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EFFECT OF PB TOXIN ON ALZHEIMER'S INCIDENCE IN SURABAYA, INDONESIA

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Abstract

Background: Alzheimer's disease represents a significant public health challenge globally, with environmental factors increasingly recognized as important contributors to its pathogenesis. Lead (Pb) exposure has been identified as a potential risk factor through multiple mechanisms, including oxidative stress induction. Surabaya, as Indonesia's second-largest city with substantial industrial and transportation activities, presents environmental conditions conducive to Pb pollution.

Objective: This study aimed to analyze the relationship between environmental Pb exposure, malondialdehyde (MDA) levels as an oxidative stress biomarker, and Alzheimer's incidence among residents of Surabaya.

Methods: A cross-sectional study was conducted with 100 participants selected from 150 eligible residents of Surabaya aged 60-80 years. Environmental Pb samples were collected from particulate matter (PM2.5 and PM10), while blood Pb and MDA levels were measured using atomic absorption spectrometry and the thiobarbituric acid reactive substances (TBARS) method, respectively. Alzheimer's diagnosis was confirmed using standardized cognitive assessment tools. Multiple linear regression analysis was employed with statistical significance set at $p < 0.05$.

Results: The study revealed significant variability in environmental Pb concentrations across Surabaya, with the highest levels detected in industrial areas (1.8 ± 0.3 μg/m³). Blood Pb levels showed a strong positive correlation with MDA concentrations ($r = 0.72$, $p < 0.001$). Participants with Alzheimer's disease exhibited significantly higher blood Pb levels (6.8 ± 1.2 μg/dL) and MDA concentrations (4.1 ± 0.8 nmol/mL) compared to healthy controls (2.1 ± 0.7 μg/dL and 1.9 ± 0.5 nmol/mL, respectively). Multiple regression analysis indicated that blood Pb levels significantly predicted both MDA levels ($\beta = 0.61$, $p < 0.001$) and Alzheimer's incidence ($\beta = 0.53$, $p < 0.001$), after adjusting for age, education, and genetic factors.

Conclusion: Environmental Pb exposure is significantly associated with increased oxidative stress and higher Alzheimer's incidence among Surabaya residents. These findings underscore the importance of implementing comprehensive environmental protection policies and public health interventions to reduce Pb exposure in urban settings.

Keywords: Pb, malondialdehyde, Alzheimer, Surabaya

INTRODUCTION

Alzheimer's disease stands as the most prevalent form of dementia worldwide, accounting for approximately 60-70% of all dementia cases. The global burden of Alzheimer's continues to escalate, with current estimates indicating that over 50 million people are living with dementia, a figure projected to reach 152 million by 2050 (Bakulski et al., 2020; Rosnon et al., 2024). This progressive neurodegenerative disorder is characterized by the accumulation of amyloid-β plaques and neurofibrillary tangles in brain tissue, resulting in symptoms of progressive memory loss and cognitive dysfunction (Horton et al., 2019; Su et al., 2024). The etiology of Alzheimer's is recognized as complex and multifactorial, involving an intricate interplay between genetic predisposition and environmental factors (Bakulski et al., 2020; Meng et al., 2024).

The search for modifiable environmental risk factors has gained significant momentum in Alzheimer's research, with heavy metals emerging as potential contributors to disease pathogenesis. Among these metals, lead (Pb) has attracted considerable scientific interest due to its documented neurotoxicity and persistence in the environment (Edo et al., 2024; Ruzi et al., 2024). Lead is a ubiquitous environmental contaminant that has been extensively used as an additive in gasoline, paint, and various industrial applications, leading to widespread environmental contamination (Goh et al., 2024; Horton et al., 2019). Despite regulatory efforts to reduce Pb exposure, its environmental persistence continues to pose significant health risks, particularly in urban and industrial areas.

The neurotoxic mechanisms of Pb are multifaceted and particularly relevant to Alzheimer's pathology. Experimental studies have demonstrated that Pb exposure can increase the expression of amyloid precursor protein (APP) and beta-secretase 1 (BACE-1), thereby promoting the generation and deposition of amyloid-β peptides (Cheong et al., 2024; Wu et al., 2020) . Additionally, Pb has been shown to induce hyperphosphorylation of tau protein, another pathological hallmark of Alzheimer's (Fadila et al., 2024; Wu et al., 2020). Of particular significance is the ability of Pb to cross the blood-brain barrier, where it can accumulate and exert direct toxic effects on neuronal cells (Isman et al., 2024; Wu et al., 2020). The transport of Pb into the brain occurs primarily through its substitution for calcium, hijacking divalent metal transporters intended for essential metals (Bakulski et al., 2020; Ghazali et al., 2023; Gudadhe et al., 2024).

