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Review

Systematic and state-of the science review of the role of environmental factors in Amyotrophic Lateral Sclerosis (ALS) or Lou Gehrig's Disease

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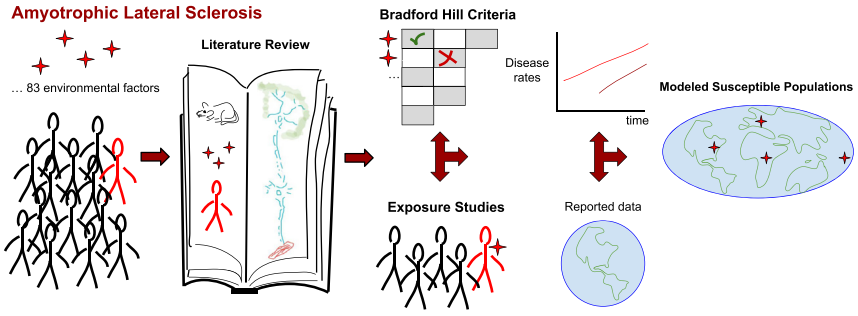
HIGHLIGHTS

- Environmental factors linked to amyotrophic lateral sclerosis (ALS) are explored.
- Stringent PRISMA literature review criteria were applied in this meta-analysis.
- Two independent methodologies point to some of the same environmental determinants.
- BMAA, formaldehyde, mercury, manganese and zinc rank highest for ALS association.
- Data gaps are identified and global disease burden was modeled for present and future.

GRAPHICAL ABSTRACT



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ABSTRACT

The etiology of sporadic amyotrophic lateral sclerosis (ALS) is still unclear. We evaluate environmental factors suspected to be associated with ALS for their potential linkage to disease causality and to model geographic distributions of susceptible populations and expected cases worldwide. A PRISMA systematic literature review was performed 2021. Bradford Hill criteria were used to identify and rank environmental factors and a secondary review of ALS diagnoses in population studies and ALS case or cohort studies was conducted. Prevalence rate projection informed estimates of impacted regions and populations. Among 1710 papers identified, 258 met the inclusion criteria, of which 173 responded to at least one of nine Bradford Hill criteria among 83 literature-identified ALS environmental factors. Environmental determinants of ALS in order of decreasing significance were *β*-*N*-methylamino-L-alanine (BMAA), formaldehyde, selenium, and heavy metals including manganese, mercury, zinc, and copper. Murine animal models were the most common methodology for exploring environmental factors. Another line of investigation of 62 population exposure studies implicated the same group of environmental agents (mean odds ratios): BMAA (2.32), formaldehyde (1.54), heavy metals (2.99), manganese (3.85), mercury (2.74), and zinc (2.78). An age-adjusted incidence model estimated current total ALS cases globally at ~85,000 people compared to only ~1600 cases projected from the reported ALS incidence in the literature. Modeling with the prevalence microscope equation forecasted an increase in U.S. ALS cases from 16,707 confirmed in 2015 to ~22,650 projected for 2040. Two orthogonal methods employed implicate BMAA, formaldehyde, manganese, mercury, and zinc as environmental factors with strong ALS associations.

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ALS cases likely are significantly underreported globally, and high vulnerability exists in regions with large aging populations. Recent studies on other diseases with environmental determinants suggest the need to consider additional potential triggers and mechanisms, including exposures to microbial agents and epigenetic modifications.

Contents

1. Introduction

Some 150 years after its initial description in the field of neuroscience (Schiffter, 2010), the etiology of sporadic amyotrophic lateral sclerosis (sALS) or Lou Gehrig's Disease remains uncertain. Whereas exposure to environmental toxins has long been suspected as playing a role in ALS onset, the only agreed-upon risk factors remain old age, male sex, and to have a predisposition from a family history with ALS (Aktekin and Uysal, 2020; Longinetti and Fang, 2019; Ingre et al., 2015). Familial ALS (fALS) represents 10% of cases linked to known gene mutations. Currently, research has focused on the 25 genes identified for Mendelian inheritance of ALS (Riancho et al., 2018). Pathogenesis attributed to hereditary factors include genes that almost always express as dominant traits (Taylor et al., 2016). Of the hereditary contributions, 60–80% have been linked to the cytoplasmic CuZn superoxide dismutase (SOD) protein first identified in 1993, the fused in sarcoma (FUS) RNA binding protein or TAR DNA binding protein (TARDBP) genes coding for TAR DNA binding protein number 43 (TDP-43) first identified in 2006, and the 9p21 chromosome C9orf72 gene expressing protein and resulting dipeptide repeat proteins (DPRs) first identified in 2011 (Taylor et al., 2016; Zufiria et al., 2016). In the United States and Europe, 40% of fALS cases have been attributed solely to genetic lesions and repeats in the C9orf72 gene (Logroscino and Piccininni, 2019). What triggers the majority of ALS cases (~60%) at present remains unclear.

Geospatial clusters of ALS continue to be reported worldwide, arguably the most famous being in the Western Pacific. Globally, the incidence rate, or rather the rate of the number of new cases given to those at risk, ranges from 0.6 to 3.8 per 100,000 person-years (Longinetti and Fang, 2019). The prevalence rate, described as those affected given a total population at a given time, ranges from 4.1 to 8.4 per 100,000 persons (Longinetti and Fang, 2019). While the Chamorros of the Mariana Islands, including Guam, saw the highest prevalence when first reported in 1956, peaking at 100 per 100,000 persons, New Guinea reached the highest prevalence ever reported in 1963 at 147 per 100,000 persons (Garruto and Yase, 1986; Logroscino and Piccininni, 2019). Today, the Chamorros people in Guam report a prevalence of 3 per 100,000 persons - like reports in the United States and European nations. As the Western Pacific ALS/PDC has experienced a significant reduction in disease burden (Chen, 1995) over the last 50 years across all foci regions, global trends project the number of people diagnosed with ALS each year to rise from 80,162 cases in 2015 to 105,693 cases in 2040 (Arthur et al., 2016). New Guinea sees a high prevalence at 73 per 100,000 persons (Logroscino and Piccininni, 2019). Comparison of disease rates between villages have ruled out genetic factors (Spencer et al., 2019), leaving environmental factors as likely culprits.

As environmental toxins can trigger genetic and epigenetic changes in the body, research has focused on finding associations between exposure events and ALS incidence. A barrage of chemicals has been associated with ALS to date. The cyanotoxin *β-N*-methylamino-*L*-alanine (BMAA) has been heavily studied in association with ALS starting with the ALS geospatial cluster in Guam (Garruto and Yase, 1986; Chen, 1995; Spencer et al., 2019; Riancho et al., 2018; Plato et al., 2003; Banack and Cox, 2018; Cox and Sacks, 2002; Cox et al., 2016). Residential, occupational, and industrial exposures to organic chemicals and metals have been under suspicion. The ability of known neurotoxins such as metals, solvents (i.e., ethanol), pharmacological agents, or mixed chemical exposures to trigger pathology is affected by endogenous factors such as genetic predisposition and gene expression (Bondy and Campbell, 2005). Although the causal linking of neurotoxins to various current diseases has been limited, history may inform on the potential for causal linkages between environmental exposures and disease outbreak (Rusyniak et al., 2005). In addition, lifestyle and nutritional choices in the environment have been shown to correlate with ALS diagnosis. However, these choices only increase the long list of potential risk factors to ALS without helping to narrow or eliminate previously suspected factors.

Established in 1965, Bradford Hill criteria present a means to measure and weigh a risk factor for disease causality by casting a wider net around multiple criteria (Davidson and Smith, 2010). Association may be bridged to causal if the following criteria are met: 1. strength of association, 2. consistency, 3. specificity, 4. temporality, 5. biological gradient, 6. plausibility, 7. coherence, 8. experiment, and 9. analogy (Fig. S1). Recent evaluations using the Bradford Hill criteria have been applied to determine disease causality (Khella et al., 2021; Sfairopoulos et al., 2021) or gaps in the literature (Feldman et al., 2020; Colebunders et al., 2021). Epidemiologists argue that

if a risk factor meets all nine criteria, that it may be considered causal. However, studies allowing for a 5% statistical error or higher may catch Type I (by chance) errors, thereby associating several environmental factors with ALS. In the same way, studies with small sample sizes are prone to Type II (random association) errors in which false-negative results may lead researchers away from factors that in fact, contribute to ALS etiology. Therefore, the second evaluation of factors using a literature search for population exposure events observed in ALS cases offers a means for validating results obtained with the Bradford Hill criteria assessment.

