SUPPLEMENTARY FOR

The amyotrophic lateral sclerosis exposome: recent advances and future directions

Stephen A. Goutman,[1,2,‡] Masha G. Savelieff,[3,‡] Dae-Gyu Jang,[1,2] Junguk Hur,[3] Eva L. Feldman[1,2,*]

[1]Department of Neurology, University of Michigan, Ann Arbor, MI 48109, USA

[2]NeuroNetwork for Emerging Therapies, University of Michigan, Ann Arbor, MI 48109, USA

[3]Department of Biomedical Sciences, University of North Dakota, Grand Forks, ND 58202, USA

[‡]These authors contributed equally.

Stephen A. Goutman	sgoutman@med.umich.edu	0000-0001-8780-6637
Masha G. Savelieff	masha.savelieff@ndus.edu	0000-0001-5575-2494
Dae-Gyu Jang	dajang@med.umich.edu	0009-0009-7966-1322
Junguk Hur	junguk.hur@med.und.edu	0000-0002-0736-2149
Eva L. Feldman	efeldman@umich.edu	0000-0002-9162-2694

*Corresponding author: Eva L. Feldman, MD, PhD

5017 AAT-BSRB, 109 Zina Pitcher Place, Ann Arbor, Michigan 48109, United States

Email: efeldman@umich.edu, Phone: (734) 763-7274 / Fax: (734) 763-7275

Supplementary Table S1. Summary of ALS cluster studies.

Results are from a PubMed search using the terms “amyotrophic lateral sclerosis” and “spatial clustering”.

Entries arranged alphabetically.

*Incomplete years of study enrollment rounded up to the indicated year.

**Limitations and strengths as cited by papers.

Study	Country & region	Time*	Study participants	Study design	Study tools	Study findings	Study limitations/strengths**
Boumédiene et al. 2022[1]	France, Rhône-Alpes, Languedoc-Roussillon, Limousin	2003-2011	47.1 million PYFU	Population-based observational	Incident ALS from ALS referral centers, hospital centers, health insurance; neurologists verified ALS diagnosis; ascertainment estimated by capture-recapture. Clusters assessed by geographical modelling by SIR, spatial distribution of incidence, certainty classification (definite cluster, probable over-incidence area, possible over-incidence area), evaluation of result robustness.	ALS standardized incidence 2.46/100,000 PYFU (95%CI 2.31-2.63); 13 spatial clusters identified, one of which, in the Rhône-Alpes region, was definite, with 100 observed versus 54.07 expected cases, SIR 1.85 (95%CI 1.50-2.25).	*Limitations*: Retrospective; potential variability of data collected by region; analysis only considered cases address at time of ALS diagnosis. *Strengths*: Large, population-based study; relied on multiple sources for case ascertainment; neurologists verified ALS cases; methodological approach to cluster analysis; excluded clusters with fewer than 3 ALS patients to minimize impact of potential inaccuracies.
Doi et al. 2010[2]	Japan	1995-2004	National ALS mortality data, n=12,173	Based on database	Mortality data from death certificates. Linear regression examined temporal trends in mortality and M/F ratio. Clusters assessed by flexible spatial scan statistic; Monte Carlo hypothesis testing.	Annual crude mortality rate 1.07/100,000 in 2004; temporal trend increased in 70+ y age group ($p<0.01$ for M, $p<0.05$ for F), decreased in < 70 y age group ($p<0.01$ for both sexes); M/F ratio constant over time; detected 3 clusters ($p<0.005$ for M, $p<0.05$ for F) in the northeast and 1 cluster ($p<0.05$ for M) in west-central Japan.	*Limitations:* Case ascertainment based on underlying cause of death from death certificates; regional disparity may affect geographic clustering; limited case-control demographic data. *Strengths:* Large-scale registered case data.
Migliaretti et al. 2013[3]	Italy, Piedmont valley	1995-2004	Piedmont and Aosta Valley Registry for ALS, n=1,216	Registry-based	Incident ALS from registry; ascertainment estimated by capture-recapture. Clusters assessed by Bayesian spatial modelling by SIR.	ALS age-standardized incidence 3.41/100,000 (95%CI 3.22-3.60); excess of risk in 3 municipalities, Cuneo, Alessandria, Vercelli (SIR>1.2).	*Limitations*: Continuous evolution of register requires reassessment of diagnosis appropriateness; map of smoothed SIR may give rise to false positives and negatives. Strengths: Uncertain diagnoses verified at follow-up visits; completeness of ascertainment estimated at 98%; Bayesian approach allows precise analysis of small clusters.
Oliveira et al. 2023[4]	Brazil, Rio Grande do Norte	2005-2018	ALS multi-disciplinary care center at the Onofre Lopes University Hospital database, ALS n=177	Based on database	Incident ALS from ALS multi-disciplinary center; neurologist verified ALS diagnosis. Eligible cases georeferenced using municipality of residence at diagnosis. Clusters assessed by Bayesian risk mapping, Moran scatter plot, and spatial correlogram. Linear regression analyzed annual increase in ALS.	Mean annual incidence 0.3769/100,000 (95%CI 0.288-0.4658); incidence higher in males than females (M=0.4516/100,000, F=0.3044/100,000); no areas of increased risk or spatial geographic dependence.	*Limitations:* Focused on only one geographical area in a socioeconomically and ethnically diverse country; data collected from tertiary services; limited number of cases with familial ALS; clinic-, not population-, based study. *Strengths:* Analyzed using two dedicated spatial statistical methods; standardized data collected; homogenous methodology; well-defined geographical area.

Povedano et al. 2018[5]	Spain, Catalonia	2011-2016	Motor Disease Functional Unit of University Hospital of Bellvitge database, n=383	Retrospective population-based nested case-control	Incident ALS from patients assessed at Motor Disease Unit. Controlled observed and unobserved confounders. Adjusted for spatio-temporal extra variability. Clusters assessed by SIR, inferences performed with Bayesian framework. Multivariate analysis using a generalized linear mixed model with binomial response and a logistic link.	ALS incidence 1.12/100,000 PY (95%CI 0.85-1.48). Identified 3 spatial clusters that could be related to environmental variables, such as agricultural chemicals (OR 5.483; 95%ICr 1.279-25.23; probability 98.93%) and urban traffic (OR 1.364; 95%ICr 0.885-2.104; probability 91.99%).	*Limitations:* Original cohort consisted of non-random sample; lack of family ALS history; use of proxies to approximate exposure to environmental variables; unicentric. *Strengths:* Case-controlled, population-based; random effects to control for unobserved confounding; adjusted for spatial extra variability inherent in all spatial design.
Rooney et al. 2014[6]	Ireland	1995-2013	Irish ALS registry, n=1,638	Registry-based	Incident ALS from Irish ALS registry. All incident cases geocoded for address at time of diagnosis. Smoothed relative risks by Bayesian conditional auto-regression. Relationship between population density and relative risk examined by Bayesian and linear regression.	Smoothed maps identified localized areas of increased risk in urban and rural areas. Stratified maps identified localized areas of relative risk. Weak relationship between population density and relative risk as determined by linear regression. Identified areas of higher incidence in younger individuals.	Limitations: Bayesian and linear regression analysis of population density and relative risk relationship gave conflicting results; asymmetric distribution of population; lacking formal cluster analysis. Strengths: Use of national prospective ALS registry; majority of case data complete.
Rooney et al. 2015[7]	Ireland	1995-2013	Irish ALS registry, n=1,684	Registry-based	Incident ALS from Irish ALS registry. All incident cases geocoded for address at time of diagnosis. Clusters assessed by formal spatial cluster analysis (SaTScan, FleXScan). Case ascertainment completeness assessed by Poisson-based, time period-stratified statistics and time-stratified Bayesian smoothed risk mapping.	Did not identify any high-risk clusters. Identified two areas of lower-than-average ALS risk (relative risk 0.53, p=0.012; relative risk 0.0, p=0.029).	*Limitations:* Results contrast with previous Bayesian analysis in Ireland; potential lack of power to detect clusters in low-population areas. *Strengths:* Used a long-running prospective ALS registry with nationwide case ascertainment; used two cluster analysis programs; covered entire national healthcare system; exploratory design.
Schwartz et al. 2017[8]	USA	1999-2014	Counties with ≥ 20 MND cases, n=923 counties	Based on database	MND age-adjusted mortality rates from 923 counties from CDC. Percent of county population with domestic self-supplied well water in 2010 from US Geological Survey. Calculated correlation between age-adjusted MND mortality rates to percent using well water; linear regression examined correlation between MND mortality rates to well water use, independent of latitude and other geographic factors. Clusters assessed by spatial clustering.	Average MND mortality rate 2.25/100,000 (SD 0.54, range 0.67-4.23). Age-adjusted MND mortality rates correlated with well water prevalence (r=0.278, p<0.0001). Counties with high MND mortality rates linked to well water usage.	Limitations: Used MND mortality rates as surrogate for ALS; selection, misclassification, and migration bias; potential exclusion of less populous, rural counties; used counties, not individuals, as unit of analysis. Strengths: Used small geographic units; results consistent with previous studies examining ALS and well water.
Torbick et al. 2014 [9]	USA, northern New England	1997-2009	ALS Center at Dartmouth Hitchcock Medical Center database (over 800 ALS cases)	Based on database	Incident ALS from registry, verified when possible; current and prior dwelling location, medical history, occupational history, environmental exposures, age at diagnosis, year of diagnosis, family history for ALS cases geocoded into spatial database. Clusters assessed by normalized excess ALS counts at census tract level across northern New England, adjusted for age, sex. Water quality assessed by satellite remote sensing. Logistic regression modeling to evaluate correlation between individual ALS case membership in census tract to higher-than-expected ALS counts and potential risk factors, including water quality.	Several ALS clusters identified; logistic regression modeling found higher metrics of poor-quality water (chlorophyll-a as cyanobacteria surrogate, total nitrogen as driver of algae growth) correlated to higher odds of belonging to an ALS cluster; Secchi depth of water body within a 30 km radius has OR 0.40 (95%CI 0.249-0.614; p=0.0001); total nitrogen of water body within a 30 km radius has OR 2.42 (95%CI 1.460-4.124; p=0.0007); chlorophyll-a of water body within a 10 km radius has OR 1.05 (95%CI 0.996-1.098; p=0.0678).	*Limitations*: Water quality and exposure within a single large lake can be variable; did not investigate environmental and occupational toxins that may be present in lake water; difficulty interpreting relationship between minimum distance to a lake and belonging to an ALS hotspot. *Strengths*: Satellite remote sensing to address field sampling limitations; examined multiple lake quality attributes.

Uenal et al. 2014[10]	Germany, Swabia	2008-2012	ALS registry Swabia (n=438 ALS cases out of a target population of ca. 8.4 million)	Registry-based	Incident ALS from registry; ascertainment estimated by capture-recapture. Clusters assessed by SIR.	ALS age-standardized incidence 2.5/100,000 PY (95%CI 2.3-2.7); mean SIR 1.1/100,000 PY (95%CI 1.0-1.2); no statistically significant clusters; mean SIR 1.1/100,000 PY (95%CI 1.0-1.2); capture-recapture estimated 18.9% missing cases leading to corrected age-standardized incidence 3.1/100,000 PY.	*Limitations*: Retrospective; no access to an independent mortality dataset. *Strengths*: Data quality evaluated; neurologists verified newly diagnosed ALS cases; high registry completeness.
Vasta et al. 2018[11]	Italy, Piedmont and Aosta valleys	1995-2014	Piedmont and Aosta Valley Register for ALS (n=2,671)	Registry-based	Incident ALS from registry. Addresses geocoded. Clusters assessed by spatial modelling by Moran's index and Kulldorff spatial scan statistic.	ALS mean annual crude incidence 3/100,000 PY; no statistically significant clusters except one small cluster of 3 individuals, which may have arisen by chance.	*Limitations*: Analysis only considered case address at the time of ALS diagnosis, and only for home, not for occupation. *Strengths*: Large, population-based study; adopted two spatial statistics; analysis performed at both municipality and census division level to eliminate contribution from differing administration.

CDC, Centers for Disease Control; CI, confidence interval; ICr, credibility intervals; F, female; M, male; MND, motor neuron disease; OR, odds ratio; PY, person-years; PYFU, person-years of follow-up; SD, standard deviation; SIR, standardized incidence ratio.

Supplementary Table S2. Summary of ALS exposome studies.

Results are from a PubMed search of English language studies dated from Jan 1, 2017, to Nov 23, 2022, identified with the search terms of “amyotrophic lateral sclerosis” and, in turn, “agriculture risk”, “air pollution”, “electromagnetic”, “environment”, “exposure”, “head trauma”, “metals”, “metals blood”, “metals plasma”, “military”, “occupational exposure”, “persistent organic pollutant”, “persistent organic pollutant blood”, “persistent organic pollutant plasma”, “pesticide”, “pesticide blood”, “pesticide plasma”, “pollutant”, “professional sports”, “traffic”, “trauma”. Studies were selected to show the range of exposures in larger populations and using novel techniques.

Entries arranged alphabetically.

*Incomplete years of study enrollment rounded up to the indicated year.

**Limitations and strengths as cited by papers.

Study	Country & region	Time *	Study participants	Exposures examined	Study design	Study tools	Study findings	Study limitations/strengths**
Andrew et al. 2017[12]	USA, New England	2009-2015	ALS (n=295); controls (n=225)	Lifestyle, avocational, environmental, occupational factors	Case-control	ALS cases enrolled from medical centers and clinics in New Hampshire, Vermont; self-reported questionnaire; logistic regression models.	Job or hobby using chemicals (OR 2.51; 95%CI 1.64-3.89), primary occupation using chemicals (OR 3.95; 95%CI 2.04- 8.3), living full-time within 2 miles of water body (OR 1.59; 95%CI 1.05-2.42); waterskiing (OR 3.89; 95%CI 1.97-8.44); boating/sailing (OR 1.51; 95%CI 1.01-2.28); adjusted for age, sex, smoking.	*Limitations*: Questionnaire did not query exposure details, e.g., dates of exposure. *Strengths*: Controls had idiopathic neurologic diseases, so they were not more likely than ALS cases to recall exposures that may have caused their illness.
Andrew et al. 2018[13]	USA, New England	2009-2016	ALS (n=46); controls (n=66)	Toenail metals	Case-control	ALS cases enrolled from medical centers and clinics in New Hampshire, Vermont; self-reported questionnaire; metals measured in toenail; logistic regression models.	Toenail mercury OR 2.49 (95%CI 1.18-5.80; p=0.024), adjusted for age, sex. Toenail mercury correlates to top quartile of fish consumption in ALS cases and controls (p=0.018).	*Limitations*: Questionnaire did not query exposure details, e.g., dates of exposure. *Strengths*: Controls had idiopathic neurologic diseases, so they were not more likely than ALS cases to recall exposures that may have caused their illness.
Andrew et al. 2020[14]	USA	2013-2015	ALS (n=70, females); controls (n=210, females)	Toenail metals	Population-based, case-control	ALS cases from the National ALS Registry; matched controls from Sister and Two Sister Studies; metals measured in toenail; logistic regression models.	Toenail mercury OR 2.3 (95%CI 1.10-4.58), adjusted for age, smoking.	*Limitations*: Nails from ALS cases collected more recently than controls; nails collected after ALS diagnosis, only measured exposure within that timeframe. *Strengths*: Not stated.