Oxidative stress represents a crucial mechanism linking Pb exposure to Alzheimer's pathology. Pb is a redox-inactive metal that induces oxidative stress by depleting thiol reserves and compromising the antioxidant defense system (Dickerson et al., 2020; Fathima et al., 2023). This oxidative damage results in lipid peroxidation, with

malondialdehyde (MDA) serving as a reliable biomarker of this process. Elevated MDA levels reflect increased cellular damage and have been documented in both Alzheimer's patients and individuals with significant Pb exposure (Akrimah et al., 2023; Bakulski et al., 2020). The resulting oxidative stress contributes to endoplasmic reticulum stress, mitochondrial dysfunction, and ultimately neuronal apoptosis (Bakulski et al., 2020; Ruzi et al., 2023).

The timing of Pb exposure appears critical to its long-term neurotoxic effects. Developmental origins of health and disease (DOHaD) research suggests that early-life exposures may program susceptibility to neurodegenerative diseases in later life (Hagemann et al., 2021; Nugroho et al., 2023). Animal studies have demonstrated that early-life Pb exposure can result in epigenetic modifications that increase Alzheimer's-related pathology in old age (Subedi et al., 2024). This is particularly relevant for understanding the latent period between exposure and disease manifestation, which may span decades.

Surabaya, as Indonesia's second-largest metropolitan center, presents environmental conditions conducive to significant Pb pollution. The city's extensive industrial activities, high traffic density, and ongoing urbanization create multiple sources of environmental Pb contamination. Previous environmental monitoring has indicated concerning levels of airborne particulate matter in Surabaya, with Pb representing a notable component of this pollution. The city's population of approximately three million people, including a substantial elderly demographic, faces potential exposure to these environmental contaminants. Despite these conditions, no comprehensive study has yet examined the relationship between Pb exposure, oxidative stress, and Alzheimer's incidence in this specific urban context.

This research gap is particularly significant given the unique environmental characteristics and population demographics of Surabaya. The current study aims to address this knowledge gap by investigating the association between environmental Pb exposure, MDA levels as a biomarker of oxidative stress, and Alzheimer's incidence among Surabaya residents. elucidation of these relationships will provide valuable evidence to inform public health policies and environmental protection measures specific to urban centers in developing countries.

METHODS

Study Design and Population

This research employed a cross-sectional design to examine the relationship between Pb exposure, malondialdehyde levels, and Alzheimer's incidence among residents of Surabaya. The study was conducted between January and December 2024, encompassing both rainy and dry seasons to account for potential seasonal variations in environmental Pb concentrations. The study population comprised 150 eligible residents of Surabaya aged 60-80 years, from which a sample of 100 participants was selected through stratified random sampling based on geographical distribution across five administrative districts (Central, North, South, East, and West Surabaya) and proximity to potential Pb sources (major roads, industrial areas).

Inclusion criteria required participants to be lifelong residents of Surabaya (minimum 30 years continuous residence), aged 60-80 years, and willing to provide informed consent. Exclusion criteria included a history of other neurological disorders (Parkinson's disease, stroke), severe psychiatric conditions, alcohol or substance abuse, or use of chelation therapy. The sample size determination considered a statistical power of 80%, alpha of 0.05, and expected medium effect size based on previous environmental health studies.

Table 1: Sample Distribution Across Surabaya Administrative Districts

Administrative District	Population	Sample	Percentage
Central Surabaya	30	20	20%
North Surabaya	32	21	21%
South Surabaya	28	19	19%
East Surabaya	35	23	23%
West Surabaya	25	17	17%
Total	**150**	**100**	**100%**

Data Collection

Environmental Pb Assessment

Environmental Pb concentrations were measured through systematic air monitoring at designated stations in each administrative district. Particulate matter samples (PM2.5 and PM10) were collected using high-volume air samplers with quartz fiber filters, following the National Ambient Air Quality Monitoring Methods. Sampling was performed over 24-hour periods at each location, repeated weekly for three months in each season to account for temporal variations. Pb analysis was conducted using atomic absorption spectrometry (AAS) following sample digestion with acid mixture, with quality control procedures including blank samples, duplicates, and standard reference materials. The detection limit for Pb analysis was 0.01 μg/m³.

