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RESEARCH ARTICLE

# Impact of the National Amyotrophic Lateral Sclerosis Registry: Analysis of Registry-funded Research

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## Abstract

**Objective**: This research aims to examine the impact of the National Amyotrophic Lateral Sclerosis (ALS) Registry-funded research activities. **Methods**: Registry-funded research and related publications were identified through the National ALS Registry website, the National Institutes of Health (NIH) Reporter website, and verified by Principal Investigators. Key study characteristics (e.g., study population, sample size) and key impact features (e.g., risk factors) were abstracted and recorded on study abstraction forms. Descriptive statistics were used to analyze the volume, productivity, and findings of the Registry-funded research. **Results**: Since 2012, the National ALS Registry funded 21 research projects. Of these, 14 were through extramural research grants and included in the analysis. These studies are often related to environmental, medical conditions, and genetic risk factors. On average, the funded grants produced 1 to 2 publications which were cited 114 times by other researchers. The relative citation ratio averaged 1.81 with a weighted relative citation ratio of 16.28. These studies supported the identification and confirmation of candidate risk factors. Environmental and occupational risk factors typically related to heavy metal exposure (e.g., lead, mercury) and agricultural chemicals (e.g., pesticides, herbicides), and the occupations associated with exposure to these substances were most frequently explored. **Interpretation**: The National ALS Registry is a multifaceted research platform, one component of which is funded research. This Registry-funded research fills an essential gap in the overall ALS scientific community as it is difficult to prevent and treat a disease without a deeper understanding of its causes.

## Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive, fatal neurodegenerative disease of motor neurons. In 2017, up to 32,000 individuals (9.9 per 100,000 population) were estimated to be living with ALS in the United States (U.S.),[1] and the age-adjusted standardized incidence rate was 1.6 per 100,000 population.[2] Most persons with ALS (PALS) receive a diagnosis 10–16 months after symptom onset[3] and survive 2–5 years after receiving the ALS diagnosis.[4,5] ALS is among a list of neurological and psychiatric disorders attributed to the environment that presents a significant health burden to the U.S. population.[6]

The mission of the federal Agency for Toxic Substances and Disease Registry (ATSDR), a part of the Centers for Disease Control and Prevention (CDC), includes the establishment of disease registries associated with exposures to toxic substances. In 2008, the U.S. Congress passed the ALS Registry Act,[7] which authorized the creation and maintenance of the National ALS Registry by ATSDR. The main goals of this multifaceted research platform are to better describe the epidemiological trends of ALS in the U.S., to identify and examine risks and


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potential etiologies (environmental and occupational factors), and to determine the disease's public health burden.

The registry includes data from existing national databases such as Medicare, Medicaid, the Veterans Health Administration (VHA), and the Veterans Benefits Administration (VBA) and information from PALS who sign up through an online web portal to participate (www.cdc.gov/als). Through registration, PALS gains access to participate in this multifaceted research platform. For example, individuals may opt to receive emails about clinical trials and epidemiological studies, donate specimens at no cost to them to the affiliated National ALS Biorepository (Biorepository), complete risk factor surveys, and access informational resources.

Once an individual completes the online Registry enrollment, they are eligible to voluntarily complete 18 surveys related to possible risk factors of ALS (e.g., environmental exposure, job history, physical activity, pesticide use, head and neck injuries). Researchers can access these data to support their research hypotheses and studies. In 2019, for example, Raymond et al.[8] used the clinical survey module to characterize ALS clinical features in a large cohort population. This study examined such areas as the site of onset, the time between symptom onset and ALS diagnosis, intervention use, and end-of-life care. The findings from this publication were used in support of 14 additional papers exploring topics from treatment effectiveness, ALS epidemiology, and etiology.

The Registry maintains an online research notification mechanism (RNM), where PALS can elect to be notified of new research opportunities such as clinical trials and epidemiological studies. Researchers wishing to use the RNM complete a standardized application, including proof of Institutional Review Board approval and study eligibility. Once approved, researchers' study materials and contact information will be emailed to PALS meeting study eligibility criteria. This function of the Registry connects PALS to ongoing research and assists researchers in recruitment efforts. Personal information about PALS, such as names or emails, is not disclosed to the researchers. Between 2013 and 2019, 46 institutions used the RNM, sending 638,760 emails to consented patients, resulting in thousands of Registry patients joining clinical trials and epidemiological studies.[9] Mehta et al. further describe the impact of the RNM and its role in facilitating successful ALS research.[9]

