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ARTICLE

Air pollution and risk of hospitalization for epilepsy: the role of farm use of nitrogen fertilizers and emissions of the agricultural air pollutant, nitrous oxide

Poluição do ar e risco de hospitalização por epilepsia: o papel do uso agrícola de fertilizantes nitrogenados e as emissões de poluente atmosférico agrícola, óxido nitroso

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ABSTRACT

The link between various air pollutants and hospitalization for epilepsy has come under scrutiny. We have proposed that exposure to air pollution and specifically the pervasive agricultural air pollutant and greenhouse gas, nitrous oxide (N_2O), may provoke susceptibility to neurodevelopmental disorders. Evidence supports a role of N_2O exposure in reducing epileptiform seizure activity, while withdrawal from the drug has been shown to induce seizure-like activity. Therefore, we show here that the statewide use of anthropogenic nitrogen fertilizers (the most recognized causal contributor to environmental N_2O burden) is significantly negatively associated with hospitalization for epilepsy in all three pre-specified hospitalization categories, even after multiple pollutant comparison correction ($p<.007$), while the other identified pollutants were not consistently statistically significantly associated with hospitalization for epilepsy. We discuss potential neurological mechanisms underpinning this association between air pollutants associated with farm use of anthropogenic nitrogen fertilizers and hospitalization for epilepsy.

Keywords: epilepsy; hospitalization; air pollution; fertilizers; nitrous oxide.

RESUMO

A ligação entre vários poluentes do ar e a hospitalização por epilepsia tem sido examinada. Propusemos que a exposição à poluição do ar, especificamente ao poluente atmosférico generalizado e ao gás de efeito estufa, o óxido nitroso (N_2O), poderiam fomentar a susceptibilidade a distúrbios do desenvolvimento neurológico. A evidência apoia o papel da exposição ao N_2O na redução da atividade convulsiva epileptiforme, enquanto mostra que a retirada do fármaco induz atividade pseudo-convulsiva. Portanto, mostramos aqui que o uso a nível estatal de fertilizantes nitrogenados antropogênicos (o agente causal mais reconhecido para a carga ambiental de N_2O) está significativa e negativamente associado à hospitalização por epilepsia nas três categorias de hospitalização pré-especificadas, mesmo após a correção de comparação de poluentes múltiplos ($p <0,007$), enquanto os outros poluentes identificados não foram consistentemente associados de forma estatística com a hospitalização por epilepsia. Discutimos possíveis mecanismos neurológicos subjacentes a esta associação entre poluentes atmosféricos associados ao uso agrícola de fertilizantes nitrogenados antropogênicos, e hospitalização por epilepsia.

Palavras-chave: epilepsia; hospitalização; poluição do ar; fertilizantes; óxido nitroso.

The link between air pollution and epilepsy has come under recent scrutiny. Scorza et al.[1] have proposed that urban air pollution may be a significant factor influencing human health and, particularly, sudden unexpected death in epilepsy. As part of their analysis, the authors suggested nutritional interventions that may ameliorate epilepsy risk, including intake of omega-3 fatty acids[1]. Empirical evidence in support of a link between air pollution and epilepsy has emerged in recent years. Cakmak et al.[2] performed a daily time-series analysis of the association between gaseous and particulate matter air pollution and hospitalization for epilepsy in Chile. The authors reported pooled city estimates of relative risk for hospitalization for epilepsy associated with changes in concentrations of various pollutants including nitrogen dioxides (NO_2), carbon monoxide (CO), sulfur dioxide (SO_2), ozone (O_3)), and particulate matter (both PM_{10}) and $PM_{2.5}$). The confidence

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intervals for all the identified pollutants indicated that air pollution may be a risk factor for hospitalizations for epilepsy. A hospital-record based investigation on the role of urban air pollution in epilepsy attack in a Chinese population has shown similar result, with a possible protective effect of ozone exposure[3]. Animal studies indicate that ozone exposure may exert a protective effect against pentylenetetrazole-induced seizures through the restoration of cellular redox balance and regulation of the A1 adenosine receptor[4]. These studies cumulatively provide evidence in support of the claims made by Scorza et al.[1] for a role of air pollution in modulating the risk of hospitalization for epilepsy.