Biological Sample Collection and Analysis

Blood samples (10 mL) were collected from each participant by venipuncture after overnight fasting. Blood Pb levels were determined using graphite furnace atomic absorption spectrometry with appropriate quality control measures, including calibration curves, internal standards, and duplicate measurements. The detection limit for blood Pb was 0.1 μg/dL.

Malondialdehyde levels were measured as a biomarker of lipid peroxidation using the thiobarbituric acid reactive substances (TBARS) method. Briefly, blood samples were centrifuged to separate plasma, which was then reacted with thiobarbituric acid under acidic conditions. The resulting pink chromogen was measured spectrophotometrically at 532 nm, with MDA concentrations calculated using a molar extinction coefficient of 1.56 × 10^5 M^-1cm^-1. Results were expressed as nmol MDA per mL of plasma.

Alzheimer's Diagnosis

Alzheimer's disease diagnosis was confirmed using a comprehensive cognitive assessment protocol including the Mini-Mental State Examination (MMSE), Clinical Dementia Rating (CDR) scale, and neurological examination following DSM-5 criteria for major neurocognitive disorder. Participants scoring below 24 on the MMSE and exhibiting functional impairment consistent with CDR ≥1 underwent further evaluation including brain imaging (MRI) to rule out other causes of cognitive impairment. The diagnosis was established by a panel of neurologists and geriatricians blind to participants' Pb exposure status.

Covariate Assessment

Data on potential confounding variables were collected through structured interviews and medical record review. These included demographic characteristics (age, gender, education level), lifestyle factors (smoking status, alcohol consumption, dietary patterns), residential history (duration of residence in Surabaya, proximity to major roads), occupational history (potential occupational exposures to heavy metals), and medical history (cardiovascular conditions, diabetes, hypertension). Genetic risk assessment included APOE ε4 genotyping using polymerase chain reaction (PCR) techniques.

Data Analysis

Data analysis was performed using SPSS version 26.0. Descriptive statistics including means, standard deviations, frequencies, and percentages were calculated for all variables. The relationship between environmental Pb concentrations, blood Pb levels, MDA concentrations, and Alzheimer's incidence was analyzed using multiple linear regression with statistical significance set at $p < 0.05$. The regression models were specified as follows:

$$MDA = \beta_0 + \beta_1(Pb\_blood) + \beta_2(age) + \beta_3(education) + \beta_4(APOE4) + \beta_5(smoking) + \varepsilon$$

$$Alzheimer's = \beta_0 + \beta_1(Pb\_blood) + \beta_2(MDA) + \beta_3(age) + \beta_4(education) + \beta_5(APOE4) + \beta_6(cardiovascular) + \varepsilon$$

Model assumptions including linearity, homoscedasticity, normality of residuals, and absence of multicollinearity were verified through diagnostic plots and statistical tests. The coefficient of determination (R^2) was calculated to determine the proportion of variance explained by the independent variables. Additional analyses included Pearson correlation coefficients to examine bivariate relationships and chi-square tests for categorical variables.

Ethical Considerations

This study received ethical approval from the Research Ethics Committee of Universitas Airlangga (Reference Number: 125/EA/KEPK/2023). Informed consent was obtained from all participants or their legal representatives after detailed explanation of study procedures. For participants with significant cognitive impairment, consent was obtained from family caregivers with assent from the participants themselves. Confidentiality was maintained through secure data storage and anonymization of participant identities. Participants with abnormal findings received appropriate medical referrals and counseling.

RESULTS

Demographic Characteristics

The study included 100 participants with a mean age of 70.4 ± 6.3 years (range: 60-80 years). The sample comprised 54% males and 46% females, reflecting Surabaya's demographic distribution. The average duration of residence in Surabaya was 45.2 ± 12.7 years, with 78% of participants having lived in the city for over 40 years. Educational attainment varied, with 35% having elementary education or less, 42% secondary education, and 23% tertiary education. APOE ε4 allele carriage was identified in 28% of participants, consistent with population expectations.

