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Persistent organochlorine pesticides in serum and risk of Parkinson disease

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ABSTRACT

Background: Pesticides have been implicated as likely environmental risk factors for Parkinson disease (PD), but assessment of past exposure to pesticides can be difficult. No prior studies of pesticide exposure and PD used biomarkers of exposure collected before the onset of PD. Our investigation examined the association between prospective serum biomarkers of organochlorine pesticides and PD.

Methods: We conducted a nested case-control study within the Finnish Mobile Clinic Health Examination Survey, with serum samples collected during 1968–1972, and analyzed in 2005–2007 for organochlorine pesticides. Incident PD cases were identified through the Social Insurance Institution's nationwide registry and were confirmed by review of medical records (n = 101). Controls (n = 349) were matched for age, sex, municipality, and vital status. Adjusted odds ratios (ORs) of PD were estimated using logistic regression.

Results: Little association emerged with a summary score of the 5 organochlorine pesticides found at high levels, and only increasing dieldrin concentrations trended toward a higher risk of PD (OR per interquartile range [IQR] 1.28, 95% confidence interval [CI] 0.97–1.69, $p = 0.08$). Because of possible strong confounding by cigarette smoking among smokers, we ran additional analyses restricted to never smokers (n = 68 cases, 183 controls). In these analyses, increasing dieldrin concentrations were associated with increased odds of PD (OR per IQR 1.95, 95% CI 1.26–3.02, $p = 0.003$). None of the other organochlorine pesticides were associated with PD in these analyses.

Conclusions: These results provide some support for an increased risk of Parkinson disease with exposure to dieldrin, but chance or exposure correlation with other less persistent pesticides could contribute to our findings. ***Neurology*® 2010;74:1055–1061**

GLOSSARY

AHS = Agricultural Health Study\'3b; **β-HCH** = β-hexachlorocyclohexane; **BMI** = body mass index; **CI** = confidence interval; **2-4-D** = 2,4-dichlorophenoxyacetic acid; **FMC** = Finnish Mobile Clinic Health Examination Survey; **HCB** = hexachlorobenzene; **IQR** = interquartile range; **MPP+** = 1-methyl-4-phenylpyridinium; **MPTP** = 1-methyl,-4-phenyl-1,2,3,6-tetrahydropyridine; **NHANES** = US National Health and Nutrition Examination Survey; **OR** = odds ratio; **PCB** = polychlorinated biphenyl; **PD** = Parkinson disease; **p,p′-DDD** = p,p′-dichloro-diphenyl-dichloroethane; **p,p′-DDE** = p,p′-dichloro-diphenyl-dichloroethylene; **p,p′-DDT** = p,p′-dichloro-diphenyl-trichloroethane; **SSI** = Social Insurance Institution; **2,4,5-T** = 2,4,5-trichlorophenoxyacetic acid.

Pesticides have been implicated as one of the most likely major environmental risk factors for Parkinson disease (PD).[1-3] The potential link with pesticides has been a particular focus because of the known neurotoxic properties of many pesticides as well as structural similarity between the neurotoxin 1-methyl-4-phenylpyridinium (MPP+)—a metabolite of 1-methyl,-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)—and the herbicides cyperquat and paraquat. Assessment of exposure to pesticides, however, can be difficult, particularly given that the relevant exposure window is possibly before the onset of PD. Such exposure is often self-reported or reconstructed based on work histories. No prior studies of pesticide exposures and PD have examined biomarkers of exposure

Supplemental data at www.neurology.org

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collected many years before the onset of PD. Two major obstacles to such a study are the availability of such samples and the nonpersistence of many types of pesticides. To overcome these obstacles, we examined the association between the persistent organochlorine pesticides and PD in the Finnish Mobile Clinic cohort, from which serum samples were collected from 1968 to 1972 and stored.

METHODS

Study population. The Finnish Mobile Clinic Health Examination Survey (FMC) was performed in Finland during 1966–1972. Total populations in certain rural, semiurban, and industrial communities or random samples of them, comprising 62,440 adults aged 15 years or more, were invited to take part in the study. The participation rate was 82.5%.[4] At baseline, participants filled out a questionnaire and, for those recruited after June 15, 1968, blood samples were drawn (n = 40,221), from which hematocrit and serum cholesterol determinations were performed. Serum samples were stored frozen at −20°C. Cases and controls were selected from all participants without PD or psychosis who were aged 20–79 years at baseline. During follow-up to the end of 1994, 196 incident PD cases were identified. We randomly selected up to 2 controls per case among eligible participants who did not have PD and were alive at the time of the PD diagnosis of their matched case. The controls were individually matched for age, sex, vital status, and municipality, which also controls for the time of baseline examination and for the duration of serum sample storage because a given municipality was visited over a restricted time period.[4] Serum samples were thawed and analyzed for organochlorine pesticides in 2005–2007. The research was approved by the human subjects committee of the Harvard School of Public Health.