Andrew et al. 2021[15]	USA, northern New England, Ohio	2016-2020	ALS (n=188); controls (n=376)	Lifestyle, avocational, occupational factors	Case-control	ALS cases enrolled from medical centers and clinics in New Hampshire, Vermont, Ohio; mailed questionnaire; logistic regression models.	Ever experienced head trauma leading to loss of consciousness OR 1.60 (95%CI 1.04-2.45), remains significant 10 to <20 and >40 y from diagnosis; ever experienced severe electrical burn/electrocution OR 2.86 (95%CI 1.37-6.03), remains significant 10 to <40 y from diagnosis; ever worked with lead OR 2.92 (95%CI 1.45-5.91), remains significant 20 to <40 y from diagnosis; ever held a mechanics (OR 2.05; 95%CI 1.10-3.79) or construction (OR 2.17; 95%CI 1.16-4.02) job; adjusted for age, sex, family history, smoking.	*Limitations*: Few ALS cases for subgroup analysis and latency; low questionnaire response rate. *Strengths*: Similar demographics of ALS questionnaire respondents to non-respondents; questionnaire included a control question to assess possible recall bias.
Andrew et al. 2021[16]	USA	2013-2019	ALS (n= 26,199); controls (n= 78,597)	Pesticides	Population-based, case-control	SYMPHONY dataset split into two groups for discovery and validation; US Geological Survey of 423 pesticide applications; logistic regression models.	Herbicides 2,4-dicholorophenoxyacetic acid (OR 1.25; 95%CI 1.17-1.34) and glyphosate (OR 1.29; 95%CI 1.19-1.39); insecticides carbaryl (OR 1.32; 95%CI 1.23-1.42) and chlorpyrifos (OR 1.25; 95%CI 1.17-1.33); adjusted for age, sex.	*Limitations*: Geospatial data limited to zip3 at diagnosis; participants may split time at different addresses; hard to estimate exposure; study did not account for personal application, diet, or occupation. *Strengths*: Large dataset.
Andrew et al. 2022[17]	USA	2013-2019	ALS (n= 26,199); controls (n= 78,597)	Airbourne contaminants	Population-based, case-control	SYMPHONY dataset split into two groups for discovery and validation; 268 airborne contaminant levels recorded by the US EPA National Emissions Inventory database for 2008; logistic regression models.	Lead (OR 1.02; 95%CI 1.01-1.03; p=0.00077) and PCBs (OR 1.01; 95%CI 1.01-1.02; p=3.60E−05). In sensitivity analyses in an independent cohort, airborne lead remained linked to ALS, adjusted for age, sex, race, SES.	*Limitations*: Exposure data collected in intervals; geospatial data limited to zip3 at diagnosis; participants may split time at different addresses. *Strengths*: Large dataset; validates findings in an independent cohort.
Bandres-Ciga et al. 2019[18]	N/A	N/A	ALS (n=20,806); controls (n=59,804)	Polygenic risk for traits	Mendelian randomization	GWAS dataset; multivariate analyses; genetic risk profiling; Bayesian colocalization	ALS polygenic risk linked positively to smoking status and moderate physical activity levels and negatively to higher cognitive performance, higher education, and light physical activity levels. Mendelian randomization suggests hyperlipidemia causal risk factor for ALS.	*Limitations*: GWAS mostly of European decent; used summary data, may bias results, though unlikely for all GWAS datasets, especially since findings were replicated; cannot exclude potential contribution from rare genetic variants. *Strengths*: Large dataset.
Beard et al. 2017[19]	USA	2005-2010	ALS (n=616)	Military service	Case-control	ALS cases enrolled in Genes and Environmental Exposures in Veterans with Amyotrophic Lateral Sclerosis study; military service, deployments, and 39 related exposures queried by standardized telephone interviews; Cox proportional hazards models.	Deployed to World War II (HR 1.97; 95%CI 1.34- 2.87) or prior to 1950 (HR 1.74; 95%CI 1.16-2.60); weighted for various clinical variables. Risk did not vary by longest service across various Military branches.	*Limitations*: Exposures self-reported, subject to recall bias; validity/reliability of self-report for military-related questions unknown; registry likely under-ascertained cases. *Strengths*: Medical record-confirmed ALS; relatively complete ascertainment; used inverse probability weights to prevent bias from confounding variables.
Beaudin et al. 2022[20]	Canada, France	2003-2012	Canada ALS (n=124), controls (n=132); France ALS (n=280), controls (n=249)	Environmental exposures	Case-control	ALS cases enrolled from clinic; phone administered questionnaire; logistic regression models.	Head trauma OR 1.50 (95%CI 1.05-2.18); electric shock OR 1.79 (95%CI 1.13-2.87), especially spinal-onset ALS; adjusted for age, sex, education, region. Occupational pesticides, residential pesticides, neck trauma, welding not linked to ALS in multivariate analysis.	*Limitations*: Potential bias for more slowly progressive ALS; controls partly from spouses and relatives, can lead to overmatching; genotype unknown; many risks considered with many of tests. *Strengths*: Controls were not more likely than ALS cases to recall exposures that may have caused their illness.

Bellomo et al. 2022[21]	Europe, USA	2017-2021	Systematic review of studies of ALS or MND cases vs controls	Professional, varsity athletes	Systematic review of 8 studies published up to 2021	Systematic review extracted data from included studies, which were assessed by Newcastle-Ottawa Scale.	Systematic review suggests higher risk of ALS from soccer and American football.	*Limitations*: Not stated. *Strengths*: Not stated.
Blecher et al. 2019[22]	Europe, USA	1976-2017	Included studies of ALS cases involved in professional and non-professional sports vs controls	Contact sports	Meta-analysis of 16 studies published up to 2017	Meta-analysis assessed risk of bias to evaluate class of evidence for each study; standardized mortality, incidence ratios, HR, OR, proportional mortality ratios, and rate ratios treated as equivalent measures of risk and referred to as rate ratio.	Professional sports prone to repetitive head and spine linked to ALS with pooled rate ratio 8.52 (95%CI 5.18-14.0) vs (i) nonprofessional sports prone to repetitive head and spine trauma (pooled rate ratio 0.60 [95%CI 0.12-3.06]), (ii) professional sports not prone to repetitive trauma (pooled rate ratio 1.35 [95%CI 0.67-2.71]); or (iii) nonprofessional sports not prone to trauma (pooled rate ratio 1.17 [95%CI 0.79-1.71]).	*Limitations*: Heterogeneity across studies, including for diagnostic ALS criteria; most included studies judged to have high or moderately high risk of bias due to study design; variation in sports exposure. *Strengths*: Accounted for heterogeneity by sensitivity and stratified analyses.
Cragg et al. 2017[23]	USA	Up to 2011	ALS (n=643, males) out of 1,007,913 (males)	Military service	Population-based	National Longitudinal Mortality Study; Cox proportional hazards models.	Veteran status (HR 1.1; 95%CI 1.0-1.3), World War II veteran (HR 1.3; 95%CI 1.1-1.6); adjusted for age, race/ethnicity, education, SES. No link to ALS for veterans of Korean War, Vietnam War, Persian Gulf War.	*Limitations*: Not stated. *Strengths*: Not stated.
Daneshvar et al. 2021[24]	USA	1960-2019	ALS (n=38); athlete controls (n=19,385); athlete controls in nested analysis (n=190)	American football	Population-based, nested case-control	ALS that developed from players in National Football League (NFL); logistic regression models.	ALS SIR (3.59; 95%CI 2.58-4.93), ALS SIR (3.94; 95%CI 2.62-5.69), adjusted for age, race, higher vs general population. In nested analysis, years played linked to ALS (OR 1.2; 95%CI 1.1-1.3). No link to ALS by position played.	*Limitations*: Retrospective; few ALS cases; lack of clinical data and case ascertainment; lack of data on repetitive head impacts and traumatic brain injury; ALS data from general population from 2009-2011 vs NFL cohort 1960-2021; lack of data on duration on non-professional play. *Strengths*: Not stated.
Dickerson et al. 2018[25]	Denmark	1982-2013	ALS (n=1,639); controls (n=151,975)	Occupational diesel exposure	Population-based, case-control	ALS cases from the Danish National Patient Registry; demographic data and occupation history obtained from the Danish Pension Fund; JEMs assessed exposures; logistic regression models.	Diesel exhaust linked to ALS risk in males only (OR 1.20; 95%CI 1.05-1.38), adjusted for SES and residential area on the index date.	*Limitations*: Did not have information on smoking to adjust potential confounding; small risk of ALS case-status misclassification. *Strengths*: Prospectively collected occupation information; estimated exposures using JEMs, instead of relying on self-reported exposure.
Dickerson et al. 2019[26]	Denmark	1982-2013	ALS (n=1,639); controls (n=151,974)	Occupational lead exposure	Population-based, case-control	ALS cases from the Danish National Patient Registry; demographic data and occupation history obtained from the Danish Pension Fund; JEMs assessed exposures; logistic regression models.	Lead exposure in 60th percentile of exposure linked to ALS risk in males only 5 y (OR 1.35; 95%CI 1.04-1.76) and 10 y (OR 1.33; 95%CI 1.0-1.72) prior to diagnosis, adjusted for SES and residential area on the index date.	*Limitations*: Did not have information on smoking to adjust potential confounding; small risk of ALS case-status misclassification; small risk of exposure misclassification. *Strengths*: Prospectively collected occupation information; estimated exposures using JEMs, instead of relying on self-reported exposure.

Dickerson et al. 2020[27]	Denmark	1982-2013	ALS (n=1,639); controls (n=168,194)	Occupational metals exposure	Population-based, case-control	ALS cases from the Danish National Patient Registry; demographic data and occupation history obtained from the Danish Pension Fund; JEMs assessed exposures; logistic regression models.	No link of occupational metals exposure (chromium, iron, nickel) to ALS risk.	*Limitations*: Small risk of ALS case-status misclassification; JEMs do not account for possible exposure differences within same job type. *Strengths*: Prospectively collected occupation information; estimated exposures using JEMs, instead of relying on self-reported exposure.
Fang et al. 2016[28]	Sweden	1989-2010	Cross-country skiers (n=212,246); general population controls (n=508,176)	Cross-country skiing	Population-based, case-control	Cohort comprised of previous competitors in Vasaloppet long-distance cross-country skiing race; unique participant identifying information and race information obtained from Vasaloppet office; non-skier control group selected from Swedish Total Population Register; ALS diagnosis obtained from Swedish Patient Register; Cox proportional hazards models.	Best performing skiers at increased ALS risk versus least well performing skiers and general population; least well performing skiers at decreased ALS risk versus general population.	*Limitations:* Lack of detailed ALS clinical data; ALS cases potentially underestimated; did not assess differences in milder injuries between ALS cases among skiers and non-skiers. *Strengths:* Large sample size; prospectively collected data on exposure and outcome; detailed skiing performance data; internal comparison between skiers and external comparison to general population.
Figueroa-Romero et al. 2020[29]	USA, Michigan	Lifetime	ALS (n=36); controls (n=31)	Lifetime metals exposure in teeth	Case-control	ALS cases enrolled from clinic; metals measured in teeth; variant of distributed lag models.	Metals higher in ALS vs controls: 1.49x chromium (95%CI 1.11-1.82; at 15 y), 1.82x manganese (95%CI 1.34-2.46; at birth), 1.65x nickel (95%CI 1.22-2.01; at 8 y), 2.46x tin (95%CI 1.65-3.30; at 2 y), 2.46x zinc (95%CI 1.49-3.67; at 6 y); adjusted for batch, sex, age at tooth extraction, smoking, and intra-participant correlated observations.	*Limitations*: Retrospective observational; small study. *Strengths*: Assessed exposures in biosamples; assessed lifetime exposure.
Filippini et al. 2020[30]	Italy, 4 provinces in northern and southern Italy	2008-2011	ALS (n=95); controls (n=135)	Clinical, lifestyle, avocational factors	Population-based, case-control	ALS registries (ERRALS, PARALS), hospital discharge records, death certificate files, drug prescription directories; mailed questionnaire; logistic regression models.	Head trauma OR 2.61 (95%CI 1.19-5.72), fish consumption OR 0.27 (95%CI 0.12-0.60), wine consumption OR 0.46 (95%CI 0.26-0.82), but not significant OR for electric shock (OR 2.09; 95%CI 0.62-7.06), private well drinking water (OR 1.38; 95%CI 0.73-2.27), herbicide gardening use (OR 1.95; 95%CI 0.88-2.27), among other factors; adjusted for age, sex, education.	*Limitations*: Observational design cannot rule out possible confounding; low response rate, reduced sample size; serious ALS cases may not have responded; self-reported exposures subject to recall bias, especially for long-term information. *Strengths*: Controls randomly selected from general population with similar characteristics to general population, suggesting little selection bias; larger study size vs prior studies by including 4 provinces of distinct populations; performed sensitivity analysis excluding cases with family history, which did not significantly affect findings.

