

Ground-Level Ozone Exposure and Cognitive Decline: Biomedical Innovations for At-Risk Brain Health

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Abstract

Ground-level ozone is a pervasive environmental pollutant and potent oxidative stressor that has been increasingly implicated in neurodegenerative processes. This study investigates the association between long-term ground-level ozone exposure and the prevalence of cognitive decline across 10 U.S. states (Arizona, California, Florida, Illinois, Massachusetts, North Carolina, New York, Ohio, Pennsylvania, and Texas) from 2021 to 2024, while exploring the role of biomedical engineering in mitigating these risks. An ecological regression analysis was conducted using state-level cognitive decline data from the CDC Behavioral Risk Factor Surveillance System (BRFSS) and daily maximum 8-hour ozone concentrations from EPA air quality datasets. Mean ground-level ozone concentrations were significantly positively correlated with cognitive decline prevalence ($p < 0.05$, $r = 0.486$). The regression model ($\beta_1 = 191.73$ per ppm; $SE = 56.67$) indicates that each 10-ppb increase in ground-level exposure is associated with a 1.92% increase in cognitive decline prevalence. Arizona exhibited the highest ozone concentrations (0.0480–0.0503 ppm), while both Arizona and Texas reported high cognitive decline prevalence. Biological literature supports these findings, linking ozone to chronic oxidative stress, neuroinflammation, and loss of synaptic plasticity in key regions such as the hippocampus. These findings highlight long-term ozone exposure as a significant environmental correlate of cognitive aging and underscore the need for biomedical engineering interventions, such as smart indoor air filtration, adaptive ventilation, real-time exposure monitoring, and neuroprotective therapeutics, to protect vulnerable populations.

Keywords: Ground-level ozone; Cognitive decline; Neurodegeneration; Biomedical engineering; Oxidative stress; Public health.

Introduction

Air pollution is increasingly recognized as a modifiable risk factor for chronic diseases, with ground-level ozone (O_3) posing a unique threat to public health due to its potent oxidative properties. Depending on geographical and seasonal factors, naturally occurring tropospheric baseline O_3 varies between 0.02 and 0.04 ppm (parts per million) (F. Gackière et al., 2011). Under the WHO Air Quality Guidelines, the threshold considered harmful to human health is an 8-hour daily maximum concentration exceeding $100 \mu\text{g}/\text{m}^3$ (approximately 50 parts per billion (ppb)). The 1943 Los Angeles photochemical smog event aroused public awareness of O_3 air pollution for the first time (Haagen-Smit, 1952; Jacobs, 2025). On July 26, 1943, a thick, blinding haze enveloped the city, reducing visibility to blocks and causing widespread respiratory and

ocular irritation. While initial public fears attributed the haze to wartime chemical attacks or emissions from a local synthetic rubber plant, the persistence of the haze led researchers to investigate unique environmental factors. O₃ was suspected as the key culprit rather than typical industrial pollutants (such as sulfur dioxide) due to distinct physical symptoms, including a sharp, bleach-like odor, unprecedented cracking of vulcanized rubber tires, and severe crop damage specific to strong oxidizers. Later lab analyses confirmed that O₃ was a secondary pollutant created through photochemical reactions between sunlight, nitrogen oxides, and unburned vehicular hydrocarbons (Haagen-Smit, 1952; Kean, 2016). While the respiratory and cardiovascular impacts of O₃ are well-documented, a growing body of evidence links long-term exposure to cognitive decline and the progression of neurodegenerative disorders (P.C. Bello-Medina et al, 2021; E. G. Cleary, 2017; Gao *et al.*, 2022; S. J. Genuis and K. L. Kelln, 2015). As populations age, understanding the environmental drivers of neurodegeneration becomes paramount for sustaining public health (D. Wood, 2024; R. Maynard *et al.*, 2023; R. E. Neale *et al.*, 2024).

This paper reviews existing literature and investigates the influence of ground-level ozone on cognitive function across 10 US states and the potential for biomedical engineering to provide protective solutions. By framing O₃ exposure within a multidisciplinary context, integrating toxicology, epidemiology, and engineering, this study aims to address the critical gaps in protecting vulnerable groups from atmospheric neurotoxins.

Background

Stratospheric vs. Ground-Level Ozone

Ozone exists in two distinct layers of the atmosphere. Stratospheric ozone, located 10 to 50 km above the Earth's surface, is essential for life as it filters harmful ultraviolet (UV) radiation. In contrast, ground- or surface-level (tropospheric) ozone is a secondary pollutant formed by photochemical reactions between nitrogen oxides (NO_x) and volatile organic compounds (VOCs) in the presence of sunlight. Ground-level ozone is a key component of urban smog and is highly reactive. Unlike stratospheric ozone, which is vital for planetary protection, tropospheric ozone acts as a powerful oxidant that directly damages biological tissues—primarily causing inflammation and cell damage in human respiratory epithelial tissues upon inhalation, while also inducing oxidative stress in exposed ocular and cutaneous tissues (EPA, 2026; Fuks et al., 2019; WHO, 2021).

Significance of Cognitive Decline in Population Health

Cognitive decline and neurodegenerative diseases, such as Alzheimer's Disease (AD) and Parkinson's Disease (PD), represent a substantial global health burden (Z. Gui et al, 2024; R. Maynard et al, 2023). The relationship between ambient air pollutants and cognitive function is particularly concerning for elderly populations, where long-term exposure to ground-level O₃ has been significantly associated with reduced performance in memory and executive function tasks

(Chen et al., 2022; Cleary et al., 2021). In large-scale cohorts, even low levels of ozone exposure have been correlated with accelerated cognitive aging (S. D. Ilango et al., 2025). Given that air pollution is a modifiable exposure, identifying its role in neurodegeneration offers a pathway for large-scale preventive measures that could reduce the severe burden on individual health and quality of life, while also alleviating the broader social and economic costs of dementia.