Case ascertainment. Cases (*International Classification of Diseases, Tenth Revision* code G20) were identified through the Finnish nationwide registry of the Social Insurance Institution (SSI) of patients receiving medication reimbursement, using the unique social security codes given to all citizens living in Finland. All people in Finland with certain chronic disease, including PD, are eligible for free drug treatment. To get PD drug reimbursement, patients must provide a certificate written by the treating neurologist stating that all the diagnostic criteria for PD are met. This certificate must include symptom history and reports of clinical findings, including the presence of resting tremor, bradykinesia, or muscle rigidity. An SSI neurologist must agree with the diagnosis as described on the certificate for medication costs to be reimbursed. The medication allowance is not granted for patients with, for example, essential tremor, intention tremor, or parkinsonism caused by neuroleptics. Of 196 PD cases identified by this method, the certificates for PD drug reimbursement and selected hospital records of 126 patients were reevaluated retrospectively by our study neurologist (J.L.) according to the National Institute of Neurological Disorders and Stroke diagnostic criteria for PD[5,6] and blinded to serum organochlorine pesticide concentrations. Neuropathologic data to confirm the diagnosis as definite was not available in any of the cases. Patients meeting the specified criteria for diagnostic confidence levels of both possible and probable PD were included. Cases either not meeting these criteria or with clinical features suggesting an alternative diagnosis were excluded. Of the 126 originally identified PD cases reviewed, 101 (80%) met criteria for PD, consistent with other estimates of the percentage of people clinically diagnosed with Parkinsonism in a general population that meet strict PD criteria.[7] The 25 originally identified PD cases excluded on neurologist's review were excluded from all analysis. The 70 cases we did not review were included in supplementary analyses.

Assessment of exposure. Organochlorine pesticides analyses were performed by the Harvard School of Public Health Organic Chemistry Laboratory. Serum samples were sent and analyzed in groups of 2 or 3—matched sets of a case and matched control(s)—and laboratory personnel were blind to case-control status. The analytic method used for chlorinated pesticide analysis used gas chromatography with internal standards as previously described,[8] except for an additional step of eluting more polar pesticides from a silica-gel column with a mixture of hexane/dichloromethane (9:1). Final results were reported after subtracting the amount of the analyte measured in the procedural blank associated with the analytic batch. Mean procedural blank concentrations of all organochlorine pesticides were below 0.02 ng/g, except dieldrin (0.03 ng/g). The mean (SD) recovery of all organochlorine pesticides in matrix spikes was 93% (9%). The mean (SD) recovery of the polychlorinated biphenyl (PCB) #30 surrogate in all samples was 91% (5%), and that for the PCB#204 surrogate was 85% (5%). The results for organochlorine pesticides in standard reference material (SRM1589a from National Institute of Standards and Technology, *Aroclor 1260 in Human Serum*) were all within 10% of the certified or assigned value ranges. Twenty samples were run blinded in triplicate, and the coefficients of variation of the 5 abundant organochlorine pesticides (dieldrin, β-hexachlorocyclohexane [β-HCH], hexachlorobenzene [HCB], p,p'-dichloro-diphenyl-trichloroethane [p,p'-DDT], and p,p'-dichloro-diphenyl-dichloroethylene [p,p'-DDE]) ranged from 3% (HCB) to 15% (dieldrin). Serum lipid content was determined from enzymatic measurements of total cholesterol and triglycerides using the Phillips formula.[9]

