	>**0.5**	0.71	0.04–3.13	>0.5
Photographic process machine	**1.50**	**0.85–2.42**	**0.13**	1.36	0.87–2.01	0.16	0.94	0.47–1.66	>0.5	0.95	0.16–2.97	>0.5
Physicians	1.69	1.19–2.60	0.008	1.33	1.00–1.83	0.069	1.08	0.79–1.46	>0.5	**1.45**	**0.71–3.09**	**0.32**
Precision textile, machine workers	0.98	0.83–1.14	>0.5	1.03	0.91–1.16	>0.5	**1.02**	**0.85–1.20**	>**0.5**	1.94	1.30–2.78	<0.001
Production inspectors	1.17	1.02–1.34	0.026	**1.11**	**1.00–1.23**	**0.046**	1.08	0.95–1.23	0.25	1.01	0.74–1.37	>0.5
Production testers	1.48	0.63–2.90	0.31	2.25	1.38–3.45	<0.001	0.87	0.35–1.79	>0.5	**0.72**	**0.04–3.20**	>**0.5**
Radiological technicians	0.69	0.29–1.37	0.33	**0.61**	**0.30–1.09**	**0.13**	1.40	0.78–2.33	0.22	**0.25**	**0.01–1.14**	**0.17**
Religious workers	1.12	0.83–1.48	0.43	1.14	0.90–1.42	0.28	**1.70**	**1.27–2.21**	<**0.001**	0.87	0.31–1.89	>0.5
Secretaries, stenographers	1.13	1.02–1.24	0.015	**1.22**	**1.13–1.31**	<**0.001**	1.35	1.22–1.49	<0.001	1.27	1.03–1.56	0.024
Social workers	**1.31**	**1.04–1.62**	**0.018**	1.21	1.01–1.45	0.034	1.44	1.14–1.80	0.002	1.41	0.96–1.99	0.065
Stock handlers and baggers	**0.85**	**0.62–1.13**	**0.27**	1.04	0.84–1.28	>0.5	**1.12**	**0.85–1.45**	**0.40**	1.39	0.81–2.21	0.20
Supervisory cleaning and bldg service	1.37	0.99–1.83	0.048	1.10	0.84–1.41	0.47	0.87	0.63–1.17	0.39	**1.13**	**0.56–1.99**	>**0.5**
Teachers, post-secondary	1.35	1.13–1.63	0.001	1.31	1.14–1.50	<0.001	**1.61**	**1.39–1.85**	<**0.001**	1.03	0.71–1.47	>0.5
Teachers, primary-secondary	**1.23**	**1.11–1.38**	<**0.001**	**1.18**	**1.08–1.28**	<**0.001**	**1.30**	**1.18–1.43**	<**0.001**	1.23	**1.01–1.50**	**0.039**
Technical, sales	1.11	1.04–1.18	0.001	**1.15**	**1.10–1.21**	<**0.001**	1.17	1.10–1.24	<0.001	1.02	—	>0.5
Veterinarians	1.22	0.52–2.42	>0.5	1.77	1.07–2.75	0.017	0.92	0.47–1.60	>0.5	**2.68**	**1.13–5.33**	**0.011**

Based on two logistic regression models for each disease category, each with approximately half of the 87 occupations individually represented with indicator terms; adjusted for age, race, gender, region and SES. Entries in bold represent occupations and outcomes observed to have significantly elevated PMRs in a previous study [Schulte et al., 1996].