This paper aimed to offer a criteria-based approach to evaluate factors currently suspected of association with ALS. We hypothesize that the scientific literature shows associative or even causal links between environmental toxin exposure and ALS. The Bradford Hill criteria are thereby used to infer causal relationships through epidemiological analysis (Fedak et al., 2015). Furthermore, we hypothesize that populations with higher exposure to environmental toxins show a higher disease incidence. A state-of-the science literature review of environmental toxin exposure through occupational means as a driver to ALS diagnosis later in life therefore was conducted, to test the hypothesis that a given confirmed exposure in a population is linked to an increased risk of ALS development. In addition, we performed geospatial mapping to expose gaps in the literature and we applied modeling to assess regional susceptibility based on demographic and possible exposure sources.

2. Methods

Two methods were utilized to decrease small sample size bias and the chance of random associations. Bradford Hill criteria defined and developed as a rubric for study assessment helped discern causality for environmental factors in the literature. Cataloged exposure studies of ALS patients were then aligned to further support the likelihood of factor association or ultimately causality (Fig. S1).

2.1. PRISMA Systematic literature review

A systematic literature review was first conducted through SCOPUS database searches for all publications available on or before March 12, 2021. ALS was searched for using {ALS} OR {amyotrophic lateral sclerosis} OR {motor neuron disease}. Environmental toxins were additionally targeted using (toxi* OR contaminant* OR poison*) AND ({exogenous} OR {external} OR {exposure}). To search for animal models, geospatial population studies, or epigenetic studies, the following keywords were used: {model} OR {database} OR geo* OR epigen* OR {methylation} (Fig. S1).

Meeting the Bradford Hill criteria would allow us to argue whether empirical evidence for the epidemiological association may be considered causal (Fedak et al., 2015). Articles eligible for analysis were limited to hypothesis-driven studies that sought to associate risk factors with ALS. Animal and human model studies were assessed alongside human population studies.

2.2. State-of-the science literature review

A state-of-the science literature review was further conducted by a SCOPUS database search on April 19, 2021. A redirected search on SCOPUS using the suspected factor, route of exposure, and occupational or industrial keywords were conducted to seek direct ties from exposure (s) to ALS diagnosis. Hypothesis-driven studies of ALS in factor-exposed populations were analyzed for odds ratios (OR), standardized mortality ratios (SMR), or standardized incidence ratios (SIR) by a factor in occupational or industrial contexts.

2.3. Prevalence rate modeling

Geospatially linked prevalence data reported in the United States were plotted to find the rate of change of the prevalence rate in 100,000 people over time. The rate of change was then used to project the prevalence rate by using the microscope equation:

$$Future\ rate = (rate\ of\ change * time\ interval) + Current\ rate$$

Population size projections every 5 years from 2015 to 2060 were referenced from Statista.com. The rate of change of the population size over time in years was then used to project population size using its microscope equation.

To determine when ALS would increase prevalence to escape orphan disease status, the prevalence rate threshold needed for ALS to surpass was calculated for 200,001 people given the population size each year. The point of intersection between the projected prevalence and the prevalence rate threshold above for orphan disease status was used to represent the year in which ALS would presumably overcome orphan disease status. Prevalence in the United States was finally calculated using the projected prevalence rate given the projected population size for each year considered.

2.4. Modeling of susceptible populations

Disease incidence in the United States and globally were modeled from literature rates and organized into a minimum, average, and maximum rate. The correlation between the percentage of people aged 65 years and older in a country's population and ALS incidence rate were then used to assign minimum, average and maximum incidence rates to non-reporting countries. When modeling the number of people susceptible to ALS across the world by country, countries whose population of 65+ year old individuals was <10% were assigned to the minimum incidence rate model. Countries with between 10% and 20% 65 years and older persons in the population were modeled after the average incidence rate, whereas countries whose 65+ year old persons exceeded 20% of the total population were calculated by applying the maximum incidence rate model.

3. Results

3.1. Bradford Hill criteria analysis

Since ALS was recognized as a disease in the mid-1800s, no environmental factor has been identified as causal to date (Fig. 1). A transition from observing incidence rates to performing laboratory investigation occurred after the first genetic link was discovered. Research using animal models increased after the SOD1 gene mutation was discovered in the early 1990s. Lou Gehrig's death lines up with an initial push for research in the 1940s and 50s, but the discovery of the SOD1 mutation in the 1990s let to an acceleration in research. The environmental movement in the 1960s and 1970s correlates with the initiation of research on environmental toxins, which was followed by an interest to link known or presumed exposures to the geography of disease cases.

We considered the nine Bradford Hill criteria of association to evaluate the role of environmental factors in the development of ALS. Numerous factors have been suspected of association with ALS, 83 of which were identified in hypothesis-driven studies (Table S1). These factors can be narrowed down to the top ranked *β-N*-methylamino-*L*-alanine (BMAA), formaldehyde, selenium, and heavy metals including manganese, mercury, zinc, and copper (Fig. 2). Among the top ranked organic chemicals were BMAA (a non-proteinogenic amino acid) and formaldehyde, a known neurotoxin. Literature reporting associations between BMAA exposure and ALS met all nine Bradford Hill criteria. Nevertheless, specificity and analogy are two criteria with minimal support. Formaldehyde, on the other hand, only met 5 Bradford Hill criteria. The criteria lacking evidence include specificity and analogy but most notably consistency. Selenium, a non-metallic mineral, along with various heavy metals, specifically mercury, manganese, zinc, and copper also rank highly. Selenium, like formaldehyde, is missing evidence in specificity and analogy, while literature reported inconsistent results across studies. Mercury lacked in specificity and had inconsistent

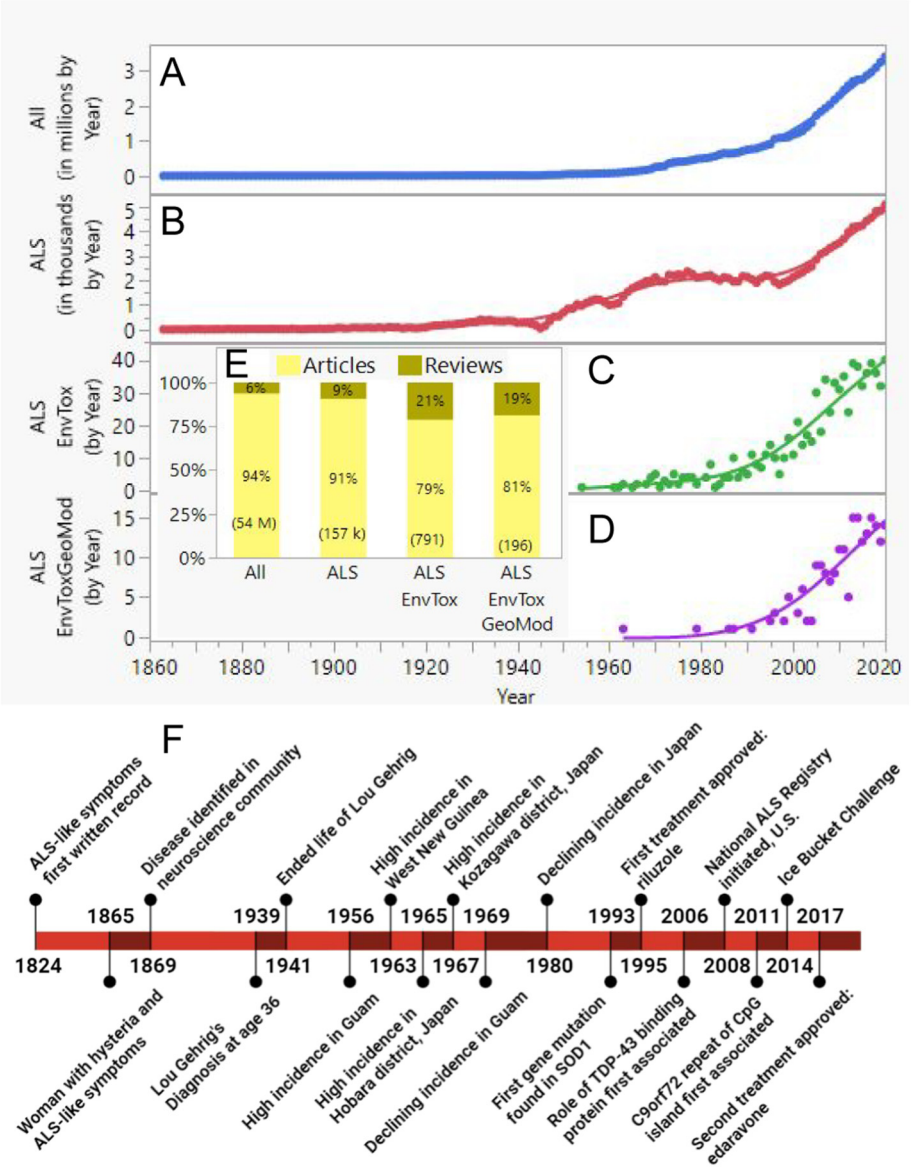

Fig. 1. ALS Trajectory. Scatter plots show frequency of publications published each year for (A) all publications, (B) ALS publications, (C) ALS and environmental toxins publications, and (D) ALS and environmental toxins publications studied with models or geographically. Stacked histograms (E) show the total number of publications and the percentages of articles compared to reviews from each SCOPUS search. (Parentheses indicate the total number of papers in each topic category). The timeline (F) shows major events occurring in ALS research and the ALS community.

literature results, especially geospatially. Manganese lacked evidence in specificity, analogy, and consistency. More research is needed overall. Zinc and copper, often studied together, lacked in specificity and analogy like the other factors. However, biological gradient through dose-response curves also lacked in evidence. Moreover, inconsistent results have been reported across the literature. Gaps in research are apparent, including specificity (identify unique outcome), biological gradient (develop dose-response curve), plausibility (track exposure event to mechanism), and coherence (establish an agreement between lab and epidemiology).