Plausible Biological Pathways

The neurotoxic effects of ozone are mediated by several interconnected pathways that bypass or penetrate the blood-brain barrier.

The primary mechanism of ozone-induced damage is chronic oxidative stress (P. C. Bello-Medina et al., 2021, S. Rivas-Arancibia et al, 2011). Inhalation of O₃ generates reactive oxygen species (ROS) and toxic byproducts that reach the brain through the circulation or olfactory pathways (S. Suresh et al., 2023). This oxidative state leads to the loss of dendritic spines and alterations in synaptic plasticity, which are critical for learning and memory. Research in animal models demonstrates that repeated ozone exposure results in neuronal death in the hippocampus, a brain region central to memory formation (S. Rivas-Arancibia et al, 2015, Mendoza-Magaña et al 2020, N. Gomez Crisostomo et al., 2014).

Recent studies suggest a bidirectional "lung-brain axis" where pulmonary inflammation induced by ozone triggers systemic immune responses that affect the central nervous system (Greve et al., 2022; Wang et al 2025; E.M. Thomson 2019). Ozone exposure activates microglia—the brain's resident immune cells—leading to neuroinflammation and the release of pro-inflammatory cytokines. In transgenic Alzheimer's models, ozone has been shown to augment amyloid-beta (A β) plaque load and impair microglial clearance, further accelerating neurodegeneration (Greve et al., 2022; Ahmed et al., 2023).

Additionally, markers like the low hippocampal NAA/Cr ratio have been identified as indicators of early-onset neurodegenerative processes initiated by pollution exposure.

Here, we investigate how long-term exposure to ground-level ozone influences cognitive decline and neurodegeneration across 10 US states from 2021 to 2024 and how biomedical engineering innovations might protect vulnerable populations.

Literature Review

The studies included in this review utilize a variety of longitudinal and cross-sectional designs to evaluate the neurotoxic effects of ozone. These methodologies vary significantly in their outcome measures, exposure assessment techniques, and statistical models.

To begin with, the definition of "dementia" varies significantly across the literature, which is a primary driver of result heterogeneity. Many studies define dementia based on clinical incidence,

often identified through doctor-reported diagnoses, medical insurance claims (e.g., Medicare in the US), or longitudinal clinical assessments (Ehsan Abolhasani et al., 2022; D. Wood et al., 2022; L. Shi et al., 2021). For example, the US national cohort study identified cases from the Medicare Chronic Conditions Warehouse, which includes both doctor visits and inpatient records (L. Shi et al., 2021). In addition, some research focuses specifically on the rate of first-time hospital admissions with a dementia-related diagnosis (F. Cerza et al., 2019, E. G. Cleary et al., 2017). The Rome longitudinal study tracked 350,844 subjects for hospitalizations related to Alzheimer's disease (AD), vascular dementia (Vd), and senile dementia (Sd). Studies in high-density urban environments have used age-specific dementia mortality as an endpoint, evaluating how ozone exposure correlates with death records (H. C. Ho et al, 2020, P.N. Parmar et al., 2025).

While population-level studies often rely on broad binary outcomes like clinical dementia diagnoses, other approaches utilize standardized screening tools, such as the Mini-Mental Status Examination (MMSE) or the Clinical Dementia Rating Sum of Boxes (CDR-SB), to evaluate cognitive decline as a continuous variable. Incorporating these individual-level clinical metrics into epidemiological cohorts allows researchers to detect subtle, subclinical cognitive changes before formal diagnosis occurs (C. Guo, 2023; E.H. Wilker et al., 2022). For instance, a study in Delhi used geocoded hospital admissions for various cognitive disorders, including depression and Parkinson's Disease, as a proxy for ozone-related cognitive risk (P. N. Parmar et al., 2025).

Exposure Assessment and Metrics

Ozone exposure is typically modeled using sophisticated spatial-temporal techniques, such as land-use regression, chemical transport models (e.g., the Community Multiscale Air Quality (CMAQ) model), or satellite-derived data (D. Wood et al., 2022; Yu-Tzu Wu et al., 2023). Common metrics include:

- Annual Average: Mean concentration over the entire year or multi-year periods, often modeled at the residential postcode or a 1x1 km grid level (D. Wood et. al, 2022).
- Warm-Season Average: Because ozone levels are typically highest during the summer months due to solar intensity, many studies use mean concentrations from May to September. The Rome study specifically used summer daily 8-hour maximum concentrations (F. Cerza et al., 2019).
- Daily Maxima and Lag Days: Short-term assessments may use the daily maximum 8-hour mean (MDA8) and evaluate its effect over several "lag days" to capture acute impacts on cognitive health (P. N. Parmar, 2025).

The use of different exposure increments (e.g., 10 $\mu\text{g}/\text{m}^3$, 5 ppb, or interquartile range (IQR) increases) complicates direct comparison between studies. For example, some studies report

risk per 10 $\mu\text{g}/\text{m}^3$, while others use IQR increments of 5.3 ppb or 9.63 ppb. This can be shown in the table below.