Once enrolled in the registry, PALS can also participate in the Biorepository. The Biorepository consists of biospecimen collections of blood, hair, urine, and fingernail-clipping samples collected from PALS in their homes. PALS may also volunteer to participate in a postmortem donation of the brain, spinal cord, cerebral spinal fluid, and other biospecimens. Biospecimens are collected and stored for future research use. The Registry expanded the availability of postmortem samples through a collaboration with the Johns Hopkins University ALS Postmortem Tissue Core in 2021. As of April 2020, details on biospecimen availability are shared in Bledsoe's analysis of the biospecimen demand and utilization of registry samples.[10] Since samples became available in 2017, more than 25 researchers inquired about sample procurement and availability; of those, 15 researchers completed an application.[10] On an annual basis, Biorepository staff conducts a utilization and demand analysis to determine the most useful biospecimen collection types and make recommendations so that the Biorepository maintains the most valuable types of biospecimen for future ALS research.

The ATSDR seeks to maximize research advancement by soliciting proposals to target research in two categories: general research that advances existing knowledge and innovative research that considers new ideas. In addition to the support provided directly to PALS, the Registry therefore also funds a wide variety of research into potential ALS risk factors. Since 2012, the Registry has funded 21 extramural research grants through the R-01 funding mechanism. These major research grants are investigator-initiated research proposals that sought to identify and evaluate ALS risk factors including, but not limited to, environmental and occupational risks, traumatic brain injuries, injury or microbial infection, nutritional intake, and pharmaceutical use.

Recent ATSDR ALS funding opportunities encouraged the development of meritorious proposals mainly focused on evaluating the role of military service, contact sports, traumatic brain injury, neuroinflammation, and infectious agents in ALS development, progression, and severity. These research projects help achieve Registry goals of better understanding the etiology of ALS. This study focused on the impact of the Registry-funded research. We aim to describe the visibility and reach of Registry-funded research through an examination of funded projects and related publications.

## Methods

### Identification of Registry-funded research

The National ALS Registry lists all Registry-funded research on its website (www.cdc.gov/als/ALSExternalResearchfundedbyRegistry.html). We identified 21 external research projects funded between 2012 and 2022 for inclusion using this website. This list of 21 projects was searched for on the NIH Reporter website (https://reporter.nih.gov/) for more detailed information. We obtained each project abstract and its relevance to

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public health statement from the NIH Reporter website. Fourteen of the 21 funded studies were found in this tool. The remaining seven were funded through different means (i.e., government contracts). A CDC/ATSDR grants administrator officer verified the accuracy of this activity.

### Identification of publications

Publications related to Registry-funded research were identified through three sources. The National ALS Registry website includes links to all Registry-related publications and reports. We selected all peer-reviewed publications (https://www.cdc.gov/als/ALSResearchPublications.html), which provided a list of 88 publications from 2012 to 2022. We further reviewed this list to identify 25 articles that were matched to Registry-funded research projects by reviewing the authors, subject matter, and funding source provided in the manuscript. Of these, 13 articles were results of grant funding and will be included in the citation analysis, while 12 were from contract funding. Next, a separate list of publications was generated from the NIH Reporter website. This website allows researchers to indicate any published articles as a result of the funding source. All articles listed on this site were captured for potential inclusion. Finally, the two lists were combined and de-duplicated. These lists were reviewed by the CDC/ATSDR grant administrator and sent to each Principal Investigator (PI) for review. The PI was provided the opportunity to modify, add, or delete any manuscript to the list. Nine of 12 (75%) PIs responded, and 2 provided additional articles, whereas 7 had no changes.

### Criteria for inclusion

To understand and summarize the impact of ALS Registry-funded research, we included only English language peer-reviewed publications published by previously and currently grant-funded research projects. This included all research projects funded between 2015 and 2021, and articles published between 2015 and 2022. We included all types of studies regardless of their design or research methodology.

### Data collection and analysis

We prepared abstraction forms to collect data separately on the sample of Registry-funded research projects and on the identified publications. For each identified research project, we abstracted information on the funding period, institutions receiving funding, and the involved lead researchers. Additionally, we mined the project abstracts and relevance statements for key themes and differentiators using inductive coding techniques. The codes were grouped into key themes using a thematic analysis approach, which was then reviewed and revised before finalization.

For each publication, we extracted information on key study characteristics (e.g., study population, design, sample size, data source, geographical reach) as well as key impact features (e.g., type and number of ALS risk factors identified, number and type of citations, area of ALS research of citing articles). The publication's relative citation ratio (RCR) score, as provided by the NIH Office of Portfolio Analysis iCite tool,[10] was documented to measure a publication's reach. The RCR represents a citation-based measure of a published article, or group of publications, reach in the scientific literature. We analyzed the extracted information to understand the volume and productivity of outputs resultant from Registry-funded research. Descriptive statistics were used to examine the number of citations and citation scores.