Moreover, the work by Cakmak et al.[2] was cited in a recent review by Chilean health authorities and government officials conducting a workshop to better understand how the economic reclassification of the country has impacted environmental health with a goal of identifying important areas for future improvement[5]. One specific recommendation made by the expert panel was to incorporate aspects of climate change in the future study of the human health effects of air pollution. Consistent with these stated goals, we have recently proposed, through empirical investigation and review, that exposure to air pollution and specifically the pervasive air pollutant and greenhouse gas, nitrous oxide (N_2O), may provoke susceptibility to neurodevelopmental disorders, like attention-deficit hyperactivity disorder (ADHD) and autism spectrum disorders (ASD)[6,7,8,9]. Epilepsy is a recognized comorbidity in both ADHD and ASD[10,11,12]. We have previously highlighted clinical case reports[13], as well as several animal studies[14,15,16], which indicated the role of N_2O exposure in reducing epileptiform seizure activity[17], while withdrawal from the drug has been shown to induce seizure-like activity[14,15,16]. Our novel environmental N_2O-mediated hypothesis of neurodevelopmental impairment is supported by recent evidence indicating N_2O hotspots in central Chile, given the following statement from the work:

> "...in our study area (off central Chile), they have ΔN_2O three times higher than the average monthly ΔN_2O... the increased N_2O production seemed to be caused by the addition of anthropogenic NO_3^- associated with strong river runoff and a subsequent reduction to N_2O (i.e., partial denitrification)[18]."

However, the aforementioned analyses by Cakmak et al.[2], Xu et al.[3], and Mallok et al.[4] do not address the air pollutant, N_2O, in the discovered association between air pollution and risk for epilepsy hospitalization. Consistent with the future goals identified by Chilean health and government officials[5], we attempt to qualify the prior work by these research groups by performing regression analyses using a state-based total of farm use of anthropogenic nitrogen fertilizer, which is thought to be the major environmental contributor to N_2O emissions[18,19]. While we attempt to document prior associations, by Cakmak et al.[2] and others, between certain air pollution exposures and hospitalization for epilepsy for years 2001 to 2005, we also wish to test our hypothesis that increasing use of anthropogenic nitrogen-based fertilizers in agriculture (the most recognized causal environmental contributor to N_2O emissions) may be significantly and negatively associated with hospitalization for epilepsy. We rationalize this hypothesis by emphasizing prior clinical reports and animal studies indicating a N_2O-induced suppression of epileptiform activity. Coupled with our prior conclusions, this hypothesis, if supported, may support the co-morbid link between epilepsy and other neurodevelopmental disorders by suggesting both are related to exposure to (i.e., ADHD and ASD) or withdrawal from (i.e., epilepsy) environmental N_2O[6,7,8,9,17].

METHODS

For years 1997 to 2006, inclusive, we have gathered data on the state sum totals of farm use of nitrogen fertilizers (in kilograms)[20], described in the authors' prior epidemiological studies[7,9]. Although the United States Geological Survey of the U.S. Department of the Interior states that "no warranty expressed or implied is made by the U.S. Geological Survey as to the accuracy of the data," we believe the use of county data on a state aggregated level is consistent with the recommendations of the United States Geological Survey[20,21]. Moreover, other government agencies, like the Environmental Protection Agency, make similar disclaimers regarding data contained on their organization's website[22], yet researchers continue to utilize the Environmental Protection Agency data on air quality emissions[23].

To replicate the work by Cakmak et al.[2], the authors averaged all locale state estimations of the annual air concentration of the pollutants between 2001 to 2005 (NOx and SO_2) [one hour] in ppb, O_3 and CO [eight hour run average] in ppm; PM_{10} total 0-10mm standard temperature and pressure [24-hour] and $PM_{2.5}$mm [local conditions, 24 hour] in micrograms/cubic meter), using air quality data from the Environmental Protection Agency[24]. Our dependent condition of interest is hospitalization for both all-listed and principal diagnoses of epilepsy, derived from data using the Healthcare Cost and Utilization Project (HCUPnet)[25], as has been performed previously[7,9].

