Exhibit 254

RESEARCH ARTICLE

Parkinson's Disease Progression and Exposure to Contaminated Water at Camp Lejeune

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ABSTRACT: Background: We recently reported an increased risk of Parkinson's disease (PD) in service members who resided at Marine Base Camp Lejeune, North Carolina, when water supplies were contaminated with trichloroethylene and other volatile organic compounds (VOCs). Prior studies suggest that environmental exposures may affect PD phenotype or progression, but this has not been reported for VOCs.

Objective: The objective of this study was to test whether PD progression is faster in individuals exposed to VOCs in water at Camp Lejeune.

Methods: A cohort of 172,128 marines residing at Camp Lejeune between 1975 and 1985 was previously assembled. We identified individuals with PD in Veterans Health Administration and Medicare databases between 2000 and 2021. Using estimates derived by the US Agency for Toxic Substances and Disease Registry, we classified individuals as exposed or unexposed to VOCs in residential water. We used Kaplan–Meier and Cox regression models to test differences between exposed and unexposed groups in the time from PD diagnosis until psychosis, fracture, fall, or death.

Results: Among 270 persons with PD, 177 (65.6%) were exposed to VOCs in residential water. Median cumulative exposure was 4970 μg/L-months, >50-fold the permissible level. Time until psychosis, fracture, and fall were all shorter in the exposed group, with adjusted hazard ratios (HRs) exceeding 2: psychosis HR, 2.19 (95% confidence interval [CI]: 0.99–4.83); fracture HR, 2.44 (95% CI: 0.91–6.55); and fall HR, 2.64 (95% CI: 0.97–7.21). A significant dose response was observed for time to fall (*P* trend, 0.032). No differences were observed for time until death.

Conclusions: PD progression may be faster in persons exposed to trichloroethylene and other VOCs in water decades earlier. © 2024 The Author(s). *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society. This article has been contributed to by U.S. Government employees and their work is in the public domain in the USA.

Key Words: Parkinson's disease; progression; trichloroethylene; solvent; exposure

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Parkinson's disease (PD) phenotype and progression are highly variable.[1,2] Differential environment may underlie some of this variability, which may reflect etiologic subtypes and/or disease modification.[3]

Several prior environmental associations with PD phenotype and progression have been reported, including caffeine, alcohol, smoking, head injury, and pesticides, but data are limited and results are inconsistent.[4-16]

To the best of our knowledge, Pezzoli et al[17] reported the only prior study of PD phenotypic differences related to solvent exposures. In a clinic-based consecutive sample of 990 patients with PD, those who reported a history of prior hydrocarbon solvent exposure were younger at PD onset and, in a subsample matched on sex and disease duration, had higher Unified Parkinson's Disease Rating Scale (UPDRS) scores and required higher doses of levodopa.

Studies in animals support the biological plausibility of this observation. Exposure to the common degreasing solvent trichloroethylene (TCE) recapitulates key pathologic characteristics of PD, including mitochondrial impairment, intraneuronal aggregation of phosphorylated α-synuclein protein, and regionally specific degeneration of nigrostriatal dopaminergic neurons.[18-22]

This study leverages our prior work investigating PD in former service members stationed at Marine Corps Base Camp Lejeune in North Carolina between 1975 and 1985.[23] Much of the water supply at Camp Lejeune was contaminated with TCE, tetrachloroethylene (PCE), and other volatile organic compounds (VOCs), including vinyl chloride and benzene, from approximately 1953 until 1987.[24-27] During 1975–1985, the period of maximal contamination, water delivered to some areas of the base dramatically exceeded US Environmental Protection Agency (EPA) maximum contaminant levels (MCLs) for TCE (Lejeune monthly median, 366 μg/L; EPA MCL, 5 μg/L), PCE (monthly median, 15.4 μg/L; MCL, 5 μg/L), and vinyl chloride (monthly median, 22.2 μg/L; MCL, 2 μg/L).[24,28] Approximately two-thirds of Lejeune residents during this period were deemed to have had at least some exposure to contaminated water at their residence. This study investigated whether PD-associated clinical symptoms may develop more rapidly in persons exposed to VOCs in residential water decades earlier.