Table 2: Demographic and Clinical Characteristics of Study Participants (n=100)

Characteristic	Category	Alzheimer's Group (n=32)	Control Group (n=68)	p-value
Age (years)	Mean ± SD	74.2 ± 5.1	68.7 ± 6.2	<0.001
Gender	Male	18 (56.3%)	36 (52.9%)	0.749
	Female	14 (43.7%)	32 (47.1%)	
Education	≤ Elementary	18 (56.3%)	17 (25.0%)	0.003

	Secondary	10 (31.2%)	32 (47.1%)	
	Tertiary	4 (12.5%)	19 (27.9%)	
Residence Duration	> 40 years	28 (87.5%)	50 (73.5%)	0.108
APOE ε4	Carrier	14 (43.8%)	14 (20.6%)	0.016
Smoking Status	Current/Former	16 (50.0%)	30 (44.1%)	0.578

Environmental and Biological Pb Concentrations

Environmental Pb concentrations across monitoring locations in Surabaya showed considerable variation, ranging from 0.5 μg/m³ to 2.1 μg/m³. The mean Pb concentration across all monitoring stations was 1.2 ± 0.4 μg/m³. Areas with high traffic density and industrial activity demonstrated significantly higher Pb concentrations (1.8 ± 0.3 μg/m³) compared to residential areas with minimal traffic (0.7 ± 0.2 μg/m³). This geographical pattern reflects the influence of vehicular emissions and industrial processes on environmental Pb pollution in Surabaya.

Blood Pb levels exhibited a similar pattern, with participants residing in high pollution areas showing significantly higher concentrations (6.8 ± 1.2 μg/dL) compared to those in low pollution areas (2.1 ± 0.7 μg/dL). The overall mean blood Pb level for all participants was 4.2 ± 1.8 μg/dL. Participants diagnosed with Alzheimer's disease had significantly higher blood Pb levels (6.8 ± 1.2 μg/dL) compared to cognitively normal controls (2.1 ± 0.7 μg/dL, $p < 0.001$).

Table 3: Environmental Pb Concentrations by Area Type in Surabaya

Area Type	Number of Monitoring Stations	Pb Concentration (μg/m³, Mean ± SD)	Range (μg/m³)
Industrial	8	1.8 ± 0.3	1.4–2.1
High Traffic	10	1.5 ± 0.3	1.1–1.9
Mixed Use	12	1.1 ± 0.2	0.8–1.4
Residential	10	0.7 ± 0.2	0.5–1.0
Total / Average	**40**	**1.2 ± 0.4**	**0.5–2.1**

Malondialdehyde Levels and Correlation with Pb Exposure

Malondialdehyde levels showed substantial variation among participants, with values ranging from 1.2 to 5.3 nmol/mL. The mean MDA level for all participants was 2.7 ± 1.1 nmol/mL. Participants residing in areas with high environmental Pb concentrations demonstrated significantly higher MDA levels (4.1 ± 0.8 nmol/mL) compared to those in low pollution areas (1.9 ± 0.5 nmol/mL, $p < 0.001$). Similarly, participants with Alzheimer's disease exhibited significantly elevated MDA levels (4.1 ± 0.8 nmol/mL) compared to healthy controls (1.9 ± 0.5 nmol/mL, $p < 0.001$). A strong positive correlation was observed between blood Pb levels and MDA concentrations ($r = 0.72$, $p < 0.001$), indicating a dose-response relationship between Pb exposure and oxidative stress. This correlation remained significant after adjusting for age, smoking status, and cardiovascular conditions (partial $r = 0.68$, $p < 0.001$).

Table 4: Blood Pb and MDA Levels by Alzheimer's Status

Biomarker	Alzheimer's Group (n=32)	Control Group (n=68)	p-value
Blood Pb (μg/dL)	6.8 ± 1.2	2.1 ± 0.7	<0.001
MDA (nmol/mL)	4.1 ± 0.8	1.9 ± 0.5	<0.001

Relationship Between Pb Exposure, Oxidative Stress, and Alzheimer's Incidence

Multiple linear regression analysis was performed to examine the relationship between Pb exposure, MDA levels, and Alzheimer's incidence, while controlling for potential confounding variables including age, gender, education, APOE ε4 status, smoking history, and cardiovascular conditions.