## Results

Registry-funded research began in 2012 as contract-funded projects. In 2015, ATSDR moved to a system of investigator-initiated R-01 grants to increase applicants' eligibility and research topic areas. Twenty-one registry-funded research studies are described on the Registry website and summarized here (Table 1; https://www.cdc.gov/als/ALSExternalResearchfundedbyRegistry.html); seven of which were funded before 2015. These seven studies explored environmental risk factors (e.g., persistent organic pollutant [POPs] exposure, cyanobacterial algal blooms, metals, pesticides), occupational risk factors (i.e., military service, occupational formaldehyde exposure), genetic risk factors (e.g., race/ethnicity) and behavioral personal risk factors (e.g., level of physical activity, smoking status, educational attainment).

The analyses described in this manuscript focus on the 14 R-01 grants funded since 2015 and identified in the NIH Reporter searchable database. Among these grants, the key topic areas were most often environmental risk factors (64%), medical condition risk factors (21%), or genetic risk factors (14%). A total of 11 academic institutions received funding. Studies most frequently used a case–control study design (8/14, 57%), while the remaining studies used a cohort design. Of the 14 funded grants, eight (57%) published peer-reviewed publications. At the time of this publication, 80% of studies whose funding period closed have produced published articles.

Overall, as of April 2022, 19 articles were published in peer-reviewed journals as a result of these grants, with an average of 1–2 publications per funded grant. Of these publications, 13 were cited by other publications and


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**Table 1.** National Amyotrophic Lateral Sclerosis Registry-funded R-01 extramural research projects (2015–2021).

| Institution | Principal investigator | Year awarded | Amount awarded | Reviewed publications |
|---|---|---|---|---|
| RFA-TS-15-001 | | | | |
| Trinity College, Dublin (Ireland) TS000242 | Hardiman, Orla | 2016 | $800,000 | Ryan, 2018[18] |
| Columbia University TS000243 | Mitsumoto, Hiroshi | 2015 | $1,197,273 | Mitsumoto, 2022[19] |
| University of Miami TS000244 | Benatar, Michael | 2016 | $799,998 | |
| Dartmouth College TS000245 | Stommel, Elijah | 2016 | $800,000 | Andrew, 2017[20]<br>Kuczmarski, 2017[21]<br>Andrew, 2018[22]<br>Andrew, 2021[23] |
| Stanford University TS000249 | Nelson, Lorene | 2015 | $1,200,000 | |
| RFA-TS-17-001 | | | | |
| University of Pittsburgh TS000272 | Talbott, Evelyn | 2017 | $997,804 | |
| Columbia University TS000285 | Shneider, Neil | 2018 | $1,250,000 | |
| RFA-TS-18-001 | | | | |
| Dartmouth Hitchcock Clinic TS000288 | Stommel, Elijah | 2018 | $1,500,000 | Andrew, 2020[24]<br>Andrew, 2021[25] |
| University of Michigan TS000289 | Feldman, Eva | 2018 | $1,530,000 | Goutman, 2020[26]<br>De Marchi, 2021[27]<br>Murdock, 2021[28]<br>Figueroa-Romero, 2022[29]<br>Goutman, 2022[30] |
| RFA-TS-19-001 | | | | |
| Northwestern University at Chicago TS000294 | Siddique, Teepu | 2019 | $899,999 | |
| RFA-TS-20-001 | | | | |
| Harvard School of Public Health TS000315 | Weisskopf, Marc | 2020 | $1,000,000 | |
| Harvard School of Public Health TS000318 | Ascherio, Alberto | 2020 | $1,000,000 | |
| RFA-TS-21-001 | | | | |
| Karolinska Institute (Sweden) TS000324 | Fang, Fang | 2021 | $499,560 | |
| University of Michigan TS000327 | Feldman, Eva | 2021 | $400,440 | |

Prior to 2015 the Registry-funded contract research in excess of $2.5 mol/L.

included in the citation analysis (see Table 1). These publications were cited 114 times, ranging from 1 to 35 per publication. The RCR of these 13 articles ranged from 0.0 to 5.44, with a mean score of 1.81 (0.53 SEM), and a weighted RCR of 16.28.

A total of 100 publications cited the original group of publications. The weighted RCR of the citing articles was 117.33. On average, these secondary articles had 3.08 citations per year and an average RCR of 3.17 (0–9.76, 0.27). The secondary articles were cited by 606 publications, with a weighted RCR of 579.75. On average, there were 2.63 citations per year and an average RCR of 2.15 (0–20.03, 0.13) for these tertiary publications (Fig. 1).