significant PSD elevations in this study: clergy, dentists, graders/sorters (MOR = 1.59, 95% CI = 1.14–2.15), hairdresser/cosmetologists (MOR = 1.23, 95% CI = 1.06–1.42), social workers (MOR = 1.31, 95% CI = 1.04–1.62), and teachers (primary/secondary) (MOR = 1.23, 95% CI = 1.11–1.38) (Table III). Where six were observed, the approximate expected number of groups showing elevations by chance with the observed levels of statistical significance of the 18 observed originally was 0.54 (one-tailed tests: sum of six *P*-values ×18/2). Similarly for AD, among 29 occupations showing prior elevations, ten were again significantly elevated where 2.1 would be expected by chance, including: aircraft mechanics (MOR = 1.35, 95% CI = 1.02–1.74), bank tellers (MOR = 1.40, 95% CI = 1.14–1.70), clergy (MOR = 1.38, 95% CI = 1.21–1.55), hairdressers/cosmetologists (MOR = 1.23, 95% CI = 1.10–1.40), painters and sculptors (MOR = 1.24, 95% CI = 1.03–1.47), secretaries (MOR = 1.22, 95% CI = 1.13–1.31), and teachers (primary/secondary) (MOR = 1.18, 95% CI = 1.08–1.28). For PD, among 24 groups showing prior elevations, 6 were significantly elevated where 0.11 would be expected, including: biological scientists (MOR = 2.04, 95% CI = 1.37–2.92), post-secondary teachers (MOR = 1.61, 95% CI = 1.39–1.85), teachers (primary/secondary) (MOR = 1.30, 95% CI = 1.18–1.43), clergy (MOR = 1.79, 95% CI = 1.58–2.02), and other religious workers (MOR = 1.70, 95% CI = 1.27–2.21). Among 20 groups for MND, four were significantly elevated where 1.2 would be expected: graders and sorters (non-agricultural) (MOR = 2.20, 95% CI = 1.00–4.13), hairdressers (MOR = 1.38, 95% CI = 1.00–1.87), teachers (primary/secondary) (MOR = 1.23, 95% CI = 1.01–1.50), and veterinarians (MOR = 2.68, 95% CI = 1.13–5.33).

Many of the 87 groups showed significantly elevated mortality for NDD categories not previously elevated in those groups (Table III). For PSD, there were ten occupations where 4.6 would be expected with those significances by chance, including: bank tellers, lawyers/judges, pest control, and physicians. The observed (and expected) numbers of groups with elevated mortality for AD were 13 (6.6), which included dental assistants, teachers (post-secondary), production test workers, and veterinarians. For PD there were ten (4.5) significant associations, including: financial records processors, secretaries, and social workers, and for MND there were six (3.3) associations including dental assistants, food counter workers, and precision textile workers. Thus dental assistants had significantly elevated AD and MND not observed in the previous study and somewhat parallel to the experience of dental laboratory workers.

Pesticides in farming

Among all farming occupations, PSD was significantly elevated only below age 65 (MOR = 1.86, 95% CI = 1.02–3.13) (Table IV). The *farmer* occupation alone, below age 65, had a stronger association (MOR = 2.22, 95% CI = 1.10–4.05). For AD, a similar but weaker pattern of association was observed, again strongest in *farmers* and limited to age below 65 (MOR = 1.76, 95% CI = 1.04–2.81) (Table IV). PD was significantly elevated across all three farming specifications in both age groups but strongest for *farmers* (MOR = 1.16, 95% CI = 1.11–1.22), with much higher risk below age 65 (MOR = 2.23, 95% CI = 1.47–3.26). MND also was significantly elevated for farming occupations of all ages, again strongest for *farmers* (MOR = 1.23, 95% CI =1.03–1.46) but with no difference on age. In other occupations where pesticide usage might be expected (e.g., *farm workers*, *horticultural specialty workers*), significant elevations were not observed although horticultural specialty workers did show a non-significant excess of PD (MOR = 1.65, 95% CI = 0.92–2.71) (data not shown).

Solvents and oxidative stress

The solvent exposure index was modeled as a continuous variable taking discrete values 0–9. In logistic regression models including an indicator of any level of solvent exposure, small but significant linear associations were observed for solvents and AD (MOR = 1.09, evaluated at highest exposure category; 95% CI = 1.03–1.15), PD (MOR = 1.07, 95% CI = 1.00–1.13), and MND (MOR = 1.16, 95% CI = 1.01–1.34) (Table V). A similar pattern was observed for benzene specifically but with lower significance and lower exposure prevalence. There were no indications of age modification in the solvent effects (data not shown). Oxidative stress, representing a constellation of occupations, showed a significant decrease below age 65 in the otherwise small elevation for PSD, and a significant but small elevation for AD at all ages (MOR = 1.05, 95% CI = 1.00–1.09) (data not shown). There was also a small but significant association with MND (MOR = 1.13, 95% CI = 1.01–1.25 $P = 0.03$) (data not shown).

