American Journal of Epidemiology
Vol. 142, No. 5
Printed in U.S.A.

Occupations with Exposure to Electromagnetic Fields: A Possible Risk Factor for Alzheimer's Disease

Eugene Sobel,[1] Zoreh Davanipour,[2] Raimo Sulkava,[3] Timo Erkinjuntti,[4] Juhani Wikstrom,[5] Victor W. Henderson,[6] Galen Buckwalter,[7] Joseph D. Bowman,[8] and Pey-Jiuan Lee[9]

The authors present analyses of data from three independent clinical series and controls indicating an association between working in occupations with probable medium to high exposure to extremely low frequency (<300 Hz) electromagnetic fields and sporadic Alzheimer's disease. Case-control analyses were carried out using data from patients examined at the following locations: the Department of Neurology, University of Helsinki, Helsinki, Finland, 1982–1985; the Koskela Hospital in Helsinki, 1977–1978; and the University of Southern California site of the Alzheimer's Disease Research Center of Los Angeles and Orange Counties, 1984–1993. The predominant occupations among medium (2–10 mG or >10 mG intermittently) to high (>10 mG or >100 mG intermittently) exposed cases were seamstress, dressmaker, and tailor. The results appear to be independent of education, and the sex-combined odds ratios for the three series are quite homogeneous 2.9, 3.1, and 3.0. The odds ratio for the three series analyzed together is 3.0 ($p < 0.001$), with a 95% confidence interval of 1.6–5.4. The odds ratio for women is 3.8 ($p < 0.001$), with a 95% confidence interval of 1.7–8.6. The most obvious, possibly etiologically relevant exposure is that of electromagnetic fields, which may have biologic plausibility because they may adversely influence calcium homeostasis and/or inappropriately activate immune system cells such as microglial cells, initiating events that result in neuronal degeneration. *Am J Epidemiol* 1995;142:515–24.

Alzheimer's disease; electromagnetic fields; occupations; risk factors

Alzheimer's disease is considered the fourth leading cause of death in the United States (1). Most cases occur after age 65 years (late onset) and are sporadic as opposed to familial. The etiology of the brain lesions associated with Alzheimer's disease appears to be multifactorial (2). Genetic factors, factors related to aging, and environmental factors are likely to play important roles. In some individuals and families, one or another factor may be the single cause of Alzheimer's disease. In other individuals and families, a combination of factors may be causative. The components of brain damage found in Alzheimer's disease include 1) neuronal loss, loss of synapses, cytoskeletal alterations, and 2) the formation of neurofibrillary tangles and neuritic plaques. Plaques are associated with the deposition of β-amyloid in a process that may involve activated microglial cells and localized inflammatory reactions (2).

Work in numerous laboratories has indicated that electromagnetic fields (EMFs) may be capable of causing biologic responses that could be associated with some of these processes in a causative manner (see Discussion). We therefore decided to conduct an epidemiologic study of sporadic Alzheimer's disease and EMF-related occupations.

MATERIALS AND METHODS

Subjects

In this paper, we use the term *familial* Alzheimer's disease to mean that the Alzheimer's disease subject

Received for publication October 7, 1994, and in final form June 12, 1995.

Abbreviations: ADRC, Alzheimer's Disease Research Center; CI, confidence interval; EMF, electromagnetic field; NINCDS-ADRDA, National Institute of Neurologic and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association.

[1] Departments of Preventive Medicine and Neurology, University of Southern California, Los Angeles, CA.
[2] Department of Neurology, University of Southern California, Los Angeles, CA.
[3] Department of Community Health and General Practice, Kuopio University, Kuopio, Finland.
[4] Department of Neurology, University of Helsinki, Helsinki, Finland.
[5] Rehabilitation Research Unit, University of Helsinki, Helsinki, Finland.
[6] Departments of Neurology and Psychology and the School of Gerontology, University of Southern California, Los Angeles, CA.
[7] Department of Preventive Medicine and Andrus Gerontology Center, University of Southern California, Los Angeles, CA.
[8] National Institute for Occupational Safety and Health, Cincinnati, OH.
[9] Department of Preventive Medicine, University of Southern California, Los Angeles, CA.
Reprint requests to Dr. Eugene Sobel, Department of Preventive Medicine, Parkview Medical Building B-304, University of Southern California School of Medicine, 1420 San Pablo Street, Los Angeles, CA 90033.

has at least one first degree relative with Alzheimer's disease, dementia, or memory loss. By *sporadic* Alzheimer's disease, we mean that the subject does not have familial Alzheimer's disease. When the information was available, we performed the analyses using only sporadic Alzheimer's disease. We did this because some forms of familial Alzheimer's disease are presumably primarily genetic in nature and may not require environmental exposures for expression.

Three case series separated by distance and/or time are used in this study: 1) a Finnish case series (Finnish series 1) with patients and controls examined at the Department of Neurology, University of Helsinki, during 1982–1985; 2) a second Finnish case series (Finnish series 2) with patients and controls examined at the Koskela Hospital in Helsinki during 1977–1978; and 3) patients and controls (recruited between 1984 and 1993) at the University of Southern California site of the Alzheimer's Disease Research Center of Los Angeles and Orange Counties. All data were collected prior to any consideration or hypotheses that working in occupations with EMF exposure might be a risk factor for Alzheimer's disease. Table 1 summarizes the Alzheimer's disease subtypes (sporadic/familial) of the cases used in the analyses, types of controls, and ascertainment period for each series.

