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Rapid Scoping Review of the Epidemiological Evidence for Mercury Exposure and Prevalence of Alzheimer's Disease

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Rapid Scoping Review of the Epidemiological Evidence for Mercury Exposure and Prevalence of Alzheimer's Disease

Rebecca Mattingly Lanham

Background

The purpose of this rapid scoping review is to examine the current body of epidemiologic research evaluating the potential linkage between environmental exposure to mercury and Alzheimer's disease (AD). We will conduct a scoping review of relevant studies to summarize the state of the literature and identify gaps for future research.

Alzheimer's disease (AD), which accounts for 60-80% of all neurodegenerative disease in the United States, was the seventh leading cause of death in Kentucky in 2020 [1]. The Alzheimer's Association estimated 75,000 individuals aged 65 and older were living with AD in Kentucky in 2020 [2]. This number is projected to increase by 14.7% to 86,000 by 2025 [2].

AD is a progressive brain disorder that affects memory, thinking skills, and behavior. The early symptoms of AD include mild memory loss and difficulty in completing familiar tasks. As the disease progresses, people may have trouble with language, experience mood swings, and they may have difficulty recognizing family and friends. In later stages, they may lose the ability to communicate, become bedridden, and require around-the-clock care. The exact etiology of AD needs further investigation; however, environmental factors such as pesticides, arsenic, cadmium, lead, and mercury have been correlated with development of AD lesions, cognitive decline, and AD [3, 4].

Mercury is a toxic metal that can be found in air, water, and soil, both from natural and human-made sources. There are three primary forms of mercury: elemental, inorganic, and organic. Elemental mercury, also known as "quicksilver," is primarily obtained from refining mercury sulfide in cinnabar ore and is used in various human activities, such as electrical equipment and dental amalgams. A link between the mercury exposure from dental amalgams and potential risk of AD has been examined. Studies have not found a positive association between the number, size, location, or time in the mouth of dental amalgams and Alzheimer's disease [5]. While these fillings do release mercury through vapor, and increase occupational mercury exposure risk, most is excreted via the mouth [6].

The most accurate way to measure mercury exposure in the body is to test a person's blood or urine for levels of mercury [7]. The two most common forms of mercury found in the body are methylmercury and inorganic mercury. Methylmercury is primarily found in fish and seafood and is the form that is most easily absorbed by the body. Inorganic mercury, on the other hand, is found in dental amalgams and other products and is typically less easily absorbed. Blood tests can measure both methylmercury and inorganic mercury levels, while urine tests primarily measure inorganic mercury level [7]. The half-life of mercury in the body depends on the form of mercury and the specific tissues where it

accumulates. The half-life is the amount of time it takes for the body to eliminate half of the mercury that has been absorbed. Methylmercury, the form of mercury found in fish and seafood, has a half-life of about 50 days in the blood [8] . However, it can accumulate in the body over time, primarily in the brain and kidneys, where it can persist for months or even years. Inorganic mercury, which is found in dental amalgam and some industrial settings, has a shorter half-life of around 30 to 90 days in the blood, but can accumulate in the kidneys, brain, and other organs [8].

The anthropogenic use of mercury contributes to atmospheric pollution and poses a significant risk to human health and the environment. Inorganic mercury compounds are formed when mercury combines with other elements such as chlorine, sulfur, and oxygen and is used in the production of batteries, polyvinyl chloride, and pigments. The different forms of mercury vary in their harmful and toxic properties. Methylmercury, the organic form of mercury, is the most toxic and is formed when inorganic mercury is methylated or combined with organic agents. Inorganic mercury exposure mainly occurs through occupational exposure via inhalation, while organic mercury, particularly methylmercury, is primarily acquired through the diet, especially through the consumption of fish and shellfish. Mercury bioaccumulates in organisms, as demonstrated in a study that found increasing blood mercury levels in women from 1999-2006 [9]. When mercury enters the brain, it phosphorylates the tau proteins which leads to a higher quantity of neurofibrillary tangles (NFT) and decreased cognitive function [10, 11].

Notable mercury exposures via ingestion in Japan and Iraq illustrate the metal's neurotoxin properties. In both cases, a local population was exposed to mercury through ingestion of fish and grain, respectively. In Japan, a vast amount of industrial waste containing large quantities of mercury was deposited into the Minamata Bay. The local population was exposed to the mercury through ingestion of fish and experienced severe symptoms of mercury poising including ataxia, speech impairment, visual field constriction, sensory disturbance, deafness, blindness, tremors, involuntary movements, mental retardation, coma, and death after. Infants whose mothers were infected developed mental retardation, peripheral neuropathy, cerebral palsy, and blindness. These changes became known as Minamata disease or Russell-Hunter syndrome [12]. Infants whose mothers were infected developed mental retardation, peripheral neuropathy, cerebral palsy, and blindness [12]. In Iraq, mercury poisoning occurred in 1971 when wheat grains were treated with fungicides containing organic mercury. This poisoning killed over 500 people who ate bread made with contaminated wheat [6, 7].