Filippini et al. 2020[31]	Italy, 3 provinces Catania, Modena, Reggio Emilia	2008-2011	ALS (n=95); controls (n=135)	Environmental, occupational exposures	Population-based, case-control	ALS registries (ERRALS, PARALS), hospital discharge records, death certificate files, drug prescription directories; mailed questionnaire; logistic regression models.	Prior agricultural work (OR 2.53; 95%CI 1.15-5.57; stays significant ≥10 y), occupational exposure to thinner (OR 2.27; 95%CI 1.14-4.54) and metal (OR 4.20; 95%CI 1.88-9.38; significant for lead, but not for mercury, selenium, cadmium), residence near EMFs (OR 2.41; 95%CI 1.13-5.12) and water body (OR 1.83; 95%CI 1.04-3.21); adjusted for age, sex, education.	*Limitations*: Low response rate, possible selection bias, though study sample characteristics similar to general population; may have missed cases that were already deceased or with severe symptoms, though caregiver could have filled questionnaire; possible residual confounding. *Strengths*: Population-based design; study area encompassed regions with different lifestyle, environmental exposures, possibly genetic background; sensitivity analysis that excluded ALS cases with family history.
Filippini et al. 2021[32]	Brazil, Denmark, Italy, Netherlands, Switzerland	2009-2020	Meta-analysis of ALS cases vs controls	Residential EMF exposure	Meta-analysis and dose-response meta-analysis of 6 studies published up to 2021	Meta-analysis assessed heterogeneity and bias; extracted study location, design, recruitment period, case numbers, total population, methods to estimate EMF, assessed outcome, risk estimates and 95%CI from most adjusted model with variables.	No link of residential EMFs exposure to ALS risk.	*Limitations*: Small sample size limited interpretation; few studies that did not allow dose-response analysis; potential residual confounding since few studies accounted for potential confounders; limited evidence of small-study bias, but slight publication bias. *Strengths*: Included studies had individual and accurate address information to determine geographical coordinates and assess exposure.
Filippini et al. 2021[33]	Italy, Modena	1994-2015	ALS (n=52); controls (n=80)	Air pollution (PM_{10})	Case-control	ALS cases enrolled from clinic; residences geocoded; PM_{10} exposure modeled; logistic regression models.	No link of PM_{10} exposure to ALS risk.	*Limitations*: Small study; limited to one exposure, PM_{10}; did not account for participants changing residence. *Strengths*: Not stated.
Goutman et al. 2019[34]	USA, Michigan	2012-2015	ALS (n=167)	Plasma POPs	Prospective	ALS cases enrolled from clinic; POPs measured in plasma; Cox proportional hazards models.	Cases in highest vs lowest ERS quartile HR 2.07 (95%CI 1.13-3.80; p=0.018); plasma pollutants with largest contribution to ERS were PBDE-154 (HR 1.53; 95%CI 0.90-2.61), PCB-118 (HR 1.50; 95%CI 0.95-2.39), PCB-138 (HR 1.69; 95%CI 0.99-2.90), PCB-151 (HR 1.46; 95%CI 1.01-2.10), PCB-175 (HR 1.53; 95%CI 0.98-2.40), p,p'-DDE (HR 1.39; 95%CI 1.07-1.81); adjusted for various clinical and lifestyle factors.	*Limitations*: Targeted; one-time exposure assessment may not represent lifetime exposures; potential disease progression bias; missing data. *Strengths*: Prospective; assessed exposures in biosamples; ERS assesses cumulative effect from multiple pollutants; sensitivity analysis to assess imputation.
Goutman et al. 2022[35]	USA, Michigan	N/A	ALS (n=381); controls (n=272)	Occupational exposures	Case-control	ALS cases enrolled from clinic; self-reported questionnaire on exposure to PM, VOC, pesticides, metals, biologicals, combustion/diesel exhaust, EMFs, radiation, corrosives; jobs coded by Standard Occupational Classification (SOC); logistic regression model.	ALS linked to higher duration-adjusted exposure to PM (OR 1.45; 95%CI 1.19-1.78), VOC (OR 1.22; 95%CI 1.02-1.45), metals (OR 1.48; 95%CI 1.21-1.82), combustion/diesel exhaust (OR 1.20; 95%CI 1.01-1.43), adjusted for age, sex, military service. In multivariable models, metals exposure remained significant (OR 1.56; 95%CI 1.11-2.20), but an adaptive elastic net model selected PM (OR 1.20), pesticides (OR 1.02), metals (1.33) as risk factors. Work in SOC code “Production Occupations” linked to ALS.	*Limitations*: Retrospective; exposures and jobs self-reported, subject to recall bias; possible selection bias; did not differentiate full-time from part-time jobs, which could affect exposure duration. *Strengths*: ALS cases diagnosed by neurologists; detailed questionnaire; SOC codes complemented by exposures; SOC codes were curated.

Goutman et al. 2022[36]	USA, Michigan	2010-2020	ALS (n=378)	Occupation	Prospective	ALS cases enrolled from clinic; self-reported questionnaire; jobs coded by Standard Occupational Classification (SOC); Cox proportional hazards models.	Poorer survival linked to SOC code "Production Occupations" and marginally with work in "Military Occupation"; poor survival linked to self-reported pesticide exposure in adjusted models. Onset segment linked to various SOC codes and self-reported exposures.	*Limitations*: Exposures and jobs self-reported, subject to recall bias; possible selection bias; did not differentiate full-time from part-time jobs, which could affect exposure duration; did not fully adjust for confounding, e.g., physical activity level. *Strengths*: Prospective; ALS cases diagnosed by neurologists; detailed questionnaire; SOC codes complemented by exposures; SOC codes were curated.
Goutman et al. 2022[37]	USA, Michigan	N/A	ALS (n=381); controls (n=266)	Presymptomatic BMI	Case-control	ALS cases enrolled from clinic; participants self-reported height and weight at diagnosis and 5 and 10 y prior; generalized estimating equations; accelerated failure time models.	10 y BMI trends differed in ALS vs controls; 10 y drop in BMI linked to 27.1% shorter ALS survival; BMI changes linked to metabolomic changes in ALS, especially lipids.	*Limitations*: Retrospective; weight self-reported, subject to recall bias; BMI queried at relatively long intervals; no data on diet or physical activity. *Strengths*: ALS cases diagnosed by neurologists; BMI assessed longitudinally.
Gu et al. 2021[38]	Worldwide	1980-2020	Meta-analysis of ALS (n=18,390) vs controls (n=6,519,391)	Trauma	Meta-analysis of 29 studies published up to 2020	Meta-analysis assessed heterogeneity and bias and extracted multivariable OR (age-adjusted or crude OR if multivariable not available), RR, HR, SMR, 95%CI, adjusted variables, trauma outcomes (number of events, years since last event).	Trauma OR 1.51 (95%CI 1.33-1.73; p=1.20E-09); significant at head OR 1.47 (95%CI 1.21-1.77; p=7.49E-05), trunk OR 1.91 (95%CI 1.29-2.84; p=0.001), lower limb OR 1.38 (95%CI 1.09-1.75; p=0.008); significant for more events (n≥2) OR 1.21 (95%CI 1.07-1.38; p=0.002); significant for trauma ≤5 y (OR 1.84; 95%CI 1.56-2.17; p=7.49E-05), >5 y (OR 1.24; 95%CI 1.12-1.38; p=4.13E-05), >10 y (OR 1.28; 95%CI 1.10-1.49; p=0.002) from diagnosis.	*Limitations*: Many included studies were hospital-based, with potential selection bias; large extent of study heterogeneity; some relevant studies excluded due to insufficient data; some trauma types, e.g., wound, electric shock, were not included; MND studies included, partly distinct from ALS; not all included studies fully adjusted; funnel plot found no evidence of publication bias, but studies with negative findings may not have been published. *Strengths*: Assessed heterogeneity, sensitivity analysis, publication bias; subgroup and meta-regression analysis.
Gunnarsson, Bodin 2018[39]	Worldwide	Up to 2017	Meta-analysis and systematic review of studies of ALS vs controls	Occupational exposures	Meta-analysis and systematic review of 79 studies published up to 2017	Meta-analysis assessed heterogeneity and bias; quality assessed by MOOSE and GRADE.	Occupational exposures to heavy physical work (RR 1.29; 95%CI 0.97-1.72), professional sports (RR 3.98; 95%CI 2.04-7.77), metals (RR 1.45; 95%CI 1.07-1.96), chemicals (RR 1.19; 95%CI 1.07-1.33), EMFs or working with electricity (RR 1.18; 95%CI 1.07-1.31), nurse or physician occupation (RR 1.18; 95%CI 1.05-1.34).	*Limitations*: Analysis of published data will reflect their inherent weaknesses. *Strengths*: Assessed quality of included studies by MOOSE and GRADE; assessed possible sources of bias, e.g., funding.
Iverson et al. 2023[40]	Worldwide	Up to 2022	Systematic review of mental health or neurological diseases in amateur and professional athletes	Trauma, sport-related concussion, exposure to repetitive head impacts	Systematic review of 10 studies of former amateur athletes, 18 studies of former professional athletes	Articles selected based on criteria; risk of bias assessed using a modified version of Scottish Intercollegiate Guidelines Network criteria; assessed methodology and limitations of studies included in the systematic review.	No higher risk of mental health or neurological diseases in former amateur athletes with RHI exposure; potential higher risk of neurological disorders, such as ALS and dementia, in former professional athletes.	*Limitations*: Not stated. *Strengths*: Not stated.

Koeman et al. 2017[41]	Netherlands	1986-2003	ALS (n=76, M, n=60, F); controls (n=2,092, M, n=2,074, F)	Occupational exposures to solvents, pesticides, metals, ELF-EMF, electric shock	Prospective population-based, case-control	ALS deaths identified from Netherlands Cohort Study; baseline self-administered questionnaire; ISCO-88 coded jobs; JEMs assessed exposures; Cox proportional hazards models.	Ever holding job with high ELF-EMF exposure vs background HR 2.19 (95%CI 1.02-4.73) in males; highest tertile of cumulative ELF-EMF exposure vs background HR 1.93 (95%CI 1.05-3.55) in males; adjusted for education. HRs nonsignificant from electric shock, total, aromatic, and chlorinated solvents, metals, pesticides, insecticides, herbicides, fungicides.	*Limitations*: Used code for MND to identify ALS; ALS deaths were not ascertained but aligned with expected rate; only baseline occupational information available, but most would have retired shortly after; JEMs broadly categorize exposures. *Strengths*: Used JEMs, instead of self-reported exposure; extensive cohort information to address potential confounding; up to five jobs queried at baseline, covering most job history.
Korner et al. 2019[42]	Germany, Hannover	2016-2017	ALS (n=117); controls (n=93)	Lifestyle, environmental factors	Case-control	ALS cases enrolled from clinic; controls enrolled from case spouses, hospital staff, other acquaintances; interview.	No link of diet, smoking, physical activity, occupational factors to ALS risk or progression.	*Limitations*: Retrospective, interview-based, potential recall bias; difficulty of selecting controls. *Strengths*: Assessed impact on progression as well as risk.
Lee et al. 2020[43]	Australia	N/A	ALS (n=50); controls (n=40)	Formaldehyde	Case-control	ALS cases enrolled from Motor Neuron Disease clinic at the Royal Brisbane & Women's Hospital; Plasma formaldehyde quantified by detection assays and formaldehyde metabolites by MRM/MS.	Plasma formaldehyde levels higher in ALS versus controls; formaldehyde metabolite levels did not differ in ALS versus controls; no link in formaldehyde levels to ALS disability, disease duration, or age.	*Limitations:* Limited to one formaldehyde measurement; did not account for diurnal variation or collect data regarding possible formaldehyde exposures (*e.g.*, occupation or diet). *Strengths:* Not stated.
Lian et al. 2019[44]	China, Beijing	2013-2016	ALS (n=123); controls (n=239)	Lifestyle, environmental factors	Case-control	ALS cases enrolled from clinic; structured questionnaire; logistic regression models.	Head trauma (OR 4.045; 95%CI 1.185-13.807; p=0.026); low BMI (OR 1.341; 95%CI 1.202-1.496; p=0.000); mild activity (OR 1.363; 95%CI 1.073-1.731; p=0.011); moderate activity (OR 1.327; 95%CI 1.049-1.679; p=0.018); smoking (OR 0.471; 95%CI 0.272-0.818; p=0.007); reading (OR 0.795; 95%CI 0.677-0.932; p=0.005); severe activity (OR 0.800; 95%CI 0.666-0.960; p=0.016); in multivariate model adjusted for significant factors from univariate model.	*Limitations*: Not stated. *Strengths*: Not stated.
Luna et al. 2019[45]	France, Limousin	2000-2012	ALS (n=312), population (approx. 7 million)	Residential UHF-EMF exposure	Population-based	ALS registry (FRALim); ascertainment estimated by capture-recapture; address and GSM data; EMF exposure modeled; Poisson regression.	HRs nonsignificant in non-exposure vs higher exposure categories, adjusted for age, sex, clinical factors; significant trend in gradient effect between UHF-EMF exposure and ALS incidence; UHF-EMF non-exposure vs highest exposure category RR 1.78 (95%CI 1.28-2.48) in non-cumulative model and 1.83 (95%CI 1.32-2.54) in cumulative model.	*Limitations*: Full residential history unavailable, may have changed; UHF-EMF exposure hard to estimate, GSM antennas transmit signals continuously, but level depends on call volume; only unidirectional, not omnidirectional, antennas considered, underestimating UHF-EMF exposure; only network considered, without distinguishing antenna generation; modeling was 2-dimensional, but 3-dimensional more relevant in urban setting. *Strengths*: ALS cases ascertained; addresses geocoded; modeling accounted for age, sex; UFH-EMF exposure consistent with official French report; exposure censored to consider temporality criteria.

Malek et al. 2022[46]	USA	1993-2017	ALS (n=256, F); controls (n=2,486, F)	Air pollution	Nested case-control	ALS deaths identified from Women's Health Initiative cohort; geocoded addresses; US EPA Air Quality System data $PM_{2.5}$, PM_{10}, PM_{coarse}, NO_2, NO_x, SO_2, O_3; exposure modeled spatiotemporally; logistic regression models.	No significant link from air pollution on ALS risk.	*Limitations*: Participants all male and race/ethnicity not representative of general population; significant missing data; exposure data not available for the very early and late ALS deaths; could not account for in-house exposures. *Strengths*: Prospectively collected baseline information.
McKay et al. 2021[47]	Worldwide	2000-2018	Systematic review of studies of ALS cases vs controls	Military service	Systematic review of 19 studies published up to 2018	Systematic review, assessed quality of included meta-analyses by A MeaSurement Tool to Assess systematic Reviews and observational studies by the Newcastle-Ottawa Scale.	Systematic review suggests a possible risk of ALS from military service, but limited evidence overall due to small sample sizes and inadequate follow-up time.	*Limitations*: Included studies small, mostly of males of European descent with short follow-up, may have survivor bias; none of the included studies explored cumulative risk scores. *Strengths*: Search of 3 large databases, screened by multiple trained reviewers; publication bias possible, but half of included studies reported null findings.
Mitsumoto et al. 2022[48]	USA	Survival assessed up to 2020	ALS (n=103); sibling controls (n=40); population controls (n=67)	Occupational exposures	Case-control	ALS cases enrolled from CDC National ALS Registry through ATSDR Risk Epidemiologic Study of ALS; structured interview; oxidative stress measured from fasting urine; logistic regression models.	Exposure to lead (OR 2.3; 95%CI 1.1- 4.6;), agricultural chemicals (OR 2.4, 95%CI 1.2-4.6), both lead/agricultural chemicals (OR 7.2; 95%CI 2.0- 26.1) vs pooled controls, adjusted for age. Urine oxidative stress marker significantly higher in ALS, but not linked to lead or agricultural chemical exposure.	*Limitations*: Possible selection bias and unknown generalizability to entire ALS population; did not adjust for many covariates; telephone-based interview time-consuming, may have deterred participation; exposures coded by one person, potential for systematic misclassification. *Strengths*: Broad geographic range; exposures coded by one person, consistency in ratings.
Myung et al. 2019[49]	South Korea	2008-2014	ALS (n=617)	Air pollution	Time-stratified case-crossover	Database of emergency department information in South Korea; air monitoring for $PM_{2.5}$, PM_{10}, NO_2, SO_2, O_3, CO; logistic regression models; single lag and moving average lag model.	ALS symptom exacerbation linked to IQR increase in $PM_{2.5}$ (OR 1.21; 95%CI 1.08-1.35), PM_{10} (OR 1.13; 95%CI 1.02-1.25), SO_2 (OR 1.19; 95%CI 1.01-1.41), CO (OR 1.19, 95%CI 1.03-1.36); adjusted for ambient temperature, relative humidity, air pressure, influenza epidemics, holidays.	*Limitations*: Aggregated city-level air pollution to estimate exposure; did not examine long-term exposure; did not assess relevant risk factors, e.g., smoking or occupations, or other confounders; potential misclassification bias from relying on recorded information to identify ALS cases. *Strengths*: Assessed all regulated, common air pollutants; case-crossover design adjusted time-invariant characteristics, e.g., genetics, slowly varying factors.
Nunez et al. 2022[50]	USA, New York	2000-2014	5,655 ALS-related hospitalizations	Air pollution ($PM_{2.5}$)	Observational	Hospitalization data; $PM_{2.5}$ (black carbon, nitrate, sulfate, organic matter, sea salt, soil mass).	$PM_{2.5}$ organic matter rate ratio 1.17 (95%CI 1.11-1.24, per SD increase), $PM_{2.5}$ soil rate ratio 0.91 (95%CI 0.86-0.97) for ALS hospitalizations, adjusted for total $PM_{2.5}$ mass and temporal and geographical confounders.	*Limitations*: Did not perform individual-level time-to-event analysis; limited to county-level analysis; did not assess participant change of address; modeled exposures, did not measure; did not evaluate potential pollutant interactions or additive effects; data may not have captured aggravated cases that did not seek hospitalization. *Strengths*: Assessed $PM_{2.5}$ subtypes over the long-term.