Finnish series 1 consists of a total of 73 Alzheimer's disease patients and 88 vascular dementia patients. The diagnostic protocol for Alzheimer's disease followed the criteria of the National Institute of Neurologic and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (3) and is described in Erkinjuntti et al. (4–7). Agreement between the clinical diagnoses and autopsy diagnoses is approximately 90 percent for both Alzheimer's disease and vascular dementia patients in this series (6, 7). Next of kin were questioned about first degree family members with possible dementia. Whenever possible, this information was followed up with clinical examinations or a review of clinical records. Sporadic Alzheimer's disease cases are defined as those without a living first degree relative in whom Alzheimer's disease could be documented and without a deceased first degree relative in whom dementia could be documented. Sporadic vascular dementia cases are similarly defined. There are 53 sporadic Alzheimer's disease cases and 70 sporadic vascular dementia cases. These cases were used in the analyses.

Finnish series 2 is an older series, and the diagnoses were made prior to the NINCDS-ADRDA criteria. All subjects who were admitted in 1977 and 1978 to the Koskela Hospital, an institution for geriatric patients in Helsinki, and who were diagnosed as having Alzheimer's disease were eligible for inclusion. The criteria of Roth for the diagnosis of Alzheimer's disease were followed (8, 9). These criteria are similar to the NINCDS-ADRDA criteria (3). Sulkava et al. (10) reported 82 percent agreement between the clinical diagnosis of Alzheimer's disease cases and the neuropathologic diagnosis in a sample of cases. Controls were selected from the long-stay internal medicine

TABLE 1. Description of the clinical series and controls and respective occupations associated with medium to high EMF* exposure

Category	Finnish series 1†	Finnish series 2‡	USC ADRC series§
Cases	Sporadic AD* (n = 53)	Sporadic and familial AD (n = 198)	Sporadic AD (n = 136)
Controls	Sporadic vascular dementia patients (n = 70)	Hospital controls essentially without neurologic diseases, including dementia (n = 299)	Nondemented neurologically normal neighborhood subjects (n = 106)
Ascertainment period	1982–1985	1977–1978	1982–1993
Medium to high EMF-exposed occupations (no. of cases, no. of controls)	Dressmaker (5, 1) Electrical fitter (1, 0) Carpenter (0, 2)	Dressmaker/seamstress/tailor (13, 6) Electrical fitter (1, 0) Carpenter (4, 3) Locomotive engineer (1, 0) Telephone line/connector (0, 1)	Dressmaker/seamstress/tailor (5, 1) Carpenter (1, 1) Electrician (1, 0) Electronics assembler (1, 0) Electrical engineer (1, 1) Electrical technician (1, 0) Tool and dye maker (1, 0)

* EMF, electromagnetic field; AD, Alzheimer's disease.
† Department of Neurology, University of Helsinki, Helsinki, Finland, 1982–1985.
‡ Koskela Hospital, Helsinki, Finland, 1977–1978.
§ University of Southern California site of the Alzheimer's Disease Research Center of Los Angeles and Orange Counties, 1984–1993.

wards at Koskela Hospital. Subjects with a diagnosis of dementia, brain atrophy, psychosis, depression, general or brain arteriosclerosis, parkinsonism, multiple sclerosis, or mental retardation were excluded. Using the alphabetic listing of all inpatients in 1978, the first 299 inpatients who met the study criteria were selected as controls. Specific occupations have not been associated with a wide range of chronic diseases, especially the more common ones. Thus, using controls from a long-term care hospital is unlikely to introduce much, if any, bias into the study. Sufficient information could not be collected to determine the familial/sporadic status of the cases. We therefore have analyzed all cases and controls together in this data set. Finnish series 2 has 198 Alzheimer's disease cases and 299 controls. These subjects were used in the analyses.

The University of Southern California Alzheimer's Disease Research Center (ADRC) series was ascertained between 1984 and 1993. All cases were diagnosed according to NINCDS-ADRDA criteria. The agreement between clinical and autopsy diagnoses is >98 percent (V. Henderson, personal communication, 1994). Nondemented, neurologically normal controls are recruited primarily through outreach efforts within the communities from which the cases came. Controls are neuropsychologically examined each year and are not demented. Sporadic cases and controls are defined as those with no known history of dementia or memory problems among first degree relatives. Information concerning first degree relatives was obtained from the next of kin. The University of Southern California ADRC series has 240 Alzheimer's disease cases and 143 controls, of which 136 and 106 are sporadic cases and controls, respectively, which were used in the analyses.

Occupational EMF exposure data

Occupational information was obtained by in-person interview of the most knowledgeable surrogate for the Alzheimer's disease and vascular dementia subjects and by direct interview of the other (nondemented) control subjects. The subject's primary lifetime occupation was obtained. Space was provided on the appropriate form for the interviewer to record the subject's primary occupation in the words used by the surrogate or subject. Information about length of employment in an occupation was not collected often enough to be used in the analyses. After review of the actual information recorded on the data collection forms, each occupation was blindly assessed for its probable exposure to extremely low-frequency magnetic fields by a certified industrial hygienist (J. D. B.). The industrial hygienist had no knowledge of any subject's case/control status when assessing the occupational information. The 11 "electrical" occupations of Milham (11) were classified as having medium or high exposure based on measurements taken in a previous occupational study (12, 13). With the exception of dressmakers, seamstresses, and tailors, the other medium- to high-exposure occupations were so classified based on published reports, analogy, and the experience of the industrial hygienist. For example, the magnetic field close to the handle of an electric drill can be as high as 5,000 mG (14).

