Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

HHS Public Access

Author manuscript

J Neurol Sci. Author manuscript; available in PMC 2025 February 15.

Published in final edited form as:

J Neurol Sci. 2024 February 15; 457: 122899. doi:10.1016/j.jns.2024.122899.

Avocational exposure associations with ALS risk, survival, and phenotype: a Michigan-based case-control study

Stephen A Goutman, MD, MS[1,2], **Jonathan Boss, MS**[3], **Dae Gyu Jang, PhD**[1,2], **Caroline Piecuch**[1], **Hasan Farid, MS**[1], **Madeleine Batra**[1], **Bhramar Mukherjee, PhD**[3], **Eva L. Feldman, MD, PhD**[1,2], **Stuart A. Batterman, PhD**[4]

[1]Department of Neurology, University of Michigan, Ann Arbor, MI

[2]NeuroNetwork for Emerging Therapies, University of Michigan, Ann Arbor, MI

[3]Department of Biostatistics, University of Michigan, Ann Arbor, MI

[4]Department of Environmental Health Sciences, University of Michigan, Ann Arbor, MI

Abstract

Introduction: Environmental exposures strongly influence ALS risk and identification is needed to reduce ALS burden. Participation in hobbies and exercise may alter ALS risk and phenotype, warranting an assessment to understand their contribution to the ALS exposome.

Methods: Participants with ALS and healthy controls were recruited from University of Michigan and self-completed a survey to ascertain hobbies, exercise, and avocational exposures. Exposure variables were associated with ALS risk, survival, onset segment, and onset age.

Results: ALS (n = 400) and control (n = 287) participants self-reported avocational activities. Cases were slightly older (median age 63.0 vs. 61.1 years, p=0.019) and had a lower educational attainment (p<0.001) compared to controls; otherwise, demographics were well balanced. Risks associating with ALS after multiple comparison correction included golfing (odds ratio (OR) 3.48, $p_{adjusted}$=0.004), recreational dancing (OR 2.00, $p_{adjusted}$=0.040), performing gardening or yard work (OR 1.71, $p_{adjusted}$=0.040) five years prior to ALS and personal (OR 1.76, $p_{adjusted}$=0.047) or family (OR 2.21, $p_{adjusted}$=0.040) participation in woodworking, and personal participation in hunting and shooting (OR 1.89, $p_{adjusted}$=0.040). No exposures associated with ALS survival and onset. Those reporting swimming (3.86 years, $p_{adjusted}$=0.016) and weightlifting (3.83 years, $p_{adjusted}$=0.020) exercise 5 years prior to ALS onset had an earlier onset age.

Discussion: The identified exposures in this study may represent important modifiable ALS factors that influence ALS phenotype. Thus, exposures related to hobbies and exercise should be captured in studies examining the ALS exposome.

Corresponding Author: Stephen A. Goutman, MD, MS, Department of Neurology, 1500 E Medical Center Dr, Ann Arbor, MI 48109-5223, Fax: 734-936-5185, sgoutman@med.umich.edu.

Author contributions

SAG: drafting/revising the manuscript for content, study concept and design, analysis and interpretation of data. JB: Drafting/revising the manuscript for content, analysis and interpretation of data. DGJ: drafting/revising the manuscript for content, analysis and interpretation of data. CP: drafting/revising the manuscript for content, data collection. HF: drafting/revising the manuscript for content, data collection. MB: drafting/revising the manuscript for content, data collection. BM: analysis and interpretation of data, drafting/revising the manuscript for content. ELF: drafting/revising the manuscript for content, study concept and design, analysis and interpretation of data. SB: drafting/revising the manuscript for content, study concept and design, analysis and interpretation of data.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Keywords

ALS; avocational risk factors; hobby risk factors; ALS exposures; exercise; sports; golf; swimming; weightlifting; woodwork; guns; firearms; shooting; hunting

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease characterized by progressive motor function loss and cognitive changes.[1,2] For most, ALS is "sporadic," meaning there is no single underlying causative genetic mutation.[1,2] It is increasingly recognized as resulting from a combination of genetic susceptibility and environmental exposures.[3] Detecting and validating exposures that increase ALS risk is critical to help prevent disease. Exposures can occur in multiple settings, including occupational, residential, and avocational environments. Several exposures that consistently associate with a higher ALS risk include pesticide use and metals.[4] Using a cohort of ALS patients we established in Michigan, we demonstrated that plasma concentrations of persistent organic pollutants, including organochlorine pesticides, associated with both ALS risk and progression.[5-7] We also obtained self-reported exposures from participants[8] and showed that work in production occupations and occupational exposures to metals, particulate matter, volatile organic compounds, combustion, and diesel exhaust significantly associated with increased ALS risk.[9] Further, we found that self-reported exposures to pesticides associated with a shorter survival and multiple exposure types associated with cervical onset disease.[10] ALS risk factors can also be encountered outside of the workplace, such as during exercise and recreational activities. However, potential connections between avocational activities and ALS risk have not been extensively investigated. As we requested participants in our Michigan-based case and control cohort to provide self-reported details on exercise and hobbies, the current study aimed to identify self-reported avocational activities associated with ALS risk, survival, onset segment, and onset age.