Coal combustion, the primary anthropogenic source of mercury emissions, has tripled since the 1970s and atmospheric mercury concentration has increased to 450% of natural levels [13]. The average

mercury content in coal from the US is 0.17/kg, which is higher than the worldwide average value of 0.1 mg/kg. Although 99% of fly ash, a coal combustion byproduct, is captured by filters, about 1% is released into the air where it eventually is inhaled or settles on surfaces including plants, soil, and water [14].

Kentucky has a high burden of coal mining and coal combustion. The fifth-largest coal-producing state in the United States, Kentucky provides coal to fuel 59 power plants across 13 states [15]. Coal constitutes 75% of Kentucky's electricity portfolio and 39% of its total energy consumption [15]. In rural Breathitt County, KY, a coal fire vent released five times the amount of elemental mercury into the atmosphere as recommended by the Occupational Safety and Health Administration [16].

With the projected increase in AD and Kentucky carrying a burden of coal combustion and related mercury exposure, it is important to scope out the potential linkage between mercury and AD through environmental exposure to inform future public health practices and research.

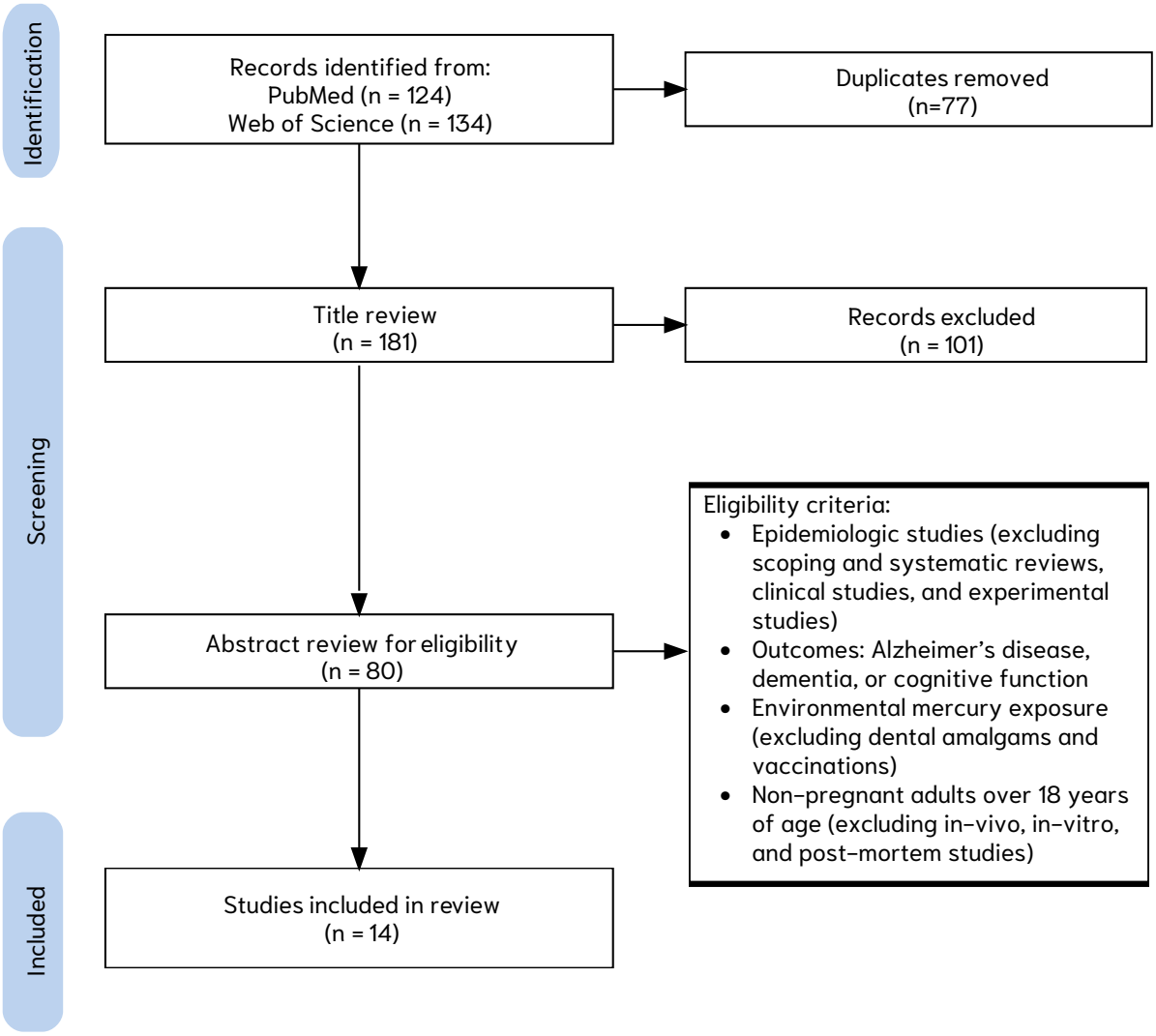
Methods

For this rapid scoping review, a search was conducted in February 2023 of two databases, PubMed and Web of Science. The search terms were “Alzheimer’s” and “mercury”, and the results were filtered to exclude papers published before January 1, 2002 or after December 31, 2022. This search yielded 124 papers from PubMed and 134 papers from Web of Science. Of these 258 total papers, 77 were duplicates and removed. The remaining 181 papers were reviewed according to the following eligibility criteria:

- Types of studies: epidemiologic studies (ecological, case-control, cohort, cross-sectional), excluding scoping and systematic reviews, clinical studies, and experimental studies
- Outcomes: Alzheimer’s disease, dementia, or cognitive function
- Primary exposure variable: environmental mercury exposure, excluding mercury exposure through dental amalgams and vaccinations
- Language: studies published in English
- Sample population: non-pregnant adults over 18 years of age, excluding in-vivo, in-vitro, and post-mortem studies