Magnetic fields

EMF (60 Hz) modeled as a continuous variable taking on ten discrete values showed a near significant association with PSD (at highest exposure stratum: MOR = 1.08, 95% CI = 0.99–1.18) and a small but significant association with AD (MOR = 1.12, 95% CI = 1.05–1.20, *P* for trend <0.001) with no age dependence (Table V). Statistically significant elevations were observed below age 65 for PD (MOR = 1.87, 95% CI = 1.14–2.98, *P* for trend = 0.015) and MND (MOR = 1.63, 95% CI = 1.10–2.39, *P* for trend = 0.014) (Table V). To investigate the possibility of an EMF-solvent interaction, models with solvent-EMF product terms were evaluated in additive relative-rate models. There was a significant negative EMF-solvent interaction for MND

($P = 0.03$) and a non-significant positive interaction for PSD ($P = 0.07$) (data not shown).

Welding

Of the four NDDs under study, only PD was associated with occupations where arc-welding of steel is performed, and only for the 20 PD deaths below age 65 (MOR = 1.77, 95% CI = 1.08–2.75) (Table VI).

DISCUSSION

Strengths and Limitations of the Study

We have observed numerous associations between NDDs and occupations that had been hypothesized from a previous study of similar design [Schulte et al., 1996]. Moreover, some limitations of the previous study were addressed. MORs were calculated excluding other diseases possibly associated with exposures under study, a source of bias with the PMR [Miettinen and Wang, 1981]. To reduce potential confounding, ten SES levels and four geographic regions were included in logistic regression models. Referral or diagnostic bias has been discussed [Tsui et al., 1999] and occupational groups here might differ on diagnostic quality, medical treatment, and accuracy or completeness of death certificates. Because all eligible cases and controls were used, selection bias was avoided. The ''healthy worker effect'' in this design should be small because it is population-based as opposed to employer-defined. However, variation in what was declared to be *usual occupation* could have depended on age or NDD status.

Cigarette smoking has a very consistent inverse relation with PD [Hubble et al., 1993; Semchuk et al., 1993; Wang et al., 1993; Hertzman et al., 1994; Gorell et al., 1999; Zorzon et al., 2002], and with AD, [Ferini-Strambi et al., 1990; Lee,

TABLE IV. Mortality Odds Ratios for Neurodegenerative Disease in Farming Occupations: Enhanced Risk Below Age 65

	All farming deaths	Presenile dementia	Alzheimers disease	Parkinson's disease	Motor neuron disease
All farm-related[a]					
Deaths, n	149,562	1,574	2,821	2,505	245
MOR		0.95	0.99	1.14	1.20
95% CI		0.90–1.01	0.95–1.03	1.08–1.19	1.02–1.41
n, age <65	22,874	15	20	35	56
MOR, age <65		1.86	1.16	1.58	1.09
95% CI		1.02–3.13	0.70–1.80	1.08–2.24	0.78–1.50
Pesticides[b]					
Deaths, n	147,688	1,561	2,781	2,478	240
MOR		0.96	0.99	1.14	1.20
95% CI		0.90–1.02	0.94–1.03	1.09–1.20	1.02–1.41
n, age <65	22,478	13	20	35	55
MOR, age <65		1.59	1.23	1.59	1.09
95% CI		0.84–2.76	0.75–1.91	1.09–2.26	0.78–1.50
Farmers, excl horticultural[c]					
Deaths, n	120,193	1,387	2,486	2,252	198
MOR		0.96	0.99	1.16	1.23
95% CI		0.90–1.03	0.94–1.04	1.11–1.22	1.03–1.46
n, age <65	11,261	11	18	30	34
MOR, age <65		2.22	1.76[d]	2.23[e]	1.12
95% CI		1.10–4.05	1.04–2.81	1.47–3.26	0.74–1.64

Adjusted for age, race, gender, region and SES. Model contains multiplicative terms for exposure and for exposure if age at death <65; thus *MOR* is estimate for deaths occurring age 65+, and MOR, age <65 is estimate of enhanced risk: age <65 versus age 65+.