Parks et al. 2022[51]	Denmark	1989-2013	ALS (n=3,937); controls (n=19,333)	Traffic-related air pollution	Population-based, case-control	ALS cases identified from Danish National Patient Register; ascertained cases; addresses obtained; average exposures to elemental carbon, NO_x, CO, $PM_{2.5}$ modeled spatiotemporally 1-, 5-, 10-y pre-ALS diagnosis.	ALS linked to SD increase in 5-y average levels to elemental carbon odds 11.5% (95%ICr -1.0%, 25.6%), NO_x odds -4.6% (95%ICr 18.1%, 8.9%), CO odds -3.2% (95%ICr 14.4%, 10.0%), but not to non-elemental carbon fine particles odds 0.7%; adjusted for age, sex, birth year, vital status, SES, civil status, last reported place of residence, place of birth. No link of ALS to joint or average traffic pollution levels.	*Limitations*: Residual potential confounding from some unavailable variables, e.g., smoking; exposure modeled, not measured; cannot rule out some misclassified ALS cases; only marital status considered, not couple cohabitation. *Strengths*: Large dataset; estimated independent, joint, average traffic-related pollutant associations.
Peters et al. 2017[52]	Sweden	1991-2010	ALS (n=5,020); controls (n=25,100)	Occupational exposures	Nested case-control	ALS cases identified from National Patient Register; occupational history from Swedish Censuses (1970, 1980, 1990); JEMs assessed exposures; logistic regression models.	Precision-tool manufacturing (OR 1.68; 95%CI 1.11-2.52); glass, pottery, tile work (OR 1.76; 95%CI 1.03-3.00); textile work (OR 0.44; 95%CI 0.21-0.91). No ALS link to any examined occupational exposure, except at younger age (<65 y) formaldehyde (OR 1.29; 95%CI 1.00- 1.65) and methylene chloride (OR 0.49; 95%CI 0.26-0.93); adjusted for age, sex.	*Limitations*: Occupation information from 10 y intervals; no information on occupational exposure variation within occupations; different occupational exposures combinations may exist in different occupations; included MND codes with ALS cases. *Strengths*: Large, nationwide, with prospectively collected occupation.
Peters et al. 2019[53]	Ireland, Italy, Netherlands	2010-2015	ALS (n=1,323); controls (n=2,704)	ELF-EMF, electric shock	Pooled population-based, case-control	ALS cases from Euro-MOTOR; replication in ALS cases from the Prospective ALS Study in the Netherlands; lifetime occupational, lifestyle history by structured questionnaire; ISCO-88 coded jobs; JEMs assessed exposures; logistic regression models; sensitivity analysis excluding *C9orf72* carriers.	Ever exposed ELF-EMF unadjusted OR 1.16 (95%CI 1.01-1.33), but nonsignificant in adjusted OR 1.10 (95%CI 0.95-1.28), both unadjusted and adjusted OR nonsignificant in replication cohort; ever exposed electric shock unadjusted OR 1.23 (95%CI 1.05-1.43), remained significant in adjusted OR 1.19 (95%CI 1.01-1.40), both unadjusted and adjusted OR nonsignificant in replication cohort. Adjusted OR were for age, sex, smoking, alcohol, education, study center.	*Limitations*: Possible recall bias, mitigated by using JEMs; possible selection bias since rapidly progressing ALS cases may be less likely to participate; risk from ever exposure to ELF-EMF and electric shock may be surrogates of other relevant exposures; some heterogeneity present in educational level. *Strengths*: Relatively large study; accounted for full occupational history; adjusted for possibly confounding lifestyle factors.
Peters et al. 2020[54]	Ireland, Italy, Netherlands	2010-2015	ALS (n=1,410); controls (n=2,616)	Smoking	Pooled population-based, case-control	ALS cases from Euro-MOTOR; investigator led interviews in Ireland, Italy; self-administered questionnaire in Netherlands with telephone follow-up to complete or clarify data when necessary; logistic regression models.	Pack-years (OR 1.26; 95%CI 1.03-1.54) for highest quartile vs never smokers, adjusted for age, sex, alcohol, education, center, driven by smoking duration (ptrend=0.001) rather than intensity (ptrend=0.86), but duration trend did not persist after adjusting for time-since-quitting. Time-since-quitting inversely linked to ALS (ptrend<0.0001). Excess OR decreased with time-since-quitting smoking, until about 10 y before disease onset.	*Limitations*: Controls more educated but *post hoc* matching found residual confounding unlikely; potential bias in cases from less likely participation of fast progressors; did not adjust for premorbid BMI, a possible confounder. *Strengths*: Population-based controls to limit selection bias; included clinically confirmed ALS cases; available detailed lifetime smoking history; excess OR model disentangled duration and intensity; sensitivity analysis of *C9orf72* status.
Peters et al. 2021[55]	Europe	1993-1999	ALS (n=107); controls (n=319)	Blood metals	Prospective, nested case-control	ALS deaths identified from European Prospective Investigation into Cancer and Nutrition cohort; age, sex, and study center-matched controls; metals measured in erythrocyte fraction of blood; logistic regression models.	Presymptomatic ALS linked to blood cadmium (OR 2.04; 95%CI 1.08-3.87), and lead (OR 1.89; 95%CI 0.97-3.67) but not to arsenic, copper, manganese, mercury, selenium; zinc protective (OR 0.50; 95%CI 0.27-0.94).	*Limitations*: Could not ascertain all included ALS cases were presymptomatic; exposure reflects a window of approx. 120 days around the time blood was collected. *Strengths*: Prospective; assessed exposures in biosamples; lifestyle factors collected prior to disease onset.

Phelps et al. 2022[56]	USA, Indiana	1964-1980	216 living players; 447 total players; controls (n=638)	College American football	Cohort	Living and deceased football players from University of Notre Dame; controls from Health and Retirement Study; online survey.	ALS SMR 2.93 (95%CI 0.36-10.59), based on age, sex, race, using US male mortality rates (1960-2014) for 119 cause-of-death categories.	*Limitations*: Homogenous cohort limiting generalizability; included participants from one era, though sports dynamics have changed; response rate moderate, potentially biasing, though sensitivity analysis found no effect on outcome. *Strengths*: Well-characterized population, matched controls from the general population.
Pupillo et al. 2018[57]	France, Ireland, Italy, Serbia, United Kingdom	2008-2012	ALS (n=575); controls (n=1,150)	Trauma	Population-based, case-control	Newly diagnosed ALS cases attending centers from EURALS Consortium; trained investigator led structured questionnaire; logistic regression models.	Trauma leading to disability OR 1.47 (95%CI 1.08-1.99; p=0.0150); head trauma leading to functional disability OR 2.04 (95%CI 1.18-3.54; p=0.0106); adjusted for age, sex, BMI, smoking, alcohol, education, coffee, physical activity type (leisure/ work/ sport), interviewee (case/proxy).	*Limitations*: Study population representative of European population-based registries; exposures five years before symptom onset censored to eliminate potential from reverse causation; highly adjusted. *Strengths*: Relatively few cases by subcategory; cannot exclude recall bias; interviewers were not blinded, possibly leading to overemphasis of traumatic events in cases; method to assess trauma unvalidated; proxy was interviewed instead of case in instances; although standardized, interview may have varied by country; did not assess genetic profile or trauma biomarker.
Pupillo et al. 2020[58]	Italy	1959-2018	ALS (n=34)	Soccer	Cohort	Cohort built from annual almanacs; ALS cases identified by multiple sources; diagnosis confirmed if by 2 sources; estimated expected mortality in general Italian population and in general Italian ALS population.	Expected cases were 17.8; SIR 1.91 (95%CI 1.32-2.67) in whole cohort; SIR 4.66 (95%CI 2.66-7.57) in participants aged less than 45 y. Mean age at diagnosis was 45.0 y vs 65.2 y in the general population.	*Limitations*: Medical details examined for only 18 cases; diagnosis age not available in some cases, was estimated; SIR used Lombardy 1998-2002 data as reference but study had cases from all Italian regions 1959-2000; lacking a registry, may have under ascertained cases; person-years exposure estimated; mortality rates in soccer players may differ from the general population. *Strengths*: Cases verified by 2 sources.
Rooney et al. 2016[59]	Ireland	1995-2013	ALS (n=1,701)	Soil constituents	Observational	ALS cases ascertained from Irish ALS registry; 45 soil constituents from the National Soils Database from the Irish EPA at 1,310 sites; Bayesian spatial smoothing by Besag-York-Mollié model.	No significant link from 45 soil constituents, including various metals, on ALS risk.	*Limitations*: Modeling assumed area level exposure linked to population risk, residential exposure, and individual exposure; did not account for other contributing variables, e.g., genetics. *Strengths*: Not stated.

Russell et al. 2021[60]	Scotland	Professional soccer players born between 1900-1977	Professional soccer players (n=7,676); general population controls (n=23,078)	Professional soccer	Cohort	Former professional soccer players from Scottish Football Museum and individual league club archives; population controls matched using community health index database; outcomes determined by records linkage to Scottish Morbidity Record, death certification data (available from 1981-2016), prescribing data (available from 2009-2016).	Neurodegenerative disease diagnoses were n=386 in former soccer players and n=366 in matched population controls; risk of neurodegenerative disease highest for defenders (HR 4.98; 95%CI 3.18-7.79) and players with professional careers longer than 15 years (HR 5.20; 95%CI 3.17-8.51) and lowest for goalkeepers (HR 1.83; 95%CI 0.93-3.60).	*Limitations:* Potential participation of control individuals in soccer; lack of information regarding extent of soccer participation outside of professional space. *Strengths:* Inclusion of all available health records to identify neurodegenerative disease cases; large cohort size; outcomes matched against general population for age, sex, and socioeconomic status.
Sagiraju et al. 2020[61]	USA	2002-2015	ALS (n=139 definite; n=87 possible); military controls (n=1,149,374)	Military service	Case-control	ALS US veterans deployed post-9/11 from Veterans Health Administration with demographic, clinical information; logistic regression models; Cox proportional hazards models.	ALS prevalence 19.7 per 100,000; higher in Air Force (33.2 per 100,000) vs other service branches; higher in tactical operation officers (51.8 per 100,000) and health care workers (29.1 per 100,000) vs general and administrative officers.	*Limitations*: Not stated. *Strengths*: Not stated.
Seals et al. 2017[62]	Denmark	1982-2009	ALS (n=3,650); controls (n=14,600)	Cumulative occupational formaldehyde exposure	Population-based, case-control	ALS cases from the Danish National Patient Registry; demographic data and occupation history obtained from the Danish Pension Fund; JEMs assessed exposures; logistic regression models.	Formaldehyde exposure linked to ALS risk (OR 1.3; 95%CI 1.2-1.4), adjusted for age, sex, calendar date, SES, marital status, residence.	*Limitations*: Small risk of case misclassification; JEMs do not account for possible exposure differences within same job type; cannot rule out confounding by unobserved factors, e.g., smoking. *Strengths*: Prospectively collected occupation information; estimated exposures using JEMs, instead of relying on self-reported exposure.
Seelen et al. 2017[63]	Netherlands	2006-2013	ALS (n=917); controls (n=2,662)	Traffic-related air pollution	Population-based, case-control	ALS cases from Prospective ALS study in Netherlands; European Study of Cohorts for Air Pollution Effects cohort; air monitoring for $PM_{2.5}$, PM_{10}, PM_{coarse}, NO_2, NO_x; participant address and land use regression models; logistic regression models.	Upper quartile exposure risks, $PM_{2.5}$ (OR 1.57; 95%CI 1.14-2.17), NO_2 (OR 1.55; 95%CI 1.08-2.21); adjusted for age, sex, BMI, smoking, alcohol, education, SES, urbanization.	*Limitations*: Retrospective; uncertainty in exposure estimates; air pollution data only available from 1992 onwards. *Strengths*: Assessed multiple pollutants.
Su et al. 2016[64]	USA, Michigan	2011-2014	ALS (n=156); controls (n=128)	Plasma POPs	Case-control	ALS cases enrolled from clinic; self-administered questionnaire; POPs measured in plasma; JEMs assessed exposures; logistic regression models.	Plasma pentachlorobenzene (OR 2.57; 95%CI 1.31-5.02), cis-chlordane (OR 6.51; 95%CI 2.05-20.73), PCB-151 (OR 1.66; 95%CI 1.03-2.67); adjusted for age, sex, education.	*Limitations*: Retrospective; did not assess lifelong exposure. *Strengths*: Assessed exposures in biosamples.