Utilizing the inclusion criteria, 167 studies were excluded. The remaining 14 epidemiologic studies became the basis for this rapid scoping review. The scoping review methodology was based on PRISMA’s scoping review guidelines [17]. See figure 1.

Fig. 1 Rapid Scoping Review of the Epidemiological Evidence for Mercury Exposure and Prevalence of Alzheimer's Disease



Review of Literature

Authors	Year	Country	Study design	Sample size	Sample population	indicators of exposure	outcome measured	major findings	Significant link?
Bocca, B; et al. [18]	2006	Italy	case-control study	n=58	AD group: 28 patients (9 males and 19 females, mean age 72.8± 7.2 years) diagnosis made according to the NINCDS-ADRDA criteria (mean duration of the disease 4.75 ± 2.10 years) Control group: 30 blood donor volunteers (12 males and 18 females, mean age: 62.5 ± 6.1) no clinical evidence of neurological disease.	Hg levels in serum Hg levels in blood	AD	- Significantly higher levels of Hg ($p < 0.01$) were found in serum (2.17 ±0.70) of the AD group compared to HS group. - No significant difference was found in blood HG levels between AD group and HS group - Authors ruled out diet as a confounder.	possible
Gerhardsson, L et al. [19]	2008	Sweden	case-control study	n=314	AD patients: n=173 (51 males, 122 females) AD patients with minor vascular components (AD + vasc): n=87 (33 males, 54 females) Healthy controls: n=54 (18 males, 36 females) Patients with severe AD were excluded from this study	Hg levels in plasma Hg levels in CSF	AD	- The plasma concentrations of total mercury were significantly higher in subjects with AD ($p < 0.001$) than in healthy controls. - Subjects with AD had significantly higher plasma Hg levels ($p = 0.013$) in comparison with patients with AD + vasc. - Subjects with AD + vasc had significantly higher CSF levels of total mercury ($p = 0.047$) than patients with AD alone. Plasma samples median and range (ug/L Hg) AD patients: 0.28 (<0.21–2.1) HS: <0.21 (<0.21–0.41)	yes
Gerhardsson, L et al. [20]	2009	Sweden	case-control studies	n=318	AD patients: n=264 (85 males, 179 females) Healthy controls: n=54 (18 males, 36 females) Patients with severe AD were excluded from this study	Hg levels in CSF presence of AD biomarkers (A Beta, T-tau and P-tau) in CSF	AD	no significant correlation found between CSF Hg levels and AD biomarkers (A Beta, T-tau and P-tau) in CSF between sample groups	no