[a]BOC occupation codes: 473–477,479,483–489.

[b]BOC occupation codes: 473,474,477,479,483–489.

[c]BOC occupation codes: 473.

[d]$P = 0.025$.

[e]$P < 0.001$.

TABLE V. Mortality Odds Ratios for Neurodegenerative Disease and Occupations With Exposures to Solvents, Benzene, Oxidative Stress, and Electromagnetic Fields (EMF, 60 Hz)

	All deaths	Presenile dementia	Alzheimers disease	Parkinson's disease	Motor neuron disease
Solvents[a]					
Deaths, n[b]	972,505	8,179	14,549	11,458	1,994
MOR		1.06	1.09[d]	1.07	1.16[e]
95% CI		0.98–1.15	1.03–1.15	1.00–1.13	1.01–1.34
Benzene[a]					
Deaths, n	624,524	4,534	8,116	6,999	1,356
MOR		1.05	1.07	1.05	1.14
95% CI		0.97–1.15	1.007–1.14	0.98–1.12	0.97–1.33
EMF[c]					
Deaths, n	2,392,040	25,999	45,379	31,797	5,965
MOR		1.08	1.12[f]	0.96	0.94
95% CI		0.99–1.18	1.05–1.20	0.88–1.04	0.73–1.20
n, age <65	626,683	296	641	696	2,120
MOR, age <65		1.30	0.85	1.87[g]	1.63[h]
95% CI		0.57–2.69	0.46–1.49	1.14–2.98	1.10–2.39

Adjusted for age, race, gender, region and SES.
[a]MOR evaluated at maximum level of intensity and probability of exposure.
[b]Number of deaths in exposed population level.
[c]MOR evaluated at maximum of ten equal width exposure strata, relative to the lowest EMF stratum; deaths with missing EMF status excluded. Model contains multiplicative terms for exposure and for exposure if age at death <65; thus MOR is estimate for deaths occurring age 65+, and MOR, age <65 is estimate of enhanced risk: age <65 versus age 65+.
[d]$P = 0.003$.
[e]$P = 0.034$.
[f]$P < 0.001$.
[g]$P = 0.015$.
[h]$P = 0.014$.

1994] and a positive association with amyotrophic lateral sclerosis (ALS, the most common form of MND) [Nelson et al., 2000]. Stratifying on SES, region, gender and race may have achieved some limited control for smoking. Other confounding of occupation-disease associations may be unaccounted for.

Some limitations of the first study [Schulte et al., 1996] remain. Mortality does not address onset of disease, and *usual* occupation does not reveal time course of potential exposure [Checkoway and Nelson, 1999]. Usual@ occupation is often reported on the death certificate, correctly or not, as *last* occupation. Jobs from death certificates had only 48% concordance with company records in an electric utility cohort for NDDs [Savitz et al., 1998a; Andrews and Savitz, 1999]. NDD are under-represented on death certificates [Finklestein and Liss, 1987] and misclassification is particularly severe with AD because autopsy is required for accurate diagnosis.

NDD occupational risk factors could differ across race and gender [Headrie et al., 2001; Tang et al., 2001]. Where heterogeneity exits, the power to detect associations could be reduced. The antioxidant effects of estrogen in women, for example, could mitigate against the effects of oxidative stressors [Behl and Holsboer, 1998], and a genetic polymorphism in metabolism or detoxification of a neurotoxin could have different distributions in white and black workers [Agzndez et al., 1995; Farrer et al., 1997; Hubble et al., 1998; Headrie et al., 2001]. However, a more important source of heterogeneity is probably exposure differences within nominal occupational categories, particularly for generic industrial occupations. In this study, elevated PSD in clergy, hairdressers, and teachers (post-secondary) was largely limited to men (data not shown), suggesting that different gender roles may be important. Higher MORs for non-white workers were observed for *pest control* (PSD), for *dental laboratory* and *production testers* (AD) and for precision textile workers (MND), based on small numbers; higher exposures for non-white workers in the same classifications could account for such differences.