Subjects and Methods

The study was approved by Institutional Review Boards of the University of California San Francisco, San Francisco VA Health Care System, and Edward Hines, Jr. VA Hospital, with a waiver of requirement for individual informed consent.

Cohort Assembly

The study cohort was previously assembled by the US Agency for Toxic Substances and Disease Registry (ATSDR) as reported by Bove et al.[24] A total of 172,128 marine and navy personnel stationed at Camp Lejeune for at least 90 days between April 1975 and December 1985 were identified from the Defense Manpower Data Center Active Duty Military Personnel Master File and US Marine Corps. This time frame was chosen because it was the period of maximal contamination at Camp Lejeune and because the Defense Manpower Data Center file did not contain information on unit location until April 1975. Among these, we identified an analytic cohort that included all individuals who ever used Veterans Health Administration (VHA) or Medicare healthcare services.

PD Ascertainment

Detailed ascertainment methods have been previously reported.[23] In brief, for individuals who used VHA services, we searched Corporate Data Warehouse[29] Outpatient, Inpatient, Community Care (care in the community paid for by VHA) and Pharmacy files for all PD diagnostic codes (International Classification of Diseases, Ninth Revision [ICD-9] 332.0 and Tenth Revision [ICD-10] G20) and dopaminergic medications between January 1, 1999, and February 17, 2021. We reviewed the medical chart notes of all individuals identified earlier to validate diagnosis and diagnosis date, and applied standard diagnostic criteria for PD based on the totality of available information.[30]

We used a parallel approach to ascertain cases in Medicare files, including outpatient claims (Part B) and inpatient and skilled nursing facilities claims (Part A) from January 1, 1997, through December 31, 2018, and pharmacy claims (Part D) from January 1, 2006, through December 31, 2018. We reviewed all available Medicare-derived information and also VHA medical charts for those who also obtained VHA care but were not directly ascertained through VHA diagnostic codes. We assigned a diagnosis of PD for individuals ascertained via Medicare if they had at least two codes by a neurologist, or at least two codes by nonneurologist providers and two dopaminergic medication prescriptions, and had no conflicting diagnostic information.

We excluded individuals diagnosed with PD before January 1, 2000, because outcome data in VHA clinical databases were incomplete prior to this date.

Definitions and Determination of PD Progression Outcomes

We defined four parameters of PD progression as the time from PD diagnosis until (1) the earliest of a psychosis diagnosis or antipsychotic medication

prescription, (2) fracture diagnosis, (3) fall diagnosis, or (4) death. We selected these parameters because they could be determined from electronic medical record ICD codes with relatively good accuracy.[31-33] ICD codes and medications for each outcome parameter are specified in Table S1. Diagnostic codes and medications were identified from VHA and Medicare databases. Vital status was determined from the VHA Vital Status File on May 31, 2021.

Exposure Determination

Estimated exposure to VOCs at Camp Lejeune was determined by ATSDR as previously reported.[27] In brief, ATSDR used historical reconstruction of groundwater fate and transport and distribution models to derive monthly average estimates of concentrations of contaminants for each residential address from 1975 to 1985. These monthly estimates were summed for each veteran to obtain cumulative residential exposure estimates for TCE, PCE, vinyl chloride, benzene, and total VOCs (TVOCs). We then classified exposure status for each contaminant as binary (exposed or unexposed) or as tertiles (none, ≤ median, > median). Because compound-specific categorical exposures were highly correlated ($r > 0.9$), we elected to focus our analyses on TVOCs.

Covariate Data

Sex, race, and ethnicity were determined from VA data if available, or from Medicare or ATSDR files if not. We determined smoking status using VA Health Factors data.[34] Rank and duration of service at Camp Lejeune were obtained from ATSDR files.