Gerhardsson, L, et al. [21]	2011	Sweden	case-control	n=318	AD patients: n=264 (85 males, 179 females) Healthy controls: n=54 (18 males, 36 females) Patients with severe AD were excluded from this study	Quotients between the Hg conc in CSF and plasma	CSF vs Plasma quotient	the CSF/plasma quotient of Hg was significantly lower in AD than the controls ($p < 0.003$) indicating high blood-cerebral spinal fluid barrier permeability for the metal however, the Hg quotient did not have a statistically significant correlation with severity of disease	yes
Lee, JY, et al. [22]	2012	Korea	case-control group	n=210	AD patients: n=80 Healthy controls: n=130	Hg levels in blood Hg levels in serum	AD	No significant difference was observed in the blood ($p = 0.27$) or serum ($p = 0.9$) Hg concentrations between AD group compared to healthy controls. No statistical significance was observed between mercury and decrease in cognitive intelligence.	no
Park, JH, et al. [23]	2013	Korea	cross sectional, case-control study	n=208	AD patients: n=89 Healthy controls: n=119 patients with MCI were excluded from the study	Hg levels in serum	cognitive status function, AD	cognitive function evaluated via CERAD-K test Serum Hg levels had a significant negative correlation with age ($P= .004$) but had no positive or negative correlation with CERAD-K subscore or AD status. Correlation between serum Hg levels and age could be due to bioaccumulation mean Hg serum concentration ug/L between groups $p=0.488$ AD patients: 1.46 ± 0.81 HS: 1.54 ± 1.04	no
Giacoppo, S., et al [24]	2014	Italy	observational case-control study	n=89	AD patients: n=15 (mean age: 73.27± 2.596 years; 12 females and three males) MS patients: n=41 (mean age: 40.63±1.509 years; 31 females and ten males) Healthy controls: n=23 (mean age: 35.07±1.888 years; nine females and 14 males) Healthy elderly controls: n=10 (mean age: 72.40±8.796 years; seven females and three males) data was obtained for each participant regarding: occupational activity, diet, location of residence, and familiar history of neurological disease	Hg levels in blood	AD	Blood concentration of Hg (mean ± SD) in healthy elderly controls vs AD patients: 3.326 ± 1.698 vs. 5.415 ± 5.803 No significant difference found in Hg blood concentration in AD patients compared to control group	no

Paglia, G., et al. [25]	2016	Italy	case-control	n=118	AD patients: n=34 (72.44 ± 7.48, nine male, 25 female) MCI patients: n=20 (68.30 ± 7.75, 4 male, 16 female) SMC patients: n=24 (68.04 ± 8.05, 10 male, 14 female) HS: n=40 (65.53 ± 6.37, 15 male, 25 female) AD patients diagnosed with MMSE	Hg levels in serum	AD	significant difference in Hg concentration of serum via ANCOVA test ($p < 0.001$) Pairwise comparison showed significant difference of serum Hg concentration between HS vs. AD,MCI, and SMC subjects ($p < 0.01$) Hg profile was found to be comparable to some essential elements, (i.e. increasing in SMC and progressively decreasing in MCI and AD)	yes
Yang, YW., et al. [26]	2018	Taiwan	case-control study	n=164	propensity-score matched population of 82 AD patients and 82 HS average age of 76.65	Hg in blood	AD risk	No observed association between Hg concentration in blood and AD risk	no
Geier, DA., et al. [27]	2019	United States	cross sectional study	n=1,821,663	Age range: 60–80 years high ethylmercury exposure group: n=961,304 low ethylmercury exposure group: n=860,359	ethyl-mercury levels in blood	Cognitive status function	Cognitive Status function measured through: 1) Consortium to Establish a Registry for Alzheimer's Disease - Word List Learning (CERAD W-L) delayed recall test, 2) animal fluency test, and 3) Digit Symbol Substitution Test Significantly increased risks for lower animal fluency test (OR = 13.652, p = 0.0029) and CERAD W-L delayed recall test (OR = 6.401, p = 0.0433) scores were observed among the higher ethyl-Hg exposure group as compared to the lower ethyl-Hg exposure group.	yes
Cabral Pinto MMS, et al. [28]	2019	Portugal	case-control study	n=79	HS: n=10 SMC: n=14 MCI: n=16 Dementia: n=39 data was obtained on each participants' diet, medical history, profession, length of residence in industrial zone, and drinking water source. Cognitive status was assessed via mini-mental state examination (MMSE) and geriatric depression scale (GDS)	Hg levels in hair Hg conc. in soil	Cognitive status function	a significant difference ($p < 0.001$) in Hg levels in hair between the four cognitive groups (healthy, subjective memory complaint, mild cognitive impairment, and dementia), increasing from healthy to dementia participants. Pairwise comparison showed significant difference between HS vs. DEM subjects for Hg ($p < 0.01$) Dementia appears to be associated with longer residence time in the industrial zone study area ($p < 0.05$), professions associated with agriculture and fisheries, and consuming local home-grown foodstuffs. Enrichment factor values indicate that 26% of the sampled agricultural soils were extremely contaminated in Hg and 65% of the samples reach significant Hg contamination.	yes

Li, XL, et al. [29]	2020	China	ecological study	n/a	22 provinces and 3 municipal districts in Mainland China	Hg conc. in soil	AD mortality	Spearman correlation coefficient for Hg in A soil horizon 0.200 (p=0.337), B soil 0.333 (p=0.104), and C soil 0.265 (p=0.201) No association was detected between Hg soil concentration and relative risk of AD.	no
Lavanya, RD, et al. [30]	2021	India	case-control study	n=48	AD patients (recently diagnosed): n=30 (mean age: 60.29 ± 10.40years (range 45–84 years) Age-matched controls: n=18	Hg levels in serum	AD	Hg serum concentration in parts per billion: AD patients: 223.1 ± 33.5, Controls: 102.5 ± 67.2 p=0.007 Significantly higher Hg concentration in serum of AD patients when compared to controls (p = 0.007) lacked information on possible confounding factors (diet, smoking status, education)	yes
Babić Leko M, et al. [31]	2022	Croatia	case control study	n=193	AD patients: n=124 Mild cognitive impairment (MCI): n=50 Healthy controls: n=19	Hg levels in plasma AD biomarkers in CSF	AD	elevated levels of Hg in CSF are positively correlated with AD protein biomarkers including p-tau181, p-tau231, VILIP-1, and NFL lacked information on possible confounding factors (diet, smoking status, education)	yes