While most suspected factors fit into the organic chemical category, all five categories of factors have shown some degree of meeting Bradford Hill criteria. Longitudinal studies and statistical analysis are most often used to identify the association between factors and ALS. However, a lack of consistency between studies is the most common evidence against a factor's causality (Fig. 2). The number of publications for experimental models used to study factors for association with ALS is most abundant for organic chemical factors. BMAA is the most studied environmental factor by far, with mercury, formaldehyde, and aluminum next in line. The overwhelming majority of publications reporting experimentation for all factors and categories used mouse and rat models (Fig. 2).

3.2. Population exposure analysis

To test whether populations with higher exposure to toxins suspected of association to ALS show a higher incidence, hypothesis-driven studies from this literature review and for known susceptible populations were queried for ALS risk levels (Table S2).

Hypothesis-driven population-based, cohort, or case-controlled studies of ALS risk have primarily focused on pesticides, electric shock and electromagnetic radiation, heavy metals and specifically lead, and lifestyle choices, such as engaging in smoking, performing athletics, and consuming vegetables. If the analysis were to be limited to these studies, the factors with the most support for its positive associated with ALS diagnosis would be exposure to factors in descending order: calcium, red meat, sodium, manganese, residential ambient air solvents, vinyl chloride, pesticides, glutamic acid, fish, heavy metals (as an aggregated category),

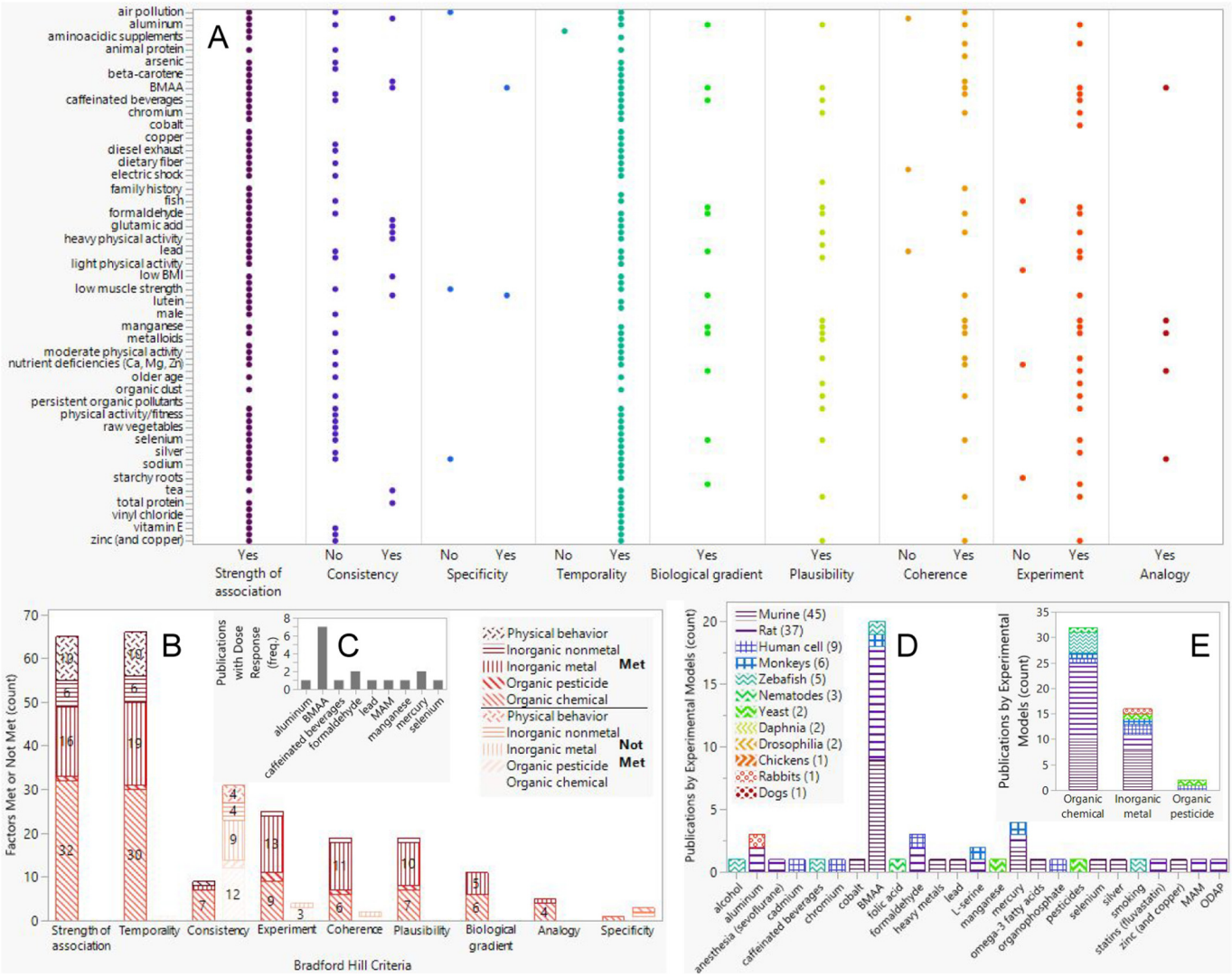

Fig. 2. Systematic literature review. Point graph (A) shows the frequency of factors considered meeting Bradford Hill criteria "Yes" or not meeting criteria "No" based on evaluation of hypothesis-driven, population-based, cohort-based, or case-controlled studies, as is shown in more detail in Table S1. Stacked histogram (B) shows the frequency of factors per the total number of factors within environmental toxin factor categories. Factor categories combine each factor considered meeting criteria "Met" or not meeting criteria "Not Met" based on evaluation of hypothesis-driven, population-based, cohort-based, or case-controlled studies, as is shown in more detail in Table S1. Histogram (C) shows frequency of publications with factor dose response data. Stacked histogram (D) shows the number of publications by factors and experimental model type. (Parentheses show the number of publications by experimental model type). Histogram (E) shows the number of publications by experimental model type used in ALS and environmental toxins studied by factor categories.

fertilizer, protein, lead, aminoacidic supplements, zinc, mercury, dietary fat, electric shock, nickel, low-frequency magnetic fields, BMAA, silica, radon, arsenic, and formaldehyde. Likewise, the factors with the most support for a protective quality against ALS diagnosis included caffeine, tea, dietary fiber, silver, fruits, methylene chloride, whole wheat, beta-carotene and raw vegetables (Fig. 3). Electrical, construction, and agriculture occupations have been studied the most. However, occupations not defined or identified in exposure studies could not be linked to factors in our analysis. Industries studied for posing and increased risk for development of ALS given known exposures to environmental toxins include construction, paper work, agriculture, electrical work, medical professions, military service, and manufacturing.

When aligning the results from the systematic review of ranked factors with those obtained by the state-of-the science population exposure assessment, BMAA exposures likely were derived from the ingestion of seafood harvested from waters contaminated with cyanobacteria or from ingestion of the cycad plant. Populations in the farming and fishing industries and residential populations with a diet affected by cyanobacterial blooms in local environmental surface water reported odds ratios in case-controlled studies from Lake Mascoma in New Hampshire of the United States (2.32 OR) as well as from the Limousin (1.25 OR) and Thau (2.02 OR) regions of France (Boumédiène et al., 2011; Masseret et al., 2013; Caller et al., 2009).