Vinceti et al. 2017[65]	Italy, 4 provinces in northern and southern Italy	1998-2011	ALS (n=703); controls (n=2,737)	Non-occupational pesticide exposure through proximity to agricultural crop	Population-based, case-control	ALS registry (ERRALS), hospital discharge records, death certificate files, drug prescription directories; ascertained residential address of ALS cases at diagnosis date; remote sensing, land use, residential history using a geographical information system.	No link of proximity to agricultural crop to ALS risk.	*Limitations*: Used current and "official" address for ALS cases; hard to account for all factors related to estimating exposure, e.g., time spent home, meteorological events; did not assess potential occupational exposures; limited information on other environmental, lifestyle, genetic factors, so possible residual confounding. *Strengths*: Included two agricultural areas with different lifestyle and environmental characteristics; used validated indicators of pesticide exposure; study radius defined by crop acreage; accounted for long-term prior pesticide exposure; using public data avoided some selection bias.
Vinceti et al. 2017[66]	Italy, 4 provinces in northern and southern Italy	1998-2011	ALS (n=703); controls (n=2,737)	Non-occupational exposure to high-voltage power lines	Population-based, case-control	ALS registry (ERRALS), hospital discharge records, death certificate files, drug prescription directories; ascertained residential address of ALS cases at diagnosis date; modeled exposure based on geodata on high-voltage power lines (≥132 kV) during 1998-2011; logistic regression models.	No link of EMF exposure from high-voltage power lines to ALS risk.	*Limitations*: Observational, cannot rule out possible confounding; model to assess EMF exposure estimates some power line and residence dimensions, but minor errors likely averaged; did not collect historical residence prior to 1979, omitting earlier exposure relevant to a disease with a possible latent phase; did not collect information about occupational exposure to EMFs. *Strengths*: Assessed exposure, including long-term, using a validated model and geodata of power lines, not solely based on distance to case residence.
Vinceti et al. 2017[67]	Italy, Emilia-Romagna	1998-2011	ALS (n=38); controls (n=38)	CSF metals	Prospective	ALS cases enrolled from clinic; age- and sex-matched controls from clinic; metals measured in CSF; logistic regression models.	ALS vs controls had higher median lead (155 vs 132 ng/L) but lower median cadmium (36 vs 72 ng/L) and mercury (196 vs 217 ng/L). No significant OR in highest tertile of exposure. Overall, no link of CSF metals to ALS risk.	*Limitations*: Small study; did not assess lifelong exposure. *Strengths*: Assessed exposures in biosamples linked to the nervous system.
Vinceti et al. 2017[68]	Italy, Emilia-Romagna	1994-2013	ALS (n=38); controls (n=38)	CSF POPs	Prospective	ALS cases enrolled from clinic; age- and sex-matched controls from clinic; POPs measured in CSF; logistic regression models.	No link of CSF OCPs, PCBs, PAHs to ALS risk.	*Limitations*: Small study; did not assess lifelong exposure. *Strengths*: Assessed exposures in biosamples linked to the nervous system.
Visser et al. 2019[69]	Ireland, Italy, Netherlands	2011-2014	ALS (n=1,557); controls (n=2,922)	Occupational exposures	Population-based, case-control	ALS cases from Euro-MOTOR; questionnaire; ISCO coded jobs; JEMs assessed exposures; logistic regression models.	Silica dust (OR 1.73; 95%CI 1.28-2.33), organic dust (OR 1.33; 95%CI 1.11-1.59); adjusted for age, sex, smoking, alcohol, education, cohort, background exposure as reference category.	*Limitations*: Questionnaire-based, possible recall bias; JEMs do not account for possible exposure differences within same job type. *Strengths*: Participants blinded to hypothesis, questionnaire contained questions about other domains; assessed various regions characterized by distinct factors; estimated exposures using JEMs, instead of relying on self-reported exposure.

Walt et al. 2018[70]	USA	Since 2006	155 ALS brain specimens	Trauma, CTE	Case-only	Brain specimens banked in the Veterans Affairs Biorepository Brain Bank	Of 155 specimens, 9 (5.8%) had ALS+CTE, linked to TBI history, duty in first Persian Gulf War, more severe tau pathology, bulbar onset, behavioral/mood changes; most common exposures to head impacts included contact sports and military service.	*Limitations*: Initial enrollment passive, may introduce bias; TBI / RHI assessed retrospectively; generalizability to general population uncertain; relatively few participants with ALS+CTE, limits power. *Strengths*: Not stated.
Wang et al. 2017[71]	Worldwide	1970-2016	Meta-analysis and systematic review of studies of ALS vs controls	Lifestyle, occupational factors	Meta-analysis and systematic review of 133 studies published up to 2016	Meta-analysis assessed heterogeneity and bias and extracted relevant data.	Exposure to lead (OR 1.72; 95%CI 1.33-2.23), metals (OR 1.69; 95%CI 1.13-2.52), pesticides (OR 1.48; 95%CI 1.18-1.86), agricultural chemicals (OR 3.08; 95%CI 1.43-6.63), solvents (OR 1.43; 95%CI 1.10-1.86), prior trauma (OR 1.73; 95%CI 1.43-2.09), electric shock (OR 3.27; 95%CI 1.87-5.73).	*Limitations*: Not stated. *Strengths*: Not stated.
Yu et al. 2021[72]	Netherlands	2006-2018	ALS (n=1,636); controls (n=4,024)	Ultrafine particles, PM	Population-based, case-control	ALS cases and controls enrolled from the Prospective ALS in the Netherlands study; exposure estimated using geocoded residential addresses and land use regression models developed within the European Study of Cohorts for Air Pollution Effects and Exposomics projects; logistic regression models.	Strongest links to $PM_{\leq 2.5}$ (OR 1.19; 95%CI 1.10-1.28), NO_2 (OR 1.25; 95%CI 1.15-1.34), NO_x (OR 1.14; 95%CI 1.07-1.22), adjusted for age (at diagnosis for cases, at recruitment for controls), sex, BMI, smoking, alcohol, education, SES.	*Limitations*: Used disease onset date in cases to estimate exposure, differing to estimates for controls; used pollutant data from 2010 to 2014 to estimate historical exposures. *Strengths*: Not stated.

BMI, body mass index; CI, confidence interval; CO, carbon monoxide; CSF, cerebrospinal fluid; CTE, chronic traumatic encephalopathy; DDE dichlorodiphenyldichloroethylene; ELF, extremely low-frequency; EMF, electromagnetic magnetic field; EPA, Environmental Protection Agency; ERRALS, Emilia-Romagna Registry for ALS; ERS, environmental risk score; EURALS, European amyotrophic lateral sclerosis; Euro-MOTOR, European Multidisciplinary ALS Network Identification to Cure Motor Neurone Degeneration; F, female; FRALim, ALS French register in Limousin; GRADE, grading of recommendations, assessment, development and evaluations; GSM, Global System for Mobile communication antennas; GWAS, genome-wide association study; HR, hazard ratio; ICr, credibility intervals; IQR, interquartile range; ISCO-88, International Standard Classification of Occupations 1988; JEM, job exposure matrix; M, male; MND, motor neuron disease; MOOSE, meta-analysis of observational studies in epidemiology; N/A, not applicable; NO, nitric oxide; NO_2, nitrogen dioxide; NO_x, nitrogen oxides; OCP, organochlorine pesticide; OR, odds ratio; PAH, polycyclic aromatic hydrocarbon; PARALS, Piedmont and Valle d'Aosta Register for ALS; PBDE, polybrominated diphenyl ether; PCB, polychlorinated biphenyl; PM, particulate matter; POP, persistent organic pollutant; RHI, repetitive head impact; RR, relative risk; SD, standard deviation; SES, socioeconomic status; SIR, standardized incidence ratio; SMR, standardized morbidity ratio; SNP, single nucleotide polymorphism; SO_2, sulfur dioxide; TBI, traumatic brain injury; VOC, volatile organic compounds; UHF, ultra-high frequency.

Supplementary Table S3. Summary of ALS exposome studies - microbiome, inflammation, immunity, and new treatment

Results from a PubMed search of English language studies dated up to Jun 22, 2023, identified with the search terms of "amyotrophic lateral sclerosis" and, in turn "clinical trial diet", "fecal microbiota transplant", "FMT", "infectious agent", "ketogenic diet", "immunity environment", "immunity exposome", "immunity exposure", "microbiome", "microbiome risk", "neuroinflammation environment", "neuroinflammation exposome", "neuroinflammation exposure", "probiotic". Studies were selected to show the range of exposures in larger populations and using novel techniques.

Entries arranged alphabetically.

*Incomplete years of study enrollment rounded up to the indicated year.

**Limitations and strengths as cited by papers.

Study	Country & region	Time*	Study participants	Exposures examined	Study design	Study tools	Study findings	Study limitations/strengths**
Brenner et al. 2018[73]	Germany	2015-2016	ALS (n=25); controls (n=32)	Microbiome	Case-control	ALS case enrollment not specified; fecal 16S rRNA sequencing; hypervariable tag sequencing for phylotype profiles; metagenome prediction.	Diversity and abundance of bacterial taxa did not differ in ALS versus control groups.	*Limitations:* Lack of diversity in study population. *Strengths:* Selected ALS patients with high revised ALS functional rating scale without bulbar or respiratory symptoms; larger study sample than previous studies.
Di Gioia et al. 2020[74]	Italy, Novara	2016-2017	ALS (n=50); controls (n=50)	Microbiome	Prospective, longitudinal case-control	ALS cases enrolled from clinic; fecal 16S rRNA sequencing; OTUs; probiotic treatment.	ALS gut microbiome differs vs controls, independent of disability degree. ALS gut microbiome composition evolves with disease progression, with fewer OTUs; 6-month probiotic treatment influenced gut microbiome composition but did not make it resemble controls nor affect disease progression.	*Limitations*: 20 cases did not complete the study and one died, restricting group size; did not consider differing lifestyles on intra-individual variability; analysis by ALS phenotype subgroup not performed. *Strengths*: Not stated.
Dorst et al. 2020[75]	Germany	2015-2018	ALS (n=80, females; n=121, males)	Diet	Prospective, parallel-group, placebo-controlled	ALS cases enrolled from sites of the network of German motor neuron disease centers; blood samples collected during LIPCAL-ALS study; serum NfL concentrations from single molecule array platform; Kaplan-Meier plots.	NfL serum levels positively linked to progression rate; HCFD linked to lower in NfL serum levels; HCFD prolonged survival of patients with high NfL serum levels versus placebo.	*Limitations:* Not stated. *Strengths:* Not stated.
Erber et al. 2020[76]	Worldwide	Up to 2019	Systematic review of studies of ALS cases and animal studies	Microbiome	Systematic review of 6 human and 6 animal studies published up to 2019	Studies related to gut microbiome in ALS patients or ALS animal models screened using PRISMA guidelines.	Gut microbiome changes linked to ALS risk and potentially progression.	*Limitations:* Not stated. *Strengths:* Not stated.

Fitzgerald et al. 2014[77]	USA	Various cohorts	Male (n=522,968); female (n=479,114)	Diet, PUFAs	Prospective, longitudinal	Cohort data from HPFS since 1986; NHS since 1976; CPS-II Nutrition since 1992; MEC since 1993-1996; NIH-AARP since 1995-1996; diet assessed by food frequency questionnaire; risk ratios estimated by Cox proportional hazards regression.	ALS cases identified, n=995; higher ω-3 PUFA intake lowered ALS risk; link between ω-3 PUFA and ALS risk due to α-linolenic acid and marine ω-3 PUFA consumption; intake of ω-6 PUFA did not affect ALS risk.	*Limitations:* Used deaths versus incidence; lack of genetic and family history information; potential error in nutrient intake estimations. *Strengths:* Prospective; large study size; used validated dietary assessments; extended follow-up; ALS patient diversity.
Goncharova et al. 2021[78]	Worldwide	2010-2020	Systematic review of studies of ALS cases versus controls	Diet, nutrients	Systematic review of 39 studies published up to 2020	Systematic review identified 39 publications that included randomized clinical trials, clinical cases, meta-analyses of ALS patients and animal models.	Systematic review suggested that vitamin B12, E, C, B1, B9, D, B2, B6, A, and B7 protect against ALS onset; vitamins and ketogenic diet with ALS therapy reduces progression of motor neuron degeneration and slows rate of disease progression; nutrient selection must be personalized.	*Limitations:* Possible some publications were missed; did not explore potential sex differences; did not explore role of nutrigenetics in nutrient absorption or microbiota in nutrient synthesis. *Strengths:* Not stated.
Gong et al. 2022[79]	China, Wuhan	2020-2021	ALS (n=35); controls (n=35)	Microbiome	Case-control	ALS cases enrolled from clinic; fecal 16S rRNA sequencing; cognitive function from Edinburgh Cognitive and Behavioral ALS Screen; metabolite mapping.	Gut microbiome and metabolome profile differed in ALS cases with and without cognitive impairment; altered bile acid profile linked to cognitive impairment in ALS.	*Limitations:* Small sample size; did not measure bile acid metabolites in serum and cerebrospinal fluid; not longitudinal. *Strengths*: First connection between gut microbiota and cognitive impairment.
Goutman et al. 2022[80]	USA, Michigan	2011-2014	ALS (cohort 1, n=125; cohort 2, n=225); controls (cohort 1, n=71; cohort 2, n=104)	Metabolome	Case-control	ALS cases enrolled from clinic; non-fasted plasma samples; Wilcoxon assessed differential metabolites in ALS versus controls; adjusted logistic regression and partial least squares-discriminant analysis; group lasso for sub-pathway level difference; metabolomics pathway enrichment analysis.	Lipid sub-pathways were altered in ALS versus controls in both cohorts; lipid sub-pathways differed in ALS females versus males.	*Limitations:* Used non-fasted plasma; no causality among observed metabolic sub-pathways; metabolome not correlated with progression; presence of batch effects. *Strengths:* Extensive number of detected and identified metabolites; large cohort size; validation of original cohort; used several statistical methods.
Hertzberg et al. 2022[81]	USA, Georgia	N/A	ALS (n=10); spousal partner as controls (n=10); control couples without ALS (n=20)	Microbiome	Case-control	ALS cases enrolled from clinic; 16S rRNA sequencing of rectal swab; inflammatory markers in plasma; ASVs; functional analysis.	ALS gut microbiome more diverse and deficient in *Prevotella* spp. vs spouses, but no differences in inflammatory markers. No differences in microbiome between partners in healthy couples. ALS microbiome had lower activity in several metabolic pathways, including carbon and butyrate metabolism.	*Limitations*: Cross-sectional, no link to progression; small sample size; bias towards male sex in ALS group; lack of detailed diet information. *Strengths*: Spouses cohabitated, which affects microbiome; use of healthy volunteer couples as second control.
Hop et al. 2022[82]	N/A	N/A	ALS (n=6,763); controls (n=2,943)	DNA methylation as a surrogate of past exposures	Epigenome-wide association study	Samples collected across 14 studies; genomic DNA isolated from blood; DNA methylation quantified by Illumina 450 k and EPIC arrays; pathway enrichment analysis; multivariate Cox regression model.	Identified 45 differentially methylated positions linked to ALS enriched for pathways related to metabolism, cholesterol biosynthesis, immunity; HDL, cholesterol, BMI, white blood cell proportions, and alcohol intake linked to ALS; cholesterol biosynthesis potentially causally related to ALS; DNA methylation patterns linked to survival.	*Limitations:* Cannot conclude causality; DNA collected from blood not brain; stringently adjusted for confounding, may block biological signals. *Strengths:* Using DNA methylation as proxy for risk factors removes recall bias and ineffective data capture by self-report; large sample size.