Hg - Mercury

MCI – mild cognitive impairment

SMC – subjective memory concerns

HS – healthy subjects

Results

Of the 14 studies reviewed, 12 were retrospective case-control studies. The rapid scoping review yielded one ecological study and one cross sectional study.

Nine of the case-control studies utilized AD prevalence as the measured outcome, while three studies Geier, DA., et al. [27], Cabral Pinto, MMS., et al. et al [28], and Park, JH., et al. [23] utilized cognitive status function as the measured outcome. Geier et al. measured cognitive status function in three ways: 1) Consortium to Establish a Registry for Alzheimer's Disease - Word List Learning (CERAD W-L) delayed recall test, 2) animal fluency test, and 3) Digit Symbol Substitution Test. Cabral Pinto et al. used the Mini-Mental State Examination and Park et al. utilized the CERAD-K assessment. Several studies utilized cognitive function assessment scores to determine or select the sample groups but did not use cognitive function as a measured outcome.

Thirteen studies used biomonitoring samples to measure mercury levels in the sample population. Five studies measured mercury concentration in whole blood, five measured mercury concentration in serum, three measured mercury concentration in cerebral spinal fluid (CSF), one measured mercury concentration in plasma, and one utilized hair samples. Additionally, AD protein biomarkers were measured by two studies, and one measured the quotient between mercury concentration in cerebrospinal fluid (CSF) and plasma. Six of the fourteen studies utilized multiple biomarker measurements ie: serum and blood or CSF and plasma.

Two studies used soil as a marker of mercury exposure. Li et al. did not find a significant link between AD mortality risk and mercury concentration in soil. The other study, Cabral Pinton et al. found a positive relationship between soil mercury concentration and cognitive functioning. It is important to note that the two studies cannot be directly compared since they were evaluating different outcomes – AD mortality risk compared to cognitive function.

The mercury levels measured from different biomonitoring matrices show varying results. Measurements from blood components, i.e. serum and plasma, showed the most consistent findings of elevated mercury levels in AD patients compared to controls. However, whole blood samples yielded contradictory results. Of the four studies that used whole blood as the biomonitoring variable, only one study, Geier et al., found a positive correlation between mercury concentration and cognitive function. However, this study is unique in that it is the only study conducted in the United States, has the largest sample size by far (approximately 1.8 million) and was cross-sectional in nature rather than a case-control study like the other studies that used biomonitoring variables. This cross sectional study utilized

the prevalence of ethylmercury to evaluate cognitive functioning in the US population. This study differed from the 12 case-control studies which compared groups retrospectively.

Discussion

Overall, the body of research linking environmental exposure to mercury and AD seems to be inconclusive.

Human biomonitoring, defined as “the method for assessing human exposure to chemicals or their effects by measuring these chemicals, their metabolites or reaction products in human specimens”, involves the measurement of biomarkers in different body fluids (e.g., blood, serum, or CSF) or tissues (e.g., hair) as the primary means of evaluating mercury exposure to determine any subsequent risk or correlation with AD [22]. The most common biomonitoring methods; serum, whole blood, plasma, cerebral spinal fluid, and hair, were all represented in the results of this review. However, the results from this rapid scoping review did not find a consistent, significant link between mercury exposure measured through biomonitoring and AD prevalence. Possible explanations for these differing results include the population sampled and the biomarker used to measure mercury exposure.

Cabral Pinto et al. broke the sample population into four groups ranging in cognitive functioning; healthy controls (HS), mild cognitive impairment (MCI), subjective memory concerns (SMC), and dementia. The study found a significant difference in the mercury levels between the different study groups with mercury concentration in hair increasing from healthy to dementia participants. This is impactful because most of the studies measured AD prevalence as the outcome and had already assessed for cognitive function in selecting the study population. In some of the studies, this pre-screening cognitive assessment excluded patients with MCI or SMC while in others the pre-screening assessment excluded patients with advanced AD. Dividing the sample population into groups based on cognitive status indicate the continuum of Alzheimer's disease which often occurs over a period of 15–25 years. During this time, Alzheimer's disease pathology can be present without any symptoms progressing to a stage of mild cognitive impairment, then subjective memory concerns, and concluding in overt dementia. Research utilizing these stages illustrates that dementia is the result of a long-time presence of Alzheimer's disease pathology.

