EPI-01: ALS incidence in Europe: what we can learn from population-based registries

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Introduction:
Population-based disease registries are an invaluable source of annual incidence and prevalence data, collecting cases from multiple sources in a defined region and population. Many such ALS registries have been established in Europe in recent decades, and data that has been collected can enable researchers to investigate any variation in incidence rates across regions. Variation in incidence can be linked with variation in exposure to potential environmental risk factors or heritable variation in order to better understand the contributions these factors make to ALS susceptibility and disease development. The current project aims to analyse ALS incidence rates and compare lifetime risk of disease across regions in Europe by identifying all European ALS population-based registries that have published incidence data within the last decade.

Methods:
Two reviewers separately carried out a systematic search of the literature published between 2010 and 2020 using suitable MeSH terms and then compared results. Abstracts and titles were scanned to identify papers for full-text reading. Any differences were discussed with a third reviewer.

Results:
Of the 768 articles identified, 90 papers met the criteria for full review. From these, 37 unique European ALS population-based registries were identified. 24 used prospective data collection methods, 4 retrospective and 9 were national or regional governmental health databases. Age-specific incidence data was extracted.

Discussion:
There were differences in how incidence cases and rates were reported in the literature. Not all papers published age and gender stratified rates, and of those that did, several used different age ranges. There were also differences in how data was collected, either through a clinical registry, multiple sources such as specialists, hospitals, health insurance data etc, or national registries. This work demonstrates the importance of the development of a standardised protocol for publishing incidence data from population-based registries, which in turn would greater facilitate transnational epidemiological studies using a shared platform.

EPI-02: Associations between Autoimmune Diseases and Amyotrophic Lateral Sclerosis: a Register-based Study

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Background:
An association of autoimmune disease with risk of amyotrophic lateral sclerosis (ALS) has been proposed. It remains however unknown whether such association is partly attributable to familial confounding.

Objective:
We aimed to assess the associations of 43 autoimmune diseases with the subsequent risk of ALS and further evaluate the contribution of familial confounding to these associations.
Methods: We conducted a nationwide register-based nested case-control study including 3,561 ALS patients diagnosed during 1990-2013 in Sweden and 35,610 controls that were randomly selected from the general population and individually matched to the cases on age, sex, and county of birth. To evaluate the contribution of familial factors on the studied association, we additionally studied the first-degree relatives (siblings and children) of ALS patients and their controls.

Results:
Patients with ALS had a 50% higher risk of being previously diagnosed with autoimmune disease (OR 1.5, 95% confidence interval [CI] 1.3–1.6), compared with controls. Although the increased risk was greatest during the year before ALS diagnosis (likely due to misdiagnosis), an increased risk was also noted during earlier years. A positive association was noted for several autoimmune diseases, including myasthenia gravis, polymyositis or dermatomyositis, Guillain-Barre syndrome, type 1 diabetes diagnosed younger than 30 years, multiple sclerosis and hypothyreosis. First-degree relatives of ALS patients had however no increased risk of autoimmune diseases compared with first-degree relatives of controls.

Conclusions:
Although it is difficult to rule out the possibility of misdiagnosis, there is likely a positive association between autoimmune disease (such as type 1 diabetes and multiple sclerosis) and ALS, which is unlikely fully explained by shared familial confounding factors.

Acknowledgment:
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EPI-03: Dissecting the relationship between physical activity and motor neuron disease : a two-sample mendelian randomisation study.

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Background:
The role of physical activity (PA) as a risk factor for motor neuron disease (MND) remains disputed. Mendelian randomisation (MR) utilises single nucleotide polymorphisms (SNPs) as instrumental variables (IV) to assess causal relationships [1]. By utilising common SNPs associated with various measures of PA, this study aims to overcome unmeasured confounding and provide an assessment of the relationship between MND and PA.

Methods:
PA-related genome wide association study (GWAS) summary statistics were utilised to seize instrumental variables for our analysis. SNPs associated ($p < 1E-6$) with wrist worn accelerometer measured average accelerations (n=91,084) and fraction of accelerations > 425 milli-gravities (n=90,667) as well as self-reported "moderate to vigorous physical activity" (n=377,234), "vigorous physical activity" (n=261,055) and "strenuous sport or other exercise" (SSOE, n=350,492) were utilised as exposure IVs [2]. Project MinE MND data (n=36,052) were used for outcome SNPs [3]. Analysis was conducted using the "TwoSampleMR" function in R. Pleiotropy, heterogeneity and outlier SNPs were identified with Egger intercept, Cochranes Q and MR PRESSO global test. Analysis of the exposure-outcome relationship was performed with various statistical measures including inverse-variance weighted (IVW), weighted median, MR-Egger, mode-based estimation (MBE), MR PRESSO and MR-RAPS.