We conducted a Poisson regression methodology including two-way fixed effects. Briefly, a random variable Y is said to have a Poisson distribution with parameter m if it takes integer values $y = 0, 1, 2, \ldots$ with probability

$$Pr\{Y = y\} = \frac{e^{-\mu}\mu^{y}}{y!}$$

for $m > 0$. The mean and variance of this distribution can be shown to be $E(Y) = var(Y) = m$. We have a sample of

n observations of discharges related to epilepsy, y_1, y_2, ..., y_n, which are treated as realizations of independent Poisson random variables, with $Y_{ij} \sim P(m_{ij})$, where i represents a state and j an observation year. In order to test the robustness of hypothesized associations, we selected, *a priori,* several categories of epilepsy discharge diagnoses, including the clinical classification software category designations provided by HCUPnet (CCS 83: epilepsy, convulsions), using both the all-listed total and principal discharge diagnoses. The ICD9 codes that comprise this CCS category include 345.0, 345.00, 345.01, 345.1, 345.10, 345.11, 345.2, 345.3, 345.4, 345.40, 345.41, 345.5, 345.50, 345.51, 345.6, 345.60, 345.61, 345.7, 345.70, 345.71, 345.8, 345.80, 345.81, 345.9, 345.90, 345.91, 780.3, 780.31, 780.32, 780.33, 780.39. Additionally, we tested the independent ICD9 diagnostic code 345.xx for epilepsy (all-listed discharge diagnoses). We let the logarithm of the mean depend on a vector of time-varying explanatory variables, x_{ij}, such that the log-linear model is the following: $\log(m_{ij}) = x_{ij}'b_1$. Exponentiating, we have a multiplicative model for the mean discharges: $m_{ij} = \exp\{x_{ij}'b_1\}$. In each case, the exponentiated regression coefficient $\exp\{b_{1ijk}\}$ yields an incidence rate ratio, which represents a multiplicative effect of the kth predictor on the mean. Increasing x_k by one log-unit multiplies the mean by a factor $\exp\{b_{1k}\}$. All regression analyses and related diagnostics were performed using *R* (packages ggplot2 and sandwich with robust standard errors), as we have described previously[7,9].

Although we are unable to directly replicate the methodology of Cakmak et al.[2], we believe the strength of our two-way fixed effects Poisson statistical approach lies in the fact that we have both accounted for individual state-level heterogeneity among a greater number of locations (30 selected HCUP states versus seven Chilean urban centers) and controlled for correlations across a longer time series (10 years versus five years in the case of farm use of nitrogen fertilizers), thus reducing the likelihood for omitted variable bias in the modeling. While not considered by Cakmak et al.[2], this approach may be important, given the role that edaphology may play in the flux of environmental air contaminants[26], as well as the evolving legislation, especially in the United Sates, surrounding the regulation of air pollution over many decades[27].