The majority of studies included in this review relied on clinical diagnoses of AD. However, clinical diagnosis of AD can often result in misclassification errors, meaning that patients can be either over-diagnosed or under-diagnosed with the disease. This is because the symptoms of AD are similar to other types of dementia, such as vascular dementia and Lewy body dementia. Additionally, there is no single

test that can definitively diagnose AD, which can lead to subjective interpretation of test results and potential misdiagnosis. One common source of misclassification errors is the use of cognitive tests to diagnose AD. These tests can be subjective and rely heavily on a patient's self-reporting of their symptoms, which can be influenced by factors such as anxiety or depression, although most of the studies reviewed here included depression scales and excluded patients with clinical levels of depression. Furthermore, some cognitive tests may not be sensitive enough to detect the early stages of AD, leading to a delay in diagnosis and treatment.

Another limitation in this review which could have contributed to misclassification errors can also occur due to variations in diagnostic criteria and protocols across different healthcare providers and settings. For example, some clinicians may be more likely to diagnose AD based on cognitive symptoms alone, while others may require the presence of specific biomarkers or imaging findings to confirm a diagnosis.

Another possible explanation for the inconsistent results could be due to the way mercury accumulates in the body. Gerhardsson, L, et al. [14] found a high CSF vs plasma quotient, illustrating the high blood-cerebral spinal fluid barrier permeability for mercury. Post-mortem studies have established that mercury accumulates in the brain with two-fold levels of mercury concentration in AD brains. Since this review excluded post-mortem studies, brain matter was not used for biomarking mercury exposure. However, a possible hypothesis is that the mercury is not present in the body fluids of the AD patients as it had accumulated in the brain tissue.

The decision to exclude post-mortem studies in this review was based on several factors. First, rapid scoping reviews are conducted to provide a broad overview of the existing evidence on a topic, often with a limited timeframe and resources. Given the number of studies available on this topic, it was determined that excluding post-mortem studies would streamline the review process and allow the focus to be on studies that measure biomarkers in living individuals. Second, post-mortem studies have their own limitations and biases. Post-mortem studies can only provide information about the levels of mercury in the body at the time of death. These studies are limited in information regarding the route of mercury exposure or lifestyle factors. Post-mortem studies also often involve a biased sample of individuals who have already been diagnosed with AD with AD being the determined cause of death. Biomonitoring studies can identify potential sources of exposure and provide information on exposure levels in different populations, which can inform targeted interventions to reduce exposure and prevent adverse health outcomes.

However, given the frequency of misclassification of AD in clinical diagnosis, the omission of post-mortem studies may have contributed to the inconclusive results. For diseases other than those caused by single gene defects, the most accurate diagnosis is typically achieved through histological examination of tissue samples taken from affected areas. In some cases, biopsy can provide these samples during a patient's lifetime, but this has not been a viable option for Alzheimer's disease due to the high risk/benefit ratio [32]. Nevertheless, it is widely accepted that histological examination is the best way to diagnose AD. While new biomarkers may have a significant impact on clinical diagnostic practice, current biomarkers for AD show significant overlap with those found in other types of dementia, as well as in cognitively normal elderly individuals [32]. This makes it challenging to determine whether cognitive impairment is specifically due to AD or another concurrent process. In future reviews, including post-mortem studies is recommended and may illuminate additional links that were overlooked or missed in this review.

Compelling evidence from both in-vitro and in-vivo research suggests that mercury exposure is linked to neurodegeneration and AD pathology. A review by Siblerud et al clearly identifies the different ways mercury has been shown to cause symptoms of AD [33]. However, these clinical and experimental findings do not seem to translate into consistent epidemiologic findings. While there is a strong body of research in the toxicology of mercury and the etiology of Alzheimer's disease, there are gaps in epidemiologic research linking the two. While case-control studies that dominate the literature from 2002-2022 offer value and insight, they are limited in scope due to the cross-sectional nature of the population study. One advantage of the case- control studies reviewed here is the elimination of recall bias since the studies were measuring biomarkers. The current peer-reviewed research lacks longitudinal studies. Only one peer-reviewed longitudinal study was found, published in 1990, which measured the mercury levels in AD patient's nails and found that mercury concentration in nails was inversely correlated with patient's age and with the duration and severity of the dementia [34]. Longitudinal studies would be imperative in establishing any type of correlation between mercury exposure and AD.

Conclusion

Alzheimer's disease is a significant burden on both the aging population and society [2]. Current research indicates that an interplay of heredity and genetic expression alongside environmental exposure to neurotoxins, such as mercury, may influence AD. Because of human activity, the atmospheric mercury concentration has increased to 450% of natural levels [13]. Debate exists

regarding the exact contribution of mercury to AD development; several studies have found correlation between AD and mercury exposure, while other studies do not find such a link [35-38]. However, there is a consensus in the literature that there is an increasing rate of both the exposure to mercury and an inclining rate of mercury in humans [1]. In Kentucky, it is projected that in the next three years, the number of Alzheimer's cases will increase by 11,000 [1].