Statistical Analysis

We compared participant characteristics using Pearson's χ^2 statistic for categorical variables or Student *t* tests for continuous variables. We used Kaplan–Meier plots and Cox regression models adjusted for age, sex, and race (White, Black, other) to test differences between exposed and unexposed groups in the time from PD diagnosis until each of the progression outcomes defined earlier. We right-censored the period of observation at 15 years because of the low proportion of individuals with longer duration of follow-up and consequent model instability, as well as potential bias from differential loss to follow-up.[35,36] We also tested models that included rank (officer/enlisted) and smoking (ever/never), although smoking status was unknown for a substantial proportion of the cohort, and that restricted the period of observation to 10 years. We additionally performed analyses stratified by race, and tested associations with tertiles of TVOC exposure (none, ≤ median, > median).

Statistical analyses were performed using SAS, v9.4 (SAS Institute, Cary, NC).

Results

The analytic cohort included 84,824 veterans from Camp Lejeune who used VHA or Medicare healthcare services (Table 1), with a median duration of 25.0 (SD 17.4) months residence at Lejeune. A total of 270 individuals were diagnosed with PD after January 1, 2000, 227 (84.1%) of whom were White and 260 (96.3%) male. A total of 177 (65.6%) were exposed to TVOCs in residential water with a median exposure of 4970 μg/L-months. Total months of residence at Camp Lejeune was significantly longer in the exposed than the unexposed group (27.5 vs. 19.8 months, respectively; $P < 0.001$). Age at PD diagnosis averaged 55.3 (SD 6.4) years and was similar in exposed and unexposed individuals ($P = 0.11$). Length of follow-up from PD diagnosis until the 15-year maximum period of observation averaged 6.5 years. Times from PD diagnosis until psychosis, fracture, and fall were shorter in exposed individuals (Fig. 1). In adjusted Cox models, hazard ratios (HRs) in exposed individuals were increased more than 2-fold for each outcome, but exposure was not associated with time until death (Table 2). Results were similar in sensitivity models that included rank and smoking variables, or that restricted the follow-up time to a maximum of 10 years (Table S2). Associations were modestly stronger for psychosis and fracture when restricted to Whites; non-Whites comprised too small a sample to analyze independently. Analyses of TVOC exposure tertiles identified a statistically significant dose-related trend for time until a fall and near-significant trends for psychosis and fracture (Table 3).

Discussion

This is the first study to assess correlates of PD clinical symptom progression associated with prior exposure to VOCs in drinking water. The hazards of psychosis, fall, and fracture were all twice as high in former Camp Lejeune residents with PD who had been exposed to organic solvents in their residential water supply 40 years prior than in those who were not residentially exposed. Although other compounds were present, the environmentally ubiquitous solvent TCE was by far the major contaminant.

Animal studies and human epidemiology support a causal association of TCE with PD.[20] Mirroring the histopathological hallmarks of PD, rodents with chronic respiratory or oral TCE exposure manifest selective loss of nigrostriatal dopaminergic neurons, increased intraneuronal phosphorylated α-synuclein,

TABLE 1 *Demographic characteristics*

Variable	VOC Exposed (n = 177, 65.6%)	VOC Unexposed (n = 93, 34.4%)	Total (n = 270)	*P* Value[a]
Sex, n (%)				0.083
Men	173 (97.7%)	87 (93.6%)	260 (96.3%)	
Women	4 (2.3%)	6 (6.5%)	10 (3.7%)	
Race, n (%)				0.79
White	148 (83.6%)	79 (85.0%)	227 (84.1%)	
Black	25 (14.2%)	11 (11.8%)	26 (13.3%)	
Other	4 (2.3%)	3 (3.2%)	7 (2.6%)	
Ethnicity, n (%)				0.41
Hispanic	12 (6.8%)	4 (4.3%)	16 (5.9%)	
Non-Hispanic	165 (93.2%)	89 (95.7%)	254 (94.1%)	
Rank, n (%)				0.66
Officer	14 (7.9%)	6 (6.5%)	20 (7.4%)	
Enlisted	163 (92.1%)	87 (93.6%)	250 (92.6%)	
Smoker, n (%)				0.51
Ever	68 (38.4%)	37 (39.8%)	105 (38.9%)	
Never	64 (36.2%)	38 (40.9%)	102 (37.8%)	
Missing	45 (25.4%)	18 (19.4%)	63 (23.3%)	
Months lived at Lejeune, mean (SD) (range)	27.5 (18.5) (3.0–108.0)	19.8 (16.8) (3.0–93.0)	24.9 (18.3) (3.0–108.0)	<0.001
TVOC cumulative levels, μg/L-months, median (IQR)	4970.3 (1675.6–11,410.0)	n/a	n/a	n/a
Age at PD diagnosis, y, mean (SD) (range)	55.8 (6.0) (34.0–75.0)	54.5 (7.1) (37.0–72.0)	55.3 (6.4) (34.0–75.0)	0.11
Outcomes, n (%)				
Psychosis	31 (17.5%)	8 (8.6%)	39 (14.4%)	0.048
Fall	26 (14.7%)	5 (5.4%)	31 (11.5%)	0.023
Fracture	22 (12.4%)	5 (5.4%)	27 (10.0%)	0.066
Death	28 (15.8%)	10 (10.8%)	38 (14.1%)	0.26
Mean years (SD) from PD until death or 15-year follow-up	6.50 (3.85)	6.50 (4.36)	6.50 (4.03)	1.0

