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Occupational pesticide exposure and screening tests for neurodegenerative disease among an elderly population in Costa Rica ☆

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ABSTRACT

Background: Pesticides have been associated with Parkinson's disease (PD) in many studies, and with Alzheimer's disease (AD) in a few.
Methods: We conducted screening tests for neurologic disease and occupational pesticide use in a population-based sample of 400 elderly subjects at two government-run clinics in Costa Rica; 361 subjects who failed the initial screen were given both the Mini-mental States Exam (MMSE) and a modified version of a 10-item United Parkinson's Disease Rating Motor Subscale (UPDRS). Among subjects who failed either test, 144 were then examined by a neurologist.
Results: Past occupational pesticide exposure was reported by 18% of subjects. Exposed subjects performed worse on the MMSE than the non-exposed (mean 24.5 versus 25.9, $p=0.01$, adjusted for age, sex, and education). The exposed had significantly elevated risks of abnormal scores on two UPDRS items, tremor-at-rest (OR 2.58, 1.28–5.23), and finger-tapping (OR=2.94, 95% CI 1.03–8.41). Thirty-three (23%) of those examined by the neurologist were diagnosed with possible/probable PD, 3–4 times the expected based on international data; 85% of these cases had not been previously diagnosed. Among subjects who took the UPDRS, the exposed had an increased risk of PD (OR=2.57, 95% CI 0.91–7.26). No excess risk was found for a diagnosis of AD or mild cognitive impairment.
Conclusions: Elderly subjects with past occupational pesticide exposure performed significantly worse on screening tests for dementia and PD, and had an increased risk of an eventual PD diagnosis. Screening may be particularly appropriate among elderly subjects with past pesticide exposure.

1. Introduction

Exposure to pesticides, primarily occupational exposure, has been studied in relation to Parkinson's disease (PD) in over 40 epidemiologic studies, which have been recently reviewed by Van der Mark et al. (2011). These authors conducted a meta-analysis and found a relative risk of 1.62 (95% CI 1.40–1.88). Two recent studies have identified specific long-lasting organochlorine pesticides as increasing risk, (Weisskopf et al., 2010; Richardson et al., 2011) while two others have identified paraquat and/or rotenone (Tanner et al., 2011; Costello et al., 2009). However, in most of the epidemiology, the specific pesticides responsible remain largely unknown (Hatcher et al., 2008).

Exposure to pesticides has also been linked to Alzheimer's disease (AD), although there are less data than for PD, Santibáñez et al. (2007) have reviewed most of the epidemiologic studies, which are based on occupational exposure to pesticides. There have been six studies, five of which showed a positive association, two of which were statistically significant. Notably, the two cohort studies, the studies with the strongest design (the remainder were case-control) showed the strongest association (Baldi et al., 2011; Tyas et al., 2001). Case-control studies of dementia rely on informants to recall pesticide exposure, and therefore typically involve a large amount of misclassification and bias towards the null. Recently, Hayden et al. (2010) reported cohort

Abbreviations: AD, Alzheimer's disease; PD, Parkinson's disease; MCI, Mild cognitive impairment; UPDRS, United Parkinson's disease rating scale; MMSE, Mini-mental states exam; OR, Odds ratio; CI, Confidence interval; RR, Relative risk

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All authors contributed to the conduct of the study and to the preparation of the manuscript.

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data from rural Cache County in Idaho in which the rate of AD incidence was 50% higher in those reporting a history of occupational pesticide exposure (RR 1.42, 95% CI 1.06–1.91); this elevated risk was similar for those exposed to either organophosphate or organochlorine pesticides, the two most common groups used historically.

Costa Rica is a country of 4.6 million people with a life expectancy (80 years) equal to that of the US. The Costa Rican government offers free medical exams to all those aged 65 and older, and according to data from the Social Security system which runs the government health care system (personal communication, Vilma Garcia), about 2/3 of the over-65 population participates in these exams. Costa Rica has historically been an agricultural country with heavy pesticide use (Wesseling et al. 2001; Bravo et al., 2011). In Costa Rica, in the early 1970s, when the current elderly (65+) population was at their peak productive age between 25 and 50, almost 40% of the economically active population worked in agriculture (Census, 1973), and by 1985 practically 100% of the agricultural workers and farmers used pesticides (Hilje et al., 1987).