RESULTS

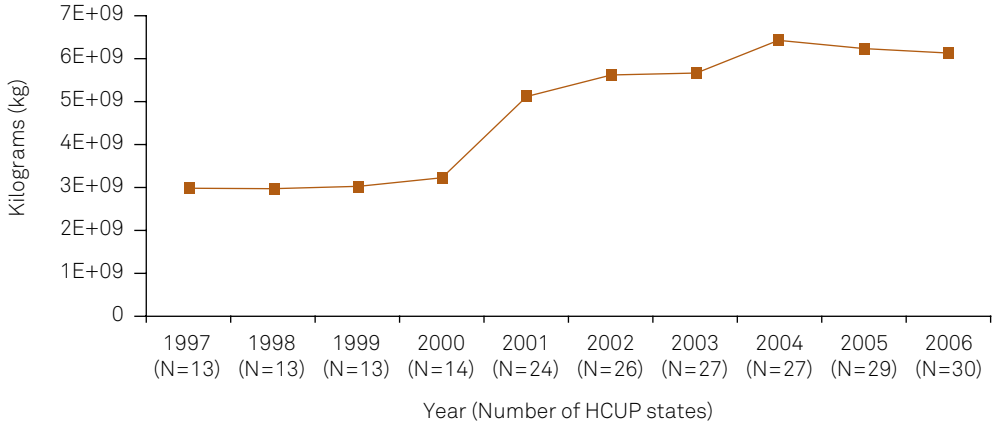
The percent changes of the various air pollutants studied in this investigation are presented in Table 1. All pollutants decreased in concentration level from 2001 to 2005, with carbon monoxide, nitrogen dioxide, and sulfur dioxide decreasing the most. Figure 1 shows the increase in the annual sum of farm use of nitrogen fertilizers for the selected HCUP available states between 1997 and 2006. Figure 2 presents the annual sum of hospitalization discharges associated with all three categories of epilepsy included in this brief report in the selected HCUP states.

Table 2 shows the results of our two-way fixed effects Poisson regression models. The data indicate that the air pollutants identified by Cakmak et al.[2] were not statistically significantly associated with hospitalization for all-listed diagnoses of epilepsy during the same time period after multiple comparison correction for the seven pollutants studied for each hospitalization category ($0.05/7 = p < 0.007$). Nitrogen dioxide concentration showed a slight protective effect against hospitalization for epilepsy (345.xx), particularly when the condition was the principal diagnosis, but the results did not retain statistical significance when adjusting for multiple pollutant

Table 1. Average (standard deviation) annual pollutant concentration across all reporting HCUP states, 2001-2005, with percent change.

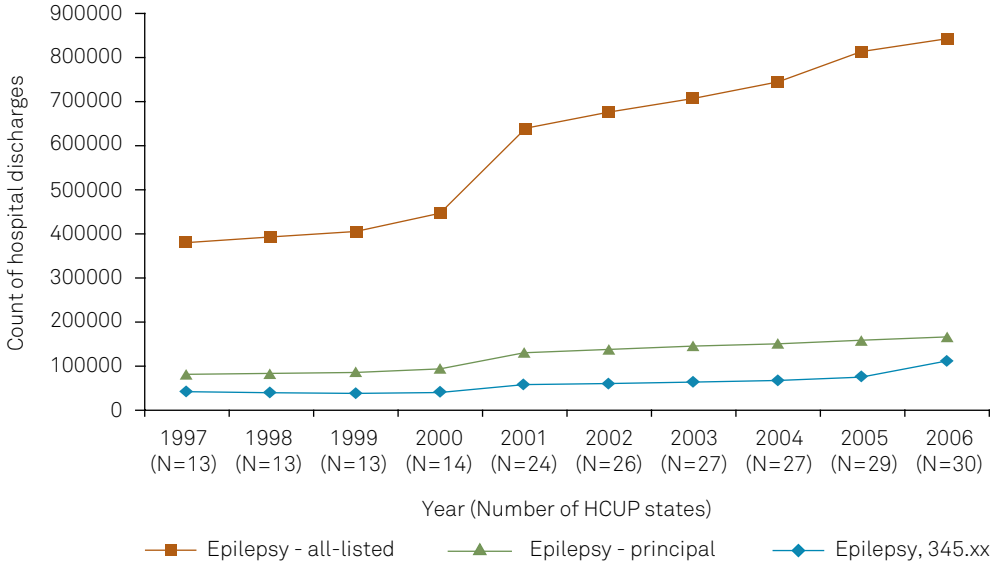
Year	Carbon monoxide (ppm)	Nitrogen dioxide (ppb)	Ozone (ppm)	PM_{10} (mg/m³)	PM_2 (mg/m³)	Sulfur dioxide (ppb)
2001	0.62 (0.22)	29.02 (7.84)	0.04630 (0.00561)	23.74 (5.28)	11.89 (2.36)	11.80 (6.68)
2002	0.63 (0.21)	27.19 (7.66)	0.04695 (0.00497)	23.47 (5.68)	11.36 (2.17)	10.64 (6.02)
2003	0.60 (0.18)	25.79 (7.60)	0.04582 (0.00411)	23.35 (4.81)	10.87 (2.25)	10.31 (5.86)
2004	0.55(0.17)	24.04 (7.31)	0.04293 (0.00382)	22.00 (4.50)	10.75 (1.98)	9.72 (5.95)
2005	0.51(0.16)	24.74 (7.07)	0.04625 (0.00475)	23.31 (4.93)	11.55 (2.38)	10.09 (5.50)
% change	-17.74	-14.75	-0.11	-1.81	-2.86	-14.49