2. Methods

2.1 Participants

Recruitment is previously published.[5,6,8-10] Briefly, all patients receiving care at the University of Michigan (UM) Pranger ALS Clinic with an ALS diagnosis meeting Gold Coast criteria are invited to participate. Neurologically healthy controls without a first- or second-degree blood relative with ALS were recruited from population outreach efforts either via the University of Michigan Health Research recruitment tool provided by the Michigan Institute for Clinical and Health Research or random address sampling. As per our prior publication, this report represents participants consented prior to the COVID-19 pandemic, at which time recruitment was interrupted.[8] Recruitment was limited to persons older than 18 years of age and verbal and written informed consent in English was obtained. The study was approved by the University of Michigan Institutional Review Board (HUM28826). Compensation for participation was provided to controls, who also provided blood and urine samples at enrollment. For ALS participants, disease characteristics,

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

including El Escorial Criteria, onset segment, and diagnostic delay variables, were pulled from medical records given their impact on prognosis.

2.2 Exposure Survey

A written questionnaire with completion instructions was provided to participants. Reminders were provided for missing surveys and follow up phone calls to respondents were made for illegible or incomplete responses. For dysarthric or deceased participants, a family member assisted with clarifications. Survey data were entered into a Redcap database and allowable ranges of responses were checked with database validation tools.

The survey was developed from instruments from the Agency for Toxic Substances and Disease Registry (ATSDR)[11] and the expertise of an exposure scientist (SAB). The questions for avocational exposures (Supplemental Table S1) captured categories of non-occupational hobbies and activities including participation in sports and exercise, such as swimming and jogging, non-occupational metals exposure, such as lead and mercury exposure, and hobbies or activities, such as hunting and shooting, woodworking, painting and fine arts, and home remodeling. Exercise and non-occupational metal exposures are self-reported binary indicators of exposure five years prior to symptom onset for cases and five years prior to survey consent for controls. Hobby and activity variables are self-reported binary indicators of whether the participant personally engaged in the activity and/or whether another member of the household engaged in the activity.

2.3 Statistical Analysis

Demographic and descriptive statistics were calculated for the cohort. For the analysis, hobby and activity variables were defined as three-level categorical variables: the participant personally engaged in the hobby, another member of the participant's household engaged in the hobby, and no one in the participant's household engaged in the hobby. For analysis of exercise, non-occupational metals, and hobby variables, any variables with less than 20 participants engaged in the respective activities were excluded.

Multiple imputation with chained equations was used to fill-in missing values in the hobbies and adjustment covariates.[12] Imputation models were stratified by case control status to incorporate case-specific variables, such as onset segment, into the case only imputation model. The control only imputation model included sex, family history of ALS, education, age at survey consent, military service, and all hobby, non-occupational metals, and exercise variables. The case only imputation model included sex, onset segment, age at symptom onset, El Escorial Criteria, family history of ALS, education, age at diagnosis, military service, the cumulative hazard rate as estimated by the Nelson-Aalen estimator, and all hobby, non-occupational metals, and exercise variables.[13] Predictive mean matching was used to impute missing continuous variables, logistic regression was used to impute missing binary variables, and polytomous regression was used to impute categorical variables with more than two levels. The only variable with more than 10% missingness was the variable indicating whether a participant golfed within five years of symptom onset for cases and within five years of survey consent for controls.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Four outcomes were evaluated: ALS risk, onset segment, post-diagnosis survival, and age at symptom onset. For the ALS risk models, single hobby logistic regression models adjusted for sex, military service, age at symptom onset for cases, age at survey consent for controls, and education were fit where the outcome was case-control status. Because logistic regression models were fit separately for each hobby, the p-values from the significance tests that tested whether a hobby was significantly associated with case-control status were corrected for multiple testing using Benjamini-Hochberg correction, with a critical value cutoff on the false discovery rate of 0.1.[14] Because the distribution of those that participate in some hobbies varied substantially by sex, sex-stratified ALS risk models were also considered. The sex-stratified ALS risk models were also adjusted for military service, age at symptom onset for cases, age at survey consent for controls, and education, with false discovery rate correction using Benjamini-Hochberg correction. To model onset segment, multinomial log-linear models were separately fit for each hobby adjusted for sex, military service, age at symptom onset, and education, with lumbar onset as the reference category. Benjamini-Hochberg correction was again used with a q-value threshold to ascertain statistical significance. Cox proportional hazards models adjusted for sex, military service, age at diagnosis, log-transformed time between symptom onset and diagnosis, family history of ALS, onset segment, El Escorial Criteria, and education were fit for each hobby to model post-diagnosis survival with subsequent Benjamini-Hochberg correction.

Sex-stratified Cox survival models were also considered with the same adjustment set as the non-stratified Cox proportional hazards models, apart from adjustment for sex. The final outcome of interest, age at symptom onset, was modeled using linear regression models separately for each hobby with adjustment for military service, sex, education, and family history of ALS with Benjamini-Hochberg correction. Sex-stratified age at symptom onset models were also considered. As with ALS risk models, sex-stratified models for the ALS case specific outcomes were also considered with Benjamini-Hochberg correction. Female only sex-stratified models for ALS case specific outcomes did not include adjustment for military service, as only one female ALS case self-reported having a history of military service.

Since certain hobbies and forms of exercise may be intrinsically associated with age, a supplementary analysis of the average difference in age between those that participated in a particular activity and those that did not engage in that activity was performed amongst controls. This supplementary analysis confirmed whether statistically significant differences in age at onset were driven by participation in that hobby or due to age differences in those that participate in that activity. Second, for ALS risk results, supplementary complete-case analyses were performed to compare results from complete cases with imputed data and ensure that the imputation strategy did not alter risk associations.

