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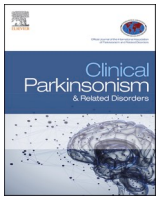

Lead service lines and Parkinson's disease prevalence in U.S. States

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ABSTRACT

Introduction: We recently showed that the prevalence of Parkinson's Disease (PD) in U.S. states is positively associated with the quantity of acid rain. Acid rain could play an etiologic role in PD by mobilizing metals, e.g., lead, from watersheds and pipes into drinking water. We assessed the correlation of PD with lead service lines, the underground pipes that connect homes to municipal water sources, which are a major aqueous source of lead.
Methods: We used multiple regression techniques to examine PD prevalence rates by state relative to the number of lead service lines. We included known or suspected aqueous risk factors, e.g., the Acid Precipitation Index (a measure of acid rain) and well water use.
Results: Age-, race-, and sex-adjusted prevalence rates for PD were significantly and positively correlated with the log number of lead service lines ($p = 0.0004$). The effect of lead service lines remained significant after adjusting for the effects of acid rain and well water use ($p = 0.0019$).
Conclusion: These findings are consistent with a role for lead in the etiology of PD. Studies of lead service line exposure in relation to PD at the individual level are warranted.

1. Introduction

Most cases of Parkinson's disease (PD) are of unknown causes ("idiopathic") but are believed to be due to environmental factors. With the exception of the synthetic chemical MPTP, few environmental risk factors have been consistently identified [1]. However, considerable evidence implicates exposure to some pesticides and metals, particularly lead [2,3]. We recently reported that state-wide prevalence rates for PD in the U.S. are highly correlated with the quantity of acid rain received per state. Acid rain (synonyms, acid precipitation, acid deposition) is precipitation with a pH < 5.6 (neutral pH = 7). Acid rain could play an etiologic role in PD by leaching lead from watersheds and plumbing into drinking water [4]. The majority of lead in tap water is derived from lead service lines (LSLs), the underground pipes that connect homes to municipal water sources. Here we examined PD prevalence in relation to the number of LSLs per state.

2. Materials and methods

Data on state-wide PD prevalence, adjusted for age, race and sex, were obtained from Mantri et al. 2019 [5]. Data on the > 6,000,000 LSLs currently in use, by state, were obtained from the 2016 National Survey of Lead Service Line Occurrence. Approximately 30% of community water systems employ LSLs in at least part of their system [6].

The National Survey recognized four categories of water systems, defined by the size of the population served: LSL1, for populations < 10,000; LSL2, for populations of 10,000–50,000; LSL3 for populations > 50,000, and LSL4, for all systems combined. We included other variables in our analyses that were previously linked to PD prevalence: the Acid Precipitation Index (a measure of the acidity and quantity of acid rain), well water use by state, and state-wide releases of sulfuric acid [4].

A full model that predicted log PD prevalence as a function of log LSLs, the Acid Precipitation Index, and well water usage was built and run as a multiple linear regression. Single linear regressions were run for each significant variable and were compared to the full model. Akaike Information Criterion (AIC) scores were used to select the variables for the multivariable model.

3. Results

Using both backward and stepwise selection, the LSL3 variable was retained; the other LSL variables and sulfuric acid were not significant and were removed from the model. Log PD prevalence was significantly predicted by the number of LSLs for the water system category > 50,000 (i.e., LSL3), the Acid Precipitation Index, and well water use ($F = 17.99$, $p < 0.0001$). PD prevalence increased as the number of LSLs increased

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Table 1
Regression models results predicting PD prevalence.

Model	*F*-Value	*p*-Value	Adjusted R^2	AICc
Full (log LSLs, API + well water)	**17.99**	**<0.0001**	**0.54**	−29.93
Log LSLs alone	14.62	0.0004	0.21	**−41.47**
API alone	19.77	<0.0001	0.29	−34.87
Well water alone	5.30	0.0257	0.08	−31.27

(β = 0.023, t = 2.63, p = 0.0019) and as the Acid Precipitation Index increased (β = 0.002, t = 4.84, p < 0.0001). Conversely, PD prevalence decreased as well water use increased (β = −0.005, t = −2.97, p = 0.0050).

The apparent protective effect of well water we observed is contrary to the results of numerous, (mostly clinic-based), case-control studies. However, it is consistent with the largest, population-based case-control study, which included > 89,000 PD cases and 21,000,000 controls [7]. We examined whether the association between LSLs and PD is influenced by collinearity between PD, well water use and acid rain by measuring the Variance Inflation Factor (VIF) for variables in the full model. All VIFs were < 2.0, which is well below the cutoff of 10 for diagnosing significant collinearity [8]. Thus, the association between LSLs and PD does not appear to be attributable to collinearity between LSLs and acid rain or well water use.

The full model, which included LSL3, the Acid Precipitation Index, and well water usage, explained 54% of the variation in PD prevalence. Table 1 shows the results of the regression models. In single models, the Acid Precipitation Index had a larger F value than log LSL3. However, the log LSL3 model had the best fit, evidenced by the lowest AIC score. Fig. 1 shows the relationship between PD prevalence and LSLs from the single model.