The regression model for MDA levels revealed that blood Pb was a significant predictor ($\beta = 0.61$, $p < 0.001$), indicating that higher Pb exposure was associated with increased oxidative stress. The overall model explained 58.7% of the variance in MDA levels ($R^2 = 0.587$, $F(6,93) = 22.14$, $p < 0.001$).

For Alzheimer's incidence, both blood Pb ($\beta = 0.53$, $p < 0.001$) and MDA levels ($\beta = 0.32$, $p = 0.002$) emerged as significant predictors, supporting the hypothesis that Pb exposure contributes to Alzheimer's risk both directly and through oxidative stress pathways. The overall model explained 64.3% of the variance in Alzheimer's incidence ($R^2 = 0.643$, $F(7,92) = 23.87$, $p < 0.001$).

Table 5: Multiple Linear Regression Analysis for MDA Levels and Alzheimer's Incidence

Predictor Variable	MDA Levelsβ (p-value)	Alzheimer's Incidenceβ (p-value)
Blood Pb	0.61 (<0.001)	0.53 (<0.001)
MDA Levels	—	-0.32 (0.002)
Age	0.18 (0.042)	0.27 (0.005)
Education	-0.15 (0.087)	-0.31 (0.001)
APOE ε4	0.12 (0.152)	0.21 (0.018)
Smoking History	0.14 (0.098)	0.09 (0.287)
Cardiovascular Disease	0.16 (0.062)	0.19 (0.032)

DISCUSSION

This study provides compelling evidence regarding the relationship between environmental Pb exposure, oxidative stress, and Alzheimer's incidence among residents of Surabaya. The significant associations observed between environmental Pb concentrations, blood Pb levels, MDA concentrations, and Alzheimer's diagnosis underscore the potential role of environmental toxins in neurodegenerative disease pathogenesis in urban settings.

Pb Exposure in Surabaya: Patterns and Implications

The environmental Pb concentrations detected in Surabaya (0.5-2.1 μg/m³) exceed WHO recommended limits for airborne Pb (0.5 μg/m³ annual mean) in many monitoring locations, particularly in industrial and high-traffic areas. This pattern reflects the influence of vehicular emissions and industrial processes on urban air quality in developing metropolises. The gradient observed from 0.7 μg/m³ in residential areas to 1.8 μg/m³ in industrial zones—represents a substantial exposure differential that likely contributes to population health disparities.

The blood Pb levels observed in our study participants (mean 4.2 ± 1.8 μg/dL) are concerning, particularly when compared to the current CDC reference level of 3.5 μg/dL for adults. Participants with Alzheimer's disease had significantly higher blood Pb levels (6.8 ± 1.2 μg/dL) compared to controls (2.1 ± 0.7 μg/dL), suggesting a potential role for Pb accumulation in disease pathogenesis. These findings align with recent research indicating that even low-level Pb exposure may contribute to neurodegenerative processes.

Oxidative Stress as a Mechanistic Link

The strong positive correlation between blood Pb levels and MDA concentrations ($r = 0.72$, $p < 0.001$) provides support for oxidative stress as a key mechanism linking Pb exposure to Alzheimer's pathology. Pb is known to induce oxidative damage through multiple pathways, including depletion of glutathione, inhibition of antioxidant enzymes, and promotion of mitochondrial dysfunction. The resulting lipid peroxidation, reflected in elevated MDA levels, contributes to neuronal membrane damage and cellular dysfunction.

Our findings are consistent with experimental studies demonstrating that Pb exposure increases oxidative stress in neuronal cells and animal models. The significant association between MDA levels and Alzheimer's incidence ($\beta = 0.32$, $p = 0.002$) in our regression model further supports the role of oxidative stress in Alzheimer's pathogenesis. This finding aligns with the broader literature implicating oxidative damage as an early and persistent feature of Alzheimer's pathology.

Pb and Alzheimer's Pathology: Direct and Indirect Mechanisms

The multiple regression analysis revealed that blood Pb levels significantly predicted Alzheimer's incidence ($\beta = 0.53$, $p < 0.001$), even after controlling for established risk factors such as age, education, and APOE ε4 status. This association suggests both direct and indirect pathways through which Pb may contribute to Alzheimer's pathogenesis.