3. Results

3.1 Participants

This analysis includes 400 ALS and 287 participants (Table 1) recruited between June 30, 2010 and February 12, 2020. ALS participants were slightly older compared to controls (median age; cases, 63.0 years; controls, 61.1 years; p=0.019). Controls also had a higher

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

educational attainment ($p<0.001$). There were no statistically significant differences in sex or military service. Characteristics of ALS cases showed a typical distribution in El Escorial Criteria and onset segment with a median diagnostic delay of 1.06 years.

3.2 Self-reported hobby and exercise associations with ALS

Responses to self-reported hobbies, exposures, and exercise, and the median age of participants stratified by whether they engaged in the queried activity for ALS and control participants are shown in Supplementary Tables S2 and S3. Exposures that most strongly associated with ALS risk ($p_{adj}<0.05$) were golfing, recreational dancing, performing gardening or yard work, personal or family woodworking, and personal history of hunting and shooting (Table 2). Activities and exposures were then stratified by male (Supplementary Table S4) and female (Supplementary Table S5) sex. Significant outcomes associated with ALS risk at $p_{adj}< 0.1$ for males were swimming, golf, personal involvement in wood working, personal involvement in hunting and gun use, gardening or yard work, and personal involvement in metal work. Interestingly, no avocational exposures were significant at $p_{adj}< 0.1$ when stratified for female sex.

3.3 Survival and onset associations

We also examined associations between avocational risk factors with onset segment and survival. No significant associations were identified using a threshold of $p_{adj}<0.1$ (Supplemental Table S6) or when the analysis was stratified by sex (data not shown). Similarly, no associations between avocational risk factors and survival were appreciated using $p_{adj}<0.1$(Supplemental Table S7) or when stratified by sex (data not shown).

3.4 Onset age associations

Onset age was associated with certain avocational exposures (Supplemental Table S8). Participation in swimming and weightlifting was associated with a younger age of ALS onset ($p_{adj}<0.05$). Under this analysis, ALS participants that reported swimming 5 years prior to ALS onset had an average onset age that was 3.86 years younger than those that did not swim. For weightlifting, the average onset age was 3.83 years earlier than ALS participants who did not weightlift. When stratified by male sex (Supplemental Table S9), weightlifting remained marginally significant (corrected $p<0.1$). Although swimming was not significant, the effect estimate was similar. The onset model stratified for females indicated no significant associations after multiple comparison corrections (Supplemental Table S10).

3.5 Complete case analysis of risk models

Lastly, a complete case analysis for ALS risk was performed to ensure that the imputation method did cause significant alterations to the risk models based on the missing data (shown in Supplemental Tables S2 and S3). Similar to the imputation model, golf, recreational dancing, performing gardening or yard work, a personal history of woodworking, and personal history of hunting and shooting were all marginally significant (corrected $p<0.1$; Supplemental Table S11), indicating that imputation did not result in spurious associations. Analysis stratified by males again showed associations with swimming, golf, personal

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

involvement in wood working, personal involvement in hunting and gun use, gardening or yard work, and personal involvement in metal work (Supplemental Table S12), whereas no associations were detected in females (Supplemental Table S13), which is again consistent with the imputed model.

4. Discussion

Understanding the key determinants that contribute to ALS risk or alter ALS phenotype is critical to mitigate potential exposure and identify factors that alter disease presentation. We contend that exposure modification to reduce ALS risk is possible, as guided by the decline in an extremely high incidence and prevalence of ALS following the transition from a traditional Chamorro diet to a North American diet, whereby food use of the poisonous cycad plant declined and disappeared.[15] Environmental exposures occur in multiple settings, including occupational, residential, and avocational contexts, and certain exposures strongly associate with ALS risk and survival. We recently described self-reported occupational ALS risk factors.[9,10] While occupational risk factors are widely researched, exposures in the avocational setting also represent important, and possibly modifiable, components of the ALS exposome. Therefore, we leveraged our detailed exposure questionnaire to determine whether particular hobbies or exercise activities associate with ALS risk, survival, and phenotype.

4.1 Hobbies

We report that personal and family participation in wood working and personal participation in hunting and shooting activities is associated with a higher ALS risk. The potential association between wood working as a hobby and the risk of ALS has not been extensively studied. In their study in Western Washington State, McGuire *et al.* investigated history of avocational wood working, but did not report any association with ALS risk[16] In this same population, occupational exposures to paints, varnish, or stains were associated with an increased, although non-statistically significant, risk of ALS. More recently, Lian *et al.* examined the relationship between ALS and physical activity in a study of ALS patients at Peking Union Medical College Hospital.[17] A history of wood working was used as a surrogate for mild physical activity, however the association between wood working and ALS risk was not reported. Wood working is of interest as a potential risk factor given the use of, and thus exposure to, formaldehyde and organic solvents during the process.[18] Additionally, some wood species naturally emit organic chemicals, including very volatile organic compounds and formaldehyde.[19,20] Occupational formaldehyde exposure was linked to ALS risk in the Danish registry,[21] although this risk was not maintained in a joint analysis with other occupational exposures.[22] Additionally, elevated plasma formaldehyde levels have also been observed in ALS patients in comparison to control participants.[23] Thus, the connection between wood working and ALS risk could be attributed to formaldehyde exposure.