We conducted screening tests for Parkinson's disease and Alzheimer's disease, and mild cognitive impairment (MCI) piggy-backed onto routine annual medical exams in a population of elderly Costa Ricans at two government clinics in San Jose. MCI is a condition that often precedes AD (Petersen and Negash, 2008). These clinics are on the outskirts of San Jose in areas that used to be agricultural. We asked subjects whether they have been occupationally exposed to pesticides. Here we compare the performance on two screening tests of those with and without past occupational exposure, and assess the risk of PD and AD/mild cognitive impairment among the pesticide exposed.

2. Methods

2.1. Population

We administered a series of screening tests for parkinsonism and dementia to 400 elderly subjects attending a routine annual free medical exam at two public clinics of the Costa Rican Social Security system near San Jose, in the county of Santo Domingo de Heredia, Costa Rica. While this county is now on the outskirts of San Jose, historically it has been an agricultural area, and partly remains so today. The subjects screened represent approximately 80% of the subjects aged 65 and older in the population served by these clinics (these clinics had higher participation rates for these annual exams than the country as a whole). The target population was aged 65 and older; however a few individuals aged 60–64 were also screened (2% of the screened population). Subjects were screened from January 2010 to January 2011.

2.2. Design

We used a three tier screening process with each tier having a higher level of specificity. Subjects who failed phase 1 passed to phase 2, and subjects who failed phase 2 passed to phase 3. The evaluation in phase 1 was brief, simple to administer by public health nurses, and of proven sensitivity to the core signs of PD and AD. Evaluations at each subsequent phase were more thorough and thus took more time. Fig. 1 provides a flow chart on the screening, with the criteria for failing at each phase.

We used very broad criteria for failure on the first phase tests, seeking to maximize sensitivity in this pilot study, with the goal of minimizing false negatives, thereby permitting a good estimation of population prevalence. As a result, almost all subjects (90%) failed at least one test during the first phase, which sent them on to phase 2. Phase 1 consisted of (1) simple questions on the consistent presence of imbalance or tremor, even if not present at the time of assessment, (2) a spiral drawing test commonly used in the assessment of parkinsonian motor signs, (3) a 3-item word recall test for memory, and (4) a category fluency test (naming of as many animals as possible in a defined time). See Fig. 1 for more details.

Here we focus primarily on those ($n=361$) who passed to the second phase, in which two additional screening tests were administered, and on phase 3, where a clinical diagnosis was made.

The two phase 2 screening tests were the Mini-mental States Exam (MMSE) and a short form (10 items) of the United Parkinson's Disease Rating Scale (UPDRS) (Louis et al. 2004). This screening phase was designed to begin separating less specific motor and cognitive complaints from more specific early signs of PD and AD using abbreviated and validated scales commonly used in the clinical assessment of these conditions. Both tests were administered by a small number of clinicians (general practitioners) trained by two neurologists (NR and JLJ) on the administration of these tests. Consistency in the assessments was reinforced and monitored by one neurologist (NR). Due to the nature of these clinics and the volume of subjects, time was of the essence.

The Mini-mental States Exam (MMSE) took about 15 min, and is a standard 10 item cognitive test (30 points, higher is better) which tests across several cognitive domains. It has been validated in Spanish (Blesa et al., 2001). Phase 2 screen failure was defined as a score of <24, without any adjustment for age, gender, or education.

A 10-item short version of the UPDRS was administered in Stage 2. This version was a modified form of the 10 item motor subscale of the UPDRS proposed by Louis et al. (2004). To facilitate administration by non-neurologists, we replaced the rigidity item (in all limbs) for postural tremor (hands) and finger tapping. Inclusion of postural tremor was intended to capture that fraction of PD subjects who develop the illness in the setting of longstanding essential tremor (ET), or who present with postural rather than rest tremor (Deuschl, 2008). Abnormalities of fine motor dexterity can present early in PD, are captured in the finger tapping task, and are part of the original UPDRS. Our internists found that these modifications were less time consuming and easier to master than the rigidity measures. As in Louis et al. (2004), other items in this screening tool were speech, facial expression, tremor at rest, posture, and body (axial) bradykinesia. Each of the 10 items was rated from 0 to 4. A rating of 1 indicated a mild abnormality, and a rating of 2 or higher indicated an abnormality of moderate or greater severity. Failure was defined as any abnormality (score ≥ 1) on the tremor-at-rest assessment, or a score >0 on at least two other test items.