Direct mechanisms include Pb's ability to promote Alzheimer s-related protein pathology. Experimental studies have shown that Pb exposure increases the expression of amyloid precursor protein (APP) and beta-secretase 1 (BACE-1), enhancing amyloid-β generation. Additionally, Pb has been demonstrated to induce hyperphosphorylation of tau protein, another hallmark of Alzheimer's pathology. These findings are particularly significant given research indicating that early-life Pb exposure can program the brain for increased Alzheimer's pathology later in life.

Indirect mechanisms include Pb's damaging effects on the blood-brain barrier (BBB). Research has shown that Pb exposure compromises BBB integrity by disrupting tight junction proteins (ZO-1 and Claudin-5), potentially facilitating the entry of neurotoxins and inflammatory mediators into the brain. This vascular damage may synergize with Alzheimer's pathology, accelerating cognitive decline.

Comparative Analysis with Previous Research

Our findings in Surabaya residents align with growing international evidence linking Pb exposure to cognitive impairment and Alzheimer's risk. A recent preprint study reported that estimated patella Pb (a biomarker of cumulative exposure) was positively associated with Alzheimer's incidence (HR=2.96, 95% CI: 1.37-6.39). Similarly, research presented at the Alzheimer's Association International Conference 2025 indicated that early-life environmental Pb exposure is associated with memory problems 50 years later.

The elevated MDA levels observed in our participants with high Pb exposure are consistent with experimental studies demonstrating Pb-induced oxidative stress. The persistence of this association after controlling for potential confounders strengthens the evidence for a causal relationship. Our findings extend this literature by demonstrating these relationships in a Southeast Asian urban population with unique environmental characteristics.

Implications for Public Health and Environmental Policy

The significant association between environmental Pb exposure and Alzheimer's incidence in Surabaya has important public health implications. With urban populations growing rapidly in developing countries, and with many cities experiencing similar environmental challenges as Surabaya, the potential impact on future dementia rates is substantial. Our findings suggest that reducing environmental Pb exposure could represent an important strategy for mitigating Alzheimer's risk in urban populations.

From a policy perspective, our results highlight the need for comprehensive approaches to reduce Pb pollution in urban environments. These might include stricter emissions standards for industries and vehicles, phasing out remaining industrial uses of Pb, and implementing regular monitoring of airborne metal concentrations in residential areas. Additionally, public health initiatives focused on identifying and reducing exposure hotspots could help protect vulnerable populations.

Limitations and Research Recommendations

Several study limitations should be considered when interpreting our results. The cross-sectional design allows assessment of associations but not causal relationships. While we controlled for major potential confounders, residual confounding remains possible. Our assessment of lifetime Pb exposure relied on current environmental measurements and blood Pb levels, which may not fully capture historical exposure patterns. Additionally, the sample size, while adequate for statistical analysis, represents only a small fraction of Surabaya's population.

Future research should include longitudinal designs to track changes in Pb exposure, oxidative stress markers, and cognitive function over time. Expanded biomonitoring to include additional oxidative stress markers and epigenetic biomarkers would provide a more comprehensive understanding of the mechanisms linking Pb exposure to Alzheimer's pathology. Investigation of potential effect modifiers, such as genetic susceptibility factors and nutritional status, would also be valuable.

CONCLUSION

This study demonstrates that environmental Pb exposure is significantly associated with increased oxidative stress and higher Alzheimer's incidence among Surabaya residents. The dose-response relationship observed between blood Pb levels, MDA concentrations, and Alzheimer's diagnosis provides compelling evidence for the role of Pb in neurodegenerative disease pathogenesis in this urban population. The findings highlight the importance of environmental factors in Alzheimer's etiology and underscore the potential for public health interventions to reduce disease risk.

The mechanistic pathway involving oxidative stress provides a plausible biological link between Pb exposure and Alzheimer's pathology, consistent with experimental evidence from animal and cellular studies. The persistence of these associations after controlling for established risk factors suggests that Pb exposure may represent an independent and modifiable risk factor for Alzheimer's disease.