The original set of publications was predominately human based, with 0.71 of the Medical Subject Headings (MeSH) terms for the articles classified as human, 0.09 categorized as animal studies, and 0.04 categorized as molecular/cellular (Fig. 2). According to the iCite portfolio analysis, there is a 35.4% average Approximate Potential to Translate (APT), an estimate of the likelihood of these articles being cited in future clinical documents.

Registry-funded research has supported the investigation of possible ALS risk factors. Key findings from the 13 publications based on R-01 research grants evaluated identified new candidate risk factors or further analyzed previously recognized risk factors (Table 2). Most

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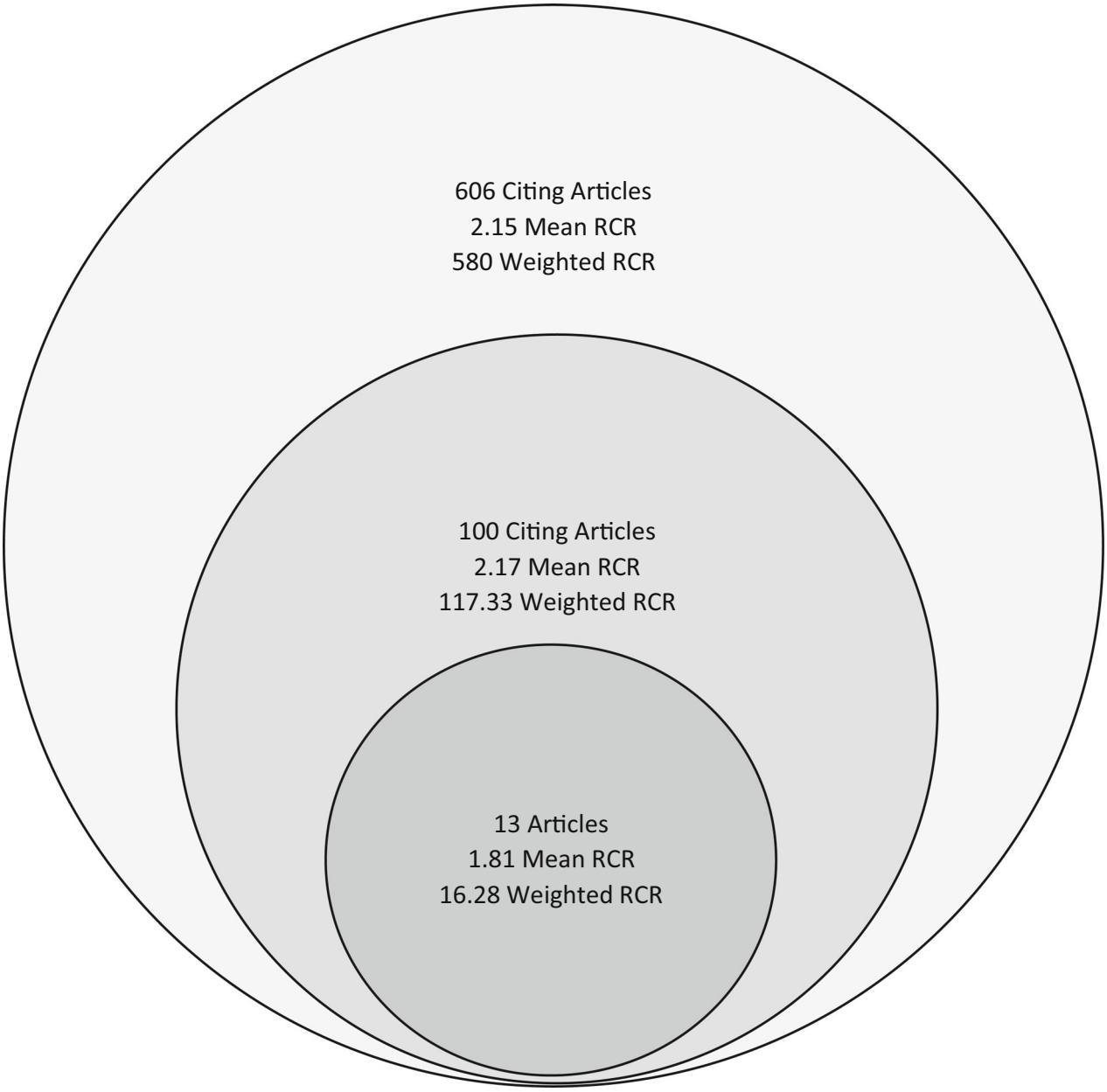


**Figure 1.** Impact of publications resulting from the National Amyotrophic Lateral Sclerosis Registry-funded research.

frequently, environmental and occupational risk factors were principally explored (6 studies), typically related to toxic metal exposure (e.g., lead, mercury) and agricultural chemicals (e.g., pesticides, herbicides), as well as occupations associated with exposure to these substances, which are also included in ATSDR's List of Priority Substances.[11] Genetic, metabolic, or immunologic risk factors were the primary focus of four studies, while medical treatment approaches were the primary focus of the remaining three studies. With a methodological focus on population-based and clinical cohort studies, the funded research programs also contributed to the identification of current limitations and future directions in ALS research (Table 3).