Formaldehyde exposure is possible in industrial production, oil extraction, funerary work, hospitals, labs, schools, construction, transportation, beauty salons. Specifically, concern for exposure by inhalation or dermal contact with formaldehyde is highest in preservatives for medical laboratories and mortuaries, chemicals, particle board, household products, glues, permanent press fabrics, paper product coatings, fiberboard, plywood, industrial fungicides, germicides and disinfectants. A case-controlled study in the Limousin (1.28 standardized incidence ratio) region of France showed a higher risk for ALS in occupational exposure in manufacturing paper and cardboard (Boumédiène et al., 2011). A study of occupational exposure in the construction industry in the United States (1.78 OR) showed a higher risk when exposures to formaldehyde occurred in the population (Rana et al., 2021). Moreover, a case-controlled study of formaldehyde exposure from a variety of occupations such as tile and textile work in Sweden showed a statistically significant association (1.29 OR) between

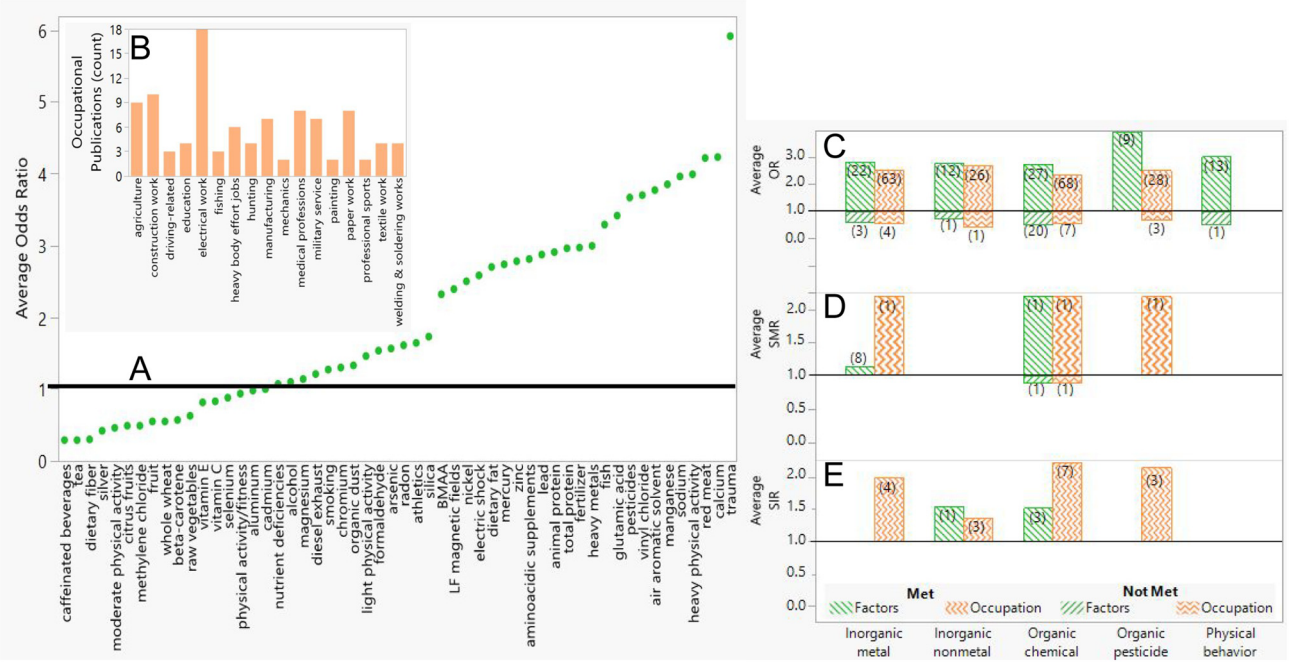

Fig. 3. State-of the science literature review. Points (A) show average odds ratios reported for factors in exposure studies. Histogram (B) shows the number of hypothesis-driven studies of ALS cases based on occupational exposures. Side-by-side histograms show hypothesis-driven studies of factor categories and linked occupations for association to ALS cases reported by average (C) odds ratios, (D) standardized mortality ratios, and (E) standardized incidence ratios. (Parentheses show the number of publications per ratio per factor category.)

documented environmental exposures to risk factors and ALS diagnosis in individuals under 65 years of age (Peters et al., 2017). Convergent validity at first glance appears to be hindered by a study of garment facilities in the United States, but the slightly lower risk of ALS (0.89 OR) reported upon formaldehyde exposure over various ages and duration was limited by power in that only 8 cases among over 11 thousand workers were analyzed (Pinkerton et al., 2013).

Selenium exposure is most likely for occupations in selenium production, processing or conversion to commercial products, electronics, and glass. Selenium is present in pigments used in plastics, paints, enamels, inks, and rubber, the preparation of pharmaceuticals, anti-dandruff shampoos, fungicides, nutritional feed additives, pesticide formulations, and rubber production. Exposure through ingestion and inhalation is possible from the diet, air, and drinking water. A population-based study in Italy of selenium supplementation supported a lower risk (0.88 OR) of ALS (Filippini et al., 2020). However, hypothesis-driven studies were not found that identified an OR for ALS given exposure to high levels of selenium in occupational or industrial cohorts.

Metals, pesticides, and some behaviors are known to alter miRNA activity in the body, leading to oxidative stress and inflammatory responses (Ferrante and Conti, 2017). Environmental factors affecting calcium homeostasis should be brought to the forefront of research attempting to find causal factors for ALS pathogenesis (Bailey et al., 2017). Heavy metal refineries are known to contaminate the air, drinking water, and dietary sources and thereby lead to the inhalation, ingestion, or dermal contact exposure routes for metals, especially of organometallic compounds. A cohort study in Ontario, Canada, tracking exposure to metals in the mining industry indicates a positive association between occupational exposure of metals (2.21 OR) and ALS (Zeng et al., 2020). In the New England region of the United States, a case-controlled study of hobbyists exposed to heavy metals showed a significantly higher risk (2.51 OR) for ALS (Andrew et al., 2017). Metal exposure in two additional case-controlled studies in Michigan and Pennsylvania further supported a positive association with ALS (4.76 OR and 3.65 OR, respectively; Yu et al., 2014, Malek et al., 2014). Although not to the degree observed in the United States studies, another case-controlled study in Rome, Italy showed that exposure to metals and associated fumes were linked to higher risk (1.84 OR) of ALS (Binazzi et al., 2009). In fact, a large population study in Spain identified deaths caused by overall heavy metal contamination (1.14 standardized mortality ratio) (Sánchez-Díaz et al., 2018).

Mercury contamination is known to result from manufacturing electrical equipment, automotive parts, fluorescent light bulb recycling facilities, chemical processing plants with mercury, and medical, dental, and health services. Dentists and dental assistants are two populations that are at particular risk from mercury exposure, due to inhalation of vapors from amalgam fillings. Fish containing high levels of methylmercury is a well-known source of mercury contamination for populations and individuals relying on a seafood-rich diet. Although a case-controlled study in the United States showed no additional risk of ALS from mercury exposure (0.6 OR) in the 1970s (Deapen and Henderson, 1986), another study of females from 2013 to 2015 showed a significantly increased risk (2.3 OR) for developing ALS (Andrew et al., 2020). A case-controlled study in Texas showed a significant increase in risk for ALS upon mercury exposure (3.85 OR) (Pierce-Ruhland and Patten, 1981) The Spanish population study of motor neuron disease-related deaths from heavy metals exposure further supported various individual metal involvement including for mercury (1.1 standardized mortality ratio) exposure (Sánchez-Díaz et al., 2018). In Park et al. (2005), mercury was not directly studied but dental occupations were associated with higher mortality from motor neuron disease (ranging from 1.39 MOR for dentists and 3.18 MOR for dental assistants).

A diet high in manganese is a concern for individuals consuming manganese above the daily recommendation. Occupational exposure to welders and other workers in industries involving ores, steel production, coal burning, and burning of wastes is also considered a risk factor for dangerous levels of manganese exposure. A single hypothesis-driven study in Texas, United States conducted some 40 years ago supported the association between manganese exposure (3.85 OR) and increased ALS incidence (Pierce-Ruhland and Patten, 1981).

While both zinc and copper ingestion from diet or drinking water contamination are a concern, human exposure to copper also can result from the inhalation of copper vapors. Zinc exposures may occur in mining, purification of zinc, lead, and cadmium, metal manufacturing industries, and

coal ash from electric utilities, sludge and fertilizer. Copper is a known risk to workers in agriculture, water treatment, and industries such as electroplating, where soluble copper compounds are used. An Italian case-controlled study showed a significantly high association (2.78 OR) to ALS upon specifically zinc exposures (Pupillo et al., 2018). In this Spanish population studied for heavy metal exposures and motor neuron disease deaths, zinc (1.13 standardized mortality ratio) and copper (1.1 standardized mortality ratio) were both considered metals that can lead to death (Sánchez-Díaz et al., 2018).

Environmental factors and occupations associated with these environmental factors agreed in association statistics overall when reported (Fig. 3). Also, all five categories showed a positive association with ALS on average, with one notable exception in studies on organic chemical factors, where 27 studies showed a positive association, whereas 20 studies showed a negligible association or a negative association. Not all categories of environmental factors and occupations have been studied in all three association statistics (odds ratios, standardized mortality ratios, or standardized incidence ratios), including physical behaviors and odds ratios for ALS.