Dressmakers, seamstresses, and tailors were judged by the industrial hygienist to have been likely to have had medium to high exposure based on their presumed use of electrical equipment producing relatively strong magnetic fields. Because the results of this study depend heavily on this single occupational classification, which had not previously been labeled an electrical occupation (probably due to a lack of consideration of these occupations), we confirmed the industrial hygienist's opinion by direct measurement of magnetic fields produced by four industrial and two home sewing machines. Observations were taken at each operator's head, chest, and left and right hands, knees, and feet. The average of these measurements, averaged over all machines, was 19.3 mG. By contrast, in the study of the 11 electrical occupations cited above (12, 13), only electric power line/cable workers and welders/flame cutters had full-shift average exposures higher than dressmakers, seamstresses, and tailors: 23.6 and 19.5 mG, respectively.

The quantitative criteria for defining occupations with high or medium exposure to magnetic fields were as follows: A high exposure occupation has an average exposure >10 mG or regular intermittent exposures >100 mG. A medium exposure occupation has exposures that average between 2 and 10 mG or are intermittently >10 mG. All other occupations were classified as low exposure.

The specific occupations classified as having medium to high EMF exposure are provided in table 1 by case/control status within each clinical series. All other occupations were classified as having low EMF exposure either because they probably did not have medium to high exposure or because there was not sufficient information for the blinded industrial hygienist to make an informed decision.

Educational and social class

Education has been identified as a probable risk factor for dementia and for Alzheimer's disease, specifically in several (e.g., 15–17), but not all (18), studies. It is therefore important to consider education as a possible confounder variable. The number of years of education was available for subjects in Finnish series 1 and the University of Southern California ADRC series.

A governmental five-level social class indicator variable based on occupation was available for Finnish series 2 (19). The lowest class consists of those with no occupation. The next lowest class consists of unskilled workers. The middle class consists of skilled workers (including dressmakers, seamstresses and tailors, and lower office personnel). The second highest class consists of tradesmen, foremen, upper office personnel, etc. The highest class consists of persons in leading positions in society (including physicians and teachers). Homemakers are classified according to the occupation of their spouse. These data were used to investigate the possible confounding effect of education on the association between occupations with EMF exposure and Alzheimer's disease in the Finnish series 2 data. Because they are based on occupation, the social class indicator and education are clearly correlated.

Possible confounding variables

In addition to education/social class, age at onset, age at examination, and sex are possible confounding variables. Age at onset is available for cases and for the vascular dementia controls in Finnish series 1. Age at examination and sex are available for all cases and controls in each series.

Statistical methods

For Finnish series 1, analyses were performed using sporadic Alzheimer's disease patients as cases and sporadic vascular dementia patients as controls. For Finnish series 2, all cases and all controls were used for analysis because no family histories were available. For the University of Southern California ADRC series, sporadic cases and controls were used for analyses. For each clinical series, the analyses were performed for women and men combined and then repeated for women and men separately. Because the results were consistent across databases for the sex-combined and female only analyses, we then combined the three databases and repeated the analyses.

In the initial set of analyses, educational attainment/social class was not used. In a forward inclusion, stepwise logistic regression model of disease risk, neither age nor sex was significant at the 0.10 significance level for any individual database or the combined database, except for the sex-combined analyses in the University of Southern California ADRC series, where the p value for age at examination was 0.097. Therefore, we did not consider age or sex as confounding variables, and we did not adjust for age or sex. Thus, we used the cross-product ratio to estimate the odds ratio. (The cross-product ratio and logistic regression without covariates procedures produce the same estimate.) We used Fisher's exact test for significance of the odds ratio estimate. Logistic regression was used for estimation of the 95 percent confidence intervals. Finally, the Mantel-Haenszel stratified odds ratio for the combined series produced essentially the same odds ratios as the cross-product ratio (20). Consequently, stratification was not necessary.

In a second set of analyses, we investigated the effect of education/social class on the association between occupations with medium to high EMF exposure and Alzheimer's disease by examining the odds ratios for occupations with medium/high EMF exposure with the education-social class variable forced into a logistic regression model. Age at onset or age at examination, as appropriate, was allowed to enter the model in all analyses if the associated p value was <0.2. Sex was similarly allowed to enter models for analyses using all subjects.

RESULTS

Finnish series 1. The sporadic Alzheimer's disease and vascular dementia cases have similar distributions for sex, age at examination, and duration of cognitive impairment (table 2). There are six (11.5 percent) cases and three (4.3 percent) controls whose primary occupation was classified as probably having had medium to high EMF exposure (table 2). The estimated odds ratio for occupations with probable medium to high EMF exposure is 2.9, 95 percent confidence interval (CI) 0.7–12.2, $p = 0.17$ for all sporadic cases and controls (table 3). Among women, the estimated odds ratio is 7.3, 95 percent CI 0.8–11.1, $p = 0.08$. Among men, the odds ratio estimate is 0.7, 95 percent CI 0.1–8.9, $p = 1.0$.

Finnish series 2. The age and sex distributions are essentially the same for the cases and controls. There are 19 (9.6 percent) cases and 10 (3.3 percent) controls with probable medium to high EMF-exposed occupations (table 2). The estimated odds ratios for occupations with probable medium to high EMF exposure are 3.1, 95 percent CI 0.7–8.9, $p < 0.006$ for all cases and controls, and 3.3, 95 percent CI 1.2–9.1, $p < 0.03$, for female cases and controls (table 3). For men the odds ratio is 2.5, 95 percent CI 0.7–8.9, $p = 0.24$.