Minnesota (MN) is an outlier in Fig. 1, due to its unusually low PD prevalence rate. The explanation for MN's low PD prevalence is unclear. Disease prevalence is related to several factors, including the number of health care providers and differential mortality rates. MN's low PD prevalence may reflect its high PD mortality rate, which is among the top 10% of U.S. states [9]. Examination of the relationship between the LSL number and PD using state mortality (rather than prevalence) rates shows that PD mortality is significantly related to LSL number (β = 0.10, t = 2.92, p = 0.033). This indicates that the relationship between PD and LSLs is robust and is not an artifact of the manner in which prevalence rates were calculated.

4. Discussion

Our analyses showed that age-, race- and sex-adjusted prevalence rates for PD are significantly correlated with the number of LSLs per state. This finding remained significant after adjustment for other risk factors, including acid rain (p = 0.0119). These findings are consistent with several epidemiologic studies in PD, including case-control studies of lead in bone and biomarkers of blood methylation [2,3].

The use of LSLs as a surrogate marker of lead exposure may be an improvement over other methods used to estimate lead exposure in PD, e.g., the use of data from the Toxic Releases Inventory (TRI) [10]. The major pathway by which lead releases recorded in the TRI affect individuals is presumably respiratory. Conversely, exposure to lead via LSLs occurs primarily by ingestion. For women of child-bearing age, the EPA estimated that in 1991, 22% of lead exposure came from water, 31% from dust (from household paint and soil), 44% from food, and only 4% from air [11]. Population-based studies demonstrate that exposure to LSLs is an independent risk factor in children for blood lead levels ≥ 5 μg/dL (the upper value of CDC's reference range for children's blood) [12].

Our study has several limitations, including the use of prevalence data as a surrogate for incidence data and the use of LSLs as a surrogate for lead exposure. For studies of disease etiology, incidence data are preferable to prevalence data because disease prevalence is affected by survivorship. State-wide incidence data for PD are not generally available. Prevalence may be a valid surrogate for incidence in PD because survivorship from PD in the US differs little by geographic region [13]. Additionally, the association between LSL and PD prevalence could reflect confounding. Because LSLs service older homes, the association between LSLs and PD might reflect the influence of factors closely associated with such homes, e.g., lead paint and/or other chemicals. We had no information about migration and the length of time individuals were exposed to LSLs. However, variation in these factors is likely to be non-differential and would bias the observed correlation toward the null. Finally, the most important limitation is that these are ecologic data; i.e., they demonstrate that state-wide PD rates increase as LSLs per

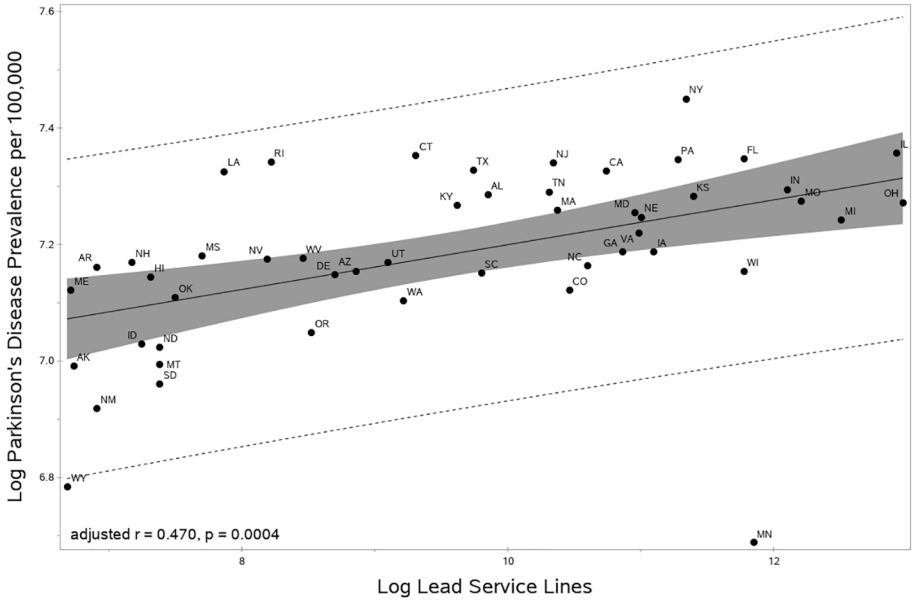

Fig. 1. Parkinson's disease and lead service lines. State-level prevalence of Parkinson's disease as a function of the number of lead service lines per state for water systems serving > 50,000 persons (β = 0.04, t = 3.82, p = 0.0004; adjusted R^2 = 0.22).

state increase and not that individuals exposed to LSLs experience increased risk.

In conclusion, our analyses show that age-, race- and sex-adjusted prevalence rates for PD in U.S. States are highly correlated with the number of LSLs, a major source of lead. These data require cautious interpretation. Epidemiologic studies of exposure to LSLs in relation to PD at the individual level are warranted.

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CRediT authorship contribution statement

Gary G. Schwartz: Conceptualization, Supervision, Writing – original draft, Writing – review & editing. **Mark R. Williamson:** Methodology, Formal analysis, Visualization, Writing – review & editing.

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