The relatively fine stratification on SES in this study helped control for diagnostic and other sources of bias. However, it may also have introduced complications. The

TABLE VI. Mortality Odds Ratios for Neurodegenerative Disease and Welding Occupations

	All welding deaths	Presenile dementia	Alzheimers disease	Parkinson's disease	Motor neuron disease
Deaths, n	44,545	321	581	540	70
MOR[a]		0.98	0.97	0.87	0.66
95% CI		0.87–1.10	0.89–1.06	0.80–0.95	0.49–0.88
n, Age <65	13,141	7	9	20	23
MOR, Age <65		1.27	0.85	1.77[b]	0.89
95% CI		0.53–2.57	0.40–1.58	1.08–2.75	0.53–1.47

Welding occupations from Bureau of Census occupation codes: 544 (millwrights), 557 (supervisors: plumbers, pipefitters, steamfitters), 585 (plumbers, pipefitters, steamfitters), 587 (apprentice: plumbers, pipefitters, steamfitters), 597 (structural metal workers), 643 (boilermakers), and 783 (welders and cutters).

[a]Evaluated in a model together with all farming occupations (Table IV). Adjusted for age, race, gender, region and SES. Model contains multiplicative terms for exposure and for exposure if age at death <65; thus *MOR* is estimate for deaths occurring age 65+, and MOR, age <65 is estimate of enhanced risk: age <65 versus age 65+.

[b]$P = 0.021$.

relatively higher risk of dementias in the lowest SES level, contrary to the general upward trend, may be a consequence of dementia reducing workers' earning abilities [Antilla et al., 2002]. Further, the strong dependence of the SES assignment algorithm on job title [Hauser and Warren, 1997] introduces unpredictable possible confounding; one would prefer an independent assessment of SES based on income, education, etc., information unavailable from death certificates.

Occupations With Elevated Odds Ratios

Hairdressers

Hairdressers are at increased risk of PSD, AD, and MND all of which were hypothesized, suggesting a role for dyes, components of hair care products, solvents, or other exposures in hair dressing and manicure. Italian investigators have reported elevated MND incidence in hairdressers [Chio et al., 1991].

Farmers

Among farming-related occupations, all four NDD elevations were highest among *farmers* and, for the dementias, were apparent only below age 65; excess PD was greater below age 65 as well. This age effect might result from early onset of NDD attributable to farming exposures, or the excess cases may not be discernable above the greatly increased background at older ages.

In a study of French farmers, elevated dementia was observed only in association with PD, particularly among women [Helmer et al., 2001]. PD has been associated in several studies with pesticide, [Hertzman et al., 1994; Seidler et al., 1996; Gorell et al., 1998; Checkoway and Nelson, 1999; Fall et al., 1999] particularly herbicide [Semchuk et al., 1992] and with farming generally [Semchuk et al., 1992; Helmer et al., 2001; Zorzon et al., 2002]. McGuire et al. [1997] observed an association between ALS and agricultural chemicals and Chio et al. [1991] observed excess MND among Italian farmers and breeders. Observing highest risk, here, among farmers as opposed to farm workers, may be a consequence of farm workers moving on to other employment such that at death, farming was not their usual work. Migrant farm workers, often those experiencing the highest pesticide exposure, may not remain in the country of employment in their final years and thus would be underrepresented in mortality registries. In this study, 113,555 deaths were observed in male *farmers* (BOC code: 473) but only 10,826 deaths among male *farm workers* (BOC code: 479).

Teachers, clergy, and other professions

Teachers at all levels had elevated risk for all four NDD outcomes (except for MND in post-secondary) and most were hypothesized. Clergy had several elevated hypothesized outcomes including PD, which was duplicated among other religious and social workers. These NDD findings in social service occupations (including lawyers and judges) are perplexing as noted previously [Schulte et al., 1996] and have been reported elsewhere [Tsui et al., 1999]. Other notable hypothesized excesses were for dentists, biological scientists and veterinarians. Professionals may have lower risks for competing causes of death (such as heart disease) due to favorable factors (e.g., less smoking, better health care) not adequately controlled by the SES stratification, and those with life-long careers may be more reliably classified, thus improving detection of excesses. Previously Ravaglia et al.