Table 1. Comparison of Ozone Exposure Metrics and Risk Estimates for Dementia Outcomes Across Included Studies

Source	Outcome	Hazard Ratio (HR)	Exposure Increment	95% CI
Wilker et al.	Clinical dementia	1.00	5 $\mu\text{g}/\text{m}^3$	0.98-1.05
Shi et al.	Incident dementia	0.990	5.3ppb	0.987-0.993
Shi et al.	Incident Alzheimer's	0.982	5.3ppb	0.977-0.986
Zhang et al.	Dementia incidence	1.01	10 $\mu\text{g}/\text{m}^3$	0.91-1.11

Evidence for Positive Associations

Significant positive associations have been reported in several targeted cohort studies, particularly those focusing on urban populations or specific dementia subtypes.

In the Rome longitudinal study, Cerza et al. (2019) analyzed a cohort of 350,844 subjects aged 65–100 years from 2001 to 2013. They found that long-term ozone exposure (measured as summer daily 8-hour means) was positively associated with first-time hospitalization for dementia. Specifically, the study reported a Hazard Ratio (HR) of 1.06 (95% CI: 1.04–1.09) per 10 $\mu\text{g}/\text{m}^3$ increment in ozone. The association was even more pronounced for senile dementia, with an HR of 1.20 (95% CI: 1.15–1.24) per 10 $\mu\text{g}/\text{m}^3$. Interestingly, while ozone and nitrogen oxides (NO_x) were positively associated with hospitalizations, nitrogen dioxide (NO_2) showed a negative association in the same cohort.

In Taiwan, Jung et al. (2015) observed a significant relationship between ozone and newly diagnosed Alzheimer's disease (Chao-Ren Jung et al., 2015). They reported an adjusted HR of 1.06 (95% CI: 1.00–1.12) per 9.63 ppb increase in baseline ozone. More strikingly, they found a 211% risk increase of AD (HR = 3.11) per 10.91 ppb increase in ozone concentrations over the follow-up period (95% CI: 2.92–3.33). This suggests that the progression of ozone concentrations over time may be a more potent risk factor than stable baseline exposure.

More recently, Qin et al. (2024) used causal inference methodologies to examine ADRD hospitalizations in a US-wide study of elderly patients (Michelle Qin et al., 2024). They found that an IQR increase in summer ozone exposure resulted in a hazard ratio of 1.045 (95% CI: 1.036–1.054). However, the study noted that the results were less conclusive when applying

generalized propensity score (GPS) matching, which attenuated the observed effects. Mortality data from Hong Kong also supports a positive link; Ho et al. (2020) found that a 10 $\mu\text{g}/\text{m}^3$ increase in daily O_3 was linked to higher dementia mortality, with an Odds Ratio (OR) of 1.034 (95% CI: 1.014–1.054) for all decedents aged 65 and older, and an OR of 1.041 (95% CI: 1.017–1.065) for those aged 85 and older.

Evidence for Null or Negative Associations

In contrast to the findings above, several large national studies have failed to find a positive association, with some reporting statistically significant null or protective effects.

A major national cohort study in the United States (2000–2018) involving approximately 12.2 million Medicare participants found no evidence of a positive link between warm-season ozone and incident dementia (L. Shi et al., May 2021; L. Shi et al., Nov 2021). The study reported a statistically significant HR of 0.990 (95% CI: 0.987, 0.993) per 5.3 ppb (IQR) increase in 5-year average warm-season ozone. This suggests a 1% reduction in risk per IQR increase, a result that stands in stark contrast to the positive associations found for $\text{PM}_{2.5}$ and NO_2 in the same study population.

In the United Kingdom, the English Longitudinal Study of Ageing (ELSA) reported similar null findings. Wood et al. (2022) found an HR of 1.01 (95% CI: 0.94, 1.09) per 10 $\mu\text{g}/\text{m}^3$ increase in annual average ozone, indicating no discernible relationship with incident dementia. In a separate study using the Cognitive Function and Ageing Study II (CFAS II) and Wales cohorts, Wu et al. (2023) described the associations between ozone and dementia as "unclear," with median exposures of 43.8 $\mu\text{g}/\text{m}^3$ not yielding significant hazard ratios. Furthermore, a study in London noted that while $\text{PM}_{2.5}$ and NO_2 were associated with dementia incidence, ozone exhibited no such relationship (D. Wood et al., 2023; M. Chandra et al., 2022)

Meta-Analytical Syntheses and Reviews

Systematic reviews and meta-analyses generally reflect the inconsistencies found in individual cohort studies. Dhiman et al. (2022) conducted a meta-analysis of epidemiological research and reported a pooled HR for Alzheimer's disease of 1.02 (95% CI: 0.96–1.08) per O_3 increment, which did not reach statistical significance. Another meta-analysis by Wilker et al. (2022) found a pooled HR of 1.00 (95% CI: 0.98–1.05) per 5 $\mu\text{g}/\text{m}^3$ increase in ozone, based on four studies, concluding that ozone had no clear association with clinical dementia.

Recent reviews by Chwiejczak et al. (2024) and Gallistl (2022) summarize this body of work by noting that while evidence for particulate matter ($\text{PM}_{2.5}$) is robust and "plentiful," the evidence for single gaseous pollutants like ozone is "less conclusive". They cite multiple studies, including Tang et al. (2023) and Abolhasani et al. (2022), which found that ozone was not clearly correlated with the development of dementia. However, some smaller studies or those using

different outcomes, such as Lo et al. (2019), have reported significant Odds Ratios (OR = 1.878; 95% CI: 1.363–2.560) for long-term ozone exposure and cognitive impairment.

Limitations of the Evidence

The current literature is hampered by several methodological and environmental factors that contribute to the conflicting findings.