Results:
Individuals who spend ≥ 2-3 days per week doing SSOE for ≥ 15-30 minutes are more likely to develop ALS than those who do not participate in SSOE (multiplicative effects IVW odds ratio 1.2, 95% confidence interval = 1.05-1.45 , p=0.01). There was no evidence of statistically significant heterogeneity, directional pleiotropy or outliers. A range of MR methods which are sensitive to violations of IV principles were applied to the SSOE data, all of which were either significant or trended toward significance (fixed effects IVW p=0.0008, multiplicative random effects IVW p=0.01, weighted median p=0.07, MR-Egger p=0.07, MR-RAPS p=0.01, MBE p=0.06). Other PA instruments did not reach statistical significance.

Conclusions:
SSOE represents a risk factor for MND, whilst other measures of PA do not reach significance. Future research should focus upon molecular mechanisms associated with SSOE and aim to identify "at-risk" individuals.

Acknowledgements:
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EPI-04: Epidemiology and Genetic Architecture of ALS in the isolated island population of Malta

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Background:
Population isolates are compelling tools for mapping genes and identifying environmental factors that increase ALS risk. The archipelago of Malta, a sovereign microstate in the south of Europe, is home to a geographically and culturally isolated population.

Objectives:
We aimed at investigating the epidemiology and genetic profile of Maltese patients with ALS, identified throughout a two-year window (2017-2018).

Methods:
Phenotypic information was gathered via a detailed questionnaire in addition to a clinical examination. The denominator for the calculation of the incident rate was the sum of total population of Malta in 2017 and 2018. The prevalence rate was estimated on 31st December 2018. Whole-genome sequencing allowed us to determine rare DNA variants that change the protein-coding sequence of ALS-associated genes.

Results:
Cases (n=24) were largely male (66.7%) with a predominant spinal onset of symptoms (70.8%). Disease onset occurred around mid-age (median age: 64 years, men; 59.5 years, female); 12.5% had familial ALS (fALS). Annual incidence rate was 2.48 (95% CI 1.59–3.68) per 100,000 person-years. Male-to-female incidence ratio was 1.93:1. Prevalence was 3.44 (95% CI 2.01–5.52) cases per 100,000 inhabitants on 31st December 2018. The southeast of mainland Malta had an increased number of ALS cases relative to other regions. One third of the ALS patients recruited had a history of heavy smoking and more than half reported an occupation associated with strenuous activity.

Intriguingly, the Maltese ALS patient cohort was found to be negative for deleterious variants in C9orf72, SOD1, TARDBP or FUS genes, which are the most commonly mutated ALS genes globally. Nonetheless, ALS-associated repeat expansions were identified in ATXN2 and NIPA1. Variants predicted to be damaging were also detected in ALS2, DAO, DCTN1, ERBB4, SETX, SCFD1 and SPG11. A total of 40% of patients with sporadic ALS had a rare and deleterious variant or repeat expansion in an ALS-associated gene, whilst the genetic cause of two thirds of fALS cases could not be pinpointed to known ALS genes or risk loci.

Discussion and conclusions:
Population-specific aspects of ALS cases in Malta overlap those reported for other neighbouring European populations, especially those in the Mediterranean including the island of Sicily and the southern region of Puglia in Italy and Cyprus. Incidence and prevalence of ALS in Malta is similar to the European median. Rare deleterious variants in the major ALS were absent in Maltese ALS patients confirming the presence of a North-South gradient in the frequency of mutations within these genes across Europe. Our initial results warrant further studies aimed at elucidating novel genes and/or environmental factors that increase ALS risk in this unique population isolate.

EPI-05: Machine Learning Models for Identifying Risk Factors and Prediction of ALS Progression

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Objectives:
Amyotrophic lateral sclerosis (ALS) is a fatal progressive neurodegenerative disease, leading to loss of upper and lower motor neurons in the motor cortex, brain stem, and spinal cord. Risk factors for ALS onset and progression are largely unknown. The gold standard for defining ALS progression is the ALS Functional Rating Scale (ALSFRS). The ALSFRS score is a measure of a patient's ability to perform certain tasks (e.g., bathing, talking, swallowing, dressing themselves, and walking) with a lower score indicating greater disability. The emergence of large-scale Electronic Health Record (EHR) data has opened up the potential of Machine Learning (ML) for identifying factors that influence the progression of ALS in a data-driven manner. However, most EHR data sets from clinical care records do not include reliable frequent ALSFRS scores, thus limiting the usefulness of a large proportion of available EHR data for identifying risk factors for ALS progression.