[2002] observed AD associated with attained level of education, however, other work has observed *negative* associations between AD and levels of education [Friedland, 1993] or cognitive [Wilson et al., 2002; Smyth et al., 2004] and leisure time activity [Scarmeas et al., 2001]. One autopsy-based study of hospital deaths found no association between AD and education or SES status [Munoz et al., 2000], perhaps reflecting the selection imposed by hospitalized subjects. Risk factors for NDD in teachers and other service workers could include stress and contact with infectious agents [Tsui et al., 1999], but other groups share those conditions.

Magnetic fields

The magnetic field job-exposure matrix would appear to assess exposures about as accurately as is possible today for a death certificate study [Bowman et al., 2005] and would be unlikely to bias estimates of NDD risks. However, 15.2% of occupations did not have measurements or reliable exposure estimates. With the job-exposure matrix, assessment error increases the variance of the categorical risk estimates [Hornung and Deddens, 1994], and thus might conceal an exposure-response relationship.

In addition to significant MORs (Table V), we observed significant linear trends across all EMF exposures for AD ($P < 0.001$) and, below age 65, for PD and MND ($P = 0.015$). At the highest exposure (geometric mean magnetic field $\geq$9.0 mG), the attributable cases constitute about 11% of AD deaths. An excess this small could be due to confounding or errors in study data and analysis. The attributable cases are more substantial (below age 65) for PD ([1.87−1.0]/1.87 = 47%) and MND ([1.63−1.0]/1.63 = 39%).

These findings display considerable concordance with other epidemiologic studies on NDD risks from magnetic fields and their recent reviews [Portier and Wolfe, 1998; Ahlbom, 2001; NRPB Advisory Group on Non-Ionizing Radiation, 2002; Li and Sung, 2003]. In addition to our original study [Schulte et al., 1996], six studies examined NDD mortality and EMF [Johansen and Olsen, 1998; Nicholas et al., 1998; Savitz et al., 1998a,b; Feychting et al., 2003; Hakansson et al., 2003], of which four had complete job histories as well as a job-exposure matrix [Johansen and Olsen, 1998; Savitz et al., 1998b; Feychting et al., 2003; Hakansson et al., 2003]. Six EMF studies examined NDD morbidity [Deapen and Henderson, 1986; Sobel et al., 1996; Davanipour et al., 1997; Feychting et al., 1998; Graves et al., 1999; Harmanci et al., 2003], one of which used a job-exposure matrix, complete job histories, and matching with twins to control for genetic factors [Feychting et al., 1998].

The reviews of this literature [Portier and Wolfe, 1998; Ahlbom, 2001; NRPB Advisory Group on Non-Ionising Radiation, 2002; Li and Sung, 2003] concurred that ‘‘there is no good ground’’ for an association with PD, ‘‘very weak evidence’’ with AD, and ‘‘substantially stronger’’ evidence for ALS [NRPB Advisory Group on Non-Ionising Radiation, 2002]. However, the ALS/MND risks attributed to EMF exposures are complicated by the association with electric shock reported by Deapen and Henderson [1986] and Jafara et al. [2001]. Subsequent studies have failed to control for this potential confounder of magnetic field effects [NRPB Advisory Group on Non-Ionising Radiation, 2002; Li and Sung, 2003]. The associations we found with AD and MND support these conclusions, but the significant MOR for PD is discordant.

Welding

Studies in the US, Europe, and Korea implicate manganese fumes from arc-welding of steel in the development of a Parkinson’s-like disorder, probably a manifestation of manganism [Sjogren et al., 1990; Kim et al., 1999; Lucchini et al., 1999; Moon et al., 1999]. The observation here that PD mortality is elevated among workers with likely manganese exposures from welding, below age 65 (based on 20 deaths), supports the welding-Parkinsonism connection. In an urban health system-based case-control incidence study, non-significantly elevated PD was observed without regard to age in a broad occupational grouping, *structural*, that would include welders (OR = 1.13, 95% CI = 0.74,1.72) [Kirkey et al., 2001]. The resistance welders in Sweden found to have no elevation of PD [Hakansson et al., 2003] would not have had significant exposure to manganese fume (as opposed to arc welders).