## Discussion

The National ALS Registry is a multifaceted research platform that provides estimates of ALS epidemiology (e.g., incidence, prevalence, mortality) in the United States,


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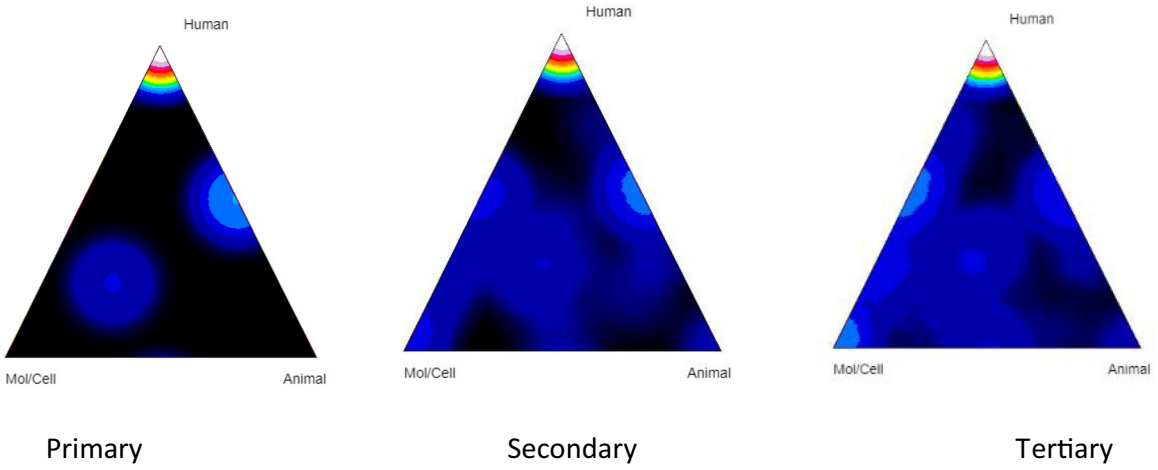


**Figure 2.** Map of research translation.

**Table 2.** Key risk factors identified by the National Amyotrophic Lateral Sclerosis Registry-funded research, 2015–2021.

| | Newly identified risk factors | Validated risk factors |
|---|---|---|
| Environmental or occupational exposures | | • Occupation: mechanics, painting, construction workers,[20–25] miners[22] |
| | • Heavy metals: bioavailable methylmercury[22] | • Heavy Metals: lead,[19,20,22] inorganic mercury[22,24] |
| | • Agricultural chemicals: MCPB (4-[2-methyl-4-chlorophenoxy]-butyric acid), Terbacil, glyphosate, paraquat, carbaryl, chlorpyrifos, Mancozeb (manganese-zinc ethylene-bis-di-thiocarbamate)[13] | • Agricultural chemicals: 2,4-D (2,4-dicholorophenoxyacetic acid), permethrin[13] |
| | • Water bodies: full-time residence within 2 miles of a water body, frequent water-related activities (water skiing, boating, sailing, kayaking)[20] | • Trauma/injury: head trauma, severe electrical burn/electrocution[25] |
| Metabolites or metabolic pathways | • Dysregulated pathways: diacylglycerol, benzoate[26] | • Dysregulated pathways: creatine, sphingolipids, polyamines, fatty acids[26,30] |
| | | • Deficiencies: glutathione[30] |
| Gene expressions or genetic variants | | • Genetic variants: ANG, C9orf72, CHCHD10, DCTN1[18] |
| Immune response or immunologic pathways | • Natural killer cell surface markers: CD11a, CD11b, CD38, CX3CR1, NKG2D, NKp46[28] | • Protective: history of antineoplastic treatment[21] |

offers researchers access to biospecimens from PALS, helps pharmaceutical companies and others recruit for clinical trials and epidemiological studies, and facilitates research by providing funding to investigate ALS risk factors and possible etiologies. The Registry is the only federal program tasked to evaluate what may cause ALS and why and measuring the public health burden of this disease. Furthermore, the Registry also conducts and disseminates research findings internally and with its academic partners to identify new data gaps or potential links to newly identified biomarkers.[12,13]

## Impact of the Registry-funded Research

Registry-funded research aids in uncovering new candidate risk factors and further developing an understanding of previously discovered risk factors. Unique environmental and occupational exposures, metabolic and immunologic pathways, and gene variants have been uncovered through these studies. Ultimately, the goal is for more in-depth research to further describe the role these risk factors play in the onset and progression of ALS.