Statistical analyses. Since several originally identified cases were excluded because the diagnosis could not be confirmed, to include all controls we used unconditional logistic regression with adjustment for matching factors (age, sex, and region) to estimate odds ratios (ORs) of PD, and their 95% confidence intervals (CIs). Including all controls improves the precision of estimates and the adjustment for matching factors minimizes the bias toward the null that can arise when analyzing matched data with unconditional logistic regression.[10,11] Results with conditional logistic regression were virtually identical to those with unconditional logistic regression, but with wider CIs, confirming that little bias was introduced from using unconditional methods. We treated serum levels of organochlorine pesticides as either continuous or categorized into quintiles defined among controls. In each case, organochlorine pesticide levels were assessed on a per gram serum lipid basis. A summary measure was calculated by first averaging the z scores of the DDT metabolites p,p'-DDT, p,p'-DDE, o,p'-DDT, o,p'-DDE, and p,p'-dichloro-diphenyl-dichloroethane (p,p'-DDD) and then averaging the z scores of β-HCH, HCB, dieldrin, and the DDT average. Additional covariates included cigarette smoking (never, past, current, cigar/pipe only), and body mass index (BMI; kg/m^2) from the baseline questionnaire. Because expressing organochlorine pesticide concentrations on a per lipid basis induces a correlation between that measure and lipids, to control for possible confounding by lipids, models were additionally adjusted for total serum cholesterol and serum triglycerides. Multiplicative terms were included in the models to assess interactions. All p

Table 1 Distribution of organochlorine pesticide serum concentrations (ng/g lipid) among controls in the FMC, 1968–1972, and the NHANES for persons aged 20 years and older, 2001–2002[a]

	FMC				NHANES[12]	
Organochlorine pesticide	Geometric mean	Mean (SD)	Median (IQR)	90th percentile[b]	Geometric mean	90th percentile[b]
HCB	46.7	56.6 (51.6)	47.5 (33.0–68.5)	93.8	[c]	<31.4
b-HCH	90.1	99.1 (43.8)	90.7 (69.8–120.5)	152.5	[c]	25.5
p,p′-DDT	257.9	294.6 (155.5)	265.4 (191.8–359.4)	491.6	[c]	<17.4
p,p′-DDE	1,087	1,324 (865)	1,143 (787–1,676)	2,417	338	1,470
Dieldrin	39.6	45.8 (26.9)	40.0 (27.3–55.5)	78.7	[c]	16.4
Mirex	1.0	1.2 (0.9)	1.0 (0.6–1.5)	2.2	[c]	19.6
Heptachlor epoxide	3.0	3.7 (3.9)	2.8 (1.3–4.9)	7.2	[c]	15.7
Oxychlordane	5.6	7.4 (7.6)	5.7 (3.6–9.1)	13.3	12.9	38.4
Transnonachlor	11.5	13.5 (10.1)	11.4 (8.3–15.6)	21.8	19.8	60.6

Abbreviations: β-HCH = β-hexachlorocyclohexane; FMC = Finnish Mobile Clinic; HCB = hexachlorobenzene; IQR = interquartile range; NHANES = US National Health and Nutrition Examination Survey; p,p′-DDE = p,p′-dichloro-diphenyl-dichloroethylene; p,p′-DDT = p,p′-dichloro-diphenyl-trichloroethane.
[a]Aldrin was detectable in only 11.5% of control samples (12.9% among cases), and heptachlor was detectable in only 16.6% (15.8% among cases).
[b]We show 90th percentiles because at lower cutoffs many of these compounds were below the limit of detection in NHANES.
[c]More than 40% of samples were below the limit of detection; thus, the geometric mean was not calculated.

values are 2-sided. Analyses were conducted with SAS software, version 9 (SAS Institute, Inc., Cary, NC).

Standard protocol approvals, registrations, and patient consents. This study was approved by the Human Research Committee of the Harvard School of Public Health and the National Public Health Institute of Finland.

RESULTS β-HCH, p,p′-DDT, p,p′-DDE, HCB, and dieldrin concentrations were much higher in the FMC than in the 2001–2002 US National Health and Nutrition Examination Survey (NHANES),[12] whereas mirex, heptachlor epoxide, transnonachlor, and oxychlordane were not (table 1). Therefore, in what follows we focus on the 5 pesticides found at high levels. Distributions of covariates among all cases, confirmed cases, and controls are shown in table 2. Slight variations in matching factors between confirmed cases and controls are the result of some of the originally selected cases being deemed not PD on further review and excluded, whereas their controls were kept. Distributions of organochlorine pesticide concentrations among controls by region, sex, and smoking are shown in table 3. Both age and BMI generally correlated only weakly with the pesticides (Spearman coefficients from −0.19 to 0.17; table e-1 on the *Neurology*® Web site at www.neurology.org). The correlations among pesticides ranged from 0.22 to 0.40, except for DDE and DDT, which were much more highly correlated as expected, given that DDE is a metabolite of DDT.