Huisman et al. 2015[83]	Netherlands	2006-2011	ALS (n=674); controls (n=2093)	Diet, BMI	Population-based, case-control	ALS cases enrolled by neurologists, rehabilitation physicians, the Dutch Neuromuscular Patient Association, and ALS study website; food frequency questionnaire for consumption; binary logistic regression for ORs; Cox proportional hazards regression for survival.	Presymptomatic total daily energy intake higher in ALS versus controls; presymptomatic BMI lower in ALS versus controls; higher premorbid total fat intake (OR 1.14; 95%CI 1.07-1.23), saturated fat (OR 1.43; 95% CI 1.25-1.64), trans-fatty acids (OR 1.03; 95%CI 1.01-1.05), cholesterol (OR 1.08; 95% CI 1.05-1.12) raised ALS risk; higher alcohol intake (OR 0.91; 95% 0.84-0.99) lowered ALS risk.	*Limitations:* Potential recall bias; questionnaire completed after symptom onset and diagnosis. *Strengths:* Large sample size; used validated questionnaire; control population representative of general population; corrected for multiple comparisons and possible confounders.
Jin et al. 2014[84]	Korea	2011-2012	ALS (n=77); controls (n=77)	Diet, fruit	Case-control	ALS cases enrolled from ALS Clinic, Hanyang University Seoul Hospital; food frequency questionnaire interviews for dietary intake; multivariate logistic regression analysis for ORs.	Beef, fish, fast food, total calcium, and animal calcium intake positively linked to ALS risk; plant calcium and beta-carotene intake negatively linked to ALS risk; vegetable and other antioxidant nutrient intake did not affect ALS risk.	*Limitations:* Small sample size; cross-sectional; questionnaire completed after symptom onset; surrogate completion of questionnaires in late-stage ALS cases; potential recall bias and residual confounding. *Strengths:* Not stated.
Kim et al. 2022[85]	USA, Texas	N/A	ALS (n=36); controls (n=20)	Microbiome	Case-control	ALS cases enrolled from South Texas ALS Clinic; fecal and saliva 16S rRNA sequencing; microbial translocation by blood LBP and 16S rRDA levels; OTU richness.	Gut dysbiosis in spinal onset ALS linked to higher microbial translocation to blood; oral dysbiosis in bulbar onset ALS linked to higher microbial translocation to blood; higher microbial translocation linked to more severe symptoms.	*Limitations*: Not stated. *Strengths:* Not stated.
Ludolph et al. 2020[86]	Germany	2015-2018	ALS (n=80, females; n=121, males)	Diet	Prospective, parallel-group, placebo-controlled	ALS cases enrolled from sites of the network of German motor neuron disease centers; received HCFD supplement or placebo; survival time as primary endpoint; change in function, body weight, and SVC as secondary endpoints.	HCFD did not prolong survival for total ALS population; post hoc analysis indicated HCFD prolonged survival in fast-progressing subgroup.	*Limitations:* Studies examining dose-response relationships and impact of food composition on efficacy and tolerability are needed; high dropout rate. *Strengths:* Not stated.
Mazzini et al. 2018[87]	Italy	N/A	ALS (n=50); controls (n=50)	Microbiome	Double-blind, case-control clinical trial	Fecal 16S rDNA sequencing; bacterial species quantified by qPCR; total eubacteria and yeast by denaturing gradient gel electrophoresis; patients treated with microorganisms or placebo for 6 mo.	High abundance of *E. coli* and enterobacteria and low abundance of total yeast in ALS cases; differences in bacterial profiles between ALS cases versus controls; bacteriotherapy currently in progress.	*Limitations:* Not stated. *Strengths:* Not stated.
Michels et al. 2023[88]	Germany, Swabia	2010-2014	ALS (n=336); controls (n=487)	Diet, lipids	Population-based, case-control	ALS cases enrolled from ALS registry Swabia; serum lipid levels measured photometrically (triglycerides) and enzymatically (HDL, LDL, total cholesterol); questionnaire-based interview to collect covariates; conditional logistic regression models for odds ratio.	High levels total cholesterol positively linked to ALS risk (OR 1.60; 95%CI 1.03-2.49); higher HDL (HR 1.72; 95%CI 1.19-2.50) and LDL (HR 1.58; 95%CI 1.11-2.26) linked to shorter ALS survival; higher triglycerides linked to longer survival (HR 0.68; 95%CI 0.48-0.96).	*Limitations:* Did not obtain genetic background data. *Strengths:* Large, prospective, population-based; matched sex, age, area of residency; used prospective long-term data; potential confounders assessed by stepwise adjusted analysis.
Niccolai et al. 2021[89]	Italy, Modena	2017-2020	ALS (n=19); controls (n=9)	Microbiome, inflammation	Case-control	ALS cases enrolled from the tertiary ALS Center in Modena; 16S rRNA sequencing; serum and fecal inflammatory cytokine levels from MixMatch Human kit.	Metabolome differed in cases versus controls and slowly progressive cases.	*Limitations:* Small cohort size. *Strengths*: Not stated.

Ngo et al. 2020[90]	Australia	2016-2018	MND (n=49); controls (n=51)	Microbiome	Case-control	ALS cases enrolled from clinic; fecal 16S rRNA sequencing; OTUs; whole-body composition; resting energy expenditure.	MND microbiome does not differ vs controls, matched for age, sex, BMI, though beta-diversity differences were present in some MND cases. Weight, BMI, metabolic and clinical features in MND cases did not correlate to microbiome. Greater risk of shorter MND survival with higher microbiome richness and diversity and Firmicutes to Bacteroidetes ratio.	*Limitations*: Mix of incident and prevalent ALS cases; used targeted 16S instead of whole genome sequencing; did not assess diet, which can impact gut microbiome. *Strengths*: Used latest 16S microbiome pipelines and range of approaches; assessed clinical outcomes.
Nicholson et al. 2021[91]	USA, Massachusetts	N/A	ALS (n=66); controls (n=61); neurodegenerative controls (n=12)	Microbiome	Case-control	ALS cases enrolled from clinic; fecal 16S rRNA sequencing; OTUs.	ALS microbiome lower in relative abundance butyrate-producing bacteria vs controls, adjusted for age, sex, constipation.	*Limitations*: Cross-sectional observational with residual possibility of confounding; did not assess diet, which can impact gut microbiome; females overrepresented in control vs ALS group. *Strengths*: Not stated.
Ning et al. 2022[92]	N/A	N/A	ALS (n=20,806); controls (n=59,804)	Microbiome	Mendelian randomization	GWAS of International Amyotrophic Lateral Sclerosis Genomics Consortium; microbiome from MiBioGen (n=18,340); metabolome from TwinsUK and KORA (n=7,824).	ALS linked through SNPs to higher levels of 2 genera (OR>1) and lower levels of 3 genera (OR<1) and to higher levels of 4 gut metabolites (OR>1). .	*Limitations*: Most findings nonsignificant after FDR, but Mendelian randomization can still detect causal relationships; 16S sequencing only to genus level; low cutoff of exposure-related SNPs (p<1×10–5); lacked data on various participant variables. *Strengths*: Large dataset; integrated analysis.
Okamoto et al. 2009[93]	Japan, Tokai	2000-2004	ALS (n=153); controls (n=306)	Diet, vegetables, fruits, antioxidants	Case-control	ALS cases enrolled from medical centers in the Tokai area of Japan; questionnaire for dietary history 3 years before diagnosis; multiple conditional logistic regression for OR.	Higher fruit and vegetable and fruit alone intake lowered ALS risk; beneficial link of vegetable intake to ALS; no dose-response relationship between beta-carotene, vitamin C, and vitamin E intake to ALS risk.	*Limitations:* Cases within 3 years of receiving diagnosis; potential survivor bias; portion of surveys completed by proxy respondents; survey completed after diagnosis. *Strengths:* Not stated.
Petimar et al. 2019[94]	Worldwide	Cohorts followed max of 12-24 years	Male (n=120,688); female (n=230,877)	Diet, caffeine	Pooled analyses of 8 prospective cohort studies	Prospective cohort studies from the Pooling Project of Prospective Studies of Diet and Cancer; food-frequency questionnaires for coffee, tea, and caffeine intake; Cox regression for risk ratios; random-effects model for pooled analyses.	ALS deaths identified, n=545; no association found between coffee, tea, or caffeine intake and ALS mortality.	*Limitations:* Limited power to detect modest links; did not assess duration/changes in caffeine intake, only baseline data available; potentially underestimated ALS cases. *Strengths:* Large study size; aggregated multiple cohorts, improved statistical power; reduced heterogeneity across studies.

Pupillo et al. 2018[95]	Italy, Lombardy, Piedmont and Aosta Valley, and Apulia	2011-2015	ALS (n=212); controls (n=212)	Diet	Population-based, case-control	ALS cases from the Euro-MOTOR collaboration; food intake habits determined by interview-based food-frequency questionnaires; macronutrients, micronutrients, fatty acids, and total energy estimated by Italian food composition database.	Coffee, tea (OR 0.29; 95%CI 0.14-0.60), whole bread (OR 0.55; 95%CI 0.31-0.99), raw vegetables (OR 0.25; 95%CI 0.13-0.52), citrus fruits (OR 0.49; 95%CI 0.25-0.97) lowered ALS risk; red meat (OR 2.96; 95%CI 1.46-5.99), pork/processed meat (OR 3.87; 95%CI 1.86-8.07), total protein (OR 2.96, 95%CI 1.08-8.10), animal protein (OR 2.91; 95%CI 1.33-6.38), sodium (OR 3.96; 95%CI 1.45-10.84), zinc (OR 2.78; 95%CI 1.01-7.83), glutamic acid (OR 3.63; 95%CI 1.08-12.2) raised ALS risk.	Limitations: Study population limited to Italy; potential recall bias and reverse causation. Strengths: Estimated intake of selected nutrients; large sample size; controls had similar dietary habits; role of food investigated during health status and in patients without a feeding tube.
Sun et al. 2019[96]	Sweden	2006-2013	ALS (n=2,484); controls (n=12,420)	Antibiotic use	Nested case-control	ALS cases from Swedish Patient Register, Migration Register, and causes of Death Register; Prescribed Drug Register for antibiotic prescription data; conditional logistic regression model for ORs.	Antibiotic use raised ALS risk, particularly use of more than two beta-lactamase sensitive penicillin prescriptions (OR 1.28; 95%CI 1.10-1.50).	*Limitations:* Potential residual confounding; antibiotic effect versus effect of underlying indication for antibiotic use; cannot determine causality; small subgroup analyses; lacked adherence to treatment data; registry did not include drugs prescribed during hospitalization; could not verity ALS diagnosis for all cases. *Strengths:* Large sample size; minimal selection and information biases.
Westenen g et al. 2021[97]	Netherlands	2006-2016	ALS C9+ (n=143); ALS C9- (n=1,322); controls (n=1,322)	Lifestyle factors	Longitudinal, population-based, case-control	ALS cases enrolled by neurologists, rehabilitation physicians, the Dutch Neuromuscular Patient Association, and the ALS Centrum website; structured questionnaires to assess BMI, physical activity, and smoking; mutation status determined using DNA extracted from blood.	Cigarette pack-years and daily energy intake at symptom onset higher in C9+ and C9- groups versus controls; current BMI and lifetime alcohol consumption lower in C9+ and C9- groups versus controls; median presymptomatic BMI lower in C9+ versus controls, but higher in C9- versus controls; BMI of C9+ group increased more slowly and was significantly lower versus controls; BMI of C9- group higher versus controls; causal effects of alcohol consumption and smoking on ALS in C9- group.	*Limitations:* Inability to reconstruct longitudinal trajectory for energy intake and alcohol consumption; unable to perform causal analyses for energy intake and physical activity; potential recall bias and confounding. *Strengths*: Not stated.
Wills et al. 2014[98]	USA	2009-2012	ALS control diet (n=6); ALS HC/HC (n=8); ALS HF/HC (n=6)	Diet	Double-blind, placebo-controlled, randomized phase 2 clinical trial	ALS cases enrolled from 12 USA participating centers randomly assigned to control diet, HC/HC, or HF/HC; diet via tube-feeding formula; primary outcomes safety and tolerability; Kaplan-Meier product-limit methods for survival curves.	HC/HC patients had fewer adverse events and deaths during follow-up versus HF/HC and control diet groups; fewer HC/HC patients discontinued the study due to adverse events versus other groups.	*Limitations:* Small study size; slow recruitment; malnourished participants with advanced disease; ALSFRS-R only measured twice during study. *Strengths:* Enteral nutritional supplements allowed tight control over calories administered; well-balanced groups; low risk of confounding.

Yu et al. 2020[99]	South Korea, Seoul	2011-2020	ALS (n=272; CSF samples, n=27)	Diet	Observational, case-only	ALS cases enrolled from the ALS clinic at Hanyang University Hospital; dietary fiber intake calculated from 24-h dietary recall survey; plasma nutritional markers measured; lumbar puncture and cytokine assay kits for CSF cytokine analysis.	Vegetable fiber intake linked to slower disease progression and longer survival; pro-inflammatory cytokine levels negatively linked to vegetable fiber intake in CSF.	*Limitations:* Data from a single hospital; fiber intake only estimated once; limited availability of CSF samples for analysis. *Strengths:* Not stated.
Zeng et al. 2020[100]	China, Hunan province	2018-2019	ALS (n=20); controls (n=20)	Fecal microbiome, metabolome	Case-control	ALS cases enrolled from clinic; fecal 16S rRNA sequencing; OTUs; shotgun sequencing; metabolomics.	ALS gut microbiome differs vs controls, with higher Bacteroidetes phylum and several genera and lower Firmicutes phylum and *Megamonas* genus. ALS microbiome had lower activity in several metabolic pathways, including lipids.	*Limitations*: Could not establish causality. *Strengths*: Not stated.
Zhang et al. 2022[101]	N/A	N/A	ALS (n=20,806); controls (n=59,804)	SNPs for microbiome, ALS	Mendelian randomization	GWAS dataset of ALS and the gut microbiome (FoCus, PopGen); bi-directional Mendelian randomization.	Two significant microbiome genera linked to ALS through SNPs: *OTU10032 unclassified Enterobacteriaceae Species-level OTU* (OR 1.04; 95%CI 1.01-1.07; p=0.011; linked to 2 SNPs, closest genes *AKAP3*, *SLC22A13*) and *Unclassified Acidaminococcaceae* (OR 1.02; 95%CI 1.01-1.04; p=0.009; linked to 4 SNPs, closest genes *ABCA13*, *C2orf83*, *LINC01137*, *SIX6*). Metabolite gamma-Glu-Phe OR 1.96 (95%CI 1.50-2.55; p=0.012).	*Limitations*: Used limited number of gut microbiota and ALS SNPs as instrumental variables; potential bias in Mendelian randomization analyses from population stratification; 16S sequencing only defines genera, limiting finer grained information. *Strengths*: Assessed gut genera and metabolites linked to ALS; used large GWAS dataset with bi-directional Mendelian randomization, minimizing confounding and reverse causation; sensitivity analyses indicate findings robustness.