Like wood working, the potential connection between hunting and shooting activities and ALS risk has not been extensively studied. Andrew *et al.* surveyed ALS patients and control individuals and reported that hobbies involving lead, including casting lead bullets, increased

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

risk.[24] The questionnaire for that study did include participation in hunting or shooting activities, but results were not reported. While our participants were not specifically questioned regarding the metal composition of the bullets used or their consumption of wild game, hunting and shooting activities could be a source of lead exposure. Shooting can lead to the aerosolization of metals, including lead, antimony, manganese, and boron, depending on the bullet composition.[25] Further, regardless of ALS status, individuals that used shooting ranges exhibited increased blood levels of lead and antimony.[26,27] Consumption of wild game presents another possible source of metal exposure. Residents of North Dakota who consumed wild game demonstrated higher blood lead levels than those who did not consume wild game.[28] In the Cree population in Quebec, Canada, elevated blood lead levels associated with hunting, use of firearms and leaded ammunition, and consumption of hunted or fished foods.[29] An additional study of the First Nations population in Ontario, Canada suggested an increased risk of lead consumption due to dietary intake of moose and dear meat.[30] Outside of lead exposure, mishandling of game meat can also lead to food borne illnesses.[31] Of note, our study population is derived from Michigan, where an estimated 59% of the population has consumed wild-harvested meat at least once.[32] and the sharing of wild game is prevalent.[33]

4.2 Sports and Physical Activity

We also found that participation in activities such as golf, recreational dancing, and gardening or yard work in the 5 years prior to ALS diagnosis or study entry associated with an elevated ALS risk. Participation in golf was significantly linked with ALS in the entire cohort after adjusting for multiple comparisons and considering sex, a finding further supported by the results of the male-only analysis. In the analysis limited to females, golf was a risk factor, though this association did not remain after multiple comparison testing. To the best of our knowledge, there are no studies linking golfing to ALS. Instead, investigations have focused on the potential association of golf with pesticide exposure.[34] A case and control study in Canada and France suggested that occupations linked to pesticide exposure—such as golf or garden maintenance—are associated with increased ALS risk.[35] however studies investigating inhalational connections are inconclusive.[36,37] It is unlikely that golf meets the threshold for strenuous activity associated with ALS.

Gardening and yardwork associated with ALS risk, but only in males during sex-stratified analysis. These results are unsurprising as similar associations were reported in several other cohorts. An Australian study showed that exposure to herbicides or pesticides due to regular gardening was associated with an elevated risk of ALS.[38] Additionally, a population-based case-control study in Northern and Southern Italy suggested an association between use of herbicides during gardening and ALS.[39] In a small population-based registry from Italy, United Kingdom, and Ireland, occupation as a farmer/gardener was associated with ALS risk,[40] however this study did not address gardening in the avocational setting. While we did not specifically inquire whether participants used pesticides or herbicides during their gardening activities, the global consistency of studies linking gardening to ALS risk suggest the possibility of a disease-relevant exposure stemming from this activity.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

In the non-stratified analysis, recreational dancing associated with ALS, though we did not investigate the intensity or duration of this activity to establish a more precise correlation with ALS. However, it is noteworthy that this association held greater significance in the analysis stratified for females compared to males. Overall, the associations identified are significant in males, but not females. While recreational dancing may be a false association, it might also represent an activity that uniquely impacts ALS in females and may be worth future investigation. Indeed, some types of recreational dancing can reach moderate to intense levels of physical activity,[41,42] which is significant given the potential role of strenuous physical activity as an ALS risk factor.[3]

In the complete cohort, weightlifting approached statistical significance after multiple testing correction, although this effect was less pronounced in the sex-stratified model, possibly due to sample size constraints. The marginally significant association between weightlifting and ALS risk in our study could reflect strenuous physical activity, which is a recognized ALS risk factor,[43] however our survey did not query the intensity of activity. In the sex-stratified models, swimming was associated with increased risk of ALS in males. While a study in New England demonstrated an association between watersports and ALS risk,[44] out study did not evaluate whether swimming took place in natural bodies of water or pools, which could be considered a limitation in our analysis.

As noted above, it is surprising that the risk factors identified in the current study appear to be specific to males. These activities might pose risks in females but are not reaching statistically significant thresholds due to the small number of females engaging in these hobbies. It is also possible that the risks here are not uniform across the population and may depend on underlying genetic susceptibility.[43] Thus, a lack of an association may be because we did not account for genetics. Alternatively, the absence of an association could be related to the study's small sample size or participant bias. Nonetheless, these results have important implications for ALS research as they suggest that the tools we currently use to investigate disease-relevant exposures in females may be insufficient.