Methods:
Using the Pooled Resource Open-Access ALS Clinical Trials (PROACT) Database, we identified factors that could serve as surrogates for ALSFRS scores with respect to disease progression. We investigated multiple ML techniques for predicting a patient's ALSFRS given a fixed period of prior vitals and laboratory results. These techniques span the spectrum of simple linear regression to sophisticated neural networks, e.g., autoencoders (AEs) and recurrent neural networks (RNNs).

Results:
Our highest performing method combines AE and RNN: a patient's inputs are first projected into the AE's latent space, then passed into an RNN to perform temporal learning over the latent features. With this method, we can predict ALSFRS 20-40 days into the future using 3 months of patient data, with a root-mean-squared-error (RMSE) of 6.596 FRS points. In contrast, an RNN alone achieves an RMSE of 7.604 FRS points. We also extract importance scores for each feature to reveal that commonly available clinical features (e.g., respiratory rate, weight, height, and pulse) are crucial in the surrogate models for ALSFRS scores. Using only these identified important factors, our RNN model achieves an RMSE within 0.3% of that of an RNN trained on the full set of variables, affirming the rich information content inherent in these factors.

Conclusions:
In summary, we demonstrated ALSFRS prediction using multiple methods on available EHR data. Our best model leverages both AE and RNN. With our model, we identified key features that are highly predictive of ALSFRS. The sparsity and irregularity of the dataset along the time dimension posed data challenges, which can be addressed by our developed surrogate models to impute missing values. Overcoming these data challenges will greatly increase the usability of EHR datasets, which are limited by infrequently sampled ALSFRS scores, in future studies to understand disease progression factors.

EPI-06: Urbanization, air pollution and water exposure: Identification of potential environmental risk factors associated with diagnosis of amyotrophic lateral sclerosis using systematic review.

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Background:
An individual ALS-related genetic mutation can have multiple clinically distinct presentations among patients (1). This has led to a hypothesis that small contributions from various genetic and environmental factors interact to cause the disease. However, the growing literature on environmental factors in ALS, particularly regarding exposures in the surrounding environment such as urbanization and air and water pollution, has yet to be fully appraised (2, 3).

Objective:
To identify and synthesize epidemiological studies relating to urbanization, air pollution and exposure to water in relation to the developmentt of ALS.

Methods:
A systematic review was conducted for each exposure of interest (n=3). Indexed articles since database inception were searched in PubMed and Scopus on March 24, 2020, using a combination of keywords/MeSH terminology and citation analysis, respectively. Articles identified had their title and abstract screened for preliminary selection, followed by a full-text screening to confirm eligibility prior to a detailed review for data extraction.

Results:
The combined search strategy for urbanization, air pollution and water exposure in the onset of ALS led to the inclusion of 16, 6 and 13 articles respectively. Most studies used either a case-control (42%) or cross-sectional design (39%). Half of these case-control studies relied on a questionnaire or interview to ascertain environmental exposures rather than quantitative geospatial data with repeated measures. Proximity to industrial activities, water treatment facilities and agricultural areas were all positively associated to increased odds of ALS in 2 spatial analysis studies each. A positive relationship between occupational exposure to diesel exhaust and increased odds of ALS was identified in 3 case-control studies. Two case-control studies identified a positive relationship between long-term exposure to air pollution, particularly NO2, and the risk of ALS. High or low levels of different minerals in drinking water was associated with an increase in ALS incidence in 6 studies on two distinct populations. A positive association between proximity to lakes with indicators of harmful algae blooms and ALS clusters was found in 3 cross-sectional studies.

Discussion:
More work is needed on mapping local climate zones. Findings suggest exposure to diesel exhaust gases and poor water quality may play a role in ALS etiology. Additional studies with longitudinal high-resolution geospatial measurements are recommended to strengthen found associations and potentially identify new underlying risk factors.

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EPI-07: Estimated Prevalence and Incidence of Amyotrophic Lateral Sclerosis, Overall and for SOD1 and C9orf72 Subtypes

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Background:
ALS is a rare neurological disorder characterized by progressive deterioration of motor neurons. Assessment of the size of the amyotrophic lateral sclerosis (ALS) population, including ALS due to genetic origin, is needed to understand the burden of disease as well as the need of clinical intervention and therapy.

Objectives:
Estimate the number of prevalent and incident cases of ALS overall and for SOD1 and C9orf72 ALS in 13 countries across geographic regions in Europe (France, Germany, Italy, Spain, UK), North America (US, Canada), Latin America (Argentina, Brazil, Colombia, Mexico), and Asia (China and Japan).