3.3. Geographic distributions

While European nations have been the most widely studied to date, reports from Hawaii, Washington, California, Texas, Florida, New Jersey, Maryland, Philadelphia, and Minnesota have indicated a slight increase in incidence from 1 to 2 cases per 100,000 person-years since the 1960s. According to linear regression plots of reports in the United States, incidence is increasing at a rate of 3.0% per year while prevalence is increasing at 7.6% per year (Fig. 4). If we extend the prevalence rate into the future

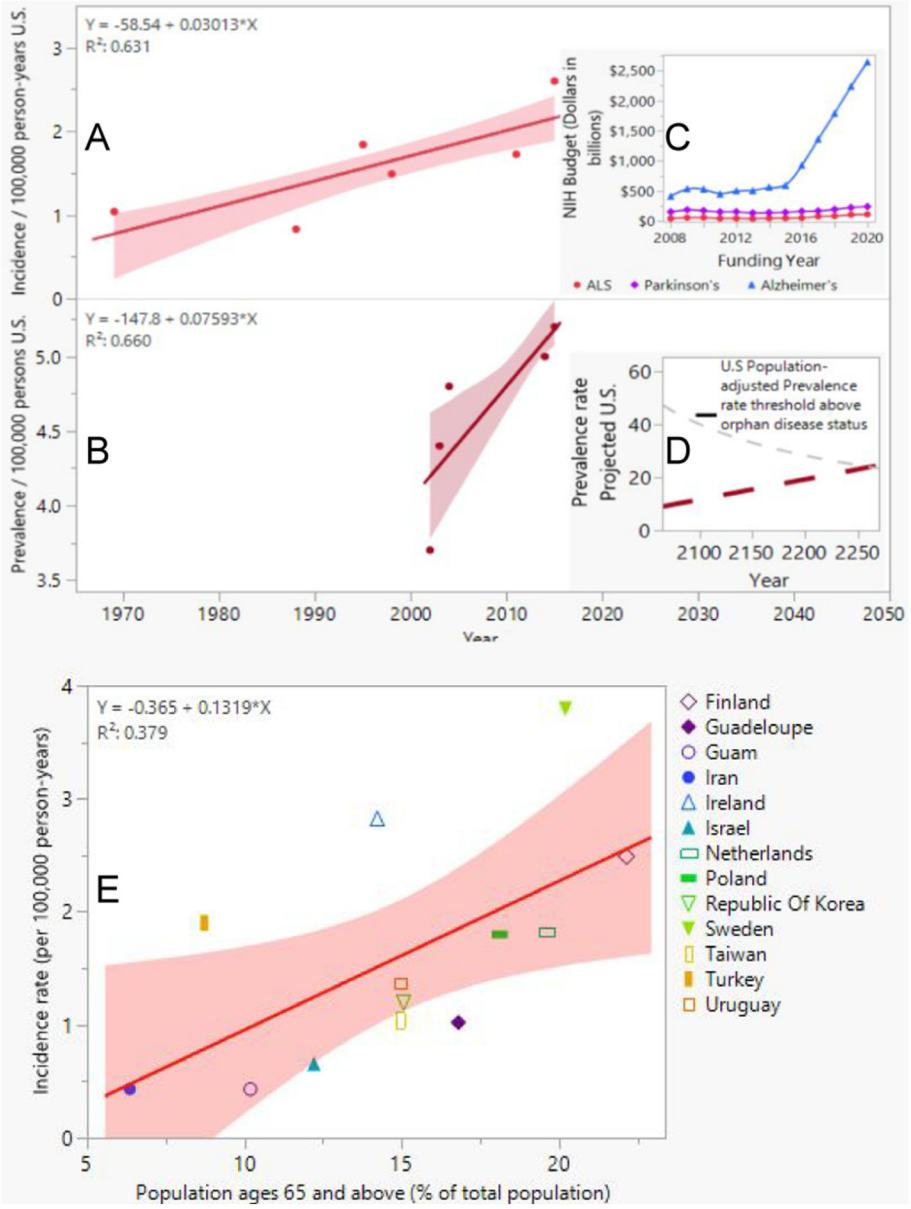

Fig. 4. Prevalence and Incidence rates. Scatter plots with linear best fit lines show (A) incidence per 100,000 person-years in the United States from 1969 to 2015 reported in Marin et al., 2016 and (B) prevalence (per 100,000 persons) in the United States from 2002 to 2015 reported in Longinetti and Fang, 2019. Line graphs (C) show NIH Budget for each of the 3 most common ND diseases magnified by the years remaining for an average patient upon diagnosis for each ND respectively. Projection plot (D) extends the prevalence rate (red dashed line) to a point of intersection with a hypothetical population-adjusted threshold for prevalence rate (grey line) representing the rate that would be considered above "orphan" status, and calculated from current and projected U.S. population estimates from Statista.com. Scatter plot (E) shows correlation between incidence rate per 100,000 person-years and the percentage of 65 years and older persons within the total population of each country reported.

using its microscope equation (Fig. 4), ALS prevalence is anticipated to increase from 16,707 ALS cases in 2015 to 22,654 ALS cases in 2040, and to 209,830 ALS cases in 2240 in the United States. Meanwhile, funding available through the National Institutes of Health (NIH) has been relatively stable for ALS and Parkinson's disease research, while Alzheimer's disease research has been increased significantly since 2015 (Fig. 4).

The most current reported incidence rates per region were used to project susceptible populations where available from the literature. If non-reporting countries were modeled given the minimum incidence model (0.42 per 100,000 persons), the minimum global ALS incidence was computed at approximately 33,000 people. An average model (1.98 per 100,000 persons) produces a mid-range estimate of 147,000 ALS-affected people, while the maximum model (4.3 per 100,000 persons) shows the upper boundary to be on the order of 314,000 people with ALS globally today. As one might expect, however, the percentage of 65 + year older persons of a country's population is moderately correlated to ALS incidence (Fig. 4). Given this age-adjusted incidence modeling, we estimate most diagnoses to be made in China (28,211), the United States (6488), and India (5934) in a single year (Fig. 5) today. The global estimate of those susceptible to ALS diagnosis each year accumulates to approximately 85,000 people.

European nations report ALS incidence rates more than any other region across the world. The global estimate of people susceptible to ALS each year would only sum to approximately 1600 people with projections from incidence rates reported in the literature alone. European nations also report the highest incidence rates globally especially in regions of Italy, France and Sweden (Fig. 5). Occupational studies almost exclusively originate in the United States and European countries (Fig. 6). Specifically, larger sample sizes in population and cohort studies are observed in United States studies compared to other nations. These studies reported particularly high sex ratios (male:female) in Scotland (5.3:1), Italy (4.2:1), and central Africa (2.9:1), compared to the United States (ranging from 1.3:1 to 1.6:1) (Fig. 6).

4. Discussion

Of the 83 factors identified for association with ALS through the systematic literature review, BMAA, formaldehyde, mercury, manganese, and zinc