We are also interested in understanding the role of exposures on the phenotypic expression of ALS to gain insight into disease triggers or heterogeneity. Contrary to our recent analysis of occupational exposures in this same cohort, we did not identify any associations with ALS survival or onset segment. However, when examining age of onset, we did observe that individuals participating in swimming and weightlifting 5 years prior to ALS diagnosis developed ALS at a younger age. These data are consistent with a recent analysis which showed that strenuous physical activity is associated with an earlier onset age of ALS.[43]

As with any retrospective case and control study of self-reported exposures, this report has limitations. A frequent limitation is recall bias, as individuals with the disease are more likely to report exposures. Additionally, some exposures may be unknown to the participant and thus go unreported. Overall, few studies have examined the association of avocational activities on ALS risk. While information on hobbies has been used to calculate lifetime physical activity or ascertain lead exposure,[24,45,46] self-reported avocational exposures represent an untapped area for future ALS exposure research. Since ALS may have a long latent period between exposure and clinical onset, a period that may span decades based

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

on evidence from longitudinal studies of the former high-incidence of ALS on Guam, our assessment of exercise in the five-year period prior to ALS onset excluded consideration of the lifetime physical activity of our participants.[47,48]

Additionally, we did not capture dietary factors in this cohort, a subject of relevance given the strong association between daily consumption of cycad seed and ALS on Guam,b and food use of False Morels by a cluster of ALS patients in the French Alps.[49] Michigan has high rates of acute poisoning from consumption of False Morels, fungi that produce monomethylhydrazine in the consumer, a genotoxin related to the principal cycad toxin methylazoxymethanol.[15] Future investigation of a possible link between ALS and food use of False Morels in Michigan would therefore be of interest. There is nevertheless an intriguing potential link of hydrazines, which cause DNA damage, to the risk factors detected in the present work.[50] For instance, in the woodworking process, some choose to fume their furniture, which could result in a release of hydrazine.[51] The chemical maleic hydride is used to prevent growth of tall fescue grass on golf courses.[52] The byproducts of disinfectants used in swimming pools may lead to hydrazine production.[53]

5. Conclusion

This analysis reveals several important avocational exposures and activities that influence ALS risk and phenotype. Further, certain risks are specific to sex, suggesting that the factors influencing ALS may differ between males and females, necessitating additional investigation. Overall, the inclusion of avocational activities in ALS exposome studies is necessary to pinpoint modifiable factors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We are indebted to the study participants that provided information. We thank Blake Swihart, Adam Patterson, Jayna Duell, RN, Daniel Berger, Amanda Williams, and Scott Dent for study support. We also thank Dr. Emily J. Koubek for expert editorial assistance.

Funding

National Institutes of Health (K23ES027221; R01ES030049; R01NS127188), National ALS Registry/CDC/ATSDR (R01TS000327, R01TS000344); the ALS Association (20-IIA-532, 20-PP-661), the NeuroNetwork for Emerging Therapies, the Robert and Katherine Jacobs Environmental Health Initiative, the NeuroNetwork Therapeutic Discovery Fund, the Peter R. Clark Fund for ALS Research, the Sinai Medical Staff Foundation, Scott L. Pranger, the University of Michigan; National Center for Advancing Translational Sciences at the National Institutes of Health (UL1TR002240).

Data availability

Sharing of non-identifiable data will be considered at the reasonable request of a qualified investigator.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

References

1. Goutman SA et al. Recent advances in the diagnosis and prognosis of amyotrophic lateral sclerosis. The Lancet. Neurology 21, 480–493, doi:10.1016/S1474-4422(21)00465-8 (2022). [PubMed: 35334233]
2. Goutman SA et al. Emerging insights into the complex genetics and pathophysiology of amyotrophic lateral sclerosis. The Lancet. Neurology 21, 465–479, doi:10.1016/S1474-4422(21)00414-2 (2022). [PubMed: 35334234]
3. Goutman SA, Savelieff MG, Jang DG, Hur J & Feldman EL The amyotrophic lateral sclerosis exposome: recent advances and future directions. Nature reviews. Neurology 19, 617–634, doi:10.1038/s41582-023-00867-2 (2023). [PubMed: 37709948]
4. Wang MD, Little J, Gomes J, Cashman NR & Krewski D Identification of risk factors associated with onset and progression of amyotrophic lateral sclerosis using systematic review and meta-analysis. Neurotoxicology 61, 101–130, doi:10.1016/j.neuro.2016.06.015 (2017). [PubMed: 27377857]
5. Goutman SA et al. High plasma concentrations of organic pollutants negatively impact survival in amyotrophic lateral sclerosis. Journal of neurology, neurosurgery, and psychiatry 90, 907–912, doi:10.1136/jnnp-2018-319785 (2019). [PubMed: 30760645]
6. Su FC et al. Association of Environmental Toxins With Amyotrophic Lateral Sclerosis. JAMA neurology 73, 803–811, doi:10.1001/jamaneurol.2016.0594 (2016). [PubMed: 27159543]
7. Goutman SA et al. Environmental risk scores of persistent organic pollutants associate with higher ALS risk and shorter survival in a new Michigan case/control cohort. Journal of neurology, neurosurgery, and psychiatry, doi:10.1136/jnnp-2023-332121 (2023).
8. Yu Y et al. Environmental Risk Factors and Amyotrophic Lateral Sclerosis (ALS): A Case-Control Study of ALS in Michigan. PloS one 9, e101186, doi:ARTN e101186 10.1371/journal.pone.0101186 (2014). [PubMed: 24979055]
9. Goutman SA et al. Associations of self-reported occupational exposures and settings to ALS: a case-control study. Int Arch Occup Environ Health 95, 1567–1586, doi:10.1007/s00420-022-01874-4 (2022). [PubMed: 35593931]
10. Goutman SA et al. Occupational history associates with ALS survival and onset segment. Amyotrophic lateral sclerosis & frontotemporal degeneration, 1–11, doi:10.1080/21678421.2022.2127324 (2022).
11. ATSDR. Taking an Exposure History. Case Studies in Environmental Medicine (2000).
12. van Buuren S & Groothuis-Oudshoorn K mice: Multivariate Imputation by Chained Equations in R. 2011 45, 67, doi:10.18637/jss.v045.i03 (2011).
13. White IR & Royston P Imputing missing covariate values for the Cox model. Statistics in medicine 28, 1982–1998, doi:10.1002/sim.3618 (2009). [PubMed: 19452569]
14. Benjamini Y & Hochberg Y Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. Journal of the Royal Statistical Society. Series B (Methodological) 57, 289–300 (1995).
15. Spencer PS et al. Early-onset, conjugal, twin-discordant, and clusters of sporadic ALS: Pathway to discovery of etiology via lifetime exposome research. Front Neurosci 17, 1005096, doi:10.3389/fnins.2023.1005096 (2023). [PubMed: 36860617]
16. McGuire V et al. Occupational exposures and amyotrophic lateral sclerosis. A population-based case-control study. American Journal of Epidemiology 145, 1076–1088 (1997). [PubMed: 9199537]
17. Lian L et al. Environmental risk factors and amyotrophic lateral sclerosis (ALS): A case-control study of ALS in China. Journal of Clinical Neuroscience 66, 12–18, doi:10.1016/j.jocn.2019.05.036 (2019). [PubMed: 31155341]
18. Thorud S, Gjølstad M, Ellingsen DG & Molander P Air formaldehyde and solvent concentrations during surface coating with acid-curing lacquers and paints in the woodworking and furniture industry. Journal of Environmental Monitoring 7, 586–591, doi:10.1039/B418887J (2005). [PubMed: 15931419]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