Methods and design:
A literature search was conducted to identify population-based studies reporting ALS prevalence and/or incidence rates. Pooled prevalence and incidence rates were obtained using either a meta-analysis approach or weighted average at the country and regional geographic level. A country level pooled estimate was used when two or more studies were available per country and geographic regional pooled estimates were used otherwise. Proportion of SOD1 and C9orf72 mutation among sporadic (SALS) and familial (FALS) cases were obtained from a previous systematic review and meta-analysis study [1].

Results:
Pooled prevalence rates (per 100,000 persons) and incidence rates (per 100,000 person-years) for ALS were 6.59 and 2.32 for Europe, 5.20 and 2.16 for North America, 3.17 and 1.19 for Latin America, 3.41 and 0.89 for China, and 10.62 and 3.24 for Japan. The estimated number of ALS cases in 2020 across the 13 countries is 116,164 prevalent and 36,659 incident cases. Total prevalent SOD1 cases were estimated at 2,861 cases of which 1,361 (48%) were FALS and 1,500 (52%) were SALS and incident cases at 874 (408 (47%) FALS, 466 (53%) SALS). Total prevalent C9orf72 cases were estimated to be 3,771 (997 (26%) FALS, 2,774 (74%) SALS) and incident cases were estimated at 1,361 (359 (26%) FALS, 1,002 (74%) SALS).

Discussion/conclusions:
Estimated number of patients with SOD1 and C9orf72 ALS suggest that while the proportions of SOD1 and C9orf72 are higher in FALS, the majority of SOD1 and C9orf72 ALS cases may be found among SALS (about 52% and 70% respectively). These results suggest that classification of familial ALS based on reported family history does not capture the full picture of ALS of genetic origin.

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EPI-08: Estimation of ALS Cases Missing from the Ohio Repository

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Background:
The Ohio ALS Repository recorded all ALS patients from October 2016 to September 2018. The distribution of cases in the 88 counties was not uniform. This incompleteness hampers accurate estimation of incidence and reliable detection of environmental risk factors to a disease. [1]

Objectives:
Estimate the number of ALS cases not recruited by the Ohio ALS Repository for each Ohio county.

Methods:
We developed a four-step procedure for the estimation. First, we identify those counties that have a normal ALS incidence rate, i.e. not too high, which may be “hot spots” due to local risk factor concentrations, and not too low, which may indicate counties where we failed to record all cases. To identify counties with a normal ALS incidence rate, we calculate the incidence rate for each county using available case counts and the county’s population data. We then rank all counties according to their rates and label those counties whose rates are within 0.5 std dev around the median of all rates as having normal rates. Second, we run a Poisson regression on the counties that have normal rates to establish a relationship between the case count and population. Third, we use the regression model to calculate the expected count of cases for those counties that are lower in the rank than those identified “normal” counties. The difference between the expected count and the actual count of a county is a preliminary estimate of the number of unrecruited cases for that county. Fourth, the preliminary estimate is adjusted by a spatial regression model[2,3].

Results:
A preliminary exploration with the described four-step procedure estimates that the total expected number of cases in the 30 low-rank counties is 65 (standard error of the modelled count 9.28, 95% confidence intervals 46-84). The number of unrecorded cases in the Ohio ALS Repository is 54, about 17% of cases actual count in the Repository. A map was created to show the spatial distribution of the unrecruited cases.

Discussion:
The way of identifying counties with normal rates, as well as the statistical models and methods, can all be further refined. Nevertheless, the proposed four-step procedure is a viable approach to addressing the under-recruitment issue of an ALS Repository and other similar databases, which in turn may improve the reliability of analyses based on those databases.

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EPI-09: Gastrointestinal biopsy and amyotrophic lateral sclerosis: a cohort study of 1.1 million individuals

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Abstract:
Background: Whether patients with gastrointestinal (GI) mucosal lesions have altered risk of amyotrophic lateral sclerosis (ALS) remains however unknown.

Methods:
We performed a nationwide matched cohort study. We firstly included individuals with a GI biopsy result of normal mucosa (n=483,442) during 1965-2016 in Sweden and their individually matched unexposed group (n=2,392,647). We then included individuals with a GI biopsy result of non-specific inflammation (n=566,663) and their individually matched unexposed group (n=2,724,515). Participants were followed from date of cohort entry until ALS diagnosis, emigration, death, or December 31, 2016, whichever came first. Stratified Cox regression models were used to estimate the associations.

Results:
Compared to individuals without GI biopsy, individuals with a GI biopsy result of normal mucosa had an increased risk of ALS (HR=1.22; 95%CI: 1.04-1.42) after excluding the first two years of follow-up to alleviate concern of surveillance bias. This increased risk was noted among male (HR=1.20; 95%CI: 0.94-1.51) and female (HR=1.23; 95%CI: 1.01-1.50), as well as among younger (<60 years; HR=1.17; 95%CI: 0.94-1.44) and older (≥60 years; HR=1.24; 95%CI: 0.99-1.56) individuals. In contrast, no association was observed for a GI biopsy result of non-specific inflammation (HR=1.00; 95%CI: 0.88-1.15). Neither of the GI biopsy results was related to the mortality risk after ALS diagnosis.