University of Southern California ADRC series. Age at examination was quite similar for cases and controls. There are 11 (8.1 percent) cases and three (2.8 percent) controls with probable medium to high EMF-exposed occupations (table 2). The estimated odds ratio is 3.0, 95 percent CI 0.8–11.1, $p = 0.10$, for

TABLE 2. Descriptive statistics for sporadic AD* cases and controls (for Finnish series 1† and USC ADRC series‡) and AD cases and controls (for Finnish series 2§)

Attribute	AD cases	Controls
Finnish series 1		
	N = 53	*N* = 70
Sex (%)		
Male	16 (30.2)	22 (31.4)
Female	37 (69.8)	48 (68.6)
Age at examination (years)		
Mean (SD*)	71.6 (10.6)	73 6 (9.4)
Range	50–96	50–91
Duration of cognitive impairment (years)		
Mean (SD)	2.3 (1 3)	1.6 (1.1)
Range	0.4–6.8	0.1–5 9
Missing	1	0
Education (%)		
0–5th grade	4 (9.5)	7 (11 1)
6th grade	24 (57 1)	39 (61.9)
7–11th grade	8 (19.0)	9 (14.3)
12th grade	1 (2 4)	3 (4.8)
>12th grade	5 (11.9)	5 (7.9)
Missing	11 (NA*)	7 (NA)
Occupational EMF* exposure (%)		
Medium to high	6 (11.5)	3 (4.3)
Low	46 (88.5)	67 (95.7)
Missing	1 (NA)	0 (NA)
Finnish series 2		
	N = 198	*N* = 299
Sex (%)		
Male	50 (25.3)	66 (22.1)
Female	148 (74.7)	233 (77.9)
Age at examination (years)		
Mean (SD)	79 3 (6.4)	79.1 (8.1)
Range	65–93	49–98
Social class (%)		
4–5 (lowest)	50 (25.6)	82 (27.4)
3	66 (33 8)	102 (34.1)
2	47 (24.1)	69 (23.1)
1 (highest)	32 (16.4)	46 (15.4)
Missing	3 (NA)	0 (NA)
Occupational EMF exposure (%)		
Medium to high	19 (9 6)	10 (3.3)
Low	179 (90 4)	289 (96.7)
Missing	0 (NA)	0 (NA)

Table continues

TABLE 2. Continued

Attribute	AD cases	Controls
USC ADRC series		
	N = 136	*N* = 106
Sex (%)		
Male	47 (34.6)	47 (44.3)
Female	89 (65 4)	59 (55.7)
Age at examination (years)		
Mean (SD)	74 4 (8.4)	76 4 (9.6)
Range	46–91	38–103
Missing	2	0
Duration of cognitive impairment (years)		
Mean (SD)	5.9 (3.6)	NA
Range	<1–17	NA
Missing	7	NA
Education (%)		
0–5th grade	3 (2.4)	0 (0.0)
6th grade	5 (4.0)	1 (1.0)
7–11th grade	27 (21.8)	11 (10.9)
12th grade	37 (29.8)	16 (15.8)
>12th grade	52 (41 9)	73 (72.3)
Missing	12 (NA)	5 (NA)
Occupational EMF exposure (%)		
Medium to high	11 (8.1)	3 (2.8)
Low	125 (91.9)	103 (97 2)
Missing	0 (NA)	0 (NA)
Combined series		
	N = 387	*N* = 475
Sex (%)		
Male	113 (29 2)	135 (28 4)
Female	274 (70 8)	340 (71.6)
Age at examination (years)		
Mean (SD)	76.6 (8.4)	77.7 (8.9)
Range	46–96	38–103
Missing	2	0
Occupational EMF exposure (%)		
Medium to high	36 (9 3)	16 (3.4)
Low	350 (90.7)	459 (96.6)
Missing	1 (NA)	0 (NA)

* AD, Alzheimer's disease; SD, standard deviation; NA, not applicable, EMF, electromagnetic field.

† Department of Neurology, University of Helsinki, Helsinki, Finland, 1982–1985. Controls are vascular dementia patients.

‡ University of Southern California site of the Alzheimer's Disease Research Center of Los Angeles and Orange Counties, 1984–1993.

§ Koskela Hospital, Helsinki, Finland, 1977–1978

all sporadic cases (table 3). (There were more female controls than female cases, 65.4 percent vs. 55.7 percent. However, in a logistic regression with sex and age included in the model, the odds ratio for high/medium occupation exposure was 3.1, essentially identical to the estimate without age and sex in the model.) Among women, the estimated odds ratio is 4.2, 95 percent CI 0.5–35.8, $p = 0.24$ (table 3). Among men, the estimated odds ratio is 2.7, 95 percent CI 0.5–13.9, $p > 0.4$.

