Original Research Article

Investigating Lagged County-Level Associations Between Agricultural Pesticide Application and Parkinson's Disease Mortality in the Conterminous United States

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ABSTRACT

Pesticide exposure is among the most studied environmental risk factors for Parkinson's disease (PD), but most evidence comes from individual-level designs, and national ecological studies rarely account for confounding or for the long interval between exposure and disease. This study examined whether county-level agricultural pesticide application from 1998 to 2002 was associated with later county-level PD mortality, and whether any association was robust to exposure definition, spatial structure, multivariable adjustment, and count-based modeling. County agricultural pesticide estimates from the U.S. Geological Survey EPest series were linked by Federal Information Processing Standard code to underlying-cause PD mortality (ICD-10 G20) from CDC WONDER for 2003–2007 and 2008–2012. In unadjusted and population-only models, log pesticide application was weakly and positively associated with age-adjusted PD mortality in 2008–2012 (r = .096; population-only $\beta = 0.240$, p = .002) and null in 2003–2007. This weak association was robust to normalizing exposure by land area and to removing high-use counties. However, it did not survive further scrutiny. Exposure and regression residuals showed strong positive spatial autocorrelation (Moran's I ≈ 0.47 and ≈ 0.20, p = .001), violating the independence assumption; adjustment for population density, region, county age structure, median household income, and racial composition reduced the 2008–2012 coefficient to essentially zero ($\beta = 0.003$, p = .97; partial $R^2 \approx 0.000$); and a negative-binomial count model with a population offset showed no significant association (incidence rate ratio ≈ 1.06, p = .14). The data therefore do not support a robust county-level association between agricultural pesticide application and later PD mortality. The apparent weak positive gradient is explained by geographic, demographic, and socioeconomic confounding. The study is ecological and hypothesis-generating; stronger inference will require longer exposure windows, incidence data, individual-level exposure, and chemical-specific histories.

Keywords: Parkinson's disease; pesticides; environmental epidemiology; ecological study; confounding; spatial autocorrelation; mortality; USGS EPest; CDC WONDER

INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disorder marked by bradykinesia, rigidity, tremor, gait dysfunction, and a wide range of nonmotor symptoms that include sleep disruption, autonomic disturbance, constipation, and cognitive decline. The National Institute of Neurological Disorders and Stroke

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identifies age, sex, heredity, and environmental exposure among the major risk factors associated with PD, while also emphasizing that most cases are sporadic rather than fully attributable to a single inherited mutation (1). That combination of partial heritability and incomplete explanation by genetics has made environmental epidemiology particularly important within Parkinson's research.

Among the environmental factors discussed in the literature, pesticides are a strong candidate. Agricultural chemicals are widespread, vary substantially across regions, and include compounds with known neurotoxic properties. Epidemiologists have therefore asked whether occupational use, residential proximity, or broader regional application patterns are associated with higher PD risk. There is growing reason to take this seriously: a Global Burden of Disease analysis estimated that the number of people living with Parkinson's disease more than doubled between 1990 and 2016 and that age-standardized prevalence rose roughly 22 percent over the same period, making PD the fastest-growing neurological disorder by several measures (2). Because environmental risk factors are more modifiable than age or inheritance, refining what is known about pesticide exposure is one of the more practical places for public health to act.

At the same time, linking pesticides to PD is methodologically difficult. Parkinson's disease develops slowly, often begins years before diagnosis, and may not appear on death certificates in every patient who lives with the disorder. Exposure itself is difficult to reconstruct retrospectively because individuals move, work in multiple settings, and encounter mixtures rather than isolated chemicals. These challenges explain why much of the literature relies on case-control designs, self-reported occupational histories, or regional exposure registries rather than national geographic comparisons. Public administrative data can nonetheless contribute a useful complementary perspective if interpreted with appropriate caution.

The broader epidemiologic literature generally supports the proposition that pesticide exposure is associated with Parkinson's disease risk, although the strength of association varies across study designs and chemical categories. One early meta-analysis reported a combined odds ratio of 1.94 for pesticide exposure overall and 2.15 for studies conducted in the United States, suggesting that the relationship was already visible across the first wave of observational studies (3). Later reviews reached similarly cautious conclusions rather than dismissing the association. A synthesis of 104 studies, for example, concluded that exposure to pesticides or solvents increases PD risk and showed that heterogeneity falls when study quality improves (4).