Failure on either of the phase 2 screening tests led to a clinical evaluation in phase 3. The majority of subjects ($n=144/163$) who failed phase 2 were formally evaluated by a neurologist specializing in disorders of aging. Diagnoses of PD were made using the UK Brain Bank criteria (Hughes et al., 1992) defined as bradykinesia plus at least one of the following: tremor at rest or cogwheel rigidity. For AD/MCI (mild cognitive impairment) diagnoses were made consistent with current guidelines (McKhann et al., 2011; Woodruff, 2011); Albert et al., 2011). The neurologist classified subjects as either possible/probable PD, Parkinsonism (bradykinesia or tremor but not both, not explained by other conditions), MCI, AD, and other neurologic or rheumatologic conditions common in the elderly such as essential tremor, mixed dementia, drug-induced states, orthopedic problems, or normal.

2.3. Pesticide exposure

Subjects were asked if they had worked in agriculture (yes/no). If they answered yes they were asked whether they had worked with pesticides (yes/no), and the number of years they had worked with pesticides. A detailed work history was not collected, however, given the time constraints for the screening; nurses were only able to add a limited amount of time for this new task added to the regular medical visit.

2.4. Statistical analysis

Statistical analysis focused on determining the difference in second phase screening tests (MMSE and UPDRS) between those with and without occupational exposure to pesticides, as well as differences in clinical diagnosis between the two groups.

T-tests and contingency tables were used to compare basic statistics between those with and without occupational exposure to pesticides. We conducted linear regression to compare the MMSE of the two groups, adjusting for years of schooling (continuous), age (continuous), and sex (dichotomous); residuals from the regression were checked for normality. We also evaluated the risk of a diagnosis of either PD or AD/mild cognitive impairment for those exposed to pesticides versus those not exposed, via logistic regression.

For the UPRDS, scores of 0 indicated normal, and above 0 some abnormality, with increasing severity. For no test item was the value above 2, and in general the data were either 0 or 1. For example, for the tremor-at-rest component, 75% of subjects had a score of 0, 22% a score of 1, and 3% a score of 2. We first summed all 10 UPDRS items and then divided the population into always normal (58%, sum=0) and at least one abnormality (42%, sum=1 to 12). We then conducted logistic regression analyses for any abnormality, with a dichotomous predictor for occupational pesticide exposure (0 or 1), and with the same covariates used in linear regression (years of schooling, age and gender). In addition to analyzing for any abnormal result across all 10 UPDRS items, we also analyzed each UPDRS item separately using the same model. The tremor-at-rest item was believed a priori to be the most predictive of PD.

We also estimated the expected prevalence of PD in our population using age-specific estimated prevalences around the world taken from de Lau and Breteler (2006). These estimates were 0.5% for ages 60–69, 1.5% for ages 70–79, and 3% for ages 80+. Estimates of AD prevalence were taken from Brookmeyer et al. (2011) using US data, and were 2% for ages 70–79, and 20% for ages 80+.

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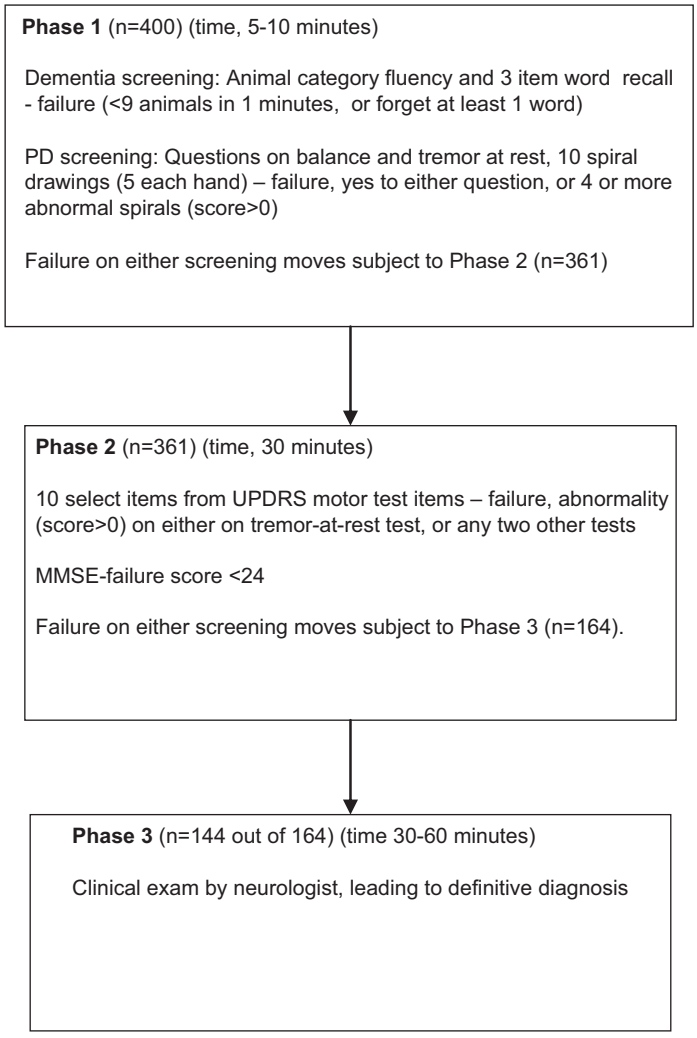