19. Skulberg KR, Nyrud AQ, Goffeng LO & Wisthaler A Health and Exposure to VOCs From Pinewood in Indoor Environments. Frontiers in Built Environment 5, doi:10.3389/fbuil.2019.00107 (2019).
20. Pohleven J, Burnard MD & Kutnar A Volatile organic compounds emitted from untreated and thermally modified wood-a review. Wood and fiber science 51, 231–254 (2019).
21. Seals RM, Kioumourtzoglou MA, Gredal O, Hansen J & Weisskopf MG Occupational formaldehyde and amyotrophic lateral sclerosis. Eur J Epidemiol 32, 893–899, doi:10.1007/s10654-017-0249-8 (2017). [PubMed: 28585120]
22. Bellavia A et al. Joint and interactive effects between health comorbidities and environmental exposures in predicting amyotrophic lateral sclerosis. International Journal of Hygiene and Environmental Health 231, 113655, doi:10.1016/j.ijheh.2020.113655 (2021). [PubMed: 33130429]
23. Lee A. et al. Plasma from some patients with amyotrophic lateral sclerosis exhibits elevated formaldehyde levels. Journal of the neurological sciences 409, 116589, doi:10.1016/j.jns.2019.116589 (2020). [PubMed: 31786407]
24. Andrew AS et al. Risk factors for amyotrophic lateral sclerosis: A regional United States case-control study. Muscle & nerve, doi:10.1002/mus.27085 (2020).
25. Lach K, Steer B, Gorbunov B, Mička V & Muir RB Evaluation of exposure to airborne heavy metals at gun shooting ranges. Ann Occup Hyg 59, 307–323, doi:10.1093/annhyg/meu097 (2015). [PubMed: 25452293]
26. Vandebroek E, Haufroid V, Smolders E, Hons L & Nemery B Occupational Exposure to Metals in Shooting Ranges: A Biomonitoring Study. Safety and Health at Work 10, 87–94, doi:10.1016/j.shaw.2018.05.006 (2019). [PubMed: 30949386]
27. Laidlaw MAS, Filippelli G, Mielke H, Gulson B & Ball AS Lead exposure at firing ranges—a review. Environmental Health 16, 34, doi:10.1186/s12940-017-0246-0 (2017). [PubMed: 28376827]
28. Iqbal S et al. Hunting with lead: association between blood lead levels and wild game consumption. Environ Res 109, 952–959, doi:10.1016/j.envres.2009.08.007 (2009). [PubMed: 19747676]
29. Liberda EN et al. Source identification of human exposure to lead in nine Cree Nations from Quebec, Canada (Eeyou Istchee territory). Environ Res 161, 409–417, doi:10.1016/j.envres.2017.11.023 (2018). [PubMed: 29197759]
30. Juric AK et al. Risk assessment of dietary lead exposure among First Nations people living on-reserve in Ontario, Canada using a total diet study and a probabilistic approach. J Hazard Mater 344, 55–63, doi:10.1016/j.jhazmat.2017.09.035 (2018). [PubMed: 29031094]
31. Hedman HD, Varga C, Duquette J, Novakofski J & Mateus-Pinilla NE Food Safety Considerations Related to the Consumption and Handling of Game Meat in North America. Vet Sci 7, doi:10.3390/vetsci7040188 (2020).
32. Goguen AD & Riley SJ Consumption of Wild-Harvested Meat in Society. Wildlife Society Bulletin 44, 553–563, doi:10.1002/wsb.1108 (2020).
33. Goguen AD, Riley SJ, Organ JF & Rudolph BA Wild-Harvested Venison Yields and Sharing by Michigan Deer Hunters. Human Dimensions of Wildlife 23, 197–212, doi:10.1080/10871209.2017.1409372 (2018).
34. Bekken MAH et al. Analyzing golf course pesticide risk across the US and Europe-The importance of regulatory environment. Sci Total Environ 874, 162498, doi:10.1016/j.scitotenv.2023.162498 (2023). [PubMed: 36863589]
35. Beaudin M, Salachas F, Pradat PF & Dupre N Environmental risk factors for amyotrophic lateral sclerosis: a case-control study in Canada and France. Amyotrophic lateral sclerosis & frontotemporal degeneration 23, 592–600, doi:10.1080/21678421.2022.2028167 (2022). [PubMed: 35084274]
36. Murphy RR & Haith DA Inhalation health risk to golfers from turfgrass pesticides at three northeastern U.S. sites. Environ Sci Technol 41, 1038–1043, doi:10.1021/es060964b (2007). [PubMed: 17328221]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