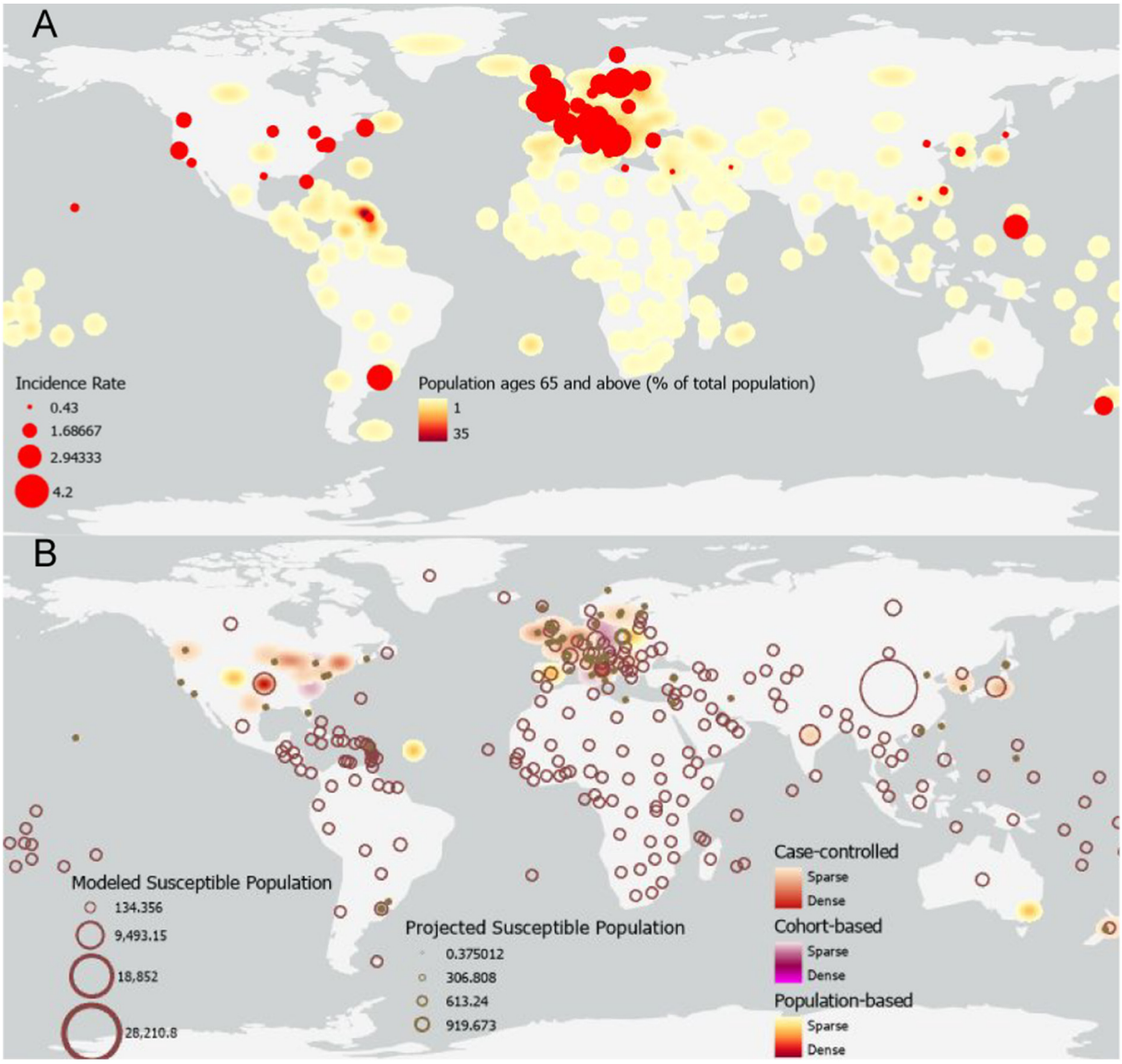

Fig. 5. Global incidence rates and susceptible populations. ArcGIS map shows (A) Incidence rate per 100,000 person-years from ALS and environmental toxins publications studied geographically accessible in SCOPUS given the percentage of 65 years and older persons by national population and (B) the modeled susceptible populations to ALS using population sizes and minimum, average, and maximum incidence rates reported (red open circles), the projected susceptible population from reported incidence rates (brown open circles), and sample sizes of case-controlled, cohort-based, and population-based hypothesis-driven studies (variations of color spectra to indicate low "Sparse " or high "Dense" sample sizes).

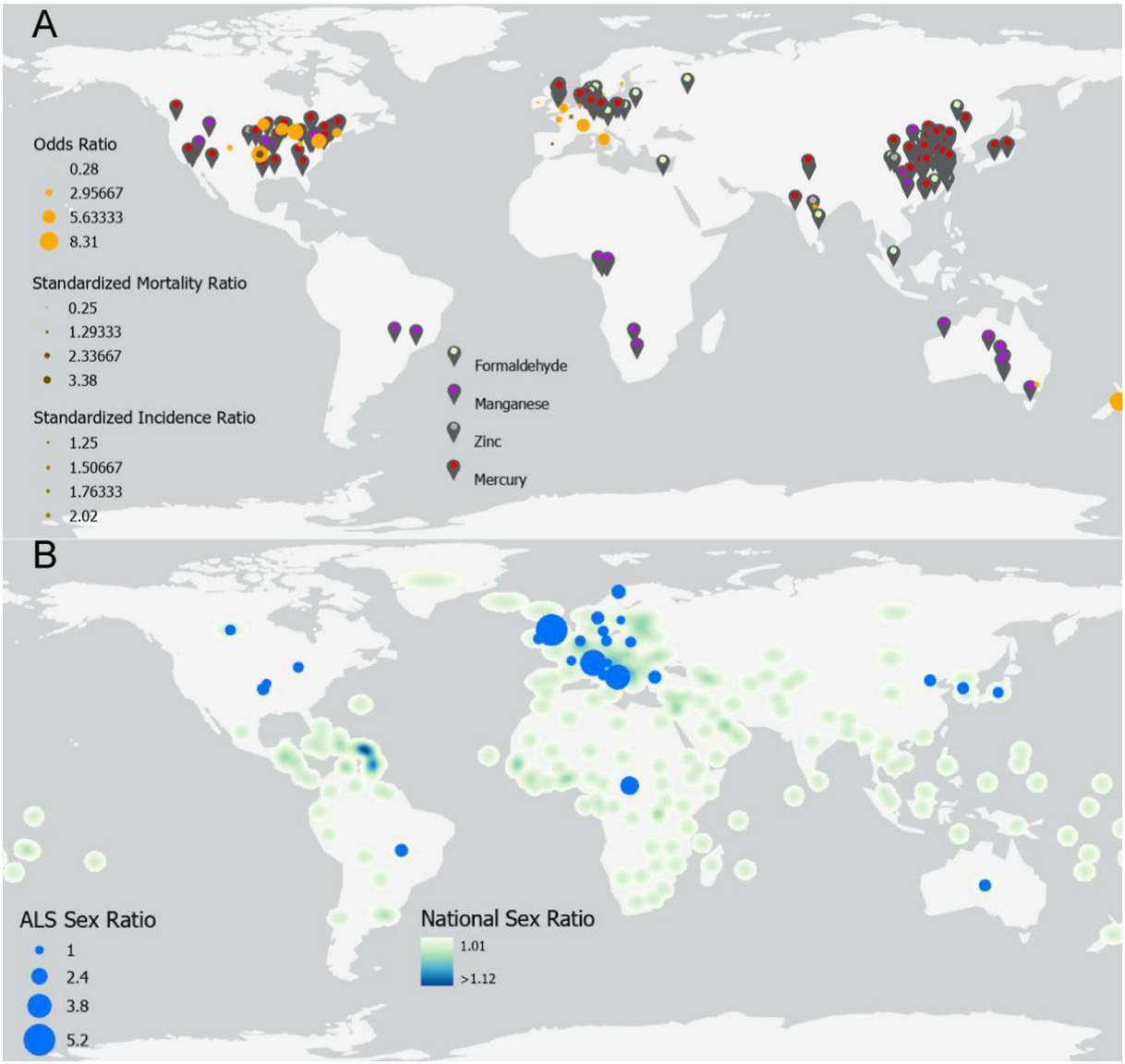

Fig. 6. ALS risk given industrial exposure and sex ratio for ALS and nationally. ArcGIS map shows (A) occupational and industry studies reporting odds ratios (orange circles), standardized mortality ratios (brown circles), or standardized incidence ratios (tan circles) as compared to sites for manufacturing and suppliers of formaldehyde (green pin), manganese (purple pin), zinc (grey pin) and mercury (red pin), and (B) the male:female sex ratio (blue circles) in reported ALS geospatial studies given the national sex ratio (white to blue color spectrum) reported by country.

have been found to rank the highest for the greatest number of Bradford Hill criteria met and for the degree of positive association with ALS in population exposure studies. While these factors may be categorized as either organic chemicals or inorganic metals, the differences between them may be important to note. BMAA is a unique cyanobacterial neurotoxin, whereas formaldehyde is a ubiquitous chemical. The Bradford Hill criteria for specificity, therefore, may be challenging to meet for a chemical such as formaldehyde.

4.1. Environmental exposure complexities

Epidemiological studies have recently begun to point to a phenomenon in which exposure events often include a multitude of environmental toxins. Therefore, it is essential that hypothesis-driven studies cast a wide net around multiple factors but with isolated exposure methods. Many studies reviewed here reported the effects from combined exposures, such as harmful mixtures from smoking, pesticides, and heavy metals. As smoking is known to result in exposure to the organic chemical formaldehyde and the inorganic compound cadmium, papers reviewed may have reported aggregated effects impossible to disaggregate. Our analysis of each factor was only able to include formaldehyde or cadmium exposures when they were reported independent of each other.

Exposures of environmental toxins over an individual's lifetime will inevitably affect health outcomes at all stages of life, recently suggested to be collected in what is termed an individual's exposome (DeBord et al., 2016). Occupational and lifestyle factors associated with ALS may be confounded by internal factors such as genetic or epigenetic signatures of an individual or by general external factors such as education and socioeconomic status.

This review supports prior evidence reporting that ALS presents opposite Alzheimer's, where males are more predisposed to ALS diagnosis (Fig. 6). The global male:female sex ratio of ALS cases is low, and ranges between 1:1–2:1 on average, but significant variation between nations have been reported (Longinetti and Fang, 2019) (Fig. 6). Interestingly, the male:female ratio of sporadic ALS (1.6:1) is double that of fALS (0.8:1) (Li et al., 1988). While one may question whether a genetic link to the X or Y chromosomes is involved, the higher sex ratio in sALS suggests an environmental trigger. Moreover, as national sex ratios of a country's total population range between 1.01 and 1.12, the high sex ratios for ALS diagnosis

reported in European and African countries cannot be attributed to sex demographics alone (Fig. 6). The high sex ratio for sporadic ALS may be due to occupational exposures, but more analyses with geographically linked occupational data are needed. The argument may be made that cumulative exposures must be assessed simultaneously to ultimately determine disease causality. As there are multiple steps through the known pathogenesis of ALS, it has also been suggested that numerous exposures or environmental toxins could be at play in the etiology of ALS (Al-Chalabi and Pearce, 2015).