Conclusions:
Individuals with a GI biopsy result of normal mucosa had a higher future risk of ALS, but not among those with a GI biopsy result of non-specific inflammation. The precise reasons underlying the contrasting result pattern need to be further investigated.

EPI-10: ITalian ALS Registry: a pilot study to assess the feasibility of a web-based, patient driven registry for Italian people with Amyotrophic Lateral Sclerosis

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Background:
ALS is rare and clinically heterogeneous disease, and to better understand the demographic characteristics of people living with ALS (PALS), the natural history of ALS across all phenotypes, and disease management in the real-world setting, requires large-scale data collection and harmonization. These data collection and harmonization can be done via several mechanisms, including: population-based disease registries, voluntary direct reporting by patients (patient-driven registry), merged databases from individual clinical research efforts, and clinic-based data repositories. This study aimed to demonstrate the feasibility of a web-based, patient driven registry for Italian people with ALS, called ITALS-Registry, and promoted by the Italian ALS Association (AISLA).

Methods:
ITALS-Registry is a web-based platform and is a part of the Italian NeuroMuscular Disease registry (http://www.registronmd.it/) that is based on an informatics technology platform, structured according to the most rigorous legal national and European requirements for management of patient sensitive data. A user-friendly web interface allows both direct patients and clinicians' participation. After the registration, PALS who join the ITALS-Registy are asked to fill 5 forms: 1 personal data and family history; 2 ALS History, level of impairment for different functions, the use of device for respiration, mobility and nutrition; 3 Verbal communication, collecting information about the existence of speech disorders and the use of device for augmented and alternative communication; 4 Participation in clinical trials; 5 Questionnaire on the degree of satisfaction about the levels of care and assistance received. The referring physician receives notification of the registration of a patient by automatic e-mail and is asked to fill a medical form that collects data bout disease phenotype (site of onset, El Escorial grid and criteria at diagnosis, ALS genetics); disease markers (ALSFRS-R at each visit); medication list at each visit, and survival.

Results:
Up to now the ITALS-Registry includes 11 ALS multidisciplinary Centers located in 6 Italian Regions. The referral population of the Centers is 32 milion of people equal to 49% of the Italian population, with an expected number of PALS ranging from 1600 to 2200 as prevalent case. Currently, in the first 4 months of activity the ITALS-Registry collected data from 117 PALS (72 men, 45 women) with a median age of 61 years.

Conclusion:
Two of the most daunting bottlenecks in clinical research are the low rates of participation in clinical trials and the current emphasis on patient privacy in research and clinical settings. In Patient-driven clinical research, patients both contribute personal clinical data and benefit from the knowledge gained through the collaboration with the researchers. The ITALS-Registry collects available deidentified data from consenting PALS in participating Italian ALS multidisciplinary Centers to enable: Quality assurance studies; Improved understanding of natural history; Epidemiologic studies; Evaluation of ALS therapies and interventions.

EPI-11: Northeast ALS Consortium National COVID-19 ALS Case Rate Census Survey – 2nd Qtr 2020

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Background:
Email/telephone survey of 7 NC ALS Multidisciplinary Clinics serving 910 ALS patients identified one COVID-19 ALS. Riluzole has antiviral/cytokine modulation effects [Achour 2009] while coronavirus protease inhibitors use the benzothiazole backbone [basic structure of riluzole] as scaffolds. Furthermore, preclinical studies have identified edaravone is a potential treatment against interstitial lung fibrosis in inflammatory induced respiratory distress [Zhi 2011, Wang 2018].

Objective:
To determine whether there is a comparable, increased, or decreased risk for COVID-19 among ALS patients.

Methods:
IRB approved protocol to survey 126 NEALS Investigator Sites with opt-in internet (Survey Monkey) portal containing 6 questions: From 1 March 2020 through 31 May 2020, (1) How many COVID–19 positive ALS patients have been identified at your center? How many patients were on (2) riluzole alone? (3) edaravone alone? (4) both riluzole and edaravone? (5) neither treatment? (6) Number of ALS patients seen at center from 1 Jan 2020 – 31 Mar 2020?

Results:
Reporting NEALS sites [26/133] identified 19 COVID-19 infections among 2926 ALS patients. The median and mode case rate was 0 but the range among sites reporting COVID-19 ALS cases varied from 5-200 COVID-19 infections per 1000 ALS patients with a mean 5.2 COVID-19 ALS cases per 1000 ALS patients [95% confidence limits = 0.7 – 9.6] across all reporting sites. There was no difference in COVID-19 incidence as a function of riluzole or edaravone use: no riluzole | no edaravone – 7 / 19 [36.8 %]; riluzole alone – 8 / 19 [42.1 %]; riluzole | edaravone – 4 / 19 [21.1 %].