Prospective and occupational studies have reinforced that general pattern. A large prospective cohort study found that participants reporting pesticide exposure had a 70 percent higher risk of Parkinson's disease than those without such exposure, an especially important finding because it reduced the concern that people with PD were merely overreporting past exposures after diagnosis (5). A case-control analysis nested within the Agricultural Health Study sharpened the argument by focusing on pesticides selected for biologic plausibility, finding that rotenone and paraquat were each associated with odds ratios of 2.5 and that the associations aligned with mechanisms already implicated in laboratory models of PD (6).

The literature is also notable for its recurring emphasis on chemical specificity. Broad categories such as "pesticides" combine herbicides, insecticides, fungicides, and persistent organochlorines that differ greatly in neurotoxic potential. Paraquat and maneb or mancozeb have been associated with about a twofold increase in risk in high-quality case-control studies (4), and a recent meta-analysis reported that organochlorine pesticide exposure was associated with higher PD risk overall, though the magnitude varied by exposure assessment and region (7). The implication is that the absence of a strong relationship for one composite exposure metric does not refute the possibility that certain chemicals matter substantially, and that national county-level analyses based on total kilograms are likely to dilute effects that are chemical-specific.

Mechanistic evidence makes pesticide exposure a credible biological candidate. A review of environmental toxicology in PD argues that toxicants, including pesticides, can reproduce elements of PD pathology in model systems (8). c-Jun N-terminal kinase 3 has been shown to mediate dopaminergic-neuron death induced by paraquat and rotenone (9), and both compounds have been framed in terms of mitochondrial dysfunction and oxidative stress (6). These findings do not prove that county-level use causes county-level mortality, but they make the hypothesis biologically plausible enough to warrant population-level testing.

The timing problem is central to interpreting any pesticide–PD association. Parkinson's disease does not begin when it is diagnosed, and diagnosis does not occur when death occurs. Patients have retrospectively reported a mean interval of 10.2 years between the onset of

prodromal symptoms and the initial diagnosis of PD (10). A much larger Veterans Affairs analysis estimated that some prodromal disorders emerge 15 to 20 years before diagnosis (11). Mortality adds yet another layer of lag: in a nationwide cohort, 46.0 percent of diagnosed patients survived 10 years after diagnosis, with relative survival still 58.8 percent at 10 years (12). For an ecological study that relies on death rather than onset, these timing studies imply that a short exposure–outcome window may miss relevant etiologic processes.

Mortality-based studies occupy an ambiguous but valuable place in this literature. Death certificates capture only cases in which Parkinson's disease is recorded as an underlying cause, yet mortality data are often more geographically comprehensive than incidence registries. One California study found that Parkinson's mortality was higher in agricultural pesticide-use counties than in nonuse counties and observed a dose-response pattern for insecticide use measured as land treated, showing that ecological mortality research can detect meaningful geographic patterns even when the design remains indirect (13).

Despite this considerable body of work, the existing literature still has clear limits when read at the population scale. First, most of the strongest causal evidence comes from individual-level designs, which answer a narrower question than whether pesticide patterns visible in administrative data track later disease burden nationally (5, 6, 13). Second, with the partial exception of the California mortality work (13), most ecological comparisons have been state-specific or regionally bounded, and few recent studies link national county-level exposure estimates (14, 15) with national county-level mortality (16). Third, and most directly motivating the original design, many ecological analyses pair exposure and outcome from roughly contemporaneous windows, which can understate a real relationship by collapsing a long induction period into a short observation period.

This study responds to these limits by linking USGS EPest data from 1998–2002 with CDC WONDER mortality records for 2003–2007 and 2008–2012, treating the difference between the two windows as a built-in lag check, and, in this revision, testing whether any observed association is robust to exposure definition, spatial dependence, multivariable confounding adjustment, and count-based modeling. The aim is deliberately narrow and hypothesis-generating: to test whether the broad national patterns predicted by individual-level studies are visible, and robust, in independent public data.