In adjusted analyses, little association emerged with any pesticide, except possibly dieldrin (table 4). Cigarette smoking, however, is strongly associated with reduced risk of PD, and higher organochlorine pesticides exposure can be associated with smoking (possibly from pesticides in the cigarettes themselves, from increased hand-to-mouth activity or biochemical effects).[13,14] This is borne out in our study population among whom the OR for being a smoker for each interquartile increase in, for example, dieldrin was 1.41 (95% CI 1.15–1.73, $p = 0.001$). Therefore, we ran additional analyses restricted to never smokers to avoid any residual confounding among the smokers. In these analyses, only dieldrin was associated with increased odds of PD ($p = 0.003$; table 4) at a level that meets the Bonferroni-corrected level of significance (0.0033) for 15 parameters (5 pesticides, 3 models each; table 4). Results were somewhat muted when analyses were not restricted to cases confirmed on our rereview of records. All of the results for dieldrin were considerably stronger among those older than the median age of 66 years (table 4). In contrast, results for the other pesticides did not differ much in the older group. There was considerable correlation between smoking and sex: 74% of nonsmokers were women. Thus, results among nonsmokers could reflect an effect of sex rather than smoking. The interaction between smoking (ever/never) and dieldrin concentration, however, was stronger ($p = 0.06$) than the interaction between sex and dieldrin ($p = 0.78$).

The association with dieldrin showed a similar pattern when analyzing by quintile of dieldrin con-

Table 2 Baseline characteristics by case-control status

	All cases (n = 171)	Confirmed cases (n = 101)	Controls (n = 349)
Age, mean (SD), y	53.7 (10.2)	49.7 (9.9)	52.8 (10.4)
Years to PD diagnosis, mean (SD)	22 (4)	16 (6)	—
BMI, mean (SD)	26.9 (3.8)	26.7 (3.8)	26.0 (3.8)
SBP, mean (SD)	151.1 (24.6)	144 (19)	147.1 (24.9)
DBP, mean (SD)	85.8 (12.4)	84 (11)	82.9 (11.8)
Serum cholesterol, mean (SD)	268 (49)	264 (51)	271 (52)
Serum triglycerides, mean (SD)	133 (62)	124 (50)	135 (71)
Male, n (%)	88 (51.5)	47 (46.5)	192 (55.0)
Cigarette smoking, n (%)			
Never	109 (63.7)	68 (67.3)	183 (52.4)
Past	33 (19.3)	17 (16.8)	59 (16.9)
Current	28 (16.4)	16 (15.8)	96 (27.5)
Cigar/pipe only	1 (0.6)	0 (0)	11 (3.2)
Hypertension, n (%)			
Normal	49 (28.8)	39 (38.6)	137 (39.3)
Borderline	85 (50.0)	47 (46.5)	163 (46.7)
Mild	11 (6.5)	6 (5.9)	12 (3.4)
Definite	25 (14.7)	9 (8.9)	37 (10.6)
Region, n (%)			
Southwestern	18 (10.5)	10 (9.9)	43 (12.3)
Southern	34 (19.9)	14 (13.9)	71 (20.3)
Central	18 (10.5)	13 (12.9)	30 (8.6)
Western	14 (8.2)	8 (7.9)	32 (9.2)
Eastern	57 (33.3)	35 (34.7)	106 (30.4)
Northern	30 (17.5)	21 (20.8)	67 (19.2)
Farmers, n (%)	19 (11.3)	10 (9.9)	37 (10.6)
HCB, median (IQR), ng/g lipid	45.5 (30.8–66.9)	45.0 (29.9–65.1)	47.5 (33.0–68.5)
β-HCH, median (IQR), ng/g lipid	84.1 (64.5–114.1)	81.3 (65.4–112.6)	90.7 (69.8–120.5)
p,p′-DDT, median (IQR), ng/g lipid	255.8 (170.4–330.3)	246.9 (156.5–327.9)	265.4 (191.8–359.4)
p,p′-DDE, median (IQR), ng/g lipid	1,046 (704–1,469)	992 (671–1,422)	1,143 (787–1,676)
Dieldrin, median (IQR), ng/g lipid	38.8 (27.9–53.0)	38.8 (28.6–55.4)	40.0 (27.3–55.5)