Series-combined analyses. For the combined data

TABLE 3. Odds ratios for medium/high versus low electromagnetic field exposure in primary occupations

Clinical series	Sex	Unadjusted			Adjusted			Exposed		Unexposed	
		OR*	95% CI*	*p* value	OR	95% CI	*p* value	Cases	Controls	Cases	Controls
Finnish series 1† Sporadic AD* vs. VaD*	Both	2.9	0.7–12.2	0.17	2.7	0.6–12.1	0.19	6	3	46	67
Finnish series 2‡ AD vs. hospital controls	Both	3.1	1.4–6.7	<0.006	3.2	1.5–7.2	0.004	19	10	179	289
USC ADRC series§ Sporadic AD vs. controls	Both	3.0	0.8–11.1	0.10	2.4¶	0.6–9.2	0.21	11	3	125	103
Finnish series 1† Sporadic AD vs. VaD	Female	7.3	0.8–65.8	0.08	10.2	1.1–95.3	0.04	5	1	32	47
Finnish series 2‡ AD vs. hospital controls	Female	3 3	1.2–9.1	<0.03	3 5	1.3–9.6	0.02	12	6	136	227
USC ADRC series§ Sporadic AD vs. controls	Female	4.2	0 5–35.8	0.24	3.7	0.4–33 6	0.24	6	1	83	58
Finnish series 1† Sporadic AD vs. VaD	Male	0.7	0.1–8.9	1.0		Did not converge		1	2	14	20
Finnish series 2‡ AD vs. hospital controls	Male	2.5	0.7–8.9	0.24	2.7	0.7–9.8	0.14	7	4	43	62
USC ADRC series§ Sporadic AD vs. controls	Male	2.7	0.5–13.9	0.44	1.7¶	0.3–10.3	0.54	5	2	42	45
Combined data sets‖	Both#	3.0	1.6–5.4	<0.001	2.9	1.6–5.4	<0.001	36	16	350	459
Combined data sets‖	Female	3.8	1.7–8.6	<0.001	3.9	1.7–8.9	0.001	23	8	251	332
Combined data sets‖	Male	2.1	0.8–5.2	0.17	1.9	0.8–5.0	0.17	13	8	99	127

* OR, odds ratio; CI, confidence interval; AD, Alzheimer's disease; VaD, vascular dementia.

† Department of Neurology, University of Helsinki, Helsinki, Finland, 1982–1985. The dichotomy for education was ≤6th grade vs. >6th grade.

‡ Koskela Hospital, Helsinki, Finland, 1977–1978. The dichotomy for social class was 3–5 (low) vs. 1–2 (high).

§ University of Southern California site of the Alzheimer's Disease Research Center of Los Angeles and Orange Counties, 1984–1993. The dichotomy for education was ≤12th grade vs. >12th grade.

‖ The dichotomy for education/social class was education ≤12th grade or social class 3–5 vs. education >12th grade or social class 1–2.

¶ Age at onset (age at examination for controls) was also in the model. The odds ratio for age decreased with increasing age. It was not significant (0.17) but entered the model with a *p* value <0.2.

\# Age at examination was also in the model. The odds ratio for age decreased with increasing age. It was not significant but entered the model with a *p* value <0.2.

set, the descriptive statistics are also provided in table 2. The rates of probable medium/high occupational EMF exposure are 9.3 percent for the combined cases and 3.4 percent for the combined controls. Among women, the rates are 8.4 percent and 2.4 percent, respectively. The estimated odds ratio for all cases/controls is 3.0 ($p < 0.001$), with a 95 percent CI of 1.6–5.4. Among women, the estimated odds ratio is 3.8 ($p < 0.001$), with a 95 percent CI of 1.7–8.6 (table 3). For men, the odds ratio is 2.1, $p = 0.17$, based on 112 cases (13 with probable medium/high exposure) and 135 controls (eight with probable medium/high exposure). The 95 percent CI is 0.8–5.2.

We also calculated odds ratios adjusted for education/social class. The best divisions in terms of balance and importance of education as a risk factor in the logistic regressions were used in the analyses. For example, for Finnish series 1, there were very few subjects with educational attainment <6th grade and very few with a ≥12th grade education. We therefore used the dichotomy ≤6th grade versus >6th grade: 70 versus 30 percent.

Table 2 provides the breakdown of education and social class by case/control status. The controls in Finnish series 1 have a slightly lower educational attainment than the cases. This is reversed in the University of Southern California ADRC series. The social class distributions in Finnish series 2 are nearly identical. Table 3 also provides the results of the logistic regression analyses with both education and occupation forced in the model. Age at onset, age at examination, and sex were allowed in the model if their associated p value was <0.2. In these analyses, the odds ratio estimates for probable medium to high EMF-exposed occupations are quite similar to the unadjusted odds ratios, as are the 95 percent confidence intervals and associated p values.

DISCUSSION

The inclusion of education in the analyses did not materially affect the analytic results. Consequently, the results appear to be independent of educational attainment. We therefore use the simple cross-product odds ratio estimates below in our discussion.

The results of this study suggest that some exposure(s) in occupations with medium to high EMF exposure are associated with the etiology of sporadic Alzheimer's disease: The estimated odds ratio of 3.0 for the combined series has a narrow 95 percent CI of 1.6–5.4 and a p value <0.001. The estimated odds ratio for women is 3.8, with a slightly wider 95 percent CI of 1.7–8.6 and a p value also <0.001. For men, however, the estimated odds ratio, 2.1, is not significant ($p = 0.17$). The 95 percent CI is 0.8–5.2. The consistency of the odds ratios for the sex-combined and female analyses is not present for the male analyses (table 3). For men, the odds ratio for the Finnish series 1 is 0.7, while for the other two series the odds ratios are 2.5 and 2.7. However, there were only 15 cases and 22 controls in this series.