Ozone concentrations exhibit high spatial and temporal variability. Using annual averages may fail to capture the importance of peak concentrations during the warm season, while studies focusing only on the warm season may ignore potential year-round chronic effects (L. Shi et al., 2021; F. Cerza et al., 2019). Moreover, most ozone exposure is modeled at the residential level, which does not account for indoor concentrations (often significantly lower) or time spent in other environments.

In addition, the distinction between hospitalization (F. Cerza et al., 2019), clinical incidence, and mortality is critical. Hospitalization may be triggered by acute health events that are exacerbated by ozone, potentially leading to the detection of existing dementia rather than causing its onset. In contrast, clinical incidence studies aim to capture the first diagnosis, which may be less sensitive to acute pollution spikes.

In urban environments, ozone is often negatively correlated with nitrogen dioxide (NO₂) due to the titration of ozone by nitric oxide (NO). Failure to adequately adjust for the "multi-exposure response" or the specific concentrations of NO_x can lead to biased estimates for ozone (J. Gallistl, 2022). The Rome study noted that NO₂ showed a negative association with dementia hospitalizations, while ozone showed a positive one, highlighting the complexity of multi-pollutant modeling (F. Cerza et al., 2019).

Lastly, the neurotoxic potential of ozone may vary based on the population's baseline health, genetic susceptibility (e.g., ApoE ε4 carriers (V. J. Williams, 2024)), and the specific chemical composition of the regional atmosphere.

Research Gaps and Future Directions

Despite the growing body of research, significant gaps remain in our understanding of the ozone-dementia nexus. The Rome study's finding of a strong association with senile dementia (F. Cerza et al., 2019) and the Hong Kong study's focus on the "old-old" (age ≥85) population (H. C. Ho et al., 2020) suggest that ozone's impact may be highly dependent on the dementia subtype and the age of the subjects. Future research should prioritize these distinctions.

While review articles (L. A. Marín-Castañeda et al., 2024; P. V. Moulton et al., 2012) suggest pathways such as neuroinflammation, oxidative stress, and blood-brain barrier disruption, more empirical research is needed to link specific ozone exposure levels to biomarkers in humans. Toxicological studies have noted that an 8-hour ozone exposure toxicity limit of 50 ppb may be

relevant for neurodegenerative risk (G. Kuo et al., 2025). The use of high-resolution models (e.g., 20x20m or 1x1 km) and the consideration of indoor-outdoor concentration ratios could provide more accurate risk estimates and reduce misclassification (Yu-Tzu Wu et al., 2023).

Emerging evidence suggests that late-life air pollution exposure, including ozone, may interact with genetic factors such as the ApoE ϵ 4 allele to modify dementia risk. Investigating these interactions could identify particularly vulnerable subpopulations.

Methods

For this study, state-level cognitive decline prevalence data among adults aged ≥ 18 years were obtained from the publicly available self-reported datasets in the CDC Behavioural Risk Factor Surveillance System (BRFSS). Daily maximum 8-hour ozone concentrations were obtained from publicly available air quality monitoring datasets in the EPA. O_3 data were aggregated to the state-year level and linked to cognitive decline data by state and by year. Associations were examined using ecological regression analyses. Because the available literature primarily reports hazard ratios rather than relative risks, a conventional comparative risk assessment was not considered appropriate. Instead, an ecological regression analysis was used to examine the association between state-level ozone exposure and cognitive decline prevalence.

This study examined the association between ground-level ozone exposure and cognitive decline prevalence during 2021-2024 across ten U.S. states (Arizona, California, Florida, Illinois, Massachusetts, North Carolina, New York, Ohio, Pennsylvania and Texas). The exposure (independent) variable was the daily maximum 8-hour ozone concentration, expressed in parts per million (ppm). The outcome variable (dependent variable) was cognitive decline prevalence, expressed as a percentage.

The association between ground-level ozone exposure and cognitive decline prevalence was evaluated using the following null (H_0) and alternative (H_1) hypotheses:

Null Hypothesis (H_0): There is no significant association between ground-level ozone exposure and cognitive decline prevalence (i.e. the ozone regression coefficient was equal to zero).

$$H_0: \beta_1 = 0$$

Alternative Hypothesis (H_1): There is a significant association between ground-level ozone exposure and cognitive decline prevalence (i.e. the ozone coefficient differed from zero).

$$H_1: \beta_1 \neq 0$$

Then, an ordinary least squares linear regression was conducted to examine the association between ground-level ozone concentration and cognitive-decline prevalence across 39 matched

state-year observations from 2021–2024 (Florida was missing cognitive decline data for the year 2021.). The model was specified as:

$$Y_i = \beta_0 + \beta_1 O_{3i} + \varepsilon_i$$

where Y_i represents cognitive decline prevalence for observation i , O_{3i} represents the daily maximum 8-hour ozone concentration in ppm, β_0 is the intercept, β_1 is the regression slope, and ε_i is the residual error term.

Statistical significance was assessed using a two-sided t-test with an alpha level of 0.05.