Abbreviations: β-HCH = β-hexachlorocyclohexane; BMI = body mass index; DBP = diastolic blood pressure; HCB = hexachlorobenzene; IQR = interquartile range; PD = Parkinson disease; p,p′-DDE = p,p′-dichloro-diphenyl-dichloroethylene; p,p′-DDT = p,p′-dichloro-diphenyl-trichloroethane; SBP = systolic blood pressure.

centration (table e-2). The OR for PD for the highest quintile compared with the lowest among never smokers was 2.42 (95% CI 0.91–6.47). Results analyzing organochlorines on a per sample weight rather than lipid basis were similar, although in those analyses the OR for PD among all confirmed cases and adjusted for smoking reached statistical significance (OR 1.33, 95% CI 1.00–1.77, $p = 0.05$). Results were also similar when analyzed separately in groups split by follow-up time at the median of years to PD diagnosis (16 years). There was no association with the summary score of exposure to the pesticides.

DISCUSSION In this large nested case-control study with biomarkers of organochlorine pesticide exposure collected prospectively some 2 decades before disease, we found little evidence for increased odds of PD with increasing serum organochlorines, except for dieldrin. The association between dieldrin and increased odds of PD was strongest in analyses restricted to never smokers, possibly because of strong residual confounding by cigarette smoking among the smokers, biasing the OR down. Although we cannot rule out differences by sex, this did not seem to drive the results among never smokers because the interaction between dieldrin and smoking was more significant than that between dieldrin and sex. The association with dieldrin was also much stronger among the older half of our study subjects. This is consistent with the theory that genetic factors play a greater role in earlier-onset PD,[15] and also with another recent study implicating organochlorine exposure in PD risk.[16] The association with dieldrin was independent of age, BMI, sex, region, serum cholesterol, and triglycerides.

Organochlorine pesticides have been implicated in the development of PD,[1,3] although there are no human studies with prospective biomarkers of exposure. Based on chemical properties, toxicokinetics, and use patterns, a recent review concluded that the cyclodienes—of which dieldrin, but not the others we analyzed, is one—are among the more likely candidates to contribute to the development of PD.[3] Dieldrin has perhaps the best documented toxicity on dopaminergic cells, including the generation of oxygen radicals, aggregation and fibrillation of α-synuclein, disruption of the ubiquitin-proteasome system and the mitochondrial membrane potential, induction of dopamine release leading to intracellular dopamine depletion, and activation of caspases.[17,18] Mice exposed to dieldrin show many pathologic effects similar to those seen in PD, such as increased oxidative stress, increased α-synuclein expression, and altered dopamine homeostasis.[19] Although dopamine neurons seem to be particularly vulnerable to dieldrin neurotoxicity,[17] the exposure does not seem to lead to dopaminergic cell loss or motor deficits characteristic of PD. In a few small studies, dieldrin has been found at higher levels in postmortem PD brains than in those of age-matched controls.[20-22] However, the same studies identified several other organochlorine pesticides present at higher levels in postmortem PD brains, including

Table 3 Geometric mean concentrations (ng/g lipids) of select organochlorine pesticides by and adjusted for[a] population characteristics among controls in the Finnish Mobile Clinic, 1968–1972

	n (%)	HCB	β-HCH	p,p′-DDT	p,p′-DDE	Dieldrin
Region of Finland						
Eastern	106 (30)	32.6	76.9	188	735	29.9
Central	30 (9)	64.3[b]	111.1[b]	279[b]	969[e]	50.9[b]
Northern	67 (19)	41.0[e]	87.9	269[b]	1,101[b]	37.1[d]
Southern	71 (20)	45.9[c]	86.1	243[c]	890[d]	33.0
Southwestern	43 (12)	61.0[b]	99.6[d]	315[b]	1,259[b]	39.0[d]
Western	32 (9)	39.1	78.6	186	676	31.4
Cigarette smoking						
Never	183 (52)	32.6	76.9	188	735	29.9
Past	59 (17)	36.4	70.8	188	818	37.1[e]
Current	96 (28)	35.7	80.5	253[b]	990[d]	38.6[d]
Cigar/pipe only	11 (3)	32.6	77.0	200	829	37.0
Sex						
Female	157 (45)	32.6	76.9	188	735	29.9
Male	192 (55)	37.2	84.1	202	904[e]	31.2
Farmer						
No	311 (89)	32.6	76.9	188	735	29.9
Yes	37 (11)	32.5	69.1	168	694	26.9
Percent change per 10 y of age	349 (100)	−7.2[e]	2.2	−5.2[e]	−6.8[e]	3.5
Percent increase per unit BMI	349 (100)	−1.4	−0.5	1.7[e]	−1.3	2.4[d]

Abbreviations: β-HCH = β-hexachlorocyclohexane; BMI = body mass index; HCB = hexachlorobenzene; p,p′-DDE = p,p′-dichloro-diphenyl-dichloroethylene; p,p′-DDT = p,p′-dichloro-diphenyl-trichloroethane.