[a]VOC exposed vs. unexposed.
Abbreviations: VOC, volatile organic compound; SD, standard deviation; TVOC, total volatile organic compound; IQR, interquartile range; n/a, not applicable; PD, Parkinson's disease.

activation of microglia with increases in markers of oxidative stress, and associated motor deficits.[19,21,22,37] TCE exposure reduces activity of mitochondrial complex I,[18,19,38] induces LRRK2 kinase activity, enhances endolysosomal dysfunction, and perturbs the rodent microbiome—all mechanisms that have been implicated in PD pathogenesis.[39,40] Proposed proximate toxicants include the potent mitochondrial complex I inhibitor 1-trichloromethyl-1,2,3,4-tetrahydro-beta-carboline,[41] which formed in vivo in the brains of mice fed TCE for 8 months,[22] as well as S-(1,2-dichlorovinyl)-L-cysteine, a by-product of the hepatic and renal metabolism of TCE.[42,43] The human epidemiology of TCE is increasingly compelling, with increased PD risk associated in analytic studies of environmental[23,44] or occupational exposure,[45] disease clusters,[18,46,47] and case reports.[48-50] Other VOCs are less well studied, but data are suggestive for PCE,[45,46,51,52] the other predominant contaminant in the Camp Lejeune water supply.

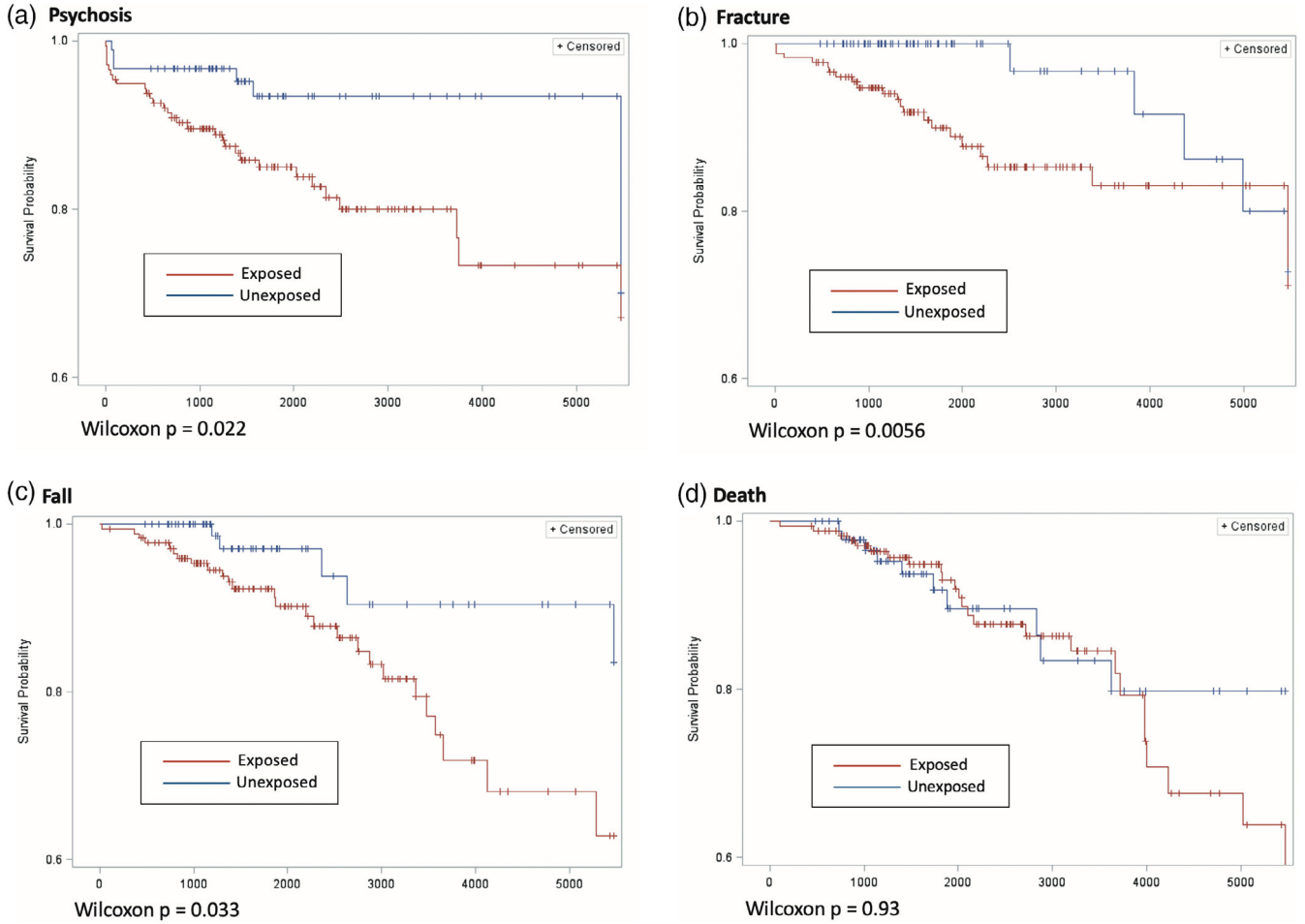

FIG. 1. Kaplan–Meier survival curves from Parkinson's disease (PD) diagnosis until outcome or 15-year follow-up in total volatile organic compound (TVOC) exposed and unexposed. (**A**) Psychosis. (**B**) Fracture. (**C**) Fall. (**D**) Death. [Color figure can be viewed at wileyonlinelibrary.com]

Similar to the outcomes observed in this study, prior reports of populations chronically exposed to TCE in well water documented neurobehavioral deficits that included increased postural sway, reduced reaction times, poorer recall, executive function, and mood.[53,54] A case–control study of workers occupationally exposed to various hydrocarbons reported higher UPDRS scores for a given PD duration among exposed workers, as well as higher levodopa doses and a lesser response to apomorphine challenge.[17] The higher risk of developing psychosis in exposed individuals in this study may reflect a similarly reduced levodopa responsiveness and need for higher medication doses.