The reported fitted equation was:

$$Y = 191.73O_3 + 7.01$$

The slope was additionally converted from a ppm scale to a 10-parts-per-billion (ppb) scale because ozone concentrations are commonly reported in ppb. Since 10 ppb equals 0.01 ppm, the estimated slope corresponds to:

$$191.73 \times 0.01 = 1.9173$$

Results

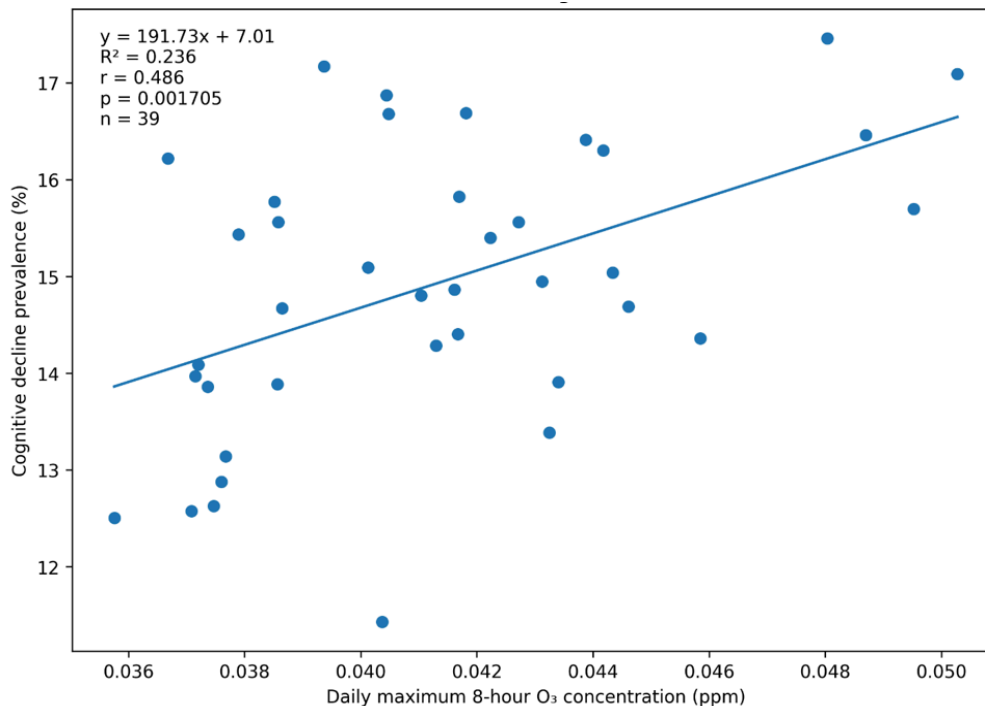


Figure 1. Association between ground-level ozone concentration and cognitive-decline prevalence, 2021–2024.

The model demonstrated a positive association between ozone concentration and cognitive-decline prevalence ($\beta = 191.73$, $r = 0.486$, $R^2 = 0.236$, $p = 0.0017$). The slope corresponds to an estimated 1.92-percentage-point increase in cognitive-decline prevalence for each 10-ppb increase in ozone concentration. This represents a change in prevalence percentage points, not a Relative Risk (RR), Odds Ratio, or percentage increase in risk.

Although the association was statistically significant, the ecological design does not establish causality.

Temporal Trends in Ground-Level Ozone and Cognitive Decline

Ground-level ozone trends.

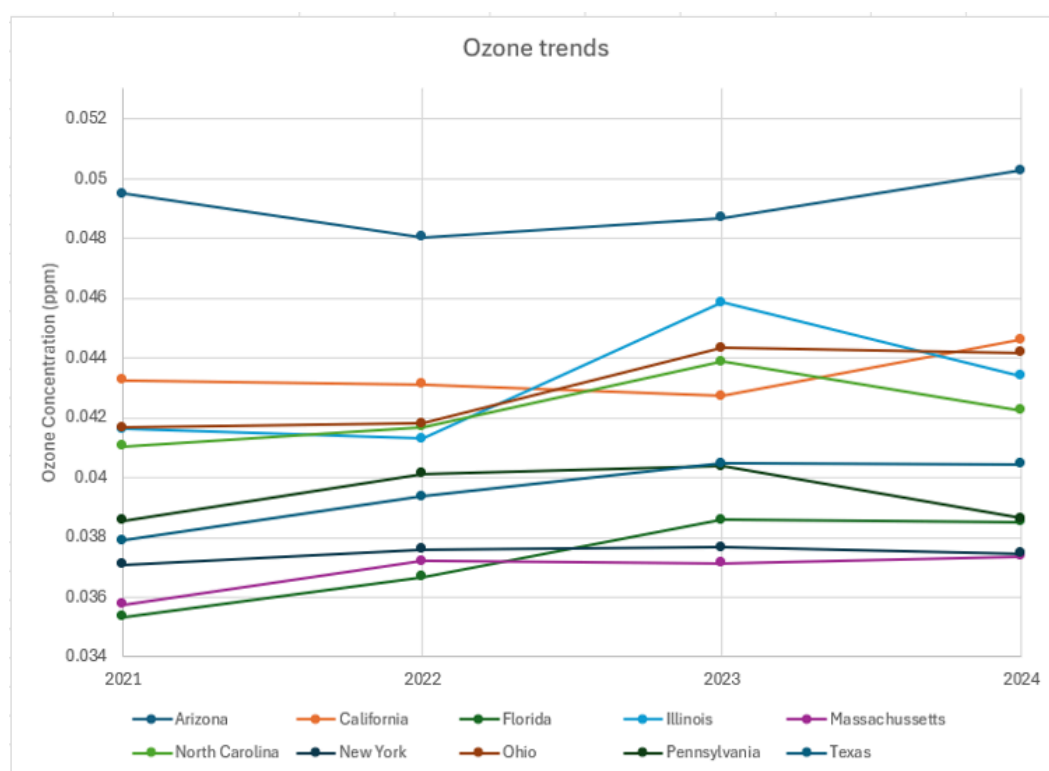


Figure 2. Ground-level ozone trends across the 10 selected states, 2021–2024.