The NIH's National Institute of Aging states in their current strategic direction for research, "Our vision is to enable all Americans to enjoy robust health and independence with advancing age" [4]. Funding research to develop a deeper understanding of neurodegenerative diseases like Alzheimer's disease is top of their list. A part of that future research should include longitudinal epidemiologic studies that look at biomarkers of individuals who live in areas of high mercury emissions. Examining rates of mercury bioaccumulation and the prevalence of Alzheimer's disease in areas of high coal emissions would benefit our current understanding of the link between Alzheimer's and mercury exposure.

Implications for Local Public Health Practitioners

In the face of inconclusive evidence, the precautionary principle states "when an activity raises threats of harm to human health or the environment, precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically" [39].

As public health practitioners, we are tasked with following these precautionary principles and therefore measures should be taken to reduce the public's mercury exposure and increase awareness of the potential harms of exposure. Recommended measures include: community education and awareness-raising campaigns, collaboration with local extension offices, and education for healthcare providers regarding the potential impact mercury exposure has on AD risk.

Community education and awareness-raising campaigns will inform individuals of steps they can take to reduce mercury exposure. For example, about 1% of fly ash is released into the air where it eventually is inhaled or settles on surfaces including plants, soil, and water. Exposure to mercury often occurs via ingestion of fish raised in mercury contaminated water or via fly ash which settled on the leaves of produce grown near coal combustion plants. Awareness of this pathway could lead individuals to health-protective behaviors related to produce consumption.

Due to elevated mercury levels in groundwater state-wide, Kentucky public health officials have issued fish consumption advisories for all groundwater. Signage posted at local fishing supply stores and near popular fishing spots is recommended to raise public awareness about the risks associated with fish

consumption (see appendix A). This signage is not intended to dissuade people from fishing or consuming fish they have caught, but rather it aims to inform the community about the potential health risks associated with consuming fish caught throughout the state. The advisories' guidance can help community members make informed decisions and minimize risks associated with consuming fish from Kentucky waters. Effective signage would include simple language and use of QR links to direct readers to the Kentucky Departments for Environmental Protection and Fish and Wildlife Resources for more information.

Washing fresh produce, particularly produce grown near coal combustion plants, is an accessible way to reduce potential mercury exposure. Local health departments can partner with coordinators of farmers markets to promote awareness of the importance of washing locally grown fruits and vegetables. Collaborative community education campaigns should be designed to target patrons of farmers markets with the goal of encouraging fresh produce consumption while educating about the importance of washing said produce. These communication campaigns can include eye-catching flyers posted at the farmers markets that encourage buyers to wash their purchased fruits and vegetables. The communication awareness campaign can also include bright vinyl stickers that are handed out at farmers markets encouraging people to "wash their produce".

Since elevated mercury levels have been found in topsoil near coal combustion plants, local health departments should partner with extension offices in counties with high coal production and/or coal burning to expand the soil testing capacity and offer mercury concentration soil testing for farmers and at-home gardeners. Currently, Kentucky extension offices offer heavy metal soil testing but only test for cadmium, chromium, nickel, lead, zinc, and copper [40]. Since mercury is a known toxin, it is important that it be included in routine soil testing.

Local health departments play a crucial role in educating healthcare providers about potential links between mercury exposure and AD. Since there is no known cure for AD, prevention is vital to reduce prevalence and burden of the disease. Healthcare professionals, particularly those working in regions of high coal producing and/or coal combustion, should be educated on the potential link between mercury exposure and AD as well as informed of how to assess exposure risk. Local health departments can develop and distribute educational resources that provide information on the potential links between mercury exposure and AD (see appendix B). These resources could include fact sheets, brochures, or online resources that are easily accessible to healthcare providers. Obtaining a detailed patient history will be important in assessing risk. Healthcare providers can ask patients about their past and current

occupations and assess whether they may have been exposed to mercury through their work. Dentistry, mining, and industrial manufacturing all have elevated mercury exposure risk. Another way to screen for potential mercury exposure is through a detailed environmental history. Healthcare providers can ask patients about their hobbies and lifestyle choices, such as consumption of certain types of fish, exposure to certain chemicals or substances, or living in proximity to industrial sites or waste dumps that may contain mercury. Once patients have been identified as potentially at risk for mercury exposure, healthcare providers can evaluate their risk for developing AD using standard screening tools, such as the Mini-Mental State Examination (MMSE) or the Montreal Cognitive Assessment (MoCA). These tools assess cognitive function and can help detect early signs of cognitive decline that may be associated with AD.

Although the evidence linking mercury exposure specifically to AD is inconclusive, the recommendations described above are important preventative measures for an array of mercury-linked outcomes.