Accordingly, the research question is: To what extent is county-level agricultural pesticide application from 1998–2002 associated with county-level Parkinson's disease mortality in 2003–2007 and 2008–2012, and does any such association persist under adjustment for confounding and appropriate model specification? The study originally hypothesized that counties with higher pesticide application would show higher PD mortality, more apparently in the later window. Because the design is ecological, the analysis is framed as hypothesis-generating rather than confirmatory.

METHODS AND MATERIALS

Data Sources

Two publicly available administrative datasets provided the basis for this analysis. The exposure data were obtained from the U.S. Geological Survey (USGS) Pesticide National Synthesis Project, which publishes annual estimated agricultural pesticide use for counties of the conterminous United States as part of the EPest series (14, 15). The five county-level files used here cover 1998 through 2002 and were drawn from USGS Data Series 752 (14). Each record reports a pesticide compound, year, state and county Federal Information Processing Standard (FIPS) codes, and two kilogram estimates labeled EPest-low and EPest-high. EPest-low treats unsurveyed pesticide–crop combinations as zero use, while EPest-high imputes a rate from neighboring Crop Reporting Districts (15). County estimates carry greater uncertainty than larger-area summaries.

The outcome data were obtained from the Centers for Disease Control and Prevention's WONDER Underlying Cause of Death system (16), queried for ICD-10 code G20 (Parkinson's disease), for 2003–2007 and 2008–2012. Each file reports county name and code, deaths, population, crude rate, age-adjusted rate, and notes. Counts of one to nine deaths are suppressed, and rates are flagged unreliable when fewer than 20 deaths underlie the rate.

For the revised analyses, county-level covariate and geographic data were added from two additional public sources. County land area and internal-point coordinates were taken from the U.S. Census Bureau 2020 county gazetteer (18), and county socioeconomic and demographic covariates (median household income, median age, and percent White) were taken from the American Community Survey (ACS) 5-year estimates (19), using the 2005–2009 release for the 2003–2007 window and the 2008–2012 release for the 2008–2012

window. Census region was derived from state FIPS. All datasets are public, contain no individual identifiers, and are joinable at the county FIPS level, which sets the unit of analysis. No personal health information was used.

Exposure, Outcomes, and Covariates

Pesticide exposure was operationalized as the midpoint of EPest-low (missing set to zero) and EPest-high (missing set to the low value), summed across all compounds within each county-year and averaged across 1998–2002. Because pesticide kilograms were highly right-skewed, exposure was transformed as $\log_{10}(kg + 1)$. To address the concern that total kilograms conflate application with county size, a normalized exposure, kilograms per square kilometer of land area, was also computed and log-transformed. The mortality outcomes were the county crude death rate per 100,000 and, where CDC WONDER did not flag it unreliable, the published age-adjusted death rate per 100,000; the age-adjusted rate is treated as the primary outcome. Covariates were $\log_{10}$ average annual population (scale), $\log_{10}$ population density (persons per square kilometer, an urbanicity/rurality proxy), county median age, $\log_{10}$ median household income, percent White, and Census region.

Data Preparation and County Matching

Metadata and footer rows were removed from the CDC WONDER files by retaining only rows with numeric five-digit county codes. Five-digit FIPS codes were generated in all datasets to support a one-to-one join, and mortality data were inner-joined to the county exposure file. After restriction to counties appearing in both the exposure and mortality data, the matched sample included 1,446 counties for 2003–2007 and 1,554 counties for 2008–2012; published age-adjusted rates were numeric for 852 and 972 counties, respectively. County crude rates were recomputed directly from deaths and population. The reconstructed pipeline reproduced the previously reported county counts, total deaths, and age-adjusted correlations exactly, and the crude-rate correlations to within 0.003; the small differences reflect the exposure-aggregation convention and do not affect any conclusion.

Statistical Analysis

Analyses proceeded from simple to fully specified. Pearson and Spearman correlations assessed association between log pesticide application and county mortality. Ordinary least squares (OLS) regression then modeled mortality on log pesticide application, following the bivariate form in Equation 1 (17), first controlling only for log population and then adding the covariates above.

$$Y = \beta_0 + \beta_1 X + \varepsilon \quad (1)$$

In Equation 1, Y is the county PD mortality rate per 100,000, X is $\log_{10}$-transformed pesticide application, β_0 is the intercept, β_1 is the slope on X, and ε is the error term. Additional predictors enter as further terms.