The dose-dependent effect of an environmental factor exposure to the body, known as hormesis or the "hockey stick" effect, must also be considered here (Fig. 2). Our findings connecting occupational exposure to environmental toxins support the possibility that exposures to factors from single events or independent of recurring occupation exposures may not be enough to drive disease etiology. Dose-dependent studies are essential for determining if extended exposure leads a factor to switch from protective to toxic (Fig. 2). For instance, the protective association seen for two studies of formaldehyde exposure would be nonsensical given its known classification as a carcinogen. In fact, dose-dependent studies of aluminum (Tanridag et al., 1999) and formaldehyde (Nie et al., 2007; Strubelt et al., 1989) observed toxicity related to ALS pathogenesis at all levels of exposure. Additionally, dose-dependent studies in animal models of BMAA (Bell, 2009; Karlsson et al., 2011, 2012; Al-Sammak et al., 2015; Anzilotti et al., 2018; Scott and Downing, 2019; Powers et al., 2017) and mercury (Day et al., 2005) have reported ALS symptoms over wide ranges of doses and after long time delays. As for survival, zebrafish dosed with caffeine showed reduced survival in high doses, neuron defects at moderate doses, and similar survival to control animals at low doses (Chen et al., 2008). Meanwhile, we suspect protective effects in the hormetic zone from low dose exposure of the nutrient selenium, yet studies have only reported on high dosage results of ALS-related toxicity (Vinceti et al., 2009). While experimental models have been used to analyze dose response curves for a variety of factors, dose-response experimentation is lacking for zinc and for copper. However, lead exposure at low levels in mice astrocyte cell cultures produced a protective, reduced inflammation effect from VEGF expression (Barbeito et al., 2010).

Of particular importance, the likelihood of exposure events to one or more factors may change over time. BMAA levels have also seen a decline in a particularly well-studied region known for ALS incidences: the Western Pacific. A drop in incidence of ALS in the Chammaros people of Guam was observed after a peak occurred in the 1950s to 1960s (Plato et al., 2003). The incidence in animal models changed from 70 per 100,000 to 7 in 100,000 from the 1960s to the 1990s (Chen, 1995). Since the American Air Force base was built on Guam in 1944 at the end of WWII, commercialization of the region changed the social and economic landscape for the Chammaros people (Plato et al., 2003). Therefore, the decline in ALS incidence from the mid-1940s and the beginning of the 1960s indicates a delay of 15 to 20 years for the removal of an exogenous factor to reduce the risk of developing ALS. On the other hand, mercury was on the decline globally as evidenced by both changing mercury emissions and concentration in fish between the 1970s and 1990s (Grieb et al., 2020). Emissions increased on the global scale between 1990 and 1995, which led to bigger international agreements such as the Minamata Treaty established in 2017 (Grieb et al., 2020). In North America, however, steady decline in mercury levels has been reported between the 1970s and 2016, followed by a plateau (Grieb et al., 2020). Mercury levels in human tissues have seen a sharp decline specifically from 1966 to 2015 (Sharma et al., 2019). In fact, the UN reported a reduction in the mercury market in most years between 1981 and 2015 (Sharma et al., 2019). After all, mercury has been substituted with alcohol in mass produced thermometers and even mercury-containing light bulbs quickly were replaced with safer alternatives globally. If BMAA and mercury exposure and causal relationships to ALS pathogenesis are alike, we may expect a reduction in ALS incidence in North America within the next 10 to 15 years.

One must also consider recent evidence pointing to other environmental triggers outside the usual suspects. Microbes may act as exogenous agent responsible for the progression of disease in the digestive and nervous systems (Sampson et al., 2020). Although not well understood yet, viruses have also been implicated as a manipulator of dysfunctional pathways leading to neurodegeneration (Celeste and Miller, 2018). Biological environmental factors need to be considered further before narrowing the search for ALS causative agents to organic and inorganic factors alone.

4.2. Genetic relationships

Since the discovery of the SOD1 gene in 1993, the literature has focused on the genetics of ALS (Fig. 1). Nevertheless, environmental triggers have yet to be significantly linked to genetic expression (Yu and Pamphlett, 2017). Environmental toxins known to trigger gene expression have been implicated in "metabolic detoxification pathways (Dardiotis et al., 2018), but the full story from exposure to genetic expression to ALS etiology remains untold.

Twin studies have supported 61% heritability of ALS through familial aggregation (Ingre et al., 2015; Al-Chalabi et al., 2010). While those afflicted with familial ALS on average present 5 years younger than sporadic ALS cases, older age is considered a risk factor for both (Longinetti and Fang, 2019; Mehta et al., 2018; Li et al., 1988). Nevertheless, lower age ranges reported by various countries for ALS may be due to an inclusion bias based on modern early diagnosis compared to the use of legacy data in registries (Hardiman et al., 2017). The higher association with the male population is also considered a risk factor but reduces in significance with increasing age (Manjaly et al., 2010).

Today, we know that genetic predisposition, lifestyle, and exposure to toxins drive epigenetic changes that lead to ALS pathogenesis with progressing age (Riancho et al., 2018). However, methylation or demethylation metabolism at the population level for ALS cases remains unstudied. The few studies considering epigenetic mechanisms are focusing on molecular level (Al-Chalabi and Pearce, 2015; Bulathsinghala and Shaw, 2014; Eid and Zawia, 2016; Jiang et al., 2017; Kisby et al., 2013; Mostafalou and Abdollahi, 2013). Methylation of lysine on histones has been detected upon exposure to another toxin found in cycad plants like BMAA, methylazoxymethanol (MAM) (Kisby et al., 2013). Lead exposure has similarly been shown to alter DNA methylation and histone modification, with the addition of mitochondrial RNA expression (Eid and Zawia, 2016). An animal study of pregnant mothers exposed to the anesthesia sevoflurane showed that offspring were more likely to develop altered methylation and arginine/proline metabolism (Jiang et al., 2017). While these epigenetic studies have been directed toward the environmental toxins themselves, other studies have considered toxin exposure directly to the patients developing neurodegenerative diseases such as Alzheimer's, Parkinson's, and multiple sclerosis (Mostafalou and Abdollahi, 2013). Studies of the epigenome directed specifically to ALS cases, or across generations are lacking.

4.3. Challenge of late diagnosis

ALS is a highly heterogeneous disease targeting either the lower spinal, corticospinal, brainstem, or cortical frontobulbar motor neurons (Taylor et al., 2016). Diagnosticians must look for a variety of muscle symptoms such as limb atrophy or flaccidity in progressive muscular atrophy, hyperflexia or spasticity in primary lateral sclerosis, tongue atrophy, thickness of speech, or difficulty swallowing in bulbar ALS, and slow or dysfunctional speech or swallowing with emotional reflexes in pseudobulbar palsy (Taylor et al., 2016). The requirement for patients to express both upper and lower motor neuron degeneration is a high bar to meet for those in the early stages of ALS pathogenesis. Diagnosis is further made difficult as standards for clinical observations and diagnostic testing such as laboratory testing have been elevated according to the Airlie House Criteria (Zarei et al., 2015). For instance, a common electrodiagnostic test finding fasciculation potentials are observed in ALS and other conditions such as benign fasciculation syndrome (BFS). Furthermore, half of the cases associated with TDP-43 abnormalities suffer from frontotemporal dementia (FTD)

instead of ALS (Taylor et al., 2016). For this reason, 17 parameters in blood tests, four cerebrospinal fluid tests, five neurophysiology presentations, and two imaging studies make up the suite of ALS diagnostic tests. The reality of diagnostic difficulties is that the delay in diagnosis or even missed diagnoses altogether are going to continue unless a biomarker for ALS is identified.

Diagnostic challenges beg another question of whether ALS incidence is under-reported globally. If only the reported incidence rates were modeled to estimate the number of people vulnerable to ALS globally, the result would be a severe underestimate. While the National Amyotrophic Lateral Sclerosis (ALS) Registry estimates 5000 people to be diagnosed with ALS each year in the United States, our prevalence modeling adjusted by the percentage of 65+ year old individuals predict 6488 diagnoses. Countries featuring aging populations are at elevated risk, and while approximately 16% of the population in the United States is 65 years or older, 28% of the population in Japan and 23% of the people in Italy are in this older age bracket. Japan's incidence rate of 2.2 per 100,000 person-years (Doi et al., 2014) would estimate approximately 2781 diagnoses for 2021, while our model would predict 5312 diagnoses for the same year. Similarly, Italy's incidence rate of 2.5 per 100,000 person-years (PARALS, 2001) estimates 1510 diagnoses this year, while our model predicts 2539 diagnoses. While the 30% difference projected for the United States seems high, the 91% difference for Japan and 68% difference for Italy suggest that the actual incidence for ALS globally potentially may be severely underestimated.