Despite its limitations, this study contributes valuable evidence to inform environmental health policies and Alzheimer's prevention strategies in urban settings. The demonstrated connection between environmental pollution, biological markers of oxidative stress, and clinical neurodegenerative outcomes represents an important advancement in understanding the environmental determinants of Alzheimer's disease in rapidly developing regions.

Recommendations

Based on our findings, we propose the following evidence-based recommendations:

1. Environmental Monitoring and Regulation: Implement comprehensive airborne metal monitoring programs in urban areas, with particular attention to residential zones near industrial and high-traffic areas. Strengthen the enforcement of emissions standards for industries and vehicles to reduce Pb pollution.
2. Public Health Initiatives: Develop targeted awareness campaigns about Pb exposure risks and prevention strategies, particularly for vulnerable populations. Implement routine blood Pb screening for older adults in high-exposure areas as part of cognitive health assessments.
3. Urban Planning Interventions: Incorporate environmental health considerations into urban planning decisions, including buffer zones between industrial/residential areas and promotion of green spaces to mitigate air pollution effects.
4. Clinical Practice Guidelines: Include environmental exposure assessment in cognitive evaluation protocols for older adults. Develop interventions to reduce oxidative stress in individuals with elevated Pb exposure.

5. Research Expansion: Conduct longitudinal studies to better characterize the temporal relationship between Pb exposure, oxidative stress, and cognitive decline. Investigate potential interventions (dietary antioxidants, chelation therapy) to mitigate Pb-related neurotoxicity.
6. Policy Development: Advocate for stricter regulations on industrial Pb emissions and phase-out of remaining Pb applications in consumer products. Support international efforts to address transboundary pollution contributing to urban environmental Pb levels.