The lag-aware comparison repeated the framework across the two mortality windows against the single 1998–2002 exposure measure, indexed explicitly in Equation 2 (17).

$$\text{Mortality}_t = \beta_0 + \beta_1 \cdot \text{Pesticide}_{(t-n)} + \varepsilon \quad (2)$$

In Equation 2, Mortality_t is the county PD mortality rate per 100,000 in window t (2003–2007 or 2008–2012), and $\text{Pesticide}_{(t-n)}$ is $\log_{10}$-transformed county pesticide application measured n years earlier (fixed at 1998–2002); β_0, β_1, and ε retain their meanings from Equation 1.

Four additional analyses were added in revision. First, spatial dependence was assessed with Moran's I using a row-standardized eight-nearest-neighbor spatial weights matrix built from county internal-point coordinates, applied to the exposure and to the OLS residuals, with significance from 999 permutations. Second, because adjacent counties are not independent, OLS models were refitted with heteroscedasticity-consistent (HC3) and state-clustered standard errors. Third, death counts were modeled directly with Poisson and negative-binomial regression using a log-population offset, which is a more principled specification than a crude rate that already contains population in its denominator; overdispersion was assessed by the Pearson χ^2/df ratio. Fourth, influential observations were examined with Cook's distance (threshold $4/n$), and the incremental contribution of pesticide application was quantified with standardized coefficients and partial R^2 (the change in R^2 from adding pesticide to the covariate model, divided by one minus the covariate-only R^2).

Statistical Software and Thresholds

Analyses were conducted in Python 3.12.3 using pandas 3.0.2, NumPy 2.4.4, SciPy 1.17.1, and statsmodels 0.14.6, with libpysal 4.15.0 and esda 2.10.0 for spatial weights and Moran's I. Statistical significance was evaluated at a two-sided $\alpha = .05$. Correlation p-values

were obtained from the t distribution and 95% confidence intervals from the Fisher z transformation; regression coefficients are reported with 95% confidence intervals and p-values.

Sensitivity Analyses, Integrity, and Ethics

Three original sensitivity checks were retained: substituting EPest-low and EPest-high for the midpoint, trimming the top 5 percent of exposure counties, and an exploratory longitudinal comparison among counties present in both windows. All calculations were executed programmatically and cross-checked against CDC WONDER's published fields; no statistics were fabricated or imputed. Because both primary data sources are public and contain no identifiers, and the study involved no human subjects, no Institutional Review Board review was required.

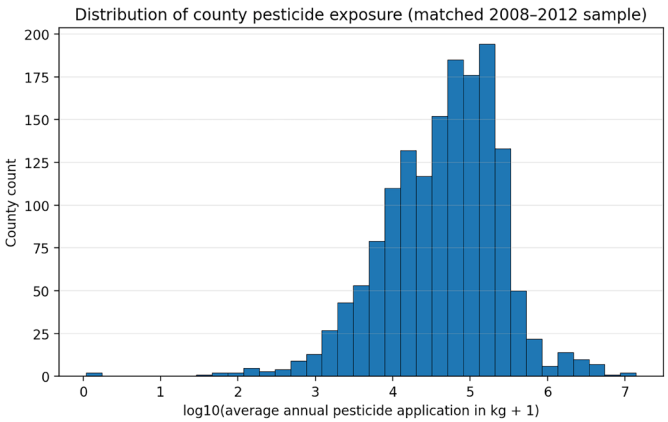

Figure 1. *Distribution of log-transformed average annual county pesticide application, 2008–2012 matched sample. The distribution remains right-skewed after log transformation, with a long upper tail of high-use counties, which motivated using log-transformed exposure in the analyses that follow.*

RESULTS

Descriptive patterns appear in Table 1. After matching, the 2003–2007 sample contained 1,446 counties (852 with reliable age-adjusted rates) and the 2008–2012 sample contained 1,554 counties (972 reliable). Crude mortality burden rose from 6.69 to 7.35 per 100,000 and mean age-adjusted mortality from 7.41 to 7.72 (Table 1).