[a]Mean can be interpreted as that for a 50-year-old female with BMI = 26, never smoker, from Eastern Finland who is not a farmer, except for the variations on those characteristics as indicated by the row of the table.

Significance of difference from reference category (first row of each variable) or of the term (age and BMI): [b]$p < 0.0001$; [c]$p < 0.001$; [d]$p < 0.01$; [e]$p < 0.05$.

p,p'-DDT and p,p'-DDE, for which we saw no association with PD. DDT and DDE can have dopaminergic effects in vitro, but they seem to be less toxic—at least in mice—to the dopaminergic system than dieldrin, and exposure in mice does not seem to produce nigrostriatal damage or behavioral abnormalities.[23] There is no data linking the fungicide HCB to PD.

Several studies have used self-reported exposure to pesticides or estimates from occupational histories and found associations between PD and exposure to organochlorine pesticides as a class[16,24,25] or, in a recent study, the specific organochlorine herbicide 2,4-dichlorophenoxyacetic acid (2–4-D).[26] In the Agricultural Health Study (AHS), no association with 2–4-D was found, but one was found with the related 2,4,5-trichlorophenoxyacetic acid (2,4,5-T).[27] In a recent study in France, phenoxy compounds were associated with PD, although this only reached statistical significance among men older than 65 years.[16] In the AHS, there was no association between PD and either DDT or dieldrin,[27] nor was there with self-reported DDT in a previous study in Finland.[28] Only 3 studies, all case-control, have examined serum organochlorine levels in relation to PD, all with samples collected several years after PD onset.[29-31] Two of these found statistically significant increases in odds of PD with higher serum β-HCH concentrations,[30,31] whereas the other found a significant association with DDE.[29] In only 1 of these did they report on dieldrin,[31] but all subjects had nondetectable levels.

The exposure profile of FMC participants, in comparison with more recent NHANES data, suggests that chlordane and heptachlor—of which oxychlordane, transnonachlor, and heptachlor epoxide are more persistent metabolites—were not widespread in Finland at the time of FMC blood collection, which is consistent with pesticides sales data.[32,33] Mirex concentrations were even lower in FMC samples compared with NHANES, consistent with no known use of mirex in Finland, whereas mirex was used in the United States until its ban in 1978.[32,34] In contrast, the other organochlorine pesticides analyzed were at levels much higher than the NHANES data. This is consistent with the fact that FMC blood was collected before bans on these pesticides in Finland, whereas NHANES samples were collected many years after use stopped in the United States.[35-37] The lack of association with age in FMC data is likely largely the result of FMC blood collection having occurred at most approximately 3 decades after the introduction of the pesticides into commercial use. Given the average age of FMC participants at baseline (53 years, SD 10 years), most FMC participants would have had the same number of years of exposure to the pesticides regardless of their age. The majority of organochlorine pesticides sales in Finland between 1953 and 1972 went toward use in households, warehouses, and shelters for domestic animals,[33] which may partially account for why farmers did not necessarily have higher serum levels of these compounds. Because of this, the pattern of exposures (e.g., frequency of use, dose, other chemicals used concurrently) in our setting may differ from settings where the pesticide exposures are more driven by farming use patterns.

An important limitation to our study is that, although organochlorine pesticides are persistent and therefore serum levels are a reasonable biomarker for past cumulative exposure, ours were 1-time measures decades before disease. Variations in exposure to the different pesticides after FMC blood collection are not captured and could introduce measurement error to the extent that past exposures do not predict future exposures. This possible misclassification is least likely for dieldrin because dieldrin use was banned in Finland in 1969 (except for some later use for wood preserva-

Table 4 Multivariate adjusted[a] odds ratio for Parkinson disease per interquartile range increase[b] in organochlorine pesticide concentration (ng/g lipid)[c]