95%CI, 95% confidence interval; ASV, amplicon sequence variant; bALS, bulbar-onset ALS; BMI, body mass index; C9+, *C9orf72* expansion mutation positive; C9-, *C9orf72* expansion mutation negative; CI, cognitive impairment; CPS-II, Cancer Prevention Study II Nutrition Cohort; CSF, cerebrospinal fluid; Euro-MOTOR, European Multidisciplinary ALS Network Identification to Cure Motor Neurone Degeneration; FA, formaldehyde; HCFD, high-caloric fatty diet; HC/HC, high-carbohydrate hypercaloric tube-fed diet; HDL, high-density lipoprotein; HF/HC, high-fat hypercaloric tube-fed diet; HPFS, Health Professionals Follow-up Study; HR, hazard ratio; LBP, lipopolysaccharide-binding protein; LC/MS, liquid chromatography-tandem mass spectrometry; LIPCAL-ALS study, lipids and calories for ALS study; MEC, Multiethnic Cohort Study; MND, motor neuron disease; MR, mendelian randomization; MRM/MS, multiple reaction monitoring mass spectrometry; MS, multiple sclerosis; NfL, neurofilament light chain; NHS, Nurses' Health Study; NIH-AARP, National Institutes of Health-AARP Diet and Health Study; OR, odds ratio; OTU, operational taxonomic unit; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PUFA, polyunsaturated fatty acid; SNP, single nucleotide polymorphism; SVC, slow vital capacity; TMAO, trimethylamine N-oxide.

References

1. Boumédiene F, Marin B, Luna J, et al. Spatio-temporal clustering of amyotrophic lateral sclerosis in France: A population-based study. *Eur J Epidemiol*. Sep 13 2022;doi:10.1007/s10654-022-00904-2
2. Doi Y, Yokoyama T, Tango T, Takahashi K, Fujimoto K, Nakano I. Temporal trends and geographic clusters of mortality from amyotrophic lateral sclerosis in Japan, 1995-2004. *J Neurol Sci*. Nov 15 2010;298(1-2):78-84. doi:10.1016/j.jns.2010.08.004
3. Migliaretti G, Berchialla P, Dalmasso P, Cavallo F, Chiò A. Amyotrophic lateral sclerosis in Piedmont (Italy): a Bayesian spatial analysis of the incident cases. *Amyotroph Lateral Scler Frontotemporal Degener*. Jan 2013;14(1):58-65. doi:10.3109/21678421.2012.733401
4. Oliveira RTG, Santana GC, Gonçalves MJ, et al. A geographical study on amyotrophic lateral sclerosis in Rio Grande Do Norte, Brazil, from 2005 to 2018. *Amyotroph Lateral Scler Frontotemporal Degener*. Feb 2023;24(1-2):117-124. doi:10.1080/21678421.2022.2102429
5. Povedano M, Saez M, Martínez-Matos JA, Barceló MA. Spatial Assessment of the Association between Long-Term Exposure to Environmental Factors and the Occurrence of Amyotrophic Lateral Sclerosis in Catalonia, Spain: A Population-Based Nested Case-Control Study. *Neuroepidemiology*. 2018;51(1-2):33-49. doi:10.1159/000489664
6. Rooney J, Heverin M, Vajda A, et al. An exploratory spatial analysis of ALS incidence in Ireland over 17.5 years (1995-July 2013). *PLoS One*. 2014;9(5):e96556. doi:10.1371/journal.pone.0096556
7. Rooney J, Vajda A, Heverin M, et al. Spatial cluster analysis of population amyotrophic lateral sclerosis risk in Ireland. *Neurology*. Apr 14 2015;84(15):1537-44. doi:10.1212/wnl.0000000000001477
8. Schwartz GG, Rundquist BC, Simon IJ, Swartz SE. Geographic distributions of motor neuron disease mortality and well water use in U.S. counties. *Amyotroph Lateral Scler Frontotemporal Degener*. May 2017;18(3-4):279-283. doi:10.1080/21678421.2016.1264975
9. Torbick N, Hession S, Stommel E, Caller T. Mapping amyotrophic lateral sclerosis lake risk factors across northern New England. *Int J Health Geogr*. Jan 2 2014;13:1. doi:10.1186/1476-072x-13-1
10. Uenal H, Rosenbohm A, Kufeldt J, et al. Incidence and geographical variation of amyotrophic lateral sclerosis (ALS) in Southern Germany--completeness of the ALS registry Swabia. *PLoS One*. 2014;9(4):e93932. doi:10.1371/journal.pone.0093932
11. Vasta R, Calvo A, Moglia C, et al. Spatial epidemiology of amyotrophic lateral sclerosis in Piedmont and Aosta Valley, Italy: a population-based cluster analysis. *Eur J Neurol*. May 2018;25(5):756-761. doi:10.1111/ene.13586
12. 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. doi:10.1159/000453359

13. Andrew AS, Chen CY, Caller TA, et al. Toenail mercury Levels are associated with amyotrophic lateral sclerosis risk. *Muscle Nerve*. Jan 4 2018;doi:10.1002/mus.26055

14. 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*. Aug 2020;21(5-6):420-427. doi:10.1080/21678421.2020.1753777

15. Andrew AS, Bradley WG, Peipert D, et al. Risk factors for amyotrophic lateral sclerosis: A regional United States case-control study. *Muscle Nerve*. Jan 2021;63(1):52-59. doi:10.1002/mus.27085

16. Andrew A, Zhou J, Gui J, et al. Pesticides applied to crops and amyotrophic lateral sclerosis risk in the U.S. *Neurotoxicology*. Dec 2021;87:128-135. doi:10.1016/j.neuro.2021.09.004

17. Andrew A, Zhou J, Gui J, et al. Airborne lead and polychlorinated biphenyls (PCBs) are associated with amyotrophic lateral sclerosis (ALS) risk in the U.S. *Sci Total Environ*. May 1 2022;819:153096. doi:10.1016/j.scitotenv.2022.153096

18. Bandres-Ciga S, Noyce AJ, Hemani G, et al. Shared polygenic risk and causal inferences in amyotrophic lateral sclerosis. *Annals of neurology*. Apr 2019;85(4):470-481. doi:10.1002/ana.25431

19. Beard JD, Engel LS, Richardson DB, et al. Military service, deployments, and exposures in relation to amyotrophic lateral sclerosis survival. *PLoS One*. 2017;12(10):e0185751. doi:10.1371/journal.pone.0185751

20. Beaudin M, Salachas F, Pradat PF, Dupré N. Environmental risk factors for amyotrophic lateral sclerosis: a case-control study in Canada and France. *Amyotroph Lateral Scler Frontotemporal Degener*. Nov 2022;23(7-8):592-600. doi:10.1080/21678421.2022.2028167

21. Bellomo G, Piscopo P, Corbo M, et al. A systematic review on the risk of neurodegenerative diseases and neurocognitive disorders in professional and varsity athletes. *Neurol Sci*. Dec 2022;43(12):6667-6691. doi:10.1007/s10072-022-06319-x

22. Blecher R, Elliott MA, Yilmaz E, et al. Contact Sports as a Risk Factor for Amyotrophic Lateral Sclerosis: A Systematic Review. *Global Spine J*. Feb 2019;9(1):104-118. doi:10.1177/2192568218813916

23. Cragg JJ, Johnson NJ, Weisskopf MG. Military Service and Amyotrophic Lateral Sclerosis in a Population-based Cohort: Extended Follow-up 1979-2011. *Epidemiology*. Mar 2017;28(2):e15-e16. doi:10.1097/ede.0000000000000589

24. Daneshvar DH, Mez J, Alosco ML, et al. Incidence of and Mortality From Amyotrophic Lateral Sclerosis in National Football League Athletes. *JAMA Netw Open*. Dec 1 2021;4(12):e2138801. doi:10.1001/jamanetworkopen.2021.38801

25. Dickerson AS, Hansen J, Gredal O, Weisskopf MG. Amyotrophic Lateral Sclerosis and Exposure to Diesel Exhaust in a Danish Cohort. *Am J Epidemiol*. Aug 1 2018;187(8):1613-1622. doi:10.1093/aje/kwy069

26. Dickerson AS, Hansen J, Specht AJ, Gredal O, Weisskopf MG. Population-based study of amyotrophic lateral sclerosis and occupational lead exposure in Denmark. *Occup Environ Med*. Apr 2019;76(4):208-214. doi:10.1136/oemed-2018-105469

27. Dickerson AS, Hansen J, Gredal O, Weisskopf MG. Study of Occupational Chromium, Iron, and Nickel Exposure and Amyotrophic Lateral Sclerosis in Denmark. *Int J Environ Res Public Health*. Nov 2 2020;17(21)doi:10.3390/ijerph17218086

28. Fang F, Hallmarker U, James S, et al. Amyotrophic lateral sclerosis among cross-country skiers in Sweden. *Eur J Epidemiol*. Mar 2016;31(3):247-53. doi:10.1007/s10654-015-0077-7

29. Figueroa-Romero C, Mikhail KA, Gennings C, et al. Early life metal dysregulation in amyotrophic lateral sclerosis. *Ann Clin Transl Neurol*. Jun 2020;7(6):872-882. doi:10.1002/acn3.51006

30. Filippini T, Fiore M, Tesauro M, et al. Clinical and Lifestyle Factors and Risk of Amyotrophic Lateral Sclerosis: A Population-Based Case-Control Study. *Int J Environ Res Public Health*. Jan 30 2020;17(3)doi:10.3390/ijerph17030857

31. Filippini T, Tesauro M, Fiore M, et al. Environmental and Occupational Risk Factors of Amyotrophic Lateral Sclerosis: A Population-Based Case-Control Study. *Int J Environ Res Public Health*. Apr 22 2020;17(8)doi:10.3390/ijerph17082882

32. Filippini T, Hatch EE, Vinceti M. Residential exposure to electromagnetic fields and risk of amyotrophic lateral sclerosis: a dose-response meta-analysis. *Sci Rep*. Jun 7 2021;11(1):11939. doi:10.1038/s41598-021-91349-2

33. Filippini T, Mandrioli J, Malagoli C, et al. Risk of Amyotrophic Lateral Sclerosis and Exposure to Particulate Matter from Vehicular Traffic: A Case-Control Study. *Int J Environ Res Public Health*. Jan 22 2021;18(3)doi:10.3390/ijerph18030973

34. Goutman SA, Boss J, Patterson A, Mukherjee B, Batterman S, Feldman EL. High plasma concentrations of organic pollutants negatively impact survival in amyotrophic lateral sclerosis. *J Neurol Neurosurg Psychiatry*. Aug 2019;90(8):907-912. doi:10.1136/jnnp-2018-319785

35. Goutman SA, Boss J, Godwin C, Mukherjee B, Feldman EL, Batterman SA. Associations of self-reported occupational exposures and settings to ALS: a case-control study. *Int Arch Occup Environ Health*. May 20 2022;doi:10.1007/s00420-022-01874-4

36. Goutman SA, Boss J, Godwin C, Mukherjee B, Feldman EL, Batterman SA. Occupational history associates with ALS survival and onset segment. *Amyotroph Lateral Scler Frontotemporal Degener*. Oct 3 2022:1-11. doi:10.1080/21678421.2022.2127324

37. Goutman SA, Boss J, Iyer G, et al. Body mass index associates with amyotrophic lateral sclerosis survival and metabolomic profiles. *Muscle Nerve*. Nov 2 2022;doi:10.1002/mus.27744

38. Gu D, Ou S, Tang M, Yin Z, Wang Z, Liu G. Trauma and amyotrophic lateral sclerosis: a systematic review and meta-analysis. *Amyotroph Lateral Scler Frontotemporal Degener*. May 2021;22(3-4):170-185. doi:10.1080/21678421.2020.1861024

39. Gunnarsson LG, Bodin L. Amyotrophic Lateral Sclerosis and Occupational Exposures: A Systematic Literature Review and Meta-Analyses. *Int J Environ Res Public Health*. Oct 26 2018;15(11)doi:10.3390/ijerph15112371

40. Iverson GL, Castellani RJ, Cassidy JD, et al. Examining later-in-life health risks associated with sport-related concussion and repetitive head impacts: a systematic review of case-control and cohort studies. *Br J Sports Med*. Jun 2023;57(12):810-821. doi:10.1136/bjsports-2023-106890

41. Koeman T, Slottje P, Schouten LJ, et al. Occupational exposure and amyotrophic lateral sclerosis in a prospective cohort. *Occup Environ Med*. Aug 2017;74(8):578-585. doi:10.1136/oemed-2016-103780

42. Korner S, Kammeyer J, Zapf A, et al. Influence of Environment and Lifestyle on Incidence and Progress of Amyotrophic Lateral Sclerosis in A German ALS Population. *Aging Dis*. Apr 2019;10(2):205-216. doi:10.14336/ad.2018.0327

43. Lee A, Arachchige BJ, Reed S, Henderson R, Aylward J, McCombe PA. Plasma from some patients with amyotrophic lateral sclerosis exhibits elevated formaldehyde levels. *J Neurol Sci*. Feb 15 2020;409:116589. doi:10.1016/j.jns.2019.116589

44. Lian L, Liu M, Cui L, et al. Environmental risk factors and amyotrophic lateral sclerosis (ALS): A case-control study of ALS in China. *J Clin Neurosci*. Aug 2019;66:12-18. doi:10.1016/j.jocn.2019.05.036

45. Luna J, Leleu JP, Preux PM, et al. Residential exposure to ultra high frequency electromagnetic fields emitted by Global System for Mobile (GSM) antennas and amyotrophic lateral sclerosis incidence: A geo-epidemiological population-based study. *Environ Res*. Sep 2019;176:108525. doi:10.1016/j.envres.2019.108525

46. Malek AM, Arena VC, Song R, et al. Long-term air pollution and risk of amyotrophic lateral sclerosis mortality in the Women's Health Initiative cohort. *Environ Res*. Oct 8 2022;216(Pt 1):114510. doi:10.1016/j.envres.2022.114510

47. McKay KA, Smith KA, Smertinaite L, Fang F, Ingre C, Taube F. Military service and related risk factors for amyotrophic lateral sclerosis. *Acta Neurol Scand*. Jan 2021;143(1):39-50. doi:10.1111/ane.13345

48. 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*. May 2022;23(3-4):190-202. doi:10.1080/21678421.2021.1936556

49. Myung W, Lee H, Kim H. Short-term air pollution exposure and emergency department visits for amyotrophic lateral sclerosis: A time-stratified case-crossover analysis. *Environ Int*. Feb 2019;123:467-475. doi:10.1016/j.envint.2018.12.042