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Appendix A

FISH CONSUMPTION GUIDELINES

CATCH & EAT SAFELY

The guidance below applies to fish from all Kentucky waters

Fish Species	General Population	Sensitive Population *	Contaminate **
Predatory fish	1 meal per month	6 meals per year	mercury
Bottom feeder fish	1 meal per week	1 meal per month	mercury
Panfish	1 meal per week	1 meal per month	mercury
All other fish	No advisory	1 meal per week	mercury

* Sensitive Populations include women of childbearing age and children 6 years and younger.

** Mercury can accumulate in the body over time and can cause neurological and developmental problems.

Predatory fish: Largemouth Bass, Smallmouth Bass, Spotted Bass, White Bass and Striped Bass and their hybrids, Yellow Bass, Flathead Catfish, Blue Catfish, Musky, Sauger and Walleye and their hybrids, Bowfin, Chain Pickerel and all Gars.

Bottom feeder fish: Channel Catfish, Drum, Carp Sucker, White Sucker, Common Carp, Bullhead species, Northern Hog Sucker, Buffalo species, Spotted Sucker, Redhorse species, Sturgeon and Creek Chub.

Panfish: Bluegill, Green Sunfish, Longear Sunfish, Redear Sunfish, Rock Bass, and Crappie species.

Other fish: Asian Carp, Trout species, Minnows, etc.

For more information visit:
https://eec.ky.gov/Environmental-Protection/Water/Monitor/Pages/Fish-Advisories.aspx

Appendix B

Mercury's Negative Effects on Brain Health

Mercury is a toxic metal that can be found in air, water, and soil, from natural and human-made sources.

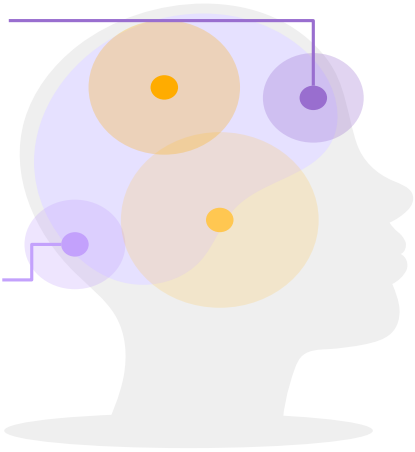
Exposure to mercury, even in small amounts, may cause serious health problems, and is a threat to the development of a child in utero and throughout life. [1]

Brain Disorders [1]

Mercury has been associated with neurological symptoms including headaches, confusion and memory loss, and decreased motor control. Some studies have linked mercury exposure to development of Alzheimer's disease

Phosphorylates Tau Proteins [2]

When mercury enters the brain it phosphorylates the tau proteins which leads to a higher quantity of tangles and decreased cognitive function.



Ways to reduce mercury exposure:

- Limit fish consumption from locally harvested waters, due to elevated mercury levels in groundwater
- Thoroughly wash fresh produce, especially if you live near (or produce is grown near) coal burning power plants

Coal combustion is the primary human-made source of mercury emissions. [3]

450% The percent to which the natural level of atmospheric mercury has increased

About 1% of fly ash, a coal combustion byproduct, is released into the air. [4]

In Kentucky, a coal fire vent released five times the amount of mercury into the atmosphere as recommended by the OSHA [5]

Mercury can occur via ingestion of fish raised in mercury contaminated water or via fly ash which settles on produce grown near coal combustion plants

1. Mercury and Health, WHO, https://www.who.int/news-room/fact-sheets/detail/mercury-and-health
2. Siblerud, Robert et al. *A Hypothesis and Evidence That Mercury May be an Etiological Factor in Alzheimer's Disease.*
3. Outridge, P.M., et al., *Updated global and oceanic mercury budgets for the United Nations Global Mercury Assessment 2018*
4. Li, R., et al., *Mercury pollution in vegetables, grains and soils from areas surrounding coal-fired power plants*
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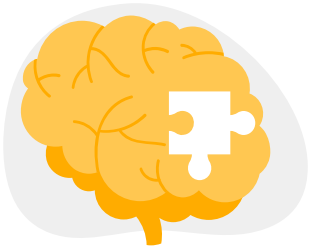
Assess for mercury exposure in patients



Occupational History

Obtain a detailed patient history including past and current occupations. Dentistry, mining, and industrial manufacturing have elevated mercury exposure risk.

Environmental History

Hobbies and lifestyle choices such as fishing, jewelry making, and consumption of locally harvested fish may increase mercury exposure as well as living in proximity to industrial sites, coal combustion plants, or waste dumps.

Evaluate Risk

Include blood mercury level testing to CBC or CMP labs for patients with high mercury exposure risk

Use cognitive screening tools, such as the Mini-Mental State Examination (MMSE) or the Montreal Cognitive Assessment (MoCA), to detect early signs of cognitive decline and Alzheimer's disease risk