37. Wong H & Haith DA Volatilization of pesticides from golf courses in the United States: mass fluxes and inhalation health risks. J Environ Qual 42, 1615–1622, doi:10.2134/jeq2013.01.0017 (2013). [PubMed: 25602402]
38. Morahan JM & Pamphlett R Amyotrophic lateral sclerosis and exposure to environmental toxins: an Australian case-control study. Neuroepidemiology 27, 130–135, doi:95552 [pii] 10.1159/000095552 (2006). [PubMed: 16946624]
39. Filippini T et al. Clinical and Lifestyle Factors and Risk of Amyotrophic Lateral Sclerosis: A Population-Based Case-Control Study. Int J Environ Res Public Health 17, doi:10.3390/ijerph17030857 (2020).
40. Beghi E et al. Amyotrophic lateral sclerosis, physical exercise, trauma and sports: results of a population-based pilot case-control study. Amyotrophic lateral sclerosis : official publication of the World Federation of Neurology Research Group on Motor Neuron Diseases 11, 289–292, doi:10.3109/17482960903384283 (2010). [PubMed: 20433412]
41. Massidda M, Cugusi L, Ibba M, Tradori I & Calo CM Energy expenditure during competitive Latin American dancing simulation. Med Probl Perform Art 26, 206–210 (2011). [PubMed: 22211197]
42. Lankford DE et al. The Energy Expenditure of Recreational Ballroom Dance. Int J Exerc Sci 7, 228–235 (2014). [PubMed: 31156758]
43. Julian TH et al. Physical exercise is a risk factor for amyotrophic lateral sclerosis: Convergent evidence from Mendelian randomisation, transcriptomics and risk genotypes. EBioMedicine 68, 103397, doi:10.1016/j.ebiom.2021.103397 (2021). [PubMed: 34051439]
44. Andrew AS et al. Environmental and Occupational Exposures and Amyotrophic Lateral Sclerosis in New England. Neurodegenerative Diseases 17, 110–116, doi:10.1159/000453359 (2017). [PubMed: 28122372]
45. Visser AE et al. Multicentre, cross-cultural, population-based, case-control study of physical activity as risk factor for amyotrophic lateral sclerosis. Journal of neurology, neurosurgery, and psychiatry 89, 797–803, doi:10.1136/jnnp-2017-317724 (2018). [PubMed: 29685899]
46. Huisman MH et al. Lifetime physical activity and the risk of amyotrophic lateral sclerosis. Journal of neurology, neurosurgery, and psychiatry 84, 976–981, doi:10.1136/jnnp-2012-304724 (2013). [PubMed: 23418211]
47. Spencer PS Guam ALS/parkinsonism-dementia: a long-latency neurotoxic disorder caused by "slow toxin(s)" in food? The Canadian journal of neurological sciences. Le journal canadien des sciences neurologiques 14, 347–357, doi:10.1017/s0317167100037732 (1987).
48. Garruto RM, Gajdusek C & Chen KM Amyotrophic lateral sclerosis among Chamorro migrants from Guam. Annals of neurology 8, 612–619, doi:10.1002/ana.410080612 (1980). [PubMed: 7212649]
49. Lagrange E et al. An amyotrophic lateral sclerosis hot spot in the French Alps associated with genotoxic fungi. Journal of the neurological sciences 427, 117558, doi:10.1016/j.jns.2021.117558 (2021). [PubMed: 34216974]
50. Spencer PS & Kisby GE Role of Hydrazine-Related Chemicals in Cancer and Neurodegenerative Disease. Chem Res Toxicol 34, 1953–1969, doi:10.1021/acs.chemrestox.1c00150 (2021). [PubMed: 34379394]
51. Coyne G How to Safely Fume Your Furniture, <https://www.wwgoa.com/post/how-to-safely-fume-your-furniture> (
52. University of Arkansas. Golf Course Pest Control, <https://www.uaex.uada.edu/farm-ranch/pest-management/docs/training-manuals/AG1159.pdf> (
53. Mustapha S et al. The Occurrence of *N*-nitrosodimethylamine (NDMA) in Swimming Pools: An Overview. Environmental Health Insights 15 (2021).

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

HIGHLIGHTS

- Participation in certain hobbies and avocational activities alters ALS risk
- Avocational activities should be included in ALS exposome studies
- Certain exercise, hobbies, and avocational ALS risk factors are sex-specific

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 1.