4.4. Alzheimer's & Parkinson's diseases

Neurotoxins have been considered as etiologic agents driving neurodegenerative diseases for decades (Shaw and Höglinger, 2008). Both ALS and Parkinson's Disease present primarily as movement disorders, while Alzheimer's presents as a dementia-related disorder (Agnihotri and Aruoma, 2020). While all three diseases list age as a risk factor, all also suspect environmental toxins contribute to pathogenesis (Agnihotri and Aruoma, 2020). Treatments are available to reduce symptoms, but mitochondrial dysfunction inherent to neurodegeneration persists in all three diseases. Agnihotri & Aruoma recommend a “healthy” diet and lifestyle to nutritionally target abnormal mitochondrial dynamics, inflammation, and oxidative stress (2020). Nevertheless, the role of environmental toxins through occupational exposure could likewise lead to the successful development of treatment strategies (Agnihotri and Aruoma, 2020).

4.5. Study limitations

As Bradford Hill stated in his 1965 address, “scientific work is incomplete”, and gaps in the research are inevitable. Epidemiological evidence reviewed and summarized here excludes some factors and reveals knowledge gaps for other factors. Data on ALS incidence and prevalence that are geospatially linked are still sparsely published. While countries with larger populations, such as China and India, are suspected to have large susceptible populations and many potential cases, few studies have reported ALS incidence regionally (Fig. 5). Moreover, while Hokkaido Island, Japan reports a 0.69 per 100,000 person-years incidence rate, the entire country of Japan may be highly susceptible to ALS, given that 28% of the total population are of age 65 or above (Fig. 5).

Furthermore, a lack of geographic linkage of exposure events and cases reported leads to incomplete reporting. Researchers hope that by identifying geographic clusters of ALS incidence, toxins associated with geography, industry, and occupation may be more readily identifiable as contributing to the disease. Manufacturing centers and regions supplying environmental agents highly ranked as risk factors, such as formaldehyde, manganese, zinc, and mercury, represent potential geographic hotspots for ALS susceptibility (Fig. 6). For instance, clusters in Guam, New Guinea, the Kii Peninsula, Skaraborg County of Sweden, Lake Macoma in New Hampshire, and Thau Lagoon in France all suspect BMAA toxin exposures from dietary intake (Riancho et al., 2018). While spatial clusters with high ALS incidence rates provide an opportunity for environmental and genetic research into causes and predisposition for ALS, small sample size and complex extraneous factors make for weak analyses. For instance, researchers have identified sources of metal contamination, most commonly copper, zinc, chromium and nickel in water and soil samples of the Briga area in Italy; but determining causality from this association is elusive (Tesauro et al., 2021). Additionally, several clusters of ALS incidence including veterans from the Middle East Gulf War, have produced conflicting odds ratios (Spencer et al., 2019). These results may not be surprising, as the aggregation of factors into categories, such as metals, heavy metals, pesticides, copper and zinc etc., makes the identification of a single factor for ALS etiology next to impossible.

Many population studies were observed to rely on databases such as the Comparative Toxicogenomic Database or the National Amyotrophic Lateral Sclerosis (ALS) Registry. While the National ALS Registry hosts an ALS Biorepository, representation of ALS patients is incomplete as contributions are made voluntarily by those diagnosed with ALS in the United States (National ALS Registry, 2021). Additional studies formed cohorts retroactively upon an exposure event or based on diagnosis records, while others further pooled participants for case-controlled studies through clinical administration. Longitudinal analysis, therefore, may be limited by a lack of representation and incomplete records. Furthermore, it is important to note that our review could be incomplete as articles written in languages other than English did not enter this analysis.

The trajectory of ALS research publication tells an unproductive story. The ratio of one review article for every 9.7 research articles is lopsided toward revisiting old data sets again and again, while new ones are lacking; furthermore, fewer hypothesis-driven studies than expected were among the 258 articles reviewed. A significant percentage (21%) of publications on environmental toxins associated with ALS have been reviewing work compared to primary articles. The low article-to-review ratio (one review for 3.7 original articles) in the study of environmental toxins associated with ALS implies that any new claim of an important environmental factor would be supported (or not supported) by few data or little evidence (Fig. 1). As this is the first known use of Bradford Hill criteria in assessing factors associated with ALS, convergent validity has yet to be established through additional studies. Moreover, if the etiology of ALS is truly caused by multiple factors, epidemiologists mostly agree that Bradford Hill criteria alone are not sufficient in assessing the effect of multiple factors (Delgado-Saborit et al., 2021; Utembe and Kamng'ona, 2021). The approach adopted here by us analyzed a large pool of associated factors, and therefore requires further support before interventions could be recommended.

Funding may also represent a barrier to action. NIH budgets are not increasing to match the increasing prevalence of ALS in the United States (Fig. 4). ALS is considered an ‘orphan disease’ in the United States as it affects fewer than 200,000 people (“Orphan Products”, 2019). Based on our prevalence rate modeling, the United States will therefore not grow out of orphan status for at least another 200 years. Even as the 1983 Orphan Drug Act was designed to encourage drug discovery for research of diseases with low incidence rates is traditionally seen as economically infeasible, slow progress has been made in the development of treatments across orphan diseases in general over time (Randhawa, 2006).

4.6. Future work

BMAA, formaldehyde, manganese, mercury, and zinc emerged as the five highest ranked environmental factors through a combination of Bradford Hill criteria analysis and association analysis of population exposure studies. These are the environmental toxins most recommended for the most immediate research. Due to extensive research of BMAA over the years, this analysis asserts causal criteria have been met. Early diagnosis for BMAA exposure is currently possible using imaging technology such as magnetic resonance (MR) and time-of-flight secondary ion mass spectrometry (ToF-SIMS) (Wilson et al., 2004; Hanrieder et al., 2014). Nevertheless, other means for early diagnosis using population health metrics may offer a means to screen for susceptible populations. Developing early diagnosis methods and treatment options would be more likely if factors ranked higher for causal criteria were focused more intentionally in future research.

To confound the research efforts undertaken, animal models may show only partial pathologies observed in humans and mixture effects may have introduced conflicting results so far. The commitment to SOD1 (G93A) transgenic murine mice and rat models begs the question as to whether the results for animal modeling increase the likelihood of effects by chance and, therefore the possibility for Type I errors. The focus on a single model, especially one that isolates one gene that has been attributed to only 20% of familial ALS (Zufiria et al., 2016), points to an elevated risk of potential misinvestment of resources. However, this review supports the continued research to develop dose-response curves for highly ranked factors, which inherently requires modeling, is essential. After all, animal models offer the research community a means to observe acute vs. chronic pathologies from genetic and/or environmental sources in what has only been seen in cell cultures or not at all (Sher, 2017). In cycad neurotoxins alone, uncertainty about causal links persists due to remaining questions such as what is the end role of BMAA for distribution and metabolism in mammals, which models adequately tests neurotoxicity, what cofactors might increase individual susceptibility to neurotoxicity, what cofactors might interact with BMAA for synergistic toxicity, what are the differences in mechanisms of acute or chronic exposure, and what protein hosts the BMAA molecule in plants and animals to finally point to the means of bioaccumulation (Karamyan and Speth, 2008). Nevertheless, the macro-perspective of epidemiology may be able to inform the micro perspective of animal models needed to support causation. Further development of models is needed that study factors which meet the nine Bradford Hill criteria. Primate and human cell models that isolate a larger range of genes associated with ALS are of particular interest.

It is important to note that still other environmental factors not yet identified may also play a role in ALS etiology. Population exposure studies have demonstrated a high association between the risk of ALS as a function of ambient air concentrations of aromatic solvents, vinyl chloride, pesticides, fertilizer, lead, nickel, and arsenic, indicating a need for additional research into cause and effects. Meanwhile, while selenium and copper ranked high in Bradford Hill criteria, conflicting results in population studies of low-exposure scenarios leave their status as causal factors unclear.

Gaps in population studies outside of European nations and the United States reveal open questions about potential exposure events and their impact on incidence rates. It has been suggested that to fill in the gaps in the geographic distribution of ALS for a risk factor such as BMAA, sampling for presence of cyanobacteria could be replaced with quantifying higher levels of total phosphorus (TP), total nitrogen, chlorophyll-*a*, and Secchi depth to measure water clarity (Serrano et al., 2015; Torbick et al., 2014). Analytical tools to sample for all five ranked environmental toxins will be needed to determine the geographic scope of susceptibility.

Finally, environmental toxins need to be researched alongside physical behaviors and demographic factors. Epigenetics research offers a window into genetic and environmental toxin relationships that could lead researchers to find common threads in the etiology of more than one neurodegenerative disease, such as ALS, Parkinson's and Alzheimer's disease.

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CRediT authorship contribution statement

Melanie Engstrom Newell: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Visualization, Writing – original draft, Writing – review & editing. **Sangeet Adhikari:** Conceptualization, Resources, Writing – review & editing. **Rolf U. Halden:** Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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