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**Table 3.** Current limitations and future Amyotrophic Lateral Sclerosis (ALS) research needs identified by the National ALS Registry-funded research, 2015–2021.

| Study designs | Commonly identified limitations | Future research needs identified |
|---|---|---|
| Population-based cohort studies (e.g., ALS registries, claims data) | Subgroup analysis: insufficient sample sizes for specific subpopulations[20,22,23,30] | • Larger cohort studies[22,23]<br>• Targeted population sampling (e.g., exposure to water bodies, specific drug/therapeutic profiles, specific familial/genetic patterns, small-area populations, geographical "hot spots")[20,22,23,30] |
| | Latency analysis: insufficient detail on exposure timing and duration in reported information[13,20,22] | • Additional information (e.g., prediagnostic exposures, residential history, weather-related exposure patterns, distance to chemical use)[13]<br>• Biological specimen (estimates for exposure dose, bioaccumulation)[13,20]<br>• Prospective cohort studies[13,22] |
| | Confounding: challenges related to identifying ideal population-based control cohorts[19] | • Standardized methodologies for control recruitment (e.g., sibling controls, matched population controls)[9,19]<br>• Prospective cohort studies[19] |
| | Causal inference: unclear cause–effect relationship between observed exposures and disease outcomes[20,22,24,30] | • Prospective cohort studies[22]<br>• Experimental studies for identified risk factors[22]<br>• Mechanistic studies for less-studied chemicals[13] |
| Clinic-based ALS cohorts (e.g., hospital, multicenter) | Subgroup analysis: insufficient representation of specific ALS subgroups in preclinical studies)[18,21,25,26,29] | • Targeted case sampling (e.g., high-exposure patients for selected environmental factors, specific genetic signatures, sex, age)[18,29] |
| | Reverse causality: insufficient detail on exposure timing and duration in reported information.[26,28] | • Prospective cohort studies (e.g., revealing temporal relationships)[21,26]<br>• Mechanistic studies (identification of prediagnostic exposure pathways, prediction of ALS course)[26] |

Together, these 13 publications have contributed more to additional research than other papers in this field (mean RCR = 1.81), as an RCR score over 1.0 indicates more citations per year than other NIH-funded papers in its field. Higher impact publications will have a higher weighted RCR, as we see here with both the initial set of publications (16.28 > 13) and the first set of citing articles (117.33 > 100). This demonstrates the value and impact of these studies on advancing the knowledge of ALS risk factors. As Registry-funded research continues to produce impactful publications, the impact on the scientific community is amplified. These findings bring scientists closer to understanding the etiology of this disease which may translate to future prevention and treatment discoveries.

As ALS risk factor research evolves, there is a need for more tailored study designs and research priorities, such as prospective cohort studies investigating specific ALS subpopulations (e.g., with a focus on defined exposure patterns or genetic factors). To better understand the temporal relationships between exposure patterns (e.g., dose, duration) and ALS onset or survival, the integration of biological specimens and more specific prediagnosis information into prospective studies is needed. Similarly, the inclusion of experimental or mechanistic studies can help establish the cause–effect relationship of observed risk factor candidates and link genetic or immunologic pathways to the ALS disease course.

Additionally, ongoing work and discoveries by other ATSDR programs likely offer new opportunities to complement ALS risk factor research, as with the identification of genotoxic markers associated with toxic substance exposure in ATSDR's Toxicological Profiles or the identification of geospatial patterns of ALS incidence and potential linkages to social vulnerability or other equity measures developed by ATSDR's Geospatial Research, Analysis, and Services Program (GRASP).[14,15]

## Limitations

There are limitations to this analysis. First, many of the publications identified by researchers have not been published long enough to be cited. Six additional publications identified during our search process have been published


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too recently for the scientific community to cite. We therefore excluded these publications from this analysis as these publications would have incorrectly underestimated the overall weighted RCR. Instead, our intention is to repeat this analysis at a future date including those and still upcoming publications to provide a more accurate representation of the impact of ongoing and future research projects. Hence, the true impact of the Registry-funded research might be greater than presented in this article. Second, this analysis focused only on peer-reviewed publications. The findings from these funded studies may have additionally been shared at scientific conferences, meetings, and other events where their resulting impact has not been measured and accounted for in this analysis. Third, the focus of this review was limited to the reach of Registry-funded research publications in the scientific community. Hence, our findings do not assess the impact of this published research on health policies or programs addressing ALS or other neurologic diseases.