Figure 2 illustrates changes in annual ground-level ozone concentrations across the 10 selected states between 2021 and 2024. Ground-level ozone concentrations varied across states and years, with some states showing relatively stable concentrations while others demonstrated greater year-to-year variation. Arizona consistently had the highest ozone concentrations, ranging from 0.0480 to 0.0503 ppm, while Massachusetts and New York generally had some of the lowest concentrations. Several states showed increases between 2022 and 2023, with Illinois showing the largest increase, rising from 0.0413 ppm to 0.0459 ppm. However, Illinois then decreased to 0.0434 ppm in 2024. Florida also showed a steady increase from 0.0353 ppm

in 2021 to 0.0386 ppm in 2023, before remaining almost unchanged in 2024. Pennsylvania increased through 2023 but then dropped to about its 2021 level in 2024. Overall, ozone concentrations differed between states and showed some year-to-year changes, but there was no consistent upward or downward trend across all 10 states.

Cognitive-decline trends.

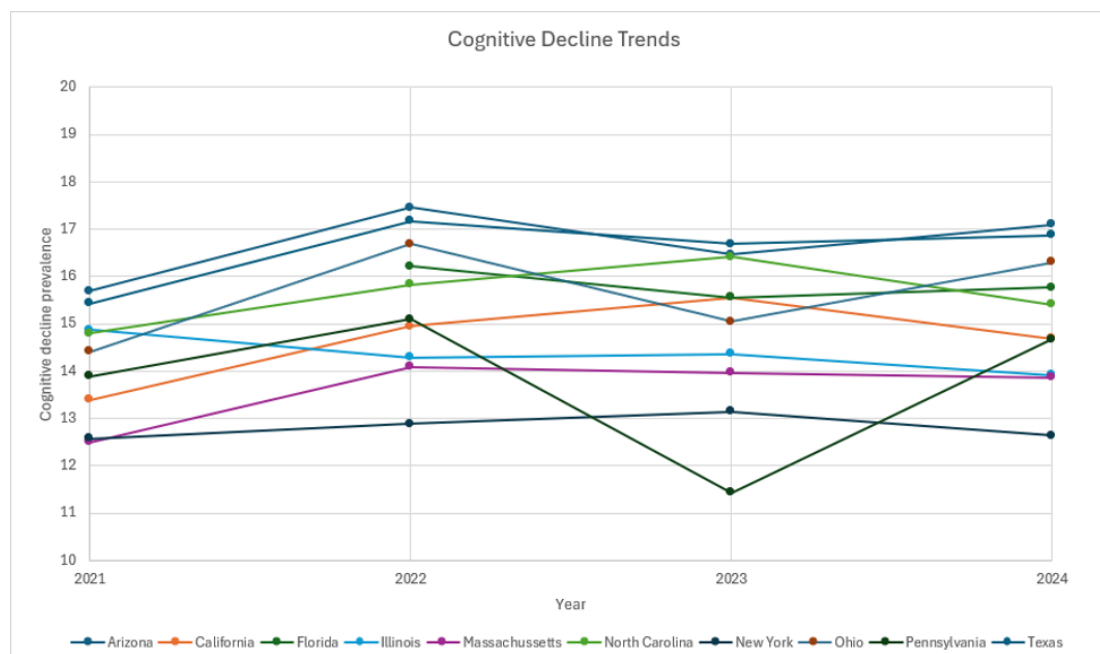


Figure 3. Cognitive-decline prevalence across the 10 selected states, 2021–2024.

Figure 3 presents changes in cognitive-decline prevalence across the selected states from 2021 to 2024. Texas and Arizona generally had some of the highest levels of cognitive-decline prevalence throughout the study period. Texas increased from 15.43% in 2021 to 17.17% in 2022, before decreasing slightly in 2023 and increasing again to 16.87% in 2024. Arizona followed a similar pattern, increasing from 15.70% in 2021 to 17.46% in 2022, then decreasing to 16.46% in 2023 before rising again to 17.09% in 2024. Pennsylvania showed the largest change over the study period, increasing from 13.89% in 2021 to 15.09% in 2022, then dropping sharply to 11.43% in 2023 before increasing to 14.67% in 2024. In contrast, New York and Massachusetts remained relatively low and stable, with both staying close to 13–14% throughout the study period. Overall, most states showed some year-to-year variation in cognitive-decline prevalence, with 2022 generally showing higher values for several states and 2023 showing declines in some states.

Discussion

The primary finding of this analysis is a significant positive association between ground-level ozone and cognitive-decline prevalence.

These results align with broader epidemiological findings that characterize ozone as a major risk factor for cognitive dysfunction. For instance, a study in Northwestern China reported that ozone was associated with poor cognitive function among elders, with an odds ratio (OR) of 2.76 per 10 $\mu\text{g}/\text{m}^3$ increment—a higher effect size than that observed for $\text{PM}_{2.5}$ or PM_{10} (Z. Gui et al., 2024). Similarly, research by Chen et al. (2017) found that each 10-ppb increase in annual ozone was cognitively equivalent to 3.5 to 5.3 years of aging-related decline (M. Chandra et al., 2022). While the current study measures prevalence percentage points rather than relative risk or years of aging, the direction and significance of the association are consistent with these international cohorts.