Unadjusted and Population-Only Associations

The core baseline associations are shown in Table 2. In the full crude-rate sample, log pesticide application and PD mortality were positively but weakly related in both periods (Pearson r = .088 in 2003–2007 and .102 in 2008–2012, both $p < .001$). In the age-adjusted subset the association was null in 2003–2007 (r = .024, p = .484) and weak but significant in 2008–2012 (r = .096, p = .003). Population-only OLS gave a 2008–2012 age-adjusted coefficient of 0.240 (95% CI 0.090 to 0.390, p = .002) and a null 2003–2007 coefficient. A formal Fisher z comparison of the two age-adjusted correlations was not significant (z = 1.54, p = .12; Figure 2), so the later window is described as showing a more apparent point estimate, not a statistically stronger association. Figure 3 visualizes the 2008–2012 age-adjusted pattern.

Robustness to Exposure Definition and Outliers

The weak positive association was not an artifact of using total kilograms or of a few high-use counties. Normalizing exposure to kilograms per square kilometer preserved the pattern and, in 2008–2012, slightly strengthened it: the age-adjusted correlation rose from r = .096 (total kilograms) to r = .120 ($p < .001$) per unit area, while the 2003–2007 age-adjusted association remained null (r = .020). Removing the top 5 percent of exposure counties raised, rather than eliminated, the later-period age-adjusted correlation (from .096 to .177) and the earlier-period correlation (from .024 to .113; Figure 4), and substituting EPest-low or EPest-high for

Table 1. *Descriptive summary of counties matched across pesticide and Parkinson's disease mortality datasets.*

Period	Matched counties	Reliable age-adjusted counties	Total deaths	Overall crude rate	Mean age-adjusted rate	Median annual pesticide kg (IQR)
2003–2007	1,446	852	85,017	6.69	7.41	54,439 (14,718–146,760)
2008–2012	1,554	972	99,180	7.35	7.72	54,119 (14,236–148,004)

Note. *Crude rates are deaths per 100,000 in the matched sample. Age-adjusted rates are means across counties not flagged unreliable. Median pesticide application refers to the midpoint of EPest-low and EPest-high, summed across compounds and averaged across 1998–2002.*

Table 2. *Baseline county-level association between average annual pesticide application (1998–2002) and later Parkinson's disease mortality.*

Period	Outcome	N	Pearson r [95% CI], p	Spearman ρ [95% CI], p	Population-only β [95% CI], p	R^2
2003–2007	County crude rate	1,446	.088 [.037, .139] p < .001	.096 [.045, .147] p < .001	0.384 [0.159, 0.609] p < .001	0.212
2003–2007	Age-adjusted rate (reliable subset)	852	.024 [−.043, .091] p = .484	.013 [−.054, .080] p = .705	0.038 [−0.118, 0.195] p = .634	0.093
2008–2012	County crude rate	1,554	.102 [.053, .151] p < .001	.096 [.046, .145] p < .001	0.517 [0.285, 0.750] p < .001	0.214
2008–2012	Age-adjusted rate (reliable subset)	972	.096 [.033, .158] p = .003	.070 [.007, .132] p = .029	0.240 [0.090, 0.390] p = .002	0.103

Note. *Pearson correlations use $\log_{10}$(total pesticide kg + 1). Correlation p-values are from the t distribution and 95% CIs from the Fisher z transformation; regression p-values from the coefficient and 95% CI. The β is from OLS including $\log_{10}$ population as the sole covariate, so these are population-only, not confounder-adjusted, estimates. R^2 largely reflects county population; see Table 3 and the text for the incremental contribution of pesticide application.*

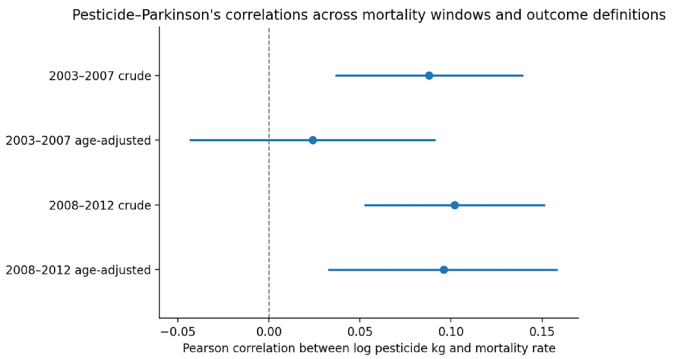

Figure 2. *Pearson correlations across mortality windows and outcome definitions, with 95 percent confidence intervals. The later mortality window shows more positive point estimates, but the confidence intervals overlap and a formal comparison did not establish a significant difference between periods.*