Conclusions:
The observed COVID-19 ALS case rate in 2926 ALS patients was 5.2 COVID-19 ALS cases per 1000 ALS patients [95% confidence limits = 0.7 – 9.6] comparable to COVID-19 case rate observed in European and USA cohorts of Parkinson's Disease (PD) and Multiple Sclerosis (MS) patients. The case rate was apparently not affected by treatment with/without riluzole, edaravone, or riluzole/edaravone together. Anecdotal reports of less severe COVID-19 disease in ALS patients on riluzole and edaravone require further investigation via a COVID-19 ALS Case registry.

EPI-12: Time trends and geographical analysis of motor neuron disease in the Netherlands

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Live Poster Session B, December 10, 2020, 5:10 PM - 5:50 PM

Objective:
To assess time trends in MND incidence, prevalence and mortality and investigate geographical clustering of MND cases in the Netherlands from 1998 to 2017, we analyzed data from the Netherlands Personal Records database, the Netherlands MND Center and the Netherlands Patient Association of Neuromuscular Diseases.

Methods:
In this prospective cohort study, Poisson regression was used to assess time trends in MND risk. We calculated age- and sex-standardized, observed and expected cases for 1,694 areas. Cox regression was used to determine whether survival, adjusted for the ENCALS individualized prediction model, has changed since 2006. Bayesian smoothed risk mapping was used to investigate geographical MND risk.

Results:
We identified 7,992 MND cases, reflecting an incidence of 2.64 (95% CI 2.62-2.67) per 100,000 person-years and a prevalence of 9.5 (95% CI 9.1-10.0) per 100,000 persons. Highest age-standardized prevalence and mortality rates occurred at a later age in men than in women (p<0.001).
In 2017, 0.31% of all recorded deaths in the Netherlands were MND-related, resulting in a lifetime risk of 1 in 323. Unadjusted mortality rates increased by 53.2% from 2.57 in 1998 to 3.86 per 100,000 person-years in 2017. After adjustment for age and sex, an increase in MND mortality rate of 14.1% (95% CI 5.7%-23.2%, p<0.001) remained. After adjustment for the ENCALS risk profile, median survival time increased from 19.6 months (95% CI 18.7-20.9) to 22.4 months (95% CI 21.1-23.7) for patients diagnosed in 2006 and 2017 (p=0.006), respectively. MND relative risk ranged from 0.78 to 1.43 between geographical areas; multiple urban and rural high-risk areas were identified.

Conclusions:
We found a significant national increase in MND mortality from 1998 through 2017, only partly explained by an ageing Dutch population, and also a geographic variability in MND risk, suggesting a role for environmental or demographic risk factors. Median survival time improved by three months from 2006 through 2017, possibly as a result of improved multidisciplinary care.

EPI-13: A comparative study of South African and Portuguese amyotrophic lateral sclerosis cohorts

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Live Poster Session C, December 11, 2020, 12:05 PM - 12:50 PM

Background:
Data on the epidemiological and clinical aspects of ALS originate from a few world regions, and very little is known about ALS in low and middle-income countries, in particular Sub-Saharan Africa. Reports on the management of ALS in low and middle-income countries is lacking, and such data are fundamental to the understanding of the global efforts that are being developed to fight ALS. Objective: This study attempts to provide preliminary perspectives on the clinical features and management of ALS in Sub-Saharan Africa by comparing two cohorts from South Africa (SA) and Portugal. Methods: The study was performed at ALS clinics at Tygerberg Hospital, Cape Town, South Africa (n = 124), and Centro Hospitalar Universitário Lisboa-Norte, Portugal)(n = 238). The study consisted of two parts – in the first part, collection of cross-sectional data at the time of diagnosis was done while, in the second part, longitudinal data on the clinical course of ALS in both cohorts. We included all patients diagnosed over a four-year period, and collected demographic and clinical data at diagnosis, longitudinal data on disease progression and management over 12 months, and mortality rates at 12 and 24 months. Statistical analysis: Differences between the two groups were compared by non-parametric Fisher's exact test for categorical variables and the Mann-Whitney test for continuous variables. Kaplan-Meier Survival curves were performed for the 12- and 24-month time points, and differences between groups were compared by means of the log-rank (Mantel-Cox) test. Results: SA patients were younger and had a higher rate of spinal-onset disease than their Portuguese counterparts. During the 12-month follow-up, NIV was introduced in half of the Portuguese patients, but only a quarter of SA patients (50.2% PT vs 25%SA; p < .001). Parenteral nutrition was introduced in less than 10% of patients in both groups. No SA patients used riluzole, while 100% of Portuguese patients did. Mortality rates were significantly higher in the SA cohort at both 12 months (35% vs 16%; p < .0001) and 24 months (63% vs 39%; p < .0001). Cox proportional hazards analysis, adjusting for multiple covariates, indicated a persistent significant survival advantage for Portuguese patients at both 12 months (HR 0.41, 95% CI 0.23 to 0.75,p = 0.004) and 24 months (HR 0.28, 95% CI 0.13 to 0.61, p =0 .001).Conclusions: Although SA patients were younger and more likely to have a spinal-onset disease, mortality was higher in this cohort. There was a significant difference in the utilization of NIV and riluzole between the two cohorts, both of which may influence survival.