Fig. 1. Screening for neurologic disease.

3. Results

Table 1 provides descriptive statistics on the subjects who took the MMSE and UPDRS, and who had data on occupational pesticide exposure. There were significant differences in Table 1 between those with and without occupational exposure for sex, mean MMSE score, and the percent who had any abnormality (score >0) on the UPDRS and on the tremor-at-rest component. Among all subjects, 58% reported having worked in agriculture, of whom 31% reported occupational pesticide exposure. The mean years of occupational exposure was 12.2 (std. dev. 14.2). Education tended to be less among those with occupational pesticide exposure, but not significantly.

Results from linear regression models for MMSE, after adjustment for age, gender, and education, are shown in Table 2. Occupational exposure to pesticides decreased the MMSE score by 1.35 points ($p=0.01$). The R-square of the model was 0.22. Use of a variable for 'years of exposure' rather than a variable of 'yes/no occupational pesticide exposure' found a significant trend of lower MMSE scores with more years of exposure (loss of 0.5 points per year, $p=0.04$). There was no effect on the MMSE for work in agricultural in general ($p=0.97$).

Results for logistic regression modeling, adjusted for covariates, are shown in Table 3; first for the sum of the 10 test items on the UPDRS (no abnormality versus some abnormality across 10 items), and then for two specific UPRDS items (any abnormality on tremor at rest, or finger tapping). There was an elevated risk of some abnormality (some test with score ≥ 1) across the 10 test items (odds ratio 1.88, $p=0.06$), which fell just short of conventional statistical significance ($p \leq 0.05$). The test item for tremor-at-rest, considered a priori to be the most specific for PD, showed a significantly increased odds ratio (OR=2.58, $p=0.008$). The pesticide exposed group also had an increased risk of abnormality on the finger tapping test item (OR=2.94, $p=0.04$). There were no marked trends in risk for any of these outcomes (overall UPDRS, two specific test items) by years of pesticide exposure. Work in agriculture per se showed no significant effect on the risk of having any abnormality on the UPDRS (OR=1.50, $p=0.10$), or for the tremor test (RR=0.90, $p=0.70$), or the finger tapping test (RR=0.50, $p=0.12$).

Of the 164 subjects who failed either the UPDRS test or the MMSE, a neurologist evaluated 144 (88%). Of these 33 were diagnosed with possible or probable PD. The expected number of prevalent PD cases in our population was only 9. Thirteen subjects were diagnosed with several types of Parkinsonism (e.g., medication-related tremor, imbalance due to other problems), and 15 subjects were diagnosed with essential tremor. The most predictive item for a PD diagnosis among those taking the UPDRS was tremor-at-rest (as expected), which had a sensitivity of 91% and specificity of 52%. In a case-control analysis via logistic regression off all subjects who took the UPDRS, adjusting for age, sex, and education, occupational pesticide exposure

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Table 1
Descriptive statistics for subjects undergoing cognitive (MMSE) and Parkinson's disease (UPDRS) screening tests.

Statistic	Combined $N=347$[a]	Occupational pesticide exposure[b] $N=66$	No occupational pesticide exposure $N=281$	p-value difference between exposed and non-exposed[c]
Mean age (s.d.)	74.0 (6.8)	74.1 (6.6)	74.1 (6.8)	0.80
Mean years education (s.d.)	6.6 (5.0)	5.8 (5.0)	6.8 (5.0)	0.15
Percent male	40%	86%	30%	<0.0001
Mean MMSE (s.d.)[d]	25.7 (4.0)	24.4 (4.8)	26.0 (3.7)	0.01
Percent any UPDRS test item ≥ 1[e]	42%	45%	41%	0.50
Percent abnormal tremor at rest ≥ 1	25%	34%	23%	0.05
Percent abnormal finger tapping ≥ 1	8%	12%	7%	0.21