Tropospheric ozone is particularly sensitive to climate change because its atmospheric formation is temperature-dependent, with warmer periods generally yielding higher ozone concentrations (Aw and Kleeman, 2003; Bell et al., 2007; Seinfeld and Pandis, 2006; Sillman and Samson, 1995). A notable observation in our results aligned with this general pattern: Arizona exhibited elevated ozone levels (0.0480–0.0503 ppm) alongside a high prevalence of cognitive decline. However, a regional discrepancy emerged where other warm-weather states, such as Florida and Texas, displayed markedly lower ozone concentrations than Arizona. This demonstrates that temperature alone does not dictate ozone levels; other factors such as precursor emissions (NO_x and VOCs), topography, and specific meteorological patterns play a determining role in regional ozone concentrations.

Susceptibility to ozone-induced cognitive decline varies significantly, with older adults consistently identified as the most vulnerable group (Thomson, 2019). In the Chinese Longitudinal Health Longevity Survey, long-term ozone exposure was significantly associated with cognitive impairment among adults aged 65 and over (Gao et al., 2022). Modification by sex has also been observed; some studies suggest stronger associations in women than men as they age (Bell et al., 2014; Mo et al., 2023), although other research has found stronger associations in males for specific pollutant reductions (X. Hu et al., 2022). In addition, association of race/ethnicity with sensitivity to ozone risk was limited, with no serious evidence (Bell et al., 2014, A. Singh S et al., 2023).

Genetic factors, particularly the presence of one or more ApoE $\epsilon 4$ alleles, have been shown to accelerate the rate of cognitive decline in individuals exposed to ozone (M. Chandra, 2022). Additionally, non-chemical stressors such as low socioeconomic position, noise, and psychosocial factors can modify the effect of ozone exposure, increasing susceptibility across the lifespan (Thomson, 2019).

It is noteworthy to recognize that biomedical engineering offers critical tools for personal and indoor protection, addressing the reality that individuals spend the majority of their time in indoor environments where ozone and its reaction products persist.

To address indoor air pollution driven by ambient ozone and its secondary chemical by-products, modern architectural and environmental engineering frameworks are increasingly turning to advanced technological interventions. Continuous, real-time indoor air quality sensing networks utilize metal-oxide semiconductor or optical sensors to dynamically track ambient ozone levels along with secondary reaction products like aldehydes and ultrafine particles. When integrated with internet-of-things (IoT) architectures, these sensors can dynamically adjust HVAC ventilation rates, balancing the influx of outdoor air against indoor pollutant accumulation (Rudavskyi & Klym, 2023). Complementing real-time monitoring, scalable filtration interventions target both primary ozone and secondary indoor oxidation products. Activated carbon, manganese dioxide catalysts, and functionalized chemical filtration media actively decompose ambient ozone before it can undergo gas-phase or surface reactions with indoor volatile organic compounds (VOCs) and skin-oil lipids (Tian et al., 2015; Weschler, 2006). By deploying these engineering controls in tandem, facilities can mitigate occupant exposure to both ground-level ozone and the hazardous toxicological by-products generated through indoor oxidation chemistry.

The use of Artificial Neural Networks (ANNs) and modern computational methods can help identify specific ozone-generation mechanisms in urban environments (García-Nieto et al., 2018; Papanastasiou et al., 2007). These models allow for the tailoring of mitigation solutions to specific metropolitan contexts, improving the efficiency of public health interventions.

Exploratory research is investigating neuroprotective agents that may alleviate the damage caused by ozone. Agents such as minocycline or antioxidant-rich dietary interventions are being studied for their potential to reduce microglial activation and oxidative damage (Rivas-Arancibia et al., 2010; Rodríguez-Martínez et al., 2016). However, these remain preliminary and require further clinical validation.

Neural Variability as a Potential Early Biomarker

An important area for future research is the use of neural variability as an early biomarker of cognitive decline and neurodegenerative disease. In a healthy brain, presenting the exact same stimulus repeatedly does not produce identical responses. Individual neurons fire in subtly different action-potential patterns from trial to trial — a property called neural (or spike-timing) variability. Far from being “noise”, this trial-to-trial variability is now understood as a signature of a flexible, well-functioning neural network: it reflects healthy synaptic plasticity and adaptive signal processing.

In early-stage vascular dementia, microvascular damage disrupts local cerebral blood flow, which in turn disrupts normal synaptic communication. This shows up in two possible directions: neural firing can become hyper-stereotyped and rigid (too little variability) or excessively noisy and disorganized (too much variability). Either direction is a departure from the healthy range,

and this disruption can begin before structural brain atrophy is visible on an MRI scan, making variability a potential early-warning signal rather than a late-stage confirmation.

Research using resting-state fMRI has found that blood-oxygen-level-dependent (BOLD) signal variability is associated with age and cognitive performance. In a longitudinal study of healthy adults, reduced BOLD signal variability over approximately 2.5 years was associated with greater cognitive decline, suggesting that changes in brain signal variability may provide an early indicator of changes in cognitive function (Fingelkurts et al., 2021).

This approach may also be useful for identifying changes associated with Alzheimer's disease before substantial cognitive impairment becomes apparent. Millar et al. (2020) examined 321 cognitively normal adults and found that BOLD variability was associated with amyloid- β and markers of neurodegeneration, including neurofilament light protein, hippocampal volume, and cortical thickness. These findings suggest that neural variability may be sensitive to biological changes associated with Alzheimer's disease even in people who are still considered cognitively normal. Earlier work also found increased BOLD variability in individuals with Alzheimer's disease compared with healthy controls, although the authors emphasized the need for larger and longitudinal studies before BOLD variability can be considered a clinical biomarker (Scarapicchia et al., 2018).