Although TCE and PCE are quickly eliminated from the body after exposure, past exposure to these and other VOCs might contribute to a more fulminant PD phenotype through several mechanisms. Inflammation, microglial activation, mitochondrial impairment, and increased intraneuronal phosphorylated α-synuclein, all demonstrated in TCE rodent models, may persist and result in a more fulminant disease course.[55,56] Indeed, persistent microglial activation and active nigral neuronal degeneration was observed in monkey models and at autopsy in persons exposed to the parkinsonism-inducing-toxicant 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine many years earlier.[57,58] Differential patterns of inflammation, potentially caused by exposure to TCE,[59] have been suggested to underlie PD phenotypic subtypes and progression.[60-62] Alternatively, microglial priming by TCE might increase susceptibility to subsequent environmental insults, as has been demonstrated for toxicants such as lipopolysaccharide and paraquat.[63-65] Another possibility is that the neuronal synuclein pathology induced by TCE might differ from that caused by other disease determinants in terms of its severity, distribution, and molecular characteristics.[66-68] Finally, persistent changes to the microbiome caused by exposure to TCE and other VOCs could potentially impact PD progression.[69-73]

Our study had several strengths. The cohort was population based, including all service members who resided at Camp Lejeune during a 10-year period of high contamination. We validated PD diagnoses by review of medical chart notes and applied accepted

diagnostic criteria. We did not rely on potentially biased self-report to determine exposure; rather, we inferred exposure using exposure reconstruction data based on residential location and time frame. We explored potential confounding by a range of variables and performed sensitivity analyses that consistently found increased HRs for three independent outcomes. The observation of a statistically significant dose–response relationship for fall risk and trends for psychosis and fracture further supports the biological plausibility of these associations.