### Future recommendations

So far, federal ALS research initiatives provide a rather siloed approach to understanding ALS. For instance, funding from the U.S. Department of Defense focuses on the preclinical development of therapeutic agents, the National Institute of Health targets basic science biomedical research to slow disease progression, and the CDC/ATSDR focuses on epidemiology and risk factor identification. Together, these initiatives will investigate the full spectrum of ALS research needs. The Registry-funded research therefore fills an essential gap within the wider ALS research landscape.

While exploratory and developmental research studies are needed to identify and evaluate those risk factors without a well-substantiated evidence base (e.g., with limited or insufficient preliminary research), those risk factors with an already well-documented evidence base would further benefit from strengthened rigorous evaluation.

Examples of such putative risk factors that may benefit from additional research include occupational radiation or electromagnetic exposures, nutrition related to heavy metal exposures, traumatic brain injuries and strenuous activity related to military service, or the role microbiome, infectious agents, nutritional deficiencies, or genomics play in the ALS etiology.

ALS studies may be further strengthened by a focus on the causal interaction between environmental chemicals and genetic factors.[16,17] For instance, the application of new alternative methods (NAMs), high-throughput screening, machine learning, or computational tools may offer suitable technologies leading to the discovery of new drugs, gene–chemical interactions, or genetic treatments in ALS. These methods may also provide additional mechanistic insights into disease etiology.

Other examples include studies that have already been demonstrated to be reproducible and for which the research outcomes have been used to inform clinical medicine practice (i.e., heavy metals, POPs, and specific exposures related to military service). Further, geographic information systems (GIS) provide simple tools for disease mapping and decision-making tools. GIS and related technologies also find widespread use in analyzing the relationships between risk factors and their geographical environments.

Last, the valuable contributions from domestic and international research institutions with access to robust ALS Registry and biorepository data sources will further strengthen existing knowledge about ALS risk factors. Further studies are therefore needed to systematically explore the literature on ALS risk factors related to environmental toxicology.

## Conclusions

Risk factor research remains an essential component of ALS research as it is difficult to prevent and treat a disease without an understanding of its causes. One of the main functions of the National ALS Registry is to examine the etiology and risk factors of the disease. Potential ALS risk factors identified thus far from Registry-funded research include specific environmental and occupational exposures, metabolic and immunologic pathways, and gene variants. More in-depth research, conducted by the Registry and others, is needed to further describe the role these and additional risk factors play in the causing and progression of ALS.

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## Conflict of Interest

The authors declared that they have no conflict of interest to disclose.

## Authors' Contributions

LR developed the study design and data collection tools with feedback from MR and PM. LR and SB conducted

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the data analysis. LR, SB, and MW drafted the manuscript. PM, MH, DKH, TL, FR, and JR provided feedback and revisions to the manuscript.