EPI-14: Combinations of Environmental Contaminants Spatially Associated With ALS Risk

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Live Poster Session C, December 11, 2020, 12:05 PM - 12:50 PM

Background:
Most ALS cases are sporadic, which gives rise to theories that environmental associations with pesticides, cyanobacteria, toxic metals, and solvents may be implicated. Knowing the identities of potential causal exposures could help in preventing ALS and modulating its progression. Large industrial facilities are permitted airborne release of certain chemicals with hazardous properties, although they are required to report the amounts to the US Environmental Protection Agency as part of its Toxics Release Inventory monitoring program.

Hypothesis:
ALS etiology may be associated with environmental risk factors, such as toxic industrial chemicals. We intend to investigate the main effects of these chemicals on the ALS rate and also their possible interactions.

Methods:
We estimated residential exposure to environmental contaminants as risk factors for ALS by using Geographical Information System methodologies applied to large medical claims databases. The Symphony Integrated Dataverse® included “zip3” regions of residence at diagnosis of ~26,000 nationally distributed ALS patients, matched 3:1 on age and gender to non-ALS controls. The outcome is the log-transformed proportion of ALS cases in each of the 863 zip3 regions nationwide. We mapped data on industrial releases of 523 airborne contaminants reported to the Toxics Release Inventory and overlaid the amount of each contaminant released in each region to estimate local exposure. In the first step of the analysis, we transformed chemicals into categorical variables based on an efficient dynamic programming algorithm, which aims to solve the problem of zero-inflation in the dataset. We then employed the variable selection algorithm lasso to select chemicals associated with ALS rate. Finally, we investigated the main effects and interactions among the selected chemicals using regression models, testing the benefit of using the interaction-effect model against the model with main effects only.

Results:
With the given tuning parameter, air releases of the following six chemicals were selected for relation to ALS as by lasso: butyl acrylate, catechol, dichloromethane, nitric acid, styrene, and trichloroethylene (P-values <0.003). These six chemicals showed statistically significant positive associations with ALS rate. We are also identifying the pairwise interaction effects. Comparison of the models with and without interactions supported the use of the interaction-effect model.

Discussion:
This project involved developing and implementing an analytic pipeline for using large healthcare claims datasets to identify geospatial environmental contaminants associated with ALS rates. Our results support future evaluation of these environmental chemicals as potential etiologic contributors to sporadic ALS risk and as targets for exposure mitigation.

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EPI-15: Motor Neuron Disease Register for England, Wales and Northern Ireland – an analysis of incidence in England

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Live Poster Session C, December 11, 2020, 12:05 PM - 12:50 PM

Introduction:
Output from the MND Register for England, Wales and Northern Ireland reported an age and sex adjusted incidence of 2.072 /100,000 person-years (95% CI 2.072, 2.073) for a subset of England in which there was adequate data for reporting. In this study we will update and expand on estimates of incidence as well as reporting on other epidemiological analyses.

Methods:
People with a diagnosis of ALS given by a consultant neurologist and whose postcode of residence is within England, Wales or Northern Ireland were eligible. The catchment area is based on data contributors that have been participating since 2018.

Results:
15 centres have been participating since 2018, significantly expanding the catchment area of the MND Register. Age- and sex- adjusted incidence will be calculated for this expanded group.

Discussion:
There are now additional centres participating in the MND Register, allowing updated incidence calculations and expanded epidemiological analysis.