Our study also had some limitations. We had diagnostic information only for cohort members who received health care through VHA or Medicare. However, because veterans are unaware of the individual-level ATSDR VOC exposure estimates, incomplete ascertainment should be nondifferential, biasing toward not finding an association. Our measures of disease progression were limited to conditions that could be reliably identified through diagnostic codes. Clinically based measures of disease progression, such as changes in UPDRS scores or reliable total levodopa equivalent doses, were not systematically available. We did not observe an earlier age at PD diagnosis in exposed individuals as has been reported for hydrocarbon-exposed workers,[17] but the attained age of the cohort is still relatively young, limiting statistical power to assess this relationship. In addition, we had exposure estimates only for residential water supplies. Veterans would also have been exposed to VOCs through water sources where they worked, trained, and exercised, in addition to potential exposure through vapor intrusion into dwellings.[74] Our inability to account for these nonresidential exposures would be expected to bias toward the null, obscuring rather than resulting in spurious associations.

In conclusion, we found a higher risk of psychosis, falling, and fracture in a cohort of veterans with PD who were exposed to TCE and other VOCs in residential water at Camp Lejeune 40 years ago. Although these findings require replication, toxicant exposure may underlie some of the phenotypic variability of PD.

Acknowledgments: We thank Dr. Frank Bove and the Agency for Toxic Substances and Disease Registry for their helpful feedback and assistance.

TABLE 2 *Cox regression model hazard ratios (95% CI) associated with TVOC exposure*

Outcome	All	Whites[a]
Adjusted for age, sex, and race		
Psychosis	2.16 (0.98–4.75)	2.56 (1.05–6.22)
Fall	2.65 (0.97–7.19)	2.31 (0.84–6.32)
Fracture	2.41 (0.89–6.49)	2.89 (0.98–8.54)
Death	1.15 (0.54–2.42)	1.60 (0.68–3.74)
Adjusted for age, sex, race, and rank		
Psychosis	2.17 (0.99–4.76)	2.56 (1.05–6.22)
Fall	2.68 (0.98–7.34)	2.36 (0.85–6.52)
Fracture	2.45 (0.90–6.62)	2.95 (0.99–8.75)
Death	1.12 (0.52–2.39)	1.60 (0.67–3.70)
Adjusted for age, sex, race, smoking, and rank		
Psychosis	2.19 (0.99–4.83)	2.59 (1.06–6.32)
Fall	2.64 (0.97–7.21)	2.27 (0.83–6.23)
Fracture	2.44 (0.91–6.55)	2.93 (0.99–8.64)
Death	1.12 (0.52–2.41)	1.57 (0.67–3.71)

[a]Non-White numbers too small to calculate stable hazard ratios.
Abbreviations: CI, confidence interval; TVOC, total volatile organic compound.

Data Availability Statement

The data that support the findings of this study are available from US Department of Veterans Affairs.

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TABLE 3 *Dose-related associations with TVOC exposure*[a]

Outcome	Unexposed (Reference)	≤ Median Exposure	> Median Exposure	*P* Trend
Psychosis	1.0	1.46 (0.98–2.18)	2.14 (1.43–3.19)	0.063
Fall	1.0	1.69 (1.05–2.73)	2.86 (1.77–4.61)	0.032
Fracture	1.0	1.46 (0.90–2.36)	2.12 (1.31–3.43)	0.13

[a]Cox regression model hazard ratios (95% CI) adjusted for age, sex, and race.
Abbreviations: TVOC, total volatile organic compound; CI, confidence interval.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.