HCUP: Healthcare Cost and Utilization Project.



HCUP: Healthcare Cost and Utilization Project

Figure 1. Annual sum of farm use of nitrogen fertilizers across all HCUP reporting states included in this analysis for all years available.



HCUP: Healthcare Cost and Utilization Project.

Figure 2. Annual sum of hospital discharge diagnoses across all HCUP reporting states included in this analysis for all years available. Categories include all-listed epilepsy discharges (Clinical Classification Software: 83), principal epilepsy discharges (Clinical Classification Software: 83), and all-listed epilepsy discharges using only ICD 9 classification code: 345.xx.

Table 2. Incident Rate Ratio of Hospitalization for Epilepsy Associated with a One Log-unit Change in Average Pollutant Concentrations using state and time fixed effects Poisson regression in R (packages ggplot2 and sandwich with robust standard errors) for all available HCUPnet states, United States, 2001–2005.

Pollutant (state-time obs)	Carbon monoxide (n = 131)		Ozone (n = 131)		Sulfur dioxide (n = 129)		Nitrogen Dioxide (n = 124)		PM_{10} (n = 131)		$PM_{2.5}$ (n = 128)		Farm nitrogen[a,b] (n = 216)	
Epilepsy Diagnosis	IRR	95%CI	IRR	95%CI	IRR	95%CI	IRR	95%CI	IRR	95%CI	IRR	95%CI	IRR	95%CI
All-listed	1.00	0.98–1.04	0.91	0.83–1.00	0.99	0.94–1.03	1.02	0.97–1.08	0.97	0.93–1.02	0.96	0.87–1.06	0.96	.93–.98*
Principal	1.02	0.96–1.08	0.91	0.78–1.07	0.98	0.93–1.03	0.93	0.88, 0.98	0.99	0.92–1.06	0.98	0.83–1.15	0.92	.88–.96*
ICD9 (345.xx)	1.09	0.98–1.21	0.76	0.59–0.97	0.99	0.91–1.08	0.85	0.74–0.97	0.95	0.85–1.07	0.95	0.77–1.17	0.82	0.74–0.90*

*p <.007, adjusted for multiple pollutant comparisons (.05/7 =.007); [a]period 1997–2006 to match the time period utilized in prior work[9] and controlling for non-farm use of nitrogen fertilizers; [b]as this variable acts as a proxy for air emissions of the agricultural pollutant, nitrous oxide (N_2O), which depend upon the total nitrogen applied, sum state totals were used and log transformed.
HCUP: Healthcare Cost and Utilization Project.

comparisons. However, a one-unit log increase in total annual farm use of nitrogen-based fertilizers in each state is significantly negatively associated with hospitalization for all three epilepsy categories studied. Further quartile analysis revealed that states above the 50th percentile of farm use of nitrogen fertilizer (i.e., heavy agricultural states) saw the greatest protective effect against hospitalization for epilepsy. States below this percentile had no protective effect (*data not shown*).