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### References

1. Mehta P, Raymond J, Punjani R, et al. Prevalence of amyotrophic lateral sclerosis in the United States using established and novel methodologies, 2017. Amyotroph Lateral Scler Frontotemporal Degener. 2022;1-9.
2. Mehta P, Raymond J, Punjani R, et al. Incidence of amyotrophic lateral sclerosis in the United States, 2014–2016. Amyotroph Lateral Scler Frontotemporal Degener. 2022;23:1-5.
3. Richards D, Morren JA, Pioro EP. Time to diagnosis and factors affecting diagnostic delay in amyotrophic lateral sclerosis. J Neurol Sci. 2020;417:117054.
4. Kjældgaard A-L, Pilely K, Olsen KS, et al. Prediction of survival in amyotrophic lateral sclerosis: a nationwide, Danish cohort study. BMC Neurol. 2021;21(1):164.
5. Mitsumoto H, Chad DA, Pioro EP. Amyotrophic Lateral Sclerosis. Contemporary Neurology Series. Oxford University Press and A F. A. Davis Co.; 1998.
6. Pugh KH, Zarus GM. The burden of environmental disease in the United States. J Environ Health. 2012;74(9):30-35.
7. ALS Registry Act. 110th Congress; 2008.
8. Raymond J, Oskarsson BÖ, Mehta P, Horton K. Clinical characteristics of a large cohort of US participants enrolled in the National Amyotrophic Lateral Sclerosis (ALS) Registry, 2010–2015. Amyotroph Lateral Scler Frontotemporal Degener. 2019;20(5–6):413-420.
9. Mehta P, Raymond J, Han MK, et al. Recruitment of patients with amyotrophic lateral sclerosis for clinical trials and epidemiological studies: descriptive study of the national ALS Registry's research notification mechanism. J Med Internet Res. 2021;23(12):e28021.
10. Bledsoe MJ, Rechtman L, Wagner L, Mehta P, Horton DK, Kaye WE. Analysis of biospecimen demand and utilization of samples from the National Amyotrophic Lateral Sclerosis Biorepository. Biopreserv Biobanking. 2021;19(5):432-437.
11. ATSDR. *Substance Priority List*. Accessed June 26, 2022. https://www.atsdr.cdc.gov/spl/
12. Raymond J, Mehta P, Larson T, Pioro EP, Horton DK. Reproductive history and age of onset for women diagnosed with amyotrophic lateral sclerosis: data from the national ALS registry: 2010–2018. Neuroepidemiology. 2021;55(5):416-424.
13. Andrew A, Zhou J, Gui J, et al. Pesticides applied to crops and amyotrophic lateral sclerosis risk in the U.S. Neurotoxicology. 2021;87:128-135.
14. ATSDR. *Toxicological Profiles*. Accessed June 26, 2022. https://www.atsdr.cdc.gov/toxprofiledocs/index.html
15. ATSDR. *Place and Health*. Accessed June 26, 2022. https://www.atsdr.cdc.gov/placeandhealth/index.html
16. ATSDR. *Division of Toxicology and Human Health Sciences (DTHHS)*. Accessed June 26, 2022. https://www.atsdr.cdc.gov/dthhs/office_of_director/comp_tox_lab.html
17. CDC. *Genomics & Precision Health*. Accessed June 26, 2022. https://www.cdc.gov/genomics/default.htm
18. Ryan M, Vaillant TZ, RL ML, et al. Comparison of the clinical and genetic features of amyotrophic lateral sclerosis across Cuban, Uruguayan and Irish clinic-based populations. J Neurol Neurosurg Psychiatry. 2019;90(6):659.
19. Mitsumoto H, Garofalo DC, Gilmore M, et al. Case-control study in ALS using the national ALS registry: lead and agricultural chemicals are potential risk factors. Amyotroph Lateral Scler Frontotemporal Degener. 2022;23(3–4):190-202.
20. Andrew AS, Caller TA, Tandan R, et al. Environmental and occupational exposures and amyotrophic lateral sclerosis in New England. Neurodegener Dis. 2017;17(2–3):110-116.
21. Kuczmarski T, Stommel EW, Riley K, et al. Medical history of chemotherapy or immunosuppressive drug treatment and risk of amyotrophic lateral sclerosis (ALS). J Neurol. 2017;264(8):1763-1767.
22. Andrew AS, Chen CY, Caller TA, et al. Toenail mercury levels are associated with amyotrophic lateral sclerosis risk. Muscle Nerve. 2018;58(1):36-41.
23. Andrew AS, Pioro EP, Li M, et al. The incidence of amyotrophic lateral sclerosis in Ohio 2016–2018: the Ohio population-based ALS registry. Neuroepidemiology. 2021;55(3):196-205.
24. Andrew AS, O'Brien KM, Jackson BP, et al. Keratinous biomarker of mercury exposure associated with amyotrophic lateral sclerosis risk in a nationwide U.S. study. Amyotroph Lateral Scler Frontotemporal Degener. 2020;21(5–6):420-427.
25. Andrew AS, Bradley WG, Peipert D, et al. Risk factors for amyotrophic lateral sclerosis: a regional United States case-control study. Muscle Nerve. 2021;63(1):52-59.
26. Goutman SA et al. Untargeted metabolomics yields insight into ALS disease mechanisms. J Neurol Neurosurg Psychiatry. 2020;91(12):1329.
27. De Marchi F, Munitic I, Amedei A, et al. Interplay between immunity and amyotrophic lateral sclerosis: clinical impact. Neurosci Biobehav Rev. 2021;127:958-978.


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28. Murdock BJ, Famie JP, Piecuch CE, et al. NK cells associate with ALS in a sex- and age-dependent manner. JCI Insight. 2021;6(11):1-15.
29. Figueroa-Romero C, Monteagudo A, Murdock BJ, et al. Tofacitinib suppresses natural killer cells in vitro and in vivo: implications for amyotrophic lateral sclerosis. Front Immunol. 2022;13:1-15.
30. Goutman SA, Guo K, Savelieff MG, et al. Metabolomics identifies shared lipid pathways in independent amyotrophic lateral sclerosis cohorts. Brain. 2022; 1-41.

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