EPI-16: The Incidence of Amyotrophic Lateral Sclerosis in Ohio 2016-2018

Dr. Angeline Andrew[1], Dr. Erik Pioro[2], Meifang Li[3], Dr. Xun Shi[3], Jiang Gui[4], Dr. Elijah Stommel[1], Tanya Butt[1], Daniel Peipert[1], Patricia Henegan[1], Dr. Maeve Tischbein[1], Pamela Cazzolli[5], Dr. John Novak[6], Dr. Adam Quick[7], Dr. Kenneth Pugar[8], Dr. Komal Sawlani[9], Dr. Bashar Katirji[9], Dr. Todd Hayes[10], Dr. Kevin Horton[11], Dr. Paul Mehta[11], Professor Walter Bradley[12]

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Live Poster Session C, December 11, 2020, 12:05 PM - 12:50 PM

Background:
Amyotrophic lateral sclerosis (ALS) results from interactions between multiple environmental and genetic factors (1, 2). The incidence of ALS varies worldwide (3). Some of this variation may be due to exposure to environmental contaminants in the local environment. To investigate gene-environment-time interactions, we have studied the incidence of ALS in Ohio, a state with industrial and agricultural toxicants and lakes with cyanobacterial blooms.

Objectives:
To collect all cases of ALS diagnosed among Ohio residents over a two-year period (October 1, 2016 to September 30, 2018).

Methods:
We developed a network of neuromuscular centers in Ohio based on the Cleveland Clinic and collected all incident cases with Awaji criteria of definite, probable, and possible ALS during the time window. Cases were mapped to their location of residence. We developed a new method to correct the incidence calculations for counties in which we hypothesize that patients were either cared for in non-participating centers or traveled outside Ohio for care.

Results:
The observed distribution of age- and gender-standardized ALS rate was not uniform across counties, ranging from 0 to 13/100,000 patient-years. We estimated the number of missing cases by selecting the counties that had adjusted incidence rates within 0.5 standard deviation around the mean adjusted rate of all counties and assumed that in these counties recruitment was complete. We then applied linear regression analyses to build the case-population relationships for the counties suspected to have an under-recruitments of cases to calculate the expected case counts. After adding the estimated missed cases, the corrected crude incidence was 1.66/100,000 patient-years and the age- and gender-standardized incidence rate for Ohio was 1.45/100,000 patient-years.

Discussion:
The overall incidence of ALS in Ohio is similar to that in other parts of the USA (4,5). The distribution of ALS cases was not uniform across all Ohio counties, with possible “hot spots” that may have higher than expected rates. We are investigating these areas using geospatial techniques, biosamples and residential and lifestyle exposures to pollutants and cyanobacteria using these ALS cases and random population-based controls to investigate ALS gene-environment interactions.

References:
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EPI-18: Trends in survival of ALS from a population-based registry

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Live Poster Session C, December 11, 2020, 12:05 PM - 12:50 PM

Objective:
To assess the trend of survival of patients with ALS comparing two periods (1998-2000 vs. 2008-2010), in general and by selected demographic and clinical variables.

Population and Methods:
The study population included adult subjects receiving a diagnosis of ALS while resident of the Lombardy region, Northern Italy, during the two study periods. All eligible patients were included in a population-based registry (SLALOM). Patients were diagnosed using the original El-Escorial criteria. Diagnostic criteria and methods of case ascertainment did not change between the two periods. ALS diagnosis was verified during follow-up and patients in whom the diagnosis was not confirmed were excluded. For each eligible case, data were collected – among others - on age at diagnosis, sex, site of onset (bulbar/generalized vs. spinal), disease duration at diagnosis, and El-Escorial diagnostic category. Patients were followed until death or last observation, whichever came first. Time to end-point (death) was measured with Kaplan-Meier curves and compared between periods with the log-rank test, in the entire sample and then in subgroups defined according to the collected demographic and clinical variables. Multivariable analysis was performed using a Cox's proportional hazards model.

Results:
A total of 235 patients were enrolled during the first period and 358 during the second period. Median survival of patients enrolled in the first period was 2.2 years (interquartile range 1.0-4.3). The 1-year, 2-year, 3-year and 5-year survival rates were 77%, 53%, 38% and 20%. The corresponding values in patients enrolled in the second period were, respectively, 2.4 years (interquartile range 1.1-5.0) and 79%, 56%, 41% and 24%. The difference between the two periods was not statistically significant. However, when adjusting for demographic and clinical variables, a significant difference in survival between the two periods was found. The adjusted hazard ratio for death for the period 2008-2010 versus the period 1998-2000 was 0.80 (95% CI 0.66-0.98). When comparing 5-year survival in subgroups of patients defined according to demographic and clinical characteristics, a significant increase in the second period was found only in patients aged 50-59 years at diagnosis (25% vs. 38%; p=0.0295), and in patients aged 70-74 years (3% vs. 22%; p=0.0049).

Conclusions:
Overall, survival of ALS has not apparently increased with time in the last decades. However, when adjusting for selected demographic and clinical variables, a significant increase was documented. The aging of the population and the benefits of comprehensive care only in selected age groups might explain our finding.