The results are heavily dependent on the professions of dressmaker, tailor, and seamstress, which comprise 21 of the 23 exposed female cases, all eight exposed female controls, two of the 13 exposed male cases, and none of the eight exposed male controls. Conceivably, an exposure other than EMF that is related to the use of sewing machines and to some of the other EMF-exposed, primarily male, occupations could account for the elevated odds ratios. Some seamstresses, dressmakers, and tailors may have worked in dry cleaning establishments in the United States, where they could have been exposed to solvents such as perchloroethylene. However, we have found no studies indicating that such solvents may be risk factors for Alzheimer's disease or dementia. In addition, clothing repair does not occur at the few drycleaning establishments in Finland. The elevated odds ratio for men engaged in occupations with probable EMF exposure, albeit not statistically significant, also argues somewhat against this idea. The cases with occupations classified as probably having had medium to high EMF exposure had ample opportunity to use electrical equipment. For example, the dressmakers, seamstresses, and tailors probably used electrical sewing machines for many years. First, each of the three clinical series were derived from subjects living in a city. Second, their ages at the end of World War II ranged from 19 years to a maximum of 50 years. The older cases had onset after age 65. They therefore had a minimum of 15 years of work experience prior to retirement. Third, seamstresses, dressmakers, and tailors are likely to continue using sewing machines at home after retirement.

Both women and men may have had significant occupational EMF exposure not identified through job descriptions, some of which were not very informative. For example, a "factory worker," "secretary," "housewife," or "homemaker" may or may not have frequently used electrical equipment. In addition, both women and men may have had significant nonoccupational exposures through hobbies. Many women sew at home as part of their homemaking responsibilities. We counted housewife/homemaker as a low exposure occupation because we had no information about home sewing. However, home sewing machines produce significant magnetic field exposures. In addition, several other home appliances, e.g., hair dryers, electric clocks, electric blankets, and some kitchen equipment such as electric mixers, produce significant magnetic field exposures up to 10^3–10^4 mG (21, 22).

Surrogate respondents were used for cases and for the vascular dementia controls in Finnish series 1. As discussed above, vague descriptions, e.g., "factory worker," led to classification in the low EMF category. Because this lack of detail happened at least as often for cases as for controls, the estimated odds ratios may be somewhat biased downward toward 1.

We are unaware of any other study that has investigated occupations with EMF exposure and Alzheimer's disease. The results of our study are not due to "multiple comparisons." We analyzed Finnish series 1 for only three exposures chosen on substantive grounds before any analyses were performed. Finnish series 2 and the University of Southern California ADRC series were analyzed, only for probable EMF-exposed occupations, after the results for Finnish series 1 were found. The most likely candidate for the putative exposure related to the occurrence of Alzheimer's disease is therefore electromagnetic fields generated by electrical equipment used in occupations.

There are substantive reasons to suspect that EMF may play a role in the etiology of Alzheimer's disease. Calcium ions may play an important role in the development of Alzheimer's disease. An inability of neurons to maintain calcium ion homeostasis can lead to cell death (23, 24). Ca^{2+}/calmodulin-dependent protein kinase has been reported to act on the tau protein to induce abnormalities associated with paired helical filaments (25), which are formed primarily from abnormal aggregations of tau proteins and are an important component of the tangles that are nearly always present in the brains of individuals with Alzheimer's disease.

Alzheimer's disease may be, at least in part, an autoimmune disorder, perhaps initiated by chronic inflammatory processes. Alzheimer's disease plaques have been found to contain monocytes and macrophages, which contribute to inflammatory responses. McGeer and colleagues have suggested that microglial cells, in addition to eliminating dead or disabled neurons, may secrete activated complement proteins that, when activated, can kill normal neurons (26). Additionally, activated microglial cells secrete other neurotoxins, including excitatory amino acids (27) and nitric oxide (28).

Exposure to electromagnetic fields may affect the human immune system and appears to affect calcium ion flux and neuronal biochemistry. Over the past decade, research has generally indicated that exposure to low levels of extremely low-frequency EMF 1) can elicit cellular biochemical changes in vitro (perhaps through Ca^{2+}-regulated activity); 2) might affect immune system function in vivo, either positively or negatively; 3) can cause neural and neuroendocrine system effects in vivo; and 4) can alter DNA transcription (29–36). EMF effects on immune responses to mitogen and antigen have been directly identified in vivo (33). Evidence has accumulated that EMF can alter Ca^{2+} regulation, homeostasis, or membrane-mediated Ca^{2+} signaling processes in immune system cells and neurons (29–31, 37–43). Similar responses have been documented in the neuroendocrine and musculoskeletal systems (29). EMF has been reported to affect biologic reactions regulated by Ca^{2+}/calmodulin (43, 44), although the evidence is mixed (45). In addition, there is evidence that exposure to alternating current and direct current magnetic fields tuned to the third harmonic for calcium ion cyclotron resonance adversely affects the performance of rats in a radial arm maze (46, 47). However, these findings have not been replicated in all attempts (e.g., 31).

EMF exposure may therefore ultimately be implicated in neuronal degeneration. This, in turn, may have important implications with respect to the etiology of Alzheimer's disease.