Solvents and oxidative stressors

This study provides some weak support for the hypothesis that solvents cause neurological diseases. The MOR estimates are small (ranging 1.06–1.13 for highest exposure stratum), raising serious concerns over uncontrolled confounding. The role of solvents in NDD has been debated in the scientific literature [Shalat et al., 1988; Graves et al., 1991; Axelson, 1995; Bleecker, 1995; Kukull et al., 1995; Graves et al., 1998; Palmer et al., 1998; Daniell et al., 1999]. On the other hand, if the present estimates are unbiased, they imply that about 10% of deaths from these neurological diseases are solvent-attributable in the highest exposure stratum. While it is plausible that agents responsible for NDD are associated with the use of, or dissolved in, solvents (such as paint or plastics resins), this conjecture cannot be evaluated with the available exposure information.

Occupations with oxidative stressors [Migliore and Coppede, 2002] exhibited a modest association with MND. The misclassification of oxidative stress was probably large owing to the limitation of death certificates; diverse manufacturing and maintenance jobs would have exposures to oxidative stressors but not be identifiable using BOC codes.

Elevations not hypothesized

Occupations with sizeable elevations in MOR not hypothesized included bank tellers (PSD), dental assistants (AD, MND), pest control (PSD), precision textile machine operators (MND), production testers (AD), and secretaries/stenographers (AD, PD). In pest control, pesticide exposures could plausibly account for some of these excesses; anti-cholinesterase effects of pesticides are well known and several studies have reported pesticides as risk factors for PD [Semchuk et al., 1993; Wang et al., 1993; Fleming et al., 1994; Fall et al., 1999]. Increased mercury levels have been reported in patients with Alzheimer's [Basun et al., 1991; Hock et al., 1998], which could account for the increased risk in both dental assistants and dental lab workers; dentists (less direct contact with mercury) exhibited a non-significant excess. PD has also been associated with elevated mercury levels [Ngim and Devathasan, 1989; Seidler et al., 1996], but PD was only modestly elevated in this study among dental workers. In addition to mercury, the elevated AD, PD, and more than two-fold elevation of MND among dental workers suggests a possible role for such agents such as methacrylate or other resin systems used in dental work [Nayebzadeh and Dufresne, 1999]. The finding of elevated MORs for Alzheimer's and MNDs in veterinarians suggests occupational origins related to unidentified biological or chemical agents. Relevant exposures for MND in precision textile workers are not obvious but formaldehyde is one possibility to be considered. For clerical work (secretaries, bank tellers), possibly important exposures might include duplicating or photocopying chemicals, and carbonless copy paper but little or no evidence has been reported.

CONCLUSION

Occupational disease surveillance based on death certificates is severely limited by the lack of work history and non-specific recording of cause of death. AD, for example encompasses clinical, neuropathological, biochemical and genetic variants, and potentially differing etiologies [Wilcock, 1992]. The probability of detecting a causal association is further degraded by the multifactoral etiology of some diseases, creating opportunities for exposure confounding; periods of prior partial disability may not be recorded as contributing to mortality. Inevitable misclassification of exposure, together with indications of positive associations, implies that baseline risks are inflated by attributable but unaccounted-for cases and that exposure-associations could be underestimated.

This study provides support for a number of previous findings on occupational factors for NDD, and supports the possibility that a substantial portion of NDD is preventable. Of particular concern are risk factors in farming, hairdressers, dental work, veterinarians, pest control workers, teachers, biological/medical scientists, and lawyers and judges. The significant exposure-response we found for magnetic fields agrees with findings for Alzheimer's and MNDs reported by most earlier studies. Findings for solvent exposures were inconclusive but merit further investigation. Studies that use morbidity rather than mortality would reduce under-reporting and provide superior diagnostic information.

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