[a] 347 subjects included here had complete data for MMSE, all 10 UPDRDS test items, and occupational pesticide exposure.
[b] Based on self-report.
[c] Unadjusted for other covariates such as age, sex, education.
[d] The Mini-Mental States Exam (MMSE) is a standard 15-min cognitive test scored from 0 to 30, with higher scores indicating better cognition.
[e] The United Parkinson's Disease Rating Scale (UPDR) used here was a modified 10 item version of the full UPDRS which takes about 20 min, and which included tests for tremor, fine motor dexterity, and bradykinesia.

Table 2
Linear regression results for the outcome MMSE score[a].

Linear regression MMSE	Regression coefficient (standard error)	p-value for coefficient
Occupational pesticide exposure (change in MMSE for those reporting exposure)	−1.35 (0.54)	0.01
Age (change in MMSE per year of age)	−0.12 (0.03)	<0.0001
Sex (male=1, female=2)	−0.16 (0.43)	0.70
Years education (change in MMSE per year)	0.31 (0.04)	<0.0001

[a] Linear regression of MMSE scores regressed on 4 predictors in table, for 353 subjects had complete data for MMSE, age, gender, education, and occupational pesticide exposure. Higher MMSE scores indicate better cognition.

increased the risk of a PD diagnosis (OR=2.57, 95% CI 0.91–7.26, $p=0.07$). The same analysis for work in agriculture showed a much less marked risk of PD (RR=1.47, $p=0.34$).

Among subjects evaluated by the neurologist, 41 were diagnosed with either AD ($n=14$) or mild cognitive impairment (MCI; $n=27$). Logistic regression analyses did not show any excess risk for being diagnosed with AD/MCI for those who had an occupational exposure to pesticides ($p=0.70$), nor were there any trends in risk by years of pesticide exposure. The expected number of prevalent AD cases in our population was 21. There are few reliable data on the expected prevalence of MCI, so we have not estimated it.

It is likely that subjects with AD were less likely to come in for their regular screening, possibly accounting for finding fewer observed AD cases than expected. If for some reason pesticide exposure was more common among AD cases not coming to their exams, this underascertainment could have also played a role in our finding of no link between pesticide exposure and AD, although we have no a priori reason to believe this to be the case.

Table 3
Logistic regression results for the outcome UPDRS[a].

Logistic regression, any abnormality on UPDRS (sum 10 tests >0)	Odds ratio (95% confidence interval)	p-value for odds ratio
Any abnormality on UPDRS (sum 10 test items >0)		
Occupational pesticide exposure[b]	1.88 (0.98–3.63)	0.06
Tremor at rest test (score ≥ 1)[c]		
Occupational pesticide exposure	2.58 (1.28–5.22)	0.008
Finger tapping test (score ≥ 1)[c]		
Occupational pesticide exposure	2.94 (1.03–8.41)	0.04

[a] Adjusted for age, sex, and education via inclusion of these variables in the logistic model. Subjects included in each analysis: 345 for any abnormality analysis, 361 for tremor at rest analysis, and 356 for finger tapping analysis; different numbers reflecting the number of subjects with complete data for that outcome.
[b] Self-reported occupational pesticide exposure.
[c] Tremor-at-rest and finger-tapping tests were two items in the 10 item UPDRS; score of 0 indicates no abnormality.

4. Discussion

Our results indicate that subjects self-reporting occupational exposure to pesticides performed significantly worse on the MMSE and on two of 10 test items used clinically to assess PD signs, including the tremor-at-rest test item, which is was the most sensitive item in the UPDRS battery for diagnosing PD in our study. Tremor is a cardinal symptom of PD. There are few prior reports in the literature regarding the MMSE and tremor test results among those exposed to pesticides.

Kamel and Hoppin (2004) have reviewed the studies of workers exposed chronically to moderate levels of a variety of pesticides; such workers have shown cognitive impairment in some but not all studies. Most studies have used a battery of cognitive test appropriate for field studies, but have not used the MMSE, perhaps the most common clinical test for cognitive deficits among the elderly. A recent exception is the large study by Baldi et al. (2011); workers directly and indirectly exposed to a variety of pesticides showed both an increased risk of poor performance on the MMSE in cross-sectional analyses, and greater deterioration over time in longitudinal analyses, compared to non-exposed farm workers; the average age of subjects was 51.