Breitner et al. (48) have found that use of antiinflammatory medications appears to be protective against Alzheimer's disease onset or progression. We have also found similar results using the Finnish series 1 data set (49). As a working hypothesis, we suggest that EMF exposure may result in the initiation of an inflammatory process that may in part be responsible for creating a cascade of pathologic processes resulting in selective neuronal cell death. An inflammatory process may result, for example, from various parts of the body receiving high levels of EMF exposure, thus activating microglial or other cells that migrate to the brain and initiate attacks on selected neurons. Alternatively, an inflammatory process may result from direct brain tissue exposure to EMF, which disrupts calcium ion homeostasis causing neuronal damage or death. Once initiated, the pathologic process need not require additional EMF exposure for its continuation.

To confirm our findings, larger case-control or historical prospective studies should be undertaken that 1) use population-based cases and matched controls, 2) obtain detailed lifetime occupational histories, 3) estimate occupational and residential lifetime EMF exposures by combining present-day exposure measurements and interview information about past exposures (12, 13), and 4) take into consideration concomitant exposures and conditions that may be confounders.

ACKNOWLEDGMENTS

Supported by National Institute on Aging (NIA) Alzheimer's Disease Research Center grant P50 AG05142, NIA grants R01 AG09238 and R01 AG08567, and a University of Southern California Zumberge award.

The authors thank Tom Trauger for performing the sewing machine measurements.

REFERENCES

1. Katzman R. The prevalence and malignancy of Alzheimer's disease. A major killer. Arch Neurol 1976;33:217–8.
2. Blass JP. Pathophysiology of the Alzheimer's syndrome. Neurology 1993;43(suppl 4):S25–38.
3. McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984;34:939–44.
4. Erkinjuntti T, Wikstrom J, Palo J, et al. Dementia among medical inpatients. Evaluation of 2,000 consecutive admissions. Arch Intern Med 1986;146:1923–6.
5. Erkinjuntti T, Sulkava R, Kovanen J, et al. Suspected dementia: evaluation of 323 consecutive referrals. Acta Neurol Scand 1987;76:359–64.
6. Erkinjuntti T. Differential diagnosis between Alzheimer's disease and vascular dementia: evaluation of common clinical methods. Acta Neurol Scand 1987;76:433–42.
7. Erkinjuntti T, Haltia M, Palo J, et al. Accuracy of the clinical diagnosis of vascular dementia: a prospective clinical and post-mortem neuropathological study. J Neurol Neurosurg Psychiatry 1988;51:1037–44.
8. Roth M. The natural history of mental disorder in old age. J Ment Sci 1955;101:281–301.
9. Roth M, Myers DH. The diagnosis of dementia. Br J Psychiatry 1975;9:87–99.
10. Sulkava R, Haltia M, Paetau A, et al. Accuracy of clinical diagnosis in primary degenerative dementia: correlation with neuropathological findings. J Neurol Neurosurg Psychiatry 1983;46:9–13.
11. Milham S Jr. Mortality from leukemia in workers exposed to electrical and magnetic fields. (Letter). N Engl J Med 1982; 307:249.
12. Bowman JD, Sobel E, London SJ, et al. Electric and magnetic field exposures and leukemia risk in "electrical" occupations. Electric Power Research Institute Contract RP 799–27, 1992.
13. London SJ, Bowman JD, Sobel E, et al. Exposure to magnetic fields among electrical workers in relation to leukemia risk in Los Angeles County. Am J Indust Med 1994;26:47–60.
14. Wu D, Ren J, Gandhi OP. Currents induced in the arm and the body by the magnetic fields of an electric hand drill. In: Abstracts of the 15th Annual Meeting of the Bioelectromagnetics Society, Los Angeles, CA, 1993:31.
15. Breteler MMB, Claus JJ, Cornelia M, et al. Epidemiology of Alzheimer's disease. Epidemiol Rev 1992;14:59–82.
16. Stern Y, Gurland B, Tatemichi TK, et al. Influence of education and occupation on the incidence of Alzheimer's disease. JAMA 1994;271:1004–10.
17. Katzman R. Education and the prevalence of dementia and Alzheimer's disease. Neurology 1993;43:13–20.
18. Fratiglioni L. Epidemiology of Alzheimer's disease. Issues of etiology and validity. Acta Neurol Scand 1993;145(suppl): 1–70.
19. Bruun K. Social groups. Helsinki, Finland: Statistical Office of Helsinki, 1954.
20. Breslow NE, Day NE, eds. Statistical methods in cancer research. Vol 1. The analysis of case-control studies. (IARC scientific publication no. 32). Lyon: International Agency for Research on Cancer, 1980.
21. Wilson B, Lovely R, Davis K, et al. Magnetic field flux density and spectral characteristics of personal appliances. In: Abstracts of the 15th Annual Meeting of the Bioelectromagnetics Society, Los Angeles, CA, 1993:32.
22. Zhang J, Morgan MG, Nair I. Effects function simulation of residential appliance field exposures. Abstracts of the 15th Annual Meeting of the Bioelectromagnetics Society, Los Angeles, CA, 1993:35.
23. Mattson MP, Lovell MA, Ehmann WD, et al. Comparison of the effects of elevated intracellular aluminum and calcium levels on neuronal survival and tau immunoreactivity. Brain Res 1993;602:21–31.
24. Mattson MP, Cheng B, Culwell AR, et al. Evidence for excitoprotective and intraneuronal calcium-regulating roles for secreted forms of the β-amyloid precursor protein. Neuron 1993;10:243–54.
25. Baudier J, Cole RD. Phosphorylation of tau proteins to a state like that in Alzheimer's brain is catalyzed by a calcium/calmodulin-dependent kinase and modulated by phospholipids. J Biol Chem 1987;36:17577–83.
26. McGeer PL, Kawamata I, Walker DG, et al. Microglia degenerative neurological disease. Glia 1993;7:84–92.
27. Piani D, Spranger M, Frei K, et al. Macrophage-induced cytotoxicity of N-methyl-D-aspartate receptor positive neurons involves excitatory amino acids rather than reactive oxygen intermediates and cytokines. Eur J Immunol 1992;22; 2429–36.
28. Boje KM, Arora PK. Microglial-produced nitric oxide and reactive nitrogen oxide mediate neuronal cell death. Brain Res 1992;587:250–6.
29. Walleczek J. Electromagnetic field effects on cells of the immune system: the role of calcium signaling. FASEB J 1992;6:3177–85.
30. Bierbaum PJ, Peters JM, eds. Proceedings of the Scientific workshop on the health effects of electric and magnetic fields on workers. Cincinnati, OH: National Institute for Occupational Health and Safety, 1991. (DHHS (NIOSH) report no. 91–111).
31. Oak Ridge Associated Universities Panel. Health effects of low-frequency electric and magnetic fields. Oak Ridge, TN: Oak Ridge Associated Universities, 1992. (Oak Ridge Associated Universities (ORAU) report no. 92/F8).
32. Cleary SF. A review of in vitro studies: low-frequency electromagnetic fields. Am Ind Hyg Assoc J 1993;54:178–85.
33. Anderson LE. Biological effects of extremely low-frequency electromagnetic fields: in vivo studies. Am Ind Hyg Assoc J 1993;54:186–96.
34. Lai H, Carino MA, Horita A, et al. Effects of a 60 Hz magnetic field on central cholinergic systems of the rat. Bioelectromagnetics 1993;14:5–15.
35. Cavopol AV, McLean MJ, Holcomb RR. Explanatory mechanism for blockade of action potentials in neural cells by external magnetic field. In: Abstracts of the 15th Annual Meeting of the Bioelectromagnetics Society, Los Angeles, CA, 1993:10.
36. McCoy SL, Freed AC, Ogden BE, et al. Reduction of in vitro production of the immunoregulatory cytokine interleukin-1 in sheep exposed to whole body EMF. In: Project abstracts of the Annual Review of Research on Biological Effects of Electric and Magnetic Fields from the Generation, Delivery, and Use of Electricity, Savannah, GA, 1993:77.
37. Walleczek J, Liburdy RP. Nonthermal 60 Hz sinusoidal magnetic-field exposure enhances $^{45}Ca^{2+}$ uptake in rat thymocytes: dependence on mitogen activation. FEBS Lett 1990;271:157–60.