50. Nunez Y, Boehme AK, Goldsmith J, et al. PM(2.5) composition and disease aggravation in amyotrophic lateral sclerosis: An analysis of long-term exposure to components of fine particulate matter in New York State. *Environ Epidemiol*. Apr 2022;6(2):e204. doi:10.1097/ee9.0000000000000204

51. Parks RM, Nunez Y, Balalian AA, et al. Long-term Traffic-related Air Pollutant Exposure and Amyotrophic Lateral Sclerosis Diagnosis in Denmark: A Bayesian Hierarchical Analysis. *Epidemiology*. Nov 1 2022;33(6):757-766. doi:10.1097/ede.0000000000001536

52. Peters TL, Kamel F, Lundholm C, et al. Occupational exposures and the risk of amyotrophic lateral sclerosis. *Occup Environ Med*. Feb 2017;74(2):87-92. doi:10.1136/oemed-2016-103700

53. Peters S, Visser AE, D'Ovidio F, et al. Associations of Electric Shock and Extremely Low-Frequency Magnetic Field Exposure With the Risk of Amyotrophic Lateral Sclerosis. *Am J Epidemiol*. Apr 1 2019;188(4):796-805. doi:10.1093/aje/kwy287

54. Peters S, Visser AE, D'Ovidio F, et al. Effect modification of the association between total cigarette smoking and ALS risk by intensity, duration and time-since-quitting: Euro-MOTOR. *J Neurol Neurosurg Psychiatry*. Jan 2020;91(1):33-39. doi:10.1136/jnnp-2019-320986

55. Peters S, Broberg K, Gallo V, et al. Blood Metal Levels and Amyotrophic Lateral Sclerosis Risk: A Prospective Cohort. *Annals of neurology*. Jan 2021;89(1):125-133. doi:10.1002/ana.25932

56. Phelps A, Alosco ML, Baucom Z, et al. Association of Playing College American Football With Long-term Health Outcomes and Mortality. *JAMA Netw Open*. Apr 1 2022;5(4):e228775. doi:10.1001/jamanetworkopen.2022.8775

57. Pupillo E, Poloni M, Bianchi E, et al. Trauma and amyotrophic lateral sclerosis: a european population-based case-control study from the EURALS consortium. *Amyotroph Lateral Scler Frontotemporal Degener*. Feb 2018;19(1-2):118-125. doi:10.1080/21678421.2017.1386687

58. Pupillo E, Bianchi E, Vanacore N, et al. Increased risk and early onset of ALS in professional players from Italian Soccer Teams. *Amyotroph Lateral Scler Frontotemporal Degener*. Aug 2020;21(5-6):403-409. doi:10.1080/21678421.2020.1752250

59. Rooney J, Vajda A, Heverin M, et al. No association between soil constituents and amyotrophic lateral sclerosis relative risk in Ireland. *Environ Res*. May 2016;147:102-7. doi:10.1016/j.envres.2016.01.038

60. Russell ER, Mackay DF, Stewart K, MacLean JA, Pell JP, Stewart W. Association of Field Position and Career Length With Risk of Neurodegenerative Disease in Male Former Professional Soccer Players. *JAMA Neurol*. Sep 1 2021;78(9):1057-1063. doi:10.1001/jamaneurol.2021.2403

61. Sagiraju HKR, Živković S, VanCott AC, et al. Amyotrophic Lateral Sclerosis Among Veterans Deployed in Support of Post-9/11 U.S. Conflicts. *Mil Med*. Mar 2 2020;185(3-4):e501-e509. doi:10.1093/milmed/usz350

62. Seals RM, Kioumourtzoglou MA, Gredal O, Hansen J, Weisskopf MG. Occupational formaldehyde and amyotrophic lateral sclerosis. *Eur J Epidemiol*. Oct 2017;32(10):893-899. doi:10.1007/s10654-017-0249-8

63. Seelen M, Toro Campos RA, Veldink JH, et al. Long-Term Air Pollution Exposure and Amyotrophic Lateral Sclerosis in Netherlands: A Population-based Case-control Study. *Environ Health Perspect*. Sep 27 2017;125(9):097023. doi:10.1289/EHP1115

64. Su FC, Goutman SA, Chernyak S, et al. Association of Environmental Toxins With Amyotrophic Lateral Sclerosis. *JAMA Neurol*. Jul 1 2016;73(7):803-11. doi:10.1001/jamaneurol.2016.0594

65. Vinceti M, Filippini T, Violi F, et al. Pesticide exposure assessed through agricultural crop proximity and risk of amyotrophic lateral sclerosis. *Environ Health*. Aug 29 2017;16(1):91. doi:10.1186/s12940-017-0297-2

66. Vinceti M, Malagoli C, Fabbi S, et al. Magnetic fields exposure from high-voltage power lines and risk of amyotrophic lateral sclerosis in two Italian populations. *Amyotroph Lateral Scler Frontotemporal Degener*. Nov 2017;18(7-8):583-589. doi:10.1080/21678421.2017.1332078

67. Vinceti M, Filippini T, Mandrioli J, et al. Lead, cadmium and mercury in cerebrospinal fluid and risk of amyotrophic lateral sclerosis: A case-control study. *J Trace Elem Med Biol*. Sep 2017;43:121-125. doi:10.1016/j.jtemb.2016.12.012

68. Vinceti M, Violi F, Tzatzarakis M, et al. Pesticides, polychlorinated biphenyls and polycyclic aromatic hydrocarbons in cerebrospinal fluid of amyotrophic lateral sclerosis patients: a case-control study. *Environ Res*. May 2017;155:261-267. doi:10.1016/j.envres.2017.02.025

69. Visser AE, D'Ovidio F, Peters S, et al. Multicentre, population-based, case-control study of particulates, combustion products and amyotrophic lateral sclerosis risk. *J Neurol Neurosurg Psychiatry*. Aug 2019;90(8):854-860. doi:10.1136/jnnp-2018-319779

70. Walt GS, Burris HM, Brady CB, et al. Chronic Traumatic Encephalopathy Within an Amyotrophic Lateral Sclerosis Brain Bank Cohort. *J Neuropathol Exp Neurol*. Dec 1 2018;77(12):1091-1100. doi:10.1093/jnen/nly092

71. 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*. Jul 2017;61:101-130. doi:10.1016/j.neuro.2016.06.015

72. Yu Z, Peters S, van Boxmeer L, et al. Long-Term Exposure to Ultrafine Particles and Particulate Matter Constituents and the Risk of Amyotrophic Lateral Sclerosis. *Environ Health Perspect*. 2021:97702. vol. 9.

73. Brenner D, Hiergeist A, Adis C, et al. The fecal microbiome of ALS patients. *Neurobiol Aging*. Jan 2018;61:132-137. doi:10.1016/j.neurobiolaging.2017.09.023

74. Di Gioia D, Bozzi Cionci N, Baffoni L, et al. A prospective longitudinal study on the microbiota composition in amyotrophic lateral sclerosis. *BMC Med*. Jun 17 2020;18(1):153. doi:10.1186/s12916-020-01607-9

75. Dorst J, Schuster J, Dreyhaupt J, et al. Effect of high-caloric nutrition on serum neurofilament light chain levels in amyotrophic lateral sclerosis. *J Neurol Neurosurg Psychiatry*. Sep 2020;91(9):1007-1009. doi:10.1136/jnnp-2020-323372

76. Erber AC, Cetin H, Berry D, Schernhammer ES. The role of gut microbiota, butyrate and proton pump inhibitors in amyotrophic lateral sclerosis: a systematic review. *Int J Neurosci*. Jul 2020;130(7):727-735. doi:10.1080/00207454.2019.1702549

77. Fitzgerald KC, O'Reilly EJ, Falcone GJ, et al. Dietary omega-3 polyunsaturated fatty acid intake and risk for amyotrophic lateral sclerosis. *JAMA Neurol*. Sep 2014;71(9):1102-10. doi:10.1001/jamaneurol.2014.1214

78. Goncharova PS, Davydova TK, Popova TE, et al. Nutrient Effects on Motor Neurons and the Risk of Amyotrophic Lateral Sclerosis. *Nutrients*. Oct 26 2021;13(11)doi:10.3390/nu13113804

79. Gong Z, Ba L, Tang J, et al. Gut microbiota links with cognitive impairment in amyotrophic lateral sclerosis: A multi-omics study. *J Biomed Res*. Dec 28 2022;37(2):125-137. doi:10.7555/JBR.36.20220198

80. Goutman SA, Guo K, Savelieff MG, et al. Metabolomics identifies shared lipid pathways in independent amyotrophic lateral sclerosis cohorts. *Brain*. Dec 19 2022;145(12):4425-4439. doi:10.1093/brain/awac025

81. Hertzberg VS, Singh H, Fournier CN, et al. Gut microbiome differences between amyotrophic lateral sclerosis patients and spouse controls. *Amyotroph Lateral Scler Frontotemporal Degener*. Feb 2022;23(1-2):91-99. doi:10.1080/21678421.2021.1904994

82. Hop PJ, Zwamborn RAJ, Hannon E, et al. Genome-wide study of DNA methylation shows alterations in metabolic, inflammatory, and cholesterol pathways in ALS. *Sci Transl Med*. Feb 23 2022;14(633):eabj0264. doi:10.1126/scitranslmed.abj0264

83. Huisman MH, Seelen M, van Doormaal PT, et al. Effect of Presymptomatic Body Mass Index and Consumption of Fat and Alcohol on Amyotrophic Lateral Sclerosis. *JAMA Neurol*. Oct 2015;72(10):1155-62. doi:10.1001/jamaneurol.2015.1584

84. Jin Y, Oh K, Oh SI, Baek H, Kim SH, Park Y. Dietary intake of fruits and beta-carotene is negatively associated with amyotrophic lateral sclerosis risk in Koreans: a case-control study. *Nutr Neurosci*. Apr 2014;17(3):104-8. doi:10.1179/1476830513Y.0000000071

85. Kim HS, Son J, Lee D, et al. Gut- and oral-dysbiosis differentially impact spinal- and bulbar-onset ALS, predicting ALS severity and potentially determining the location of disease onset. *BMC Neurol*. Feb 21 2022;22(1):62. doi:10.1186/s12883-022-02586-5

86. Ludolph AC, Dorst J, Dreyhaupt J, et al. Effect of High-Caloric Nutrition on Survival in Amyotrophic Lateral Sclerosis. *Annals of neurology*. Feb 2020;87(2):206-216. doi:10.1002/ana.25661

87. Mazzini L, Mogna L, De Marchi F, et al. Potential Role of Gut Microbiota in ALS Pathogenesis and Possible Novel Therapeutic Strategies. *J Clin Gastroenterol*. Nov/Dec 2018;52 Suppl 1, Proceedings from the 9th Probiotics, Prebiotics and New Foods, Nutraceuticals and Botanicals for Nutrition & Human and Microbiota Health Meeting, held in Rome, Italy from September 10 to 12, 2017:S68-S70. doi:10.1097/MCG.0000000000001042

88. Michels S, Kurz D, Rosenbohm A, et al. Association of blood lipids with onset and prognosis of amyotrophic lateral sclerosis: results from the ALS Swabia registry. *J Neurol*. Jun 2023;270(6):3082-3090. doi:10.1007/s00415-023-11630-4

89. Niccolai E, Di Pilato V, Nannini G, et al. The Gut Microbiota-Immunity Axis in ALS: A Role in Deciphering Disease Heterogeneity? *Biomedicines*. Jun 29 2021;9(7)doi:10.3390/biomedicines9070753

90. Ngo ST, Restuadi R, McCrae AF, et al. Progression and survival of patients with motor neuron disease relative to their fecal microbiota. *Amyotroph Lateral Scler Frontotemporal Degener*. Nov 2020;21(7-8):549-562. doi:10.1080/21678421.2020.1772825

91. Nicholson K, Bjornevik K, Abu-Ali G, et al. The human gut microbiota in people with amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Frontotemporal Degener*. May 2021;22(3-4):186-194. doi:10.1080/21678421.2020.1828475

92. Ning J, Huang SY, Chen SD, Zhang YR, Huang YY, Yu JT. Investigating Casual Associations Among Gut Microbiota, Metabolites, and Neurodegenerative Diseases: A Mendelian Randomization Study. *J Alzheimers Dis*. 2022;87(1):211-222. doi:10.3233/jad-215411

93. Okamoto K, Kihira T, Kobashi G, et al. Fruit and vegetable intake and risk of amyotrophic lateral sclerosis in Japan. *Neuroepidemiology*. 2009;32(4):251-6. doi:10.1159/000201563

94. Petimar J, O'Reilly E, Adami HO, et al. Coffee, tea, and caffeine intake and amyotrophic lateral sclerosis mortality in a pooled analysis of eight prospective cohort studies. *Eur J Neurol*. Mar 2019;26(3):468-475. doi:10.1111/ene.13840

95. Pupillo E, Bianchi E, Chio A, et al. Amyotrophic lateral sclerosis and food intake. *Amyotroph Lateral Scler Frontotemporal Degener*. May 2018;19(3-4):267-274. doi:10.1080/21678421.2017.1418002

96. Sun J, Zhan Y, Mariosa D, et al. Antibiotics use and risk of amyotrophic lateral sclerosis in Sweden. *Eur J Neurol*. Nov 2019;26(11):1355-1361. doi:10.1111/ene.13986

97. Westeneng HJ, van Veenhuijzen K, van der Spek RA, et al. Associations between lifestyle and amyotrophic lateral sclerosis stratified by C9orf72 genotype: a longitudinal, population-based, case-control study. *Lancet Neurol*. May 2021;20(5):373-384. doi:10.1016/S1474-4422(21)00042-9

98. Wills AM, Hubbard J, Macklin EA, et al. Hypercaloric enteral nutrition in patients with amyotrophic lateral sclerosis: a randomised, double-blind, placebo-controlled phase 2 trial. *Lancet*. Jun 14 2014;383(9934):2065-2072. doi:10.1016/S0140-6736(14)60222-1

99. Yu H, Kim SH, Noh MY, Lee S, Park Y. Relationship between Dietary Fiber Intake and the Prognosis of Amytrophic Lateral Sclerosis in Korea. *Nutrients*. Nov 7 2020;12(11)doi:10.3390/nu12113420

100. Zeng Q, Shen J, Chen K, et al. The alteration of gut microbiome and metabolism in amyotrophic lateral sclerosis patients. *Sci Rep*. Aug 3 2020;10(1):12998. doi:10.1038/s41598-020-69845-8

101. Zhang L, Zhuang Z, Zhang G, Huang T, Fan D. Assessment of bidirectional relationships between 98 genera of the human gut microbiota and amyotrophic lateral sclerosis: a 2-sample Mendelian randomization study. *BMC Neurol*. Jan 3 2022;22(1):8. doi:10.1186/s12883-021-02522-z