A related approach is intraindividual cognitive variability (IIV), which measures how much an individual's cognitive performance fluctuates across tests or over repeated measurements. This may be particularly useful because a person's average cognitive score can remain relatively normal even when their performance becomes less consistent. In an analysis of 1,324 participants from the Alzheimer's Disease Neuroimaging Initiative, greater cognitive variability was associated with a greater likelihood of progressing to mild cognitive impairment or Alzheimer's disease, even after accounting for factors such as age, education, baseline diagnosis, and APOE $\epsilon 4$ status (Anderson et al., 2016). More recent research has also found that greater cognitive variability is associated with amyloid, tau, neurodegeneration, and reduced cortical thickness, further supporting its potential as an early marker of emerging Alzheimer's pathology (Haynes et al., 2020).

This creates an interesting direction for biomedical engineering research. Instead of relying only on measures of cognitive performance after decline has become noticeable, future systems could combine neural signals from relatively accessible technologies such as EEG with cognitive testing and other biomarkers to detect subtle changes earlier. EEG is particularly interesting because it is non-invasive, relatively inexpensive, and has high temporal resolution. Recent reviews suggest that EEG has potential for early detection and differential diagnosis across several neurodegenerative diseases, although differences in study methods and the lack of standardized biomarkers remain important challenges (Babiloni et al., 2021; Cassani et al., 2018).

Neural variability could therefore represent a future research pathway linking environmental exposure to early brain changes. Future longitudinal studies could investigate whether individuals exposed to higher levels of ground-level ozone show changes in neural variability before measurable cognitive decline occurs. This could also help clarify the pathway between environmental exposure and cognitive outcomes: rather than examining only whether ozone exposure is associated with cognitive decline, researchers could investigate whether ozone is associated with measurable changes in brain dynamics that precede cognitive impairment. However, this remains a proposed direction rather than a conclusion supported by the present ecological analysis.

Limitations

The most significant limitation is the ecological study design, which utilizes aggregated state-year data rather than individual-level observations. This design cannot establish causality and is subject to the ecological fallacy, where associations at the group level may not reflect risks at the individual level. Furthermore, the sample size of 39 matched state-year observations from only 10 states limits the generalizability of the results.

State-level cognitive decline prevalence was estimated by calculating the arithmetic mean of county-level cognitive decline percentages. This approach assumes equal weighting across counties and does not account for differences in county population sizes, which may affect the representativeness of the state-level estimates. In addition, BRFSS data sets include self-reported values for cognitive decline prevalence so it may not adequately represent the scope of the cognitive decline in the state.

The study completely relies on secondary data and indirect indicators of cognitive decline. There is a potential for exposure misclassification, as ground-level ozone monitors may not accurately reflect the actual personal exposure of individuals (underestimation or overestimation). Additionally, residual confounding from other factors or covariates other than ozone—such as healthcare access, urban form, and other air pollutants—remains a possibility. Future studies should address this potential problem of covariates that are unaccounted for.

Public Health and Policy Significance

The findings underscore the importance of national policies focused on reducing O₃ precursors (NO_x and VOCs) to improve cognitive health outcomes. As ozone levels are sensitive to warming temperatures, cognitive resilience should be integrated into broader climate-resilience strategies. The significant association found in this study, even with an ecological design, suggests that reducing ambient ozone levels could have substantial benefits for public health, particularly for aging populations.

Conclusion

This study provides ecological evidence of a significant association between long-term exposure to ground-level ozone and the prevalence of cognitive decline across 10 U.S. states from 2021 to 2024. Higher daily maximum 8-hour ozone concentrations are strongly correlated with increased cognitive impairment, with a 10 ppb increase in ground-level ozone corresponding to a 1.92 percentage-point rise in prevalence ($p < 0.01$). These findings align with established biological mechanisms where chronic ozone inhalation triggers systemic oxidative stress, leading to neuroinflammation, microglial activation, and the loss of dendritic spines in the hippocampus and substantia nigra. Specifically, recent evidence suggests that ozone-induced neurotoxicity may be mediated by the lung-brain or liver-brain axes, involving biomarkers such as peripheral HMGB1 (High Mobility Group Box 1) and microglial synaptic phagocytosis.

Despite the clear statistical correlation, this study is subject to the limitations of ecological data, which precludes the establishment of individual-level causality. The absence of 2021 data for Florida and the lack of a uniform temporal ozone trend across all states underscore the need for high-resolution, longitudinal cohorts that track individual exposure and cognitive trajectory over time. Furthermore, the variability in geographic impacts, such as the high ozone and cognitive decline levels observed in Arizona and Texas, highlights the influence of local environmental and demographic factors.

Biomedical engineering (BME) and technological innovations are essential for translating these findings into protective strategies. Computational tools, such as artificial neural network models, can enhance the identification of ozone generation mechanisms and optimize mitigation solutions. Practical engineering interventions, including advanced indoor air filtration and adaptive ventilation systems, can significantly reduce the transport of outdoor ozone into residential and healthcare environments. Additionally, emerging neuroprotective strategies, ranging from pharmacological agents like minocycline to nutritional interventions such as curcumin and cocoa, warrant further exploration as clinical means to alleviate ozone-induced cognitive deficits. Future research should focus on validating these associations through individual-level monitoring and developing integrated BME systems that combine real-time sensing with personalized health interventions to safeguard cognitive health in an era of changing air quality. Future research should also encourage countries to systematically collect, document, and make accessible standardized long-term data on ground-level ozone and cognitive health, allowing studies like this one to be replicated across different countries and populations and helping researchers build a more complete global understanding of how air pollution may affect cognitive health.

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