Participant Demographics

Covariate	Cases (N = 400)	Controls (N = 287)	P-Value
Age (years) *	63.0 (55.5-70.2)	61.1 (54.5-68.2)	0.019
Sex			0.070
Female	184 (46.0)	153 (53.3)	
Male	216 (54.0)	134 (46.7)	
Military Service			0.070
No	336 (84.0)	252 (87.8)	
Yes	63 (15.8)	30 (10.5)	
Missing	1 (0.3)	5(1.7)	
Education			<0.001
High School or less	120 (30.0)	26 (9.1)	
Some Postsecondary	126 (31.5)	81 (28.2)	
Bachelor's Degree	91 (22.8)	83 (28.9)	
Graduate Degree	63 (15.8)	95 (33.1)	
Missing	0 (0.0)	2 (0.7)	
El Escorial Criteria			
Suspected	14 (3.5)	N/A	
Possible	39 (9.8)	N/A	
Probable, Lab Supported	105 (26.2)	N/A	
Probable	129 (32.2)	N/A	
Definite	113 (28.2)	N/A	
Onset Segment			
Bulbar	118 (29.5)	N/A	
Cervical	134 (33.5)	N/A	
Lumbar	146 (36.5)	N/A	
Missing	2 (0.5)	N/A	
Time Between Symptom Onset and Diagnosis (years)	1.06 (0.66-1.83)	N/A	

Table of descriptive statistics for the study population. For continuous variables, Median (25th – 75th percentile), and for categorical variables, N (%). P-values for continuous and categorical variables correspond to analysis of variance tests and chi-squared tests, respectively. *Age is defined at survey consent for controls and at symptom onset date for cases. N, number

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 2.

Avocational exposures risk model

All Hobby Variables (All Participants)

Models are adjusted for military service, age at symptom onset / survey consent, sex, and education.

Description	N (Exposed)	% Exposed	OR	95% CI	P-Value	Q-Value (BH)
Exercise - golf	111.65	16.3	3.48	(1.86, 6.52)	0.000	0.004
Exercise - recreational dancing	110.50	16.1	2.00	(1.24, 3.23)	0.004	0.040
Exercise - gardening or yard work	523.85	76.3	1.71	(1.17, 2.49)	0.006	0.040
Hobby - wood working - Family Only	76.65	11.2	2.21	(1.25, 3.91)	0.006	0.040
Hobby - hunting, guns, shooting skeet, trap, or targets - Personal	165.55	24.1	1.89	(1.20, 2.97)	0.006	0.040
Hobby - wood working - Personal	189.50	27.6	1.76	(1.15, 2.68)	0.009	0.047
Hobby - hunting, guns, shooting skeet, trap, or targets - Family Only	111.40	16.2	1.75	(1.07, 2.87)	0.027	0.111
Exercise - weightlifting	200.70	29.2	1.50	(1.04, 2.17)	0.031	0.111
Auto - repair and maintenance - Family Only	121.20	17.6	1.78	(1.06, 2.99)	0.031	0.111
Hobby - home remodeling, furniture refinishing - Family Only	81.05	11.8	1.85	(1.04, 3.27)	0.035	0.112
Hobby - making stained glass, pottery, or ceramics - Family Only	31.80	4.6	2.32	(0.94, 5.75)	0.069	0.187
Exercise - calisthenics	246.30	35.9	1.37	(0.97, 1.94)	0.070	0.187
Exercise - jog or run	160.55	23.4	1.40	(0.94, 2.09)	0.093	0.229
Exercise - swim	225.00	32.8	1.32	(0.93, 1.88)	0.117	0.267
Auto - repair and maintenance - Personal	305.20	44.4	0.72	(0.47, 1.11)	0.134	0.285
Hobby - home remodeling, furniture refinishing - Personal	291.80	42.5	1.29	(0.90, 1.84)	0.166	0.331
Non-work iron exposure	63.85	9.3	1.38	(0.75, 2.56)	0.302	0.569
Hobby - painting pictures or other fine arts - Family Only	56.35	8.2	1.38	(0.72, 2.68)	0.334	0.576
Non-work mercury exposure	40.20	5.9	1.43	(0.68, 2.99)	0.346	0.576
Exercise - bike	333.60	48.6	1.17	(0.84, 1.62)	0.360	0.576
Hobby - metal working - Family Only	43.80	6.4	0.73	(0.35, 1.49)	0.380	0.578
Non-work lead exposure	49.20	7.2	1.28	(0.65, 2.49)	0.477	0.650
Hobby - Car/motorcycle/boat restoration - Family Only	70.90	10.3	1.24	(0.69, 2.21)	0.477	0.650
Hobby - metal working - Personal	71.20	10.4	1.23	(0.68, 2.21)	0.487	0.650
Hobby - photograph development - Personal	47.25	6.9	1.19	(0.62, 2.29)	0.607	0.778
Hobby - making stained glass, pottery, or ceramics - Personal	75.90	11.0	0.88	(0.51, 1.53)	0.648	0.790
Hobby - Car/motorcycle/boat restoration - Personal	113.05	16.5	1.11	(0.67, 1.82)	0.690	0.790
Hobby - painting pictures or other fine arts - Personal	98.35	14.3	0.91	(0.56, 1.46)	0.691	0.790
Non-work aluminum exposure	48.45	7.1	1.13	(0.57, 2.24)	0.725	0.800
Hobby - photograph development - Family Only	27.50	4.0	0.97	(0.40, 2.37)	0.943	0.978
Exercise - aerobics	91.30	13.3	1.02	(0.62, 1.67)	0.947	0.978
Non-work exposure to welding fumes	64.25	9.4	1.00	(0.55, 1.82)	0.996	0.996

BH, Bonferroni Hochberg; CI, confidence interval; N, number; OR, odds ratio.