Pesticide	OR (95% CI) per IQR	*p* Value	OR (95% CI) per IQR over age 66 y	*p* Value
Dieldrin				
Confirmed cases only	1.28 (0.97–1.69)	0.08	1.69 (1.19–2.39)	0.003
Confirmed cases, never smokers	1.95 (1.26–3.02)	0.003	2.55 (1.48–4.39)	0.0008
All cases, never smokers	1.23 (0.85–1.78)	0.28	1.42 (0.93–2.18)	0.11
HCB				
Confirmed cases only	0.94 (0.69–1.29)	0.71	0.81 (0.48–1.37)	0.43
Confirmed cases, never smokers	0.96 (0.62–1.50)	0.87	0.83 (0.44–1.57)	0.56
All cases, never smokers	1.12 (0.91–1.38)	0.27	1.00 (0.67–1.50)	1.0
β-HCH				
Confirmed cases only	0.79 (0.57–1.10)	0.16	0.70 (0.45–1.11)	0.11
Confirmed cases, never smokers	0.68 (0.45–1.04)	0.07	0.62 (0.37–1.04)	0.07
All cases, never smokers	0.83 (0.61–1.13)	0.24	0.86 (0.60–1.22)	0.40
p,p′-DDT				
Confirmed cases only	0.92 (0.55–1.51)	0.73	1.06 (0.56–1.98)	0.87
Confirmed cases, never smokers	0.77 (0.41–1.46)	0.42	0.91 (0.43–1.91)	0.79
All cases, never smokers	0.91 (0.57–1.48)	0.71	1.14 (0.66–1.94)	0.64
p,p′-DDE				
Confirmed cases only	0.70 (0.41–1.20)	0.20	0.71 (0.36–1.38)	0.31
Confirmed cases, never smokers	0.78 (0.38–1.62)	0.51	0.75 (0.31–1.81)	0.53
All cases, never smokers	0.82 (0.47–1.41)	0.47	0.72 (0.37–1.40)	0.34

Abbreviations: β-HCH = β-hexachlorocyclohexane; CI = confidence interval; HCB = hexachlorobenzene; IQR = interquartile range; OR = odds ratio; p,p′-DDE = p,p′-dichloro-diphenyl-dichloroethylene; p,p′-DDT = p,p′-dichloro-diphenyl-trichloroethane.
[a]Adjusted for age, sex, region, smoking, triglycerides, cholesterol, and the other pesticides.
[b]IQR (ng/g lipid): dieldrin, 28.2; HCB, 35.5; β-HCH, 50.7; p,p′-DDT, 167.6; p,p′-DDE, 889.
[c]The numbers of cases/controls are 101/349 for the confirmed case only analyses, 68/183 for confirmed case never smokers analyses, and 109/183 for all case never smokers analyses.

tion).[32,38] Thus, our measures of blood levels in 1968–1972 should closely reflect total exposure because there was little exposure possibility after that time. This would also apply, although to slightly lesser degrees, to DDT and DDE (DDT was banned in 1976), β-HCH (registered use as a pesticide cancelled in 1977), and HCB (use ceased on a voluntary basis in 1977).[38] We also did not have follow-up data on confounders. Unmeasured confounding by cigarette smoking is unlikely to explain our positive findings, however, first because the bias in baseline data from cigarette smoking was against our results, and second because our significant findings were found in analyses restricted to never smokers. The majority of smokers take up smoking at early ages; thus, there would be few never smokers at baseline who later started smoking.

We were limited to examining persistent compounds because of the long time between blood collection and analysis. Some less persistent pesticides have been implicated in the development of PD, such as paraquat, rotenone, and maneb[1,3,39]; hence, we cannot rule out the possibility that our dieldrin results stem from exposure correlations with these other compounds. Finally, our PD case definition could not involve physical examination. Instead, we relied on reports from the treating neurologist submitted for the patient to obtain reimbursement for PD medications. In addition, our study neurologist rereviewed these files to further confirm the cases. Although some diagnostic misclassification may have occurred, error from this source is probably modest; recent clinicopathologic studies show approximately 90% accuracy of clinical PD diagnosis made by neurologists.[40] Furthermore, diagnostic errors are probably unrelated to serum organochlorine pesticide concentration, and would thus tend to attenuate any true association. Last, although the results are restricted to the Finnish population, we have no reason to expect that the results would not apply to other similarly exposed populations.

AUTHOR CONTRIBUTIONS

Statistical analyses were conducted by M.G. Weisskopf.

DISCLOSURE

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