Psychomotor tests (eg, finger tapping, reaction time, Santa Ana pegboard tests) have been used in a number of studies of pesticide-workers, with mixed results (Tyas et al., 2001). Data on tremor tests among those exposed to pesticides are much scarcer. Our findings of an association between tremor-at-rest and pesticides contrast

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with negative findings by London et al. (1998), but concord with an early 1965 study by Davignon et al. (1965) Both these studies were of younger workers. We studied a much older population and found a much higher prevalence of abnormality. It is not clear the degree to which our study is comparable to the two prior ones given the differences in age, differences in exposure, and the different methods of assessing tremor.

In our data, reported occupational exposure showed a borderline significant elevated risk (OR=2.57, $p=0.07$) for a diagnosis of PD among all 400 subjects in our study. There was no association, however, between occupational exposure and the diagnosis of AD/MCI.

The high prevalence of PD in our group compared to what was expected may be partly explained by the increased risk among those occupationally exposed to pesticides, assuming that pesticides increase PD risk (the exposed were 2.6 times more likely than the non-exposed to have prevalent PD). Costa Rica has had a high per capita use of pesticides compared to other populations (Wesseling et al., 2001; Bravo et al., 2011). It is noteworthy that the herbicide paraquat and fungicide maneb, two pesticides experimentally (Thiruchelvam et al., 2000) and epidemiologically (Costello et al., 2009) linked to Parkinson disease, were widely used since 1970 on coffee, the main crop in the study area (Hilje et al., 1987). Our data are based on small numbers and the estimated expected prevalence is based on rather imprecise world-wide prevalence data, (de Lau and Breteler, 2006) so this finding should be considered with caution until replicated on a larger scale. There are no registries of PD in Costa Rica, and no data on PD prevalence nation-wide. There are approximately 30 neurologists in Costa Rica (personal communication, Dr. Norbel Roman), most concentrated in the area of the capital, of whom approximately one-half are working clinically in the public sector which provides most health care. Based on the number of previously undiagnosed cases detected in this study, we suspect PD is currently under-diagnosed in Costa Rica. We plan future work to expand our screening to larger populations to see if we can replicate our findings in a larger population, including populations in more rural area with higher past pesticide use.

Our findings are limited by the lack of data on potential confounders, such as smoking and alcohol use, co-morbidities, or medications. However we have no a priori reason to think that those with and without pesticide exposure differed on these variables. A second important limitation is the cross-sectional design, which limits our ability to draw causal inferences. The most important limitation is that only one or two questions regarding pesticide exposure were possible in the context of screening where personnel had severe time constraints. A complete occupational history and data on non-occupational exposure to pesticides, as well as data on the intensity of exposure and the type of pesticide, would have obviously been preferable, and would have led to much better classification of exposure. Nonetheless, in Costa Rica about half of older men have worked professionally in agriculture and in most cases have been exposed to pesticides in that work; our data conforms to that profile, and a simple yes/no question on occupational pesticide exposure was sufficient to differentiate subjects into two groups which had significant differences on screening tests. A study is now underway to measure long-lasting organochlorine pesticides in these subjects.

From a public health standpoint, it is worth noting that programs such as these could be used to detect new cases of treatable neurologic disorders in age-appropriate populations using simple, cost effective screening tools. For instance, among our subjects, none of the subjects diagnosed with AD ($n=14$) or MCI ($n=27$) patients had been previously diagnosed, and only 5/33 (15%) subjects diagnosed with PD had been previously diagnosed. It should be noted that we have applied criteria for phase 1 screening tests which were very sensitive but not very specific, in order to be able to detect as much undiagnosed disease as possible. Application of screening tests on a broader scale would require more balance between sensitivity and specificity during initial screening.

In conclusion, our study has shown that elderly subjects with past occupational pesticide exposure performed worse on simple common screening tests for neurologic disease. Our study is the only existent study of the effect of pesticide exposure among the elderly using these types of screening tests. It may be that some of the neurologic effects of pesticide exposure do not manifest themselves until older ages. While in general these screening tests may be useful to conduct in all elderly populations to detect previously undetected neurologic disease, our findings suggest that such screening may be particularly appropriate for those with pesticide exposure. We also found a much higher than expected prevalence of PD in our sample, a finding which needs elucidation in future work. Finally our finding that the pesticide exposure carries an elevated risk of being diagnosed with PD confirms previous work.

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