38. Liburdy RP. Calcium signaling in lymphocytes and ELF fields: evidence for an electric field metric and a site of interaction involving the calcium ion channel. FEBS Lett 1992;301:53–9.
39. Yost MG, Liburdy RP. Time-varying and static magnetic fields act in combination to alter calcium signal transduction in the lymphocyte. FEBS Lett 1992;296·117–22.
40. Walleczek J, Budinger TF. Pulsed magnetic field effects on calcium signaling in lymphocytes: dependence on cell status and field intensity. FEBS Lett 1992;314:351–5.
41. Liburdy RP, Callahan DE, Harland J, et al. Experimental evidence for 60 Hz magnetic fields operating through the signal transduction cascade. FEBS Lett 1993;334:301–8.
42. Lindstrom E, Lindstrom P, Berglund A, et al. Intracellular calcium oscillations induced in a T-cell line by a weak 50 Hz magnetic field. J Cell Physiol 1993;156:395–8.
43. Shuvalova LA, Ostrovskaya MV, Sosunov EA, et al. The influence of a weak magnetic field under parametric resonance conditions on the speed of calmodulin dependent phosphorylation of myosin in solution. Proc Acad Sci USSR 1991,317: 1–6.
44. Markov MS, Ryaby JT, Kaufman JJ, et al. Extremely weak ac and dc magnetic fields significantly affect myosin phosphorylation. In: Allen MJ, Cleary SF, Sowers AE, et al, eds. Charge and field effects in biosystems. Vol. 3. Boston, MA: Birkhauser, 1992:225–30.
45. Hendee S, Christensen DA, Blumenthal DK, et al. Do weak low-frequency electromagnetic fields have cyclotron resonance effects on calcium/calmodulin interactions with myosin light chain kinase? Abstracts of the 15th Annual Meeting of the Bioelectromagnetics Society, Los Angeles, CA, 1993:19.
46. Lovely RH, Creim JHA, Miller DL, et al. Behavior of rats in a radial arm maze during exposure to magnetic fields: a test for artifact. Abstracts of the 15th Annual Meeting of the Bioelectromagnetics Society, Los Angeles, CA, 1993:64–5.
47. Lai H, Horita A, Guy AW. Neural mechanisms involved in microwave-induced deficit in radial-arm maze performance. Abstracts of the 15th Annual Meeting of the Bioelectromagnetics Society, Los Angeles, CA, 1993:64.
48. Breitner JCS, Gau BA, Welsh KA, et al. Inverse association of anti-inflammatory treatments and Alzheimer's disease: initial results of a co-twin control study. Neurology 1994;44:227–32.
49. Sulkava R, Sobel E, Davanipour Z, et al. Use of anti-inflammatory drugs may protect against Alzheimer's disease. Ann Neurol 1994;36:310–1.