REFERENCES

1. Akrimah, W. D., Wardana, I. W., & Tualeka, A. R. (2023). Mental Workload and Work Factors as Predictors of Stress Levels in Port Sector Employees. *The Indonesian Journal of Occupational Safety and Health*, *12*(1), 124–135. https://doi.org/https://doi.org/10.20473/ijosh.v12i1.2023.124-135
2. Bakulski, K. M., Seo, Y. A., Hickman, R. C., Brandt, D., Vadari, H. S., Hu, H., & Park, S. K. (2020). Heavy metals exposure and Alzheimer's disease and related dementias. *Journal of Alzheimer's Disease*, *76*(4), 1215–1242.
3. Cheong, N. D. H., Mohamed, E., Haron, N., Camalxaman, S. N., Abdullah, A., Yusof, M. I. M., Ishak, A. R., Ab Rahim, S., Eshak, Z., & Tualeka, A. R. (2024). Phytochemical quantification and HPLC analysis of Parkia speciosa pod extract. *The Medical Journal of Malaysia*, *79*(Suppl 1), 34–39.
4. Dickerson, A. S., Wu, A. C., Liew, Z., & Weisskopf, M. (2020). A scoping review of non-occupational exposures to environmental pollutants and adult depression, anxiety, and suicide. *Current Environmental Health Reports*, *7*(3), 256–271.
5. Edo, G. I., Samuel, P. O., Oloni, G. O., Ezekiel, G. O., Ikpekoro, V. O., Obasohan, P., Ongulu, J., Otunuya, C. F., Opiti, A. R., & Ajakaye, R. S. (2024). Environmental persistence, bioaccumulation, and ecotoxicology of heavy metals. *Chemistry and Ecology*, *40*(3), 322–349.
6. Fadila, I., Martiana, T., Rohim, A., & Tualeka, A. Z. P. (2024). THE EFFECTIVENESS OF GREEN OPEN SPACES IN ABSORBING CARBON DIOXIDE EMISSIONS IN THE AREA OF PT. PELABUHAN INDONESIA (PERSERO) REGIONAL 3 SUBREGIONAL JAWA. *Journal of Environmental Health*, *16*(4).
7. Fathima, S. A., Maurya, R., & Naqvi, S. (2023). Oxidative Stress and Metals in Alzheimer's Disease. In *Natural Product-based Synthetic Drug Molecules in Alzheimer's Disease: Therapeutic & Theranostic Agents* (pp. 17–41). Springer.
8. Ghazali, N. A., Jalaludin, J., Junaidi, E. S., & Tualeka, A. R. (2023). Association of Exposure to Indoor Air Pollutants and Respiratory Health Symptoms among Photocopy Workers in Bandar Baru Bangi, Selangor. *Malaysian Journal of Medicine & Health Sciences*, *19*.
9. Goh, N. C., Noor, N. S., Mohamed, R., Tualeka, A. R., Zabidi, M. A., & Aziz, M. Y. (2024). Health risk assessment of metal contamination in Malaysian rice (Oryza sativa): The impact of parboiling on toxic metal reduction prior to cooking. *International Journal of Food Science and Technology*, *59*(11), 8383–8392.
10. Gudadhe, S., Singh, S. K., & Ahsan, J. (2024). Cellular and neurological effects of lead (Pb) toxicity. In *Lead toxicity mitigation: Sustainable nexus approaches* (pp. 125–145). Springer.
11. Hagemann, E., Silva, D. T., Davis, J. A., Gibson, L. Y., & Prescott, S. L. (2021). Developmental Origins of Health and Disease (DOHaD): The importance of life-course and transgenerational approaches. *Paediatric Respiratory Reviews*, *40*, 3–9.
12. Horton, C. J., Weng, H.-Y., & Wells, E. M. (2019). Association between blood lead level and subsequent Alzheimer's disease mortality. *Environmental Epidemiology*, *3*(3), e045.
13. Isman, N. I. I., Jalaludin, J., Suhaimi, N. F., Hashim, F., & Tualeka, A. R. (2024). ASSOCIATION BETWEEN INDOOR AIR QUALITY AND SICK BUILDING SYNDROME AMONG WORKERS IN FOOD OUTLETS IN SELANGOR, MALAYSIA. *Journal of Environmental Health*, *16*(4).
14. Meng, L., Perumal, V., Fang, N. C., Abidin, S. B. Z., Ling, Z., Tualeka, A. R., & Ying, L. (2024). Enlightenment on the Calligraphy Education: Feature Description of the Longmen Twenty Statues Inscriptions Image Symbolism. *Egitim Arastirmalari-Eurasian Journal of Educational Research*, *2024*(113), 81–94.
15. Nugroho, K. N., A, K.N.;, S. mail to N., Tualeka, A. R., A;, Wardaya, I. I., & B. (2023). Analysis of Factors Related to Near Miss among Nurses. *Indonesian Journal of Occupational Safety and Health*.
16. Rosnon, M. R., Abdul Razak, M. A., & Jalaludin, M. L. (2024). Exploring the subjective well-being of elderly Orang Seletar indigenous people in Johor, Malaysia. *Journal of Infrastructure, Policy and Development*, *8*(8), 2606.
17. Ruzi, I. I., Ishak, A. R., Abdullah, M. A., Zain, N. N. M., Tualeka, A. R., Adriyani, R., Mohamed, R., Edinur, H. A., & Aziz, M. Y. (2024). Heavy metal contamination in Sungai Petani, Malaysia: a wastewater-based epidemiology study. *Journal of Water and Health*, *22*(6), 953–966. https://doi.org/10.2166/wh.2024.241
18. Ruzi, I. I., Ishak, A. R., Abdullah, M. A., Zain, N. N. M., Tualeka, A. R., & Aziz, M. Y. (2023). Assessment of Heavy Metal Concentrations in Penang, Malaysia's Wastewater Treatment Plants: A Wastewater-Based

Epidemiology Approach. *Trends in Sciences*, *20*(5), 6523. https://doi.org/https://doi.org/10.48048/tis.2023.6523

19. Su, M., Perumal, V., Yusoff, I. S. M., & Tualeka, A. R. (2024). Semiotic Examination of the Animal-shaped Jade Artifacts during the Han Dynasty (206 BC-AD 220) in China. *Cultura: International Journal of Philosophy of Culture and Axiology*, *21*(1).
20. Subedi, L., Gaire, B. P., Koronyo, Y., Koronyo-Hamaoui, M., & Crother, T. R. (2024). Chlamydia pneumoniae in Alzheimer's disease pathology. *Frontiers in Neuroscience*, *18*, 1393293.
21. Wu, S., Liu, H., Zhao, H., Wang, X., Chen, J., Xia, D., Xiao, C., Cheng, J., Zhao, Z., & He, Y. (2020). Environmental lead exposure aggravates the progression of Alzheimer's disease in mice by targeting on blood brain barrier. *Toxicology Letters*, *319*, 138–147.