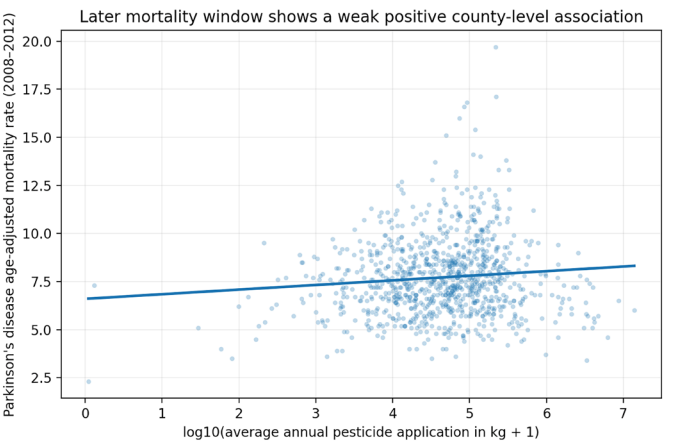

Figure 3. *County-level pesticide application and age-adjusted Parkinson's disease mortality, 2008–2012. Each point is one county with a reliable age-adjusted rate. The fitted line reflects the weak positive unadjusted association (r = .096, p = .003) that is examined for robustness in the analyses that follow.*

the midpoint produced nearly identical correlations. The association was therefore stable to how exposure was defined and was not driven by extreme counties.

Spatial Dependence

Both the exposure and the regression residuals were strongly spatially clustered, violating the OLS assumption of independent observations. Moran's I for log pesticide application was 0.455 in 2003–2007 and 0.471 in 2008–2012 (expected I ≈ 0, p = .001), and Moran's I for the residuals of the population-only age-adjusted model was 0.203 and 0.204, respectively (p = .001). Because significance tests that assume independence are therefore overstated, the population-only models were refitted with robust standard errors. HC3 standard errors left the 2008–2012 age-adjusted coefficient significant (p = .002), but clustering standard errors by state, a coarse adjustment for spatial dependence, rendered it non-significant (p = .08), a first indication that the association is geographically structured.

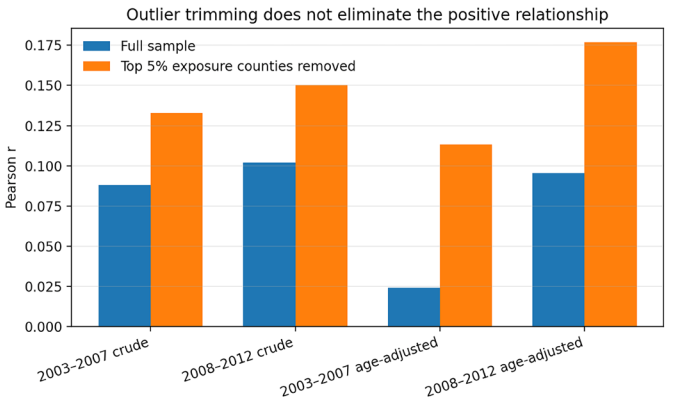

Figure 4. *Sensitivity of correlation estimates to trimming the top 5 percent of exposure counties. Positive associations persist after trimming, indicating that the baseline result is not driven by a small number of extreme high-use counties.*

Multivariable Adjustment and Count Models

The weak positive association did not survive adjustment for confounding, as shown in Table 3. Adding population density and Census region reduced the 2008–2012 age-adjusted coefficient from 0.240 to 0.059 (p = .50), and adding county age structure, median household income, and racial composition reduced it further to 0.003 (p = .97). In the earlier window the coefficient became negative once density and region were added (-0.194, p = .034) and remained negative under full adjustment (−0.238, p = .007); a negative, apparently protective coefficient is not biologically plausible and indicates that the exposure coefficient is unstable and dominated by confounding structure rather than a consistent exposure–outcome relationship. Figure 5 shows this attenuation across specifications for the 2008–2012 age-adjusted model.