DISCUSSION

The results of this brief report suggest a possible link between agricultural air pollution, particularly the farm use of anthropogenic nitrogen fertilizers and associated emissions of N_2O, and hospitalization for epilepsy in 30 states included in the HCUP database. However, this finding is reliant on the assumption that farm use of anthropogenic nitrogen fertilizers represents an accurate estimation of environmental N_2O emissions. Although others have acknowledged this relationship[19], we must exert some hesitation with the underlying interpretation of our results. For example, the potential for bias in our results cannot be discounted, as the finding that the protective effect of farm use of nitrogen fertilizers against hospitalization for epilepsy may be associated with a more rural lifestyle that is less afflicted by stress, a recognized trigger for epilepsy[28]. However, this explanation is not consistent with our prior work showing a disproportionate burden in hospitalization for other mental health comorbidities, like ADHD (1997-2006), that occurs in these less populated areas, as we have discussed[7,9]. A more consistent explanation that our collective studies now afford is that exposure to environmental anthropogenic nitrogen fertilizers used in agriculture and associated emissions of N_2O may facilitate a continuum of psychiatric impairments; that is, increasing use of anthropogenic nitrogen fertilizers in agriculture and exposure to N_2O leads to ADHD symptoms (i.e., working memory impairments and inattention), and withdrawal and/or tolerance facilitates epileptiform activity. Molecular evidence of N_2O toxicity indicates an antagonism of N-methyl-D-aspartate receptors, which may undergo a rapid upregulation in response to N_2O withdrawal and/or tolerance, resulting in receptor hyperactivation and possible seizure generation[29], as has previously been cited and discussed[6,17].

We have attempted to replicate prior associations among other commonly studied air pollutants, like CO, O_3, NOx, SOx, and particulate matter but were not able to find consistent, statistically significant associations across the pre-specified hospitalization categories during the same time period studied by Cakmak et al.[2]. Additional analyses including a longer time series (1997-2006) were not able to alter these conclusions. These results suggest that future investigations seeking to elucidate the role of air pollution in risk of hospitalization for epilepsy should be expanded to include environmental emissions of the agricultural and combustion pollutant, N_2O, especially given the clinical evidence and preclinical animal studies directly associating N_2O exposure with epileptiform activity[13,14,15,16]. While a protective effect of ozone did not meet our statistical significance after multiple pollutant comparison correction, epidemiological evidence indicating a potential protective effect of ozone in epilepsy should also consider that the effect may have to do with the possible role of N_2O as an agent of ozone depletion[30], in addition to any independent cellular mechanisms possibly at play[4]. Similarly, while nitrogen amended soils may leach N_2O emissions, nitrogen dioxide fluxes may be minimized under conditions of agricultural fertilization[31].

The current finding merges critical concepts of climate change into the growing burden of chronic human neurological illness and, in particular, suggests an important direction to take in the study of epilepsy and related comorbidity. Recent reports are indicating that current Intergovernmental Panel on Climate Change guidelines are underreporting indirect emissions of N_2O by a magnitude from three- to nine-fold[32,33], while Intergovernmental Panel on Climate Change methodologies presuming linear increases in direct soil N_2O emissions as a function of nitrogen inputs may be missing true exponential rises in global emissions, especially under conditions of heavy fertilizer use (i.e., agriculture)[19]. Our data may be particularly revealing in this regard, considering that the greatest protective effect against hospitalization for epilepsy occurs in states that report the greatest amount of nitrogen fertilizers used in agriculture.

It is also interesting to further speculate on the association between environmental sources of N_2O and risk of hospitalization for epilepsy by recognizing that diurnal variation in N_2O flux[34] (i.e., greater in the afternoon hours) may be negatively related to the early morning risk of seizure in generalized epilepsy[35]. Though, more research is needed to understand what role, if any, environmental exposure to N_2O may have in human health assessments. While our presumption that the anthropogenic use of nitrogen fertilizers is directly reflective of environmental N_2O burden is a limitation of the analysis, it remains our suggestion that scientists may need to reconfigure their thinking about particular environmental pollutants, like N_2O, recognizing that agents long thought to carry little-to-no harm in the controlled and acute medical setting may not exist in the daily environment in a similar manner.

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The authors dedicate this work to Maddie Fluegge.

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