Modeling death counts directly told the same story. Poisson models were severely overdispersed (Pearson χ^2/df ≈ 8), so their small p-values are artifacts of the specification; the appropriate negative-binomial model with a log-population offset showed no significant pesticide association even before covariates (incidence rate ratio 1.06 per tenfold increase, 95% CI 0.99 to 1.14, p = .08 in 2008–2012) and remained null after full covariate adjustment (IRR 1.06, p = .14). Consistent

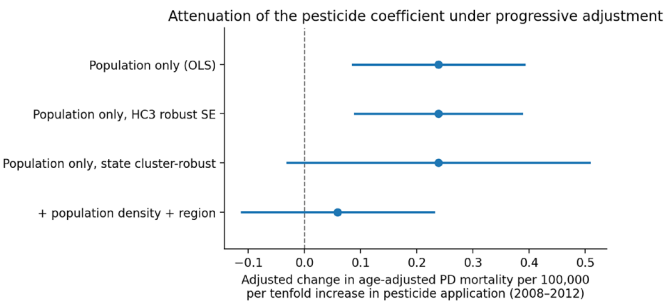

Figure 5. *Attenuation of the 2008–2012 age-adjusted pesticide coefficient under progressive adjustment. The coefficient (change in age-adjusted mortality per 100,000 per tenfold increase in application) is shown with 95 percent confidence intervals for the population-only model, the same model with HC3 and state-clustered robust standard errors, and the model further adjusted for population density and region. Adding covariates moves the estimate toward the null.*

Table 3. *Age-adjusted pesticide coefficient under progressive adjustment, and negative-binomial mortality models with a population offset.*

Model	2003–2007 estimate [95% CI], p	2008–2012 estimate [95% CI], p
OLS β, population only	0.038 [−0.118, 0.195], p = .634	0.240 [0.090, 0.390], p = .002
OLS β, + density + region	−0.194 [−0.372, −0.015], p = .034	0.059 [−0.112, 0.230], p = .497
OLS β, + age + income + race	−0.238 [−0.411, −0.064], p = .007	0.003 [−0.164, 0.171], p = .969
Negative binomial IRR, population offset	1.053 [0.983, 1.129], p = .142	1.062 [0.992, 1.136], p = .084
Negative binomial IRR, + full covariates	1.046 [0.967, 1.132], p = .257	1.061 [0.982, 1.146], p = .136

Note. *OLS β is the change in age-adjusted mortality per 100,000 per tenfold increase in pesticide application; the negative-binomial IRR is the incidence rate ratio for death counts per tenfold increase, with a log-population offset. Covariate sets are cumulative: "density + region" adds log population density and Census region; "+ age + income + race" further adds county median age, log median household income, and percent White. The 2003–2007 negative coefficient under full adjustment is not interpreted as protective; it reflects instability of the exposure coefficient under confounding. Partial R^2 for pesticide in the fully adjusted 2008–2012 age-adjusted model was 0.000.*

with this, the incremental contribution of pesticide application was negligible: its partial R^2 in the fully adjusted 2008–2012 age-adjusted model was 0.000, and its standardized coefficient in the population-only model was 0.09. Forty influential counties (Cook's distance > 4/*n*) were identified in 2008–2012; removing them left the population-only coefficient positive (0.19, p = .01), confirming that the baseline association, while not outlier-driven, is fully explained by confounding rather than by pesticide application itself.

An exploratory longitudinal comparison among counties present in both windows was consistent with the main analysis: pesticide application was only weakly associated with change in crude mortality (1,313 counties, r = .041, p = .142) and change in age-adjusted mortality (794 counties, r = .070, p = .048), and is treated as exploratory.

DISCUSSION

The revised analysis does not support the study hypothesis. County-level pesticide application from 1998–2002 showed a weak positive association with later PD mortality in unadjusted and population-only models, and that association was robust to normalizing exposure by land area and to removing high-use counties. However, once the analysis accounted for the structure of the data, the association disappeared. Exposure and residuals were strongly spatially autocorrelated; adjustment for population density, region, age structure, income, and racial composition reduced the 2008–2012 age-adjusted coefficient to essentially zero; the appropriate negative-binomial count model showed no significant association; and pesticide application contributed effectively no incremental explanatory variance. The most defensible conclusion is that the apparent weak gradient reflects confounding, not a pesticide effect.

This pattern is coherent. Agricultural pesticide application is highly clustered geographically and is correlated with rurality, regional composition, socioeconomic status, and the demographic and diagnostic characteristics of counties, all of which also shape recorded PD mortality. A population-only ecological model cannot separate a pesticide signal from those correlated features, and the strong residual spatial autocorrelation observed here shows directly that the model omits geographically structured determinants of mortality. When those determinants are partially captured by covariates, the pesticide coefficient collapses. The sign reversal in the earlier window under full adjustment underscores that the exposure coefficient is unstable rather than capturing a stable biological effect.

These null results do not contradict the individual-level literature, which uses direct exposure measures, narrower chemical categories, and diagnosed cases to report elevated risk for specific compounds such as rotenone and paraquat (4,6). Rather, they show the limits of ecological, total-kilogram, mortality-based data for detecting such effects. Ecological dilution, chemical aggregation, the use of death rather than onset, and heavy confounding by geography together make a shallow, non-robust gradient the expected result even if a true individual-level relationship exists. The earlier California ecological finding (13) was based on within-state comparisons with different exposure and design choices and is not contradicted by a national analysis that cannot adjust it away.

The lag comparison should be read cautiously. The point estimates were somewhat more positive in the later mortality window, which is compatible with the long prodromal and survival intervals reported for PD (10–12), but the two windows were not statistically distinguishable and the later-window association did not survive adjustment. The difference between windows is therefore best described as a weak temporal pattern in the unadjusted data, not as evidence of a specific biological induction period, particularly because the etiologically relevant exposure may predate the measured window and county of residence during that period is unknown.

Implications and Future Research

The public-health implication is limited and cautionary rather than actionable. The analysis provides no evidence that county pesticide application predicts PD mortality once confounding is addressed, and any surveillance or monitoring decision based on a raw geographic gradient would be vulnerable to precisely the confounding and spatial selection documented here. The more useful contribution is methodological: it shows that national county-level, total-kilogram, mortality-based designs are poorly suited to detecting pesticide–PD effects, and it quantifies how quickly an apparent association attenuates under adjustment. Future work should use longer historical and chemical-specific exposure windows, incidence or diagnosis data rather than mortality, exposure normalized to cropland or agricultural labor, individual- or small-area exposure assignment, and models that explicitly handle spatial dependence, so that a genuine toxicologic signal, if present, can be distinguished from geographic confounding.

Limitations

Several limitations bound interpretation. The design is ecological: county pesticide application is not individual exposure, and county mortality is not individual onset, so the study identifies geographic co-patterning, not personal causation. Exposure is a modeled total-kilogram burden proxy (15) that aggregates chemicals of differing toxicity; although a per-area version was tested, no chemical-specific, dose, or proximity information was available. The covariate set, while it now includes urbanicity, region, age structure, income, and race, still omits potentially important confounders such as smoking prevalence, occupational structure, well-water use, healthcare access, and diagnostic and coding practices, so residual confounding remains and the fully adjusted estimates are not causal. ACS covariates were drawn from the closest available 5-year windows and, for 2003–2007, postdate the mortality period slightly. Outcome measurement is limited by CDC WONDER's underlying-cause coding and suppression rules, which exclude small-count counties and bias the sample toward places with more recorded deaths; the age-adjusted subset is narrower still. Finally, the spatial analysis used a nearest-neighbor weights matrix and robust or clustered standard errors rather than a full spatial-econometric model; the consistent attenuation across OLS, robust, clustered, and count specifications nonetheless supports the conclusion.

CONCLUSION

Using county-level pesticide estimates from 1998–2002 and PD mortality from 2003–2007 and 2008–2012, this study found a weak positive association in unadjusted and population-only models that was robust to exposure definition and to outlier removal but did not survive adjustment for spatial dependence, geographic and demographic confounding, or count-based modeling. The fully adjusted association was null, and pesticide application added essentially no incremental explanatory value. The data therefore do not support a robust county-level association between agricultural pesticide application and later Parkinson's disease mortality; the apparent gradient is best explained by confounding. The hypothesis is not supported once the analysis is properly specified, and stronger inference will require longer and chemical-specific exposure windows, incidence data, individual- or small-area exposure, and designs built to separate a pesticide signal from the geography that surrounds it.

FUNDING SOURCES

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CONFLICT OF INTEREST

The author declares no conflicts of interest related to this work.

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