RESEARCH ARTICLE

Global Prevalence and Incidence of Amyotrophic Lateral Sclerosis

A Systematic Review

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Abstract

Background and Objectives

Amyotrophic lateral sclerosis (ALS) is a rare neurodegenerative disorder affecting upper and lower motor neurons. Due to its rarity and rapidly progressive nature, studying the epidemiology of ALS is challenging, and a comprehensive picture of the global burden of this disease is lacking. The objective of this systematic review was to describe the global incidence and prevalence of ALS.

Methods

We searched MEDLINE, Embase, Global Health, PsycInfo, Cochrane Library, and CINAHL to identify articles published between January 1, 2010, and May 6, 2021. Studies that were population based and reported estimates of prevalence, incidence, and/or mortality of ALS were eligible for inclusion. This study focuses on the incidence and prevalence. Quality assessment was performed using a tool developed to evaluate methodology relevant to prevalence and incidence studies. This review was registered with PROSPERO, CRD42021250559.

Results

This search generated 6,238 articles, of which 140 were selected for data extraction and quality assessment. Of these, 85 articles reported on the incidence and 61 on the prevalence of ALS. Incidence ranged from 0.26 per 100,000 person-years in Ecuador to 23.46 per 100,000 person-years in Japan. Point prevalence ranged from 1.57 per 100,000 in Iran to 11.80 per 100,000 in the United States. Many articles identified cases with ALS from multiple data sources.

Discussion

There is variation in reported incidence and prevalence estimates of ALS across the world. While registries are an important and powerful tool to quantify disease burden, such resources are not available everywhere. This results in gaps in reporting of the global epidemiology of ALS, as highlighted by the degree of variation (and quality) in estimates of incidence and prevalence reported in this review.

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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

ALS = amyotrophic lateral sclerosis; **GBD** = Global Burden of Disease; **MND** = motor neuron disease; **QA** = quality assessment; **UI** = uncertainty interval.

Introduction

Amyotrophic lateral sclerosis (ALS) is a rare neurodegenerative disorder affecting upper and lower motor neurons. ALS is the most common disease of a class of conditions referred to as motor neuron diseases (MND), which includes progressive bulbar palsy, primary lateral sclerosis, and progressive muscular atrophy. The course of ALS is rapidly progressive, with loss of ambulation and eventual respiratory failure leading to death. Substantial variability in published survival estimates may partly be explained by differences in diagnostic journey and/or access to specialized care.[1] Approximately 5%–10% of affected individuals have a familial form of ALS, the more common sporadic form is believed to be caused by, as yet, unspecified interactions of genetic and environmental factors. Studying the epidemiology of ALS is challenging due to the rarity of the disease, the need for specialized expertise to provide a diagnosis, and the availability of ongoing specialized care. Given these challenges, several studies have used death certificates as a proxy for incidence due to the disease's rapidly fatal course. Despite its low incidence, the burden on individuals, their family and friends, the healthcare system, and society as a whole is high.[2] The epidemiology of ALS has been the subject of investigations for many years, yet a comprehensive picture of the variability of the global burden of this disease is lacking.

In the past decade, there have been 3 published systematic reviews of the global epidemiology of ALS and 1 systematic review of the epidemiology of ALS in Africa.[3-6] Search time frames covered up to 2011,[3] up to 2015,[4] and up to 2018.[5] The main objective of this systematic review was to provide a comprehensive update on the epidemiologic landscape of ALS.

Methods

Search Strategy

We searched MEDLINE, Embase, Global Health, PsycInfo, Cochrane Library, and CINAHL to identify relevant articles published between January 1, 2010, and May 6, 2021. The search strategy was developed in consultation with a librarian (A.B.) at the McGill University Health Centre (eAppendix 1, links.lww.com/WNL/C896). No language restrictions were imposed in the initial search. This study is registered with PROSPERO under ID number CRD42021250559 and adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Relevant studies were also flagged during abstract and title screening of a second review on surveillance strategies for ALS being conducted in parallel by our group and were included (if not already) in this review.

Inclusion and Exclusion Criteria

The criteria for study inclusion were as follows: population-based observational studies reporting estimates of prevalence, incidence, and/or mortality (including survival) of ALS. The study included individuals with ALS with no restrictions on age, sex, or disease severity. Systematic reviews and meta-analyses were retained for background and their references searched but were excluded as sources of original data. Duplicate publications, conference proceedings, case reports, and clinical trials were excluded. Articles with an abstract only, where no full text was available, and articles published in a language other than French or English for which translation was not possible were also excluded. The initial search included all epidemiologic parameters, but we focus on the results of the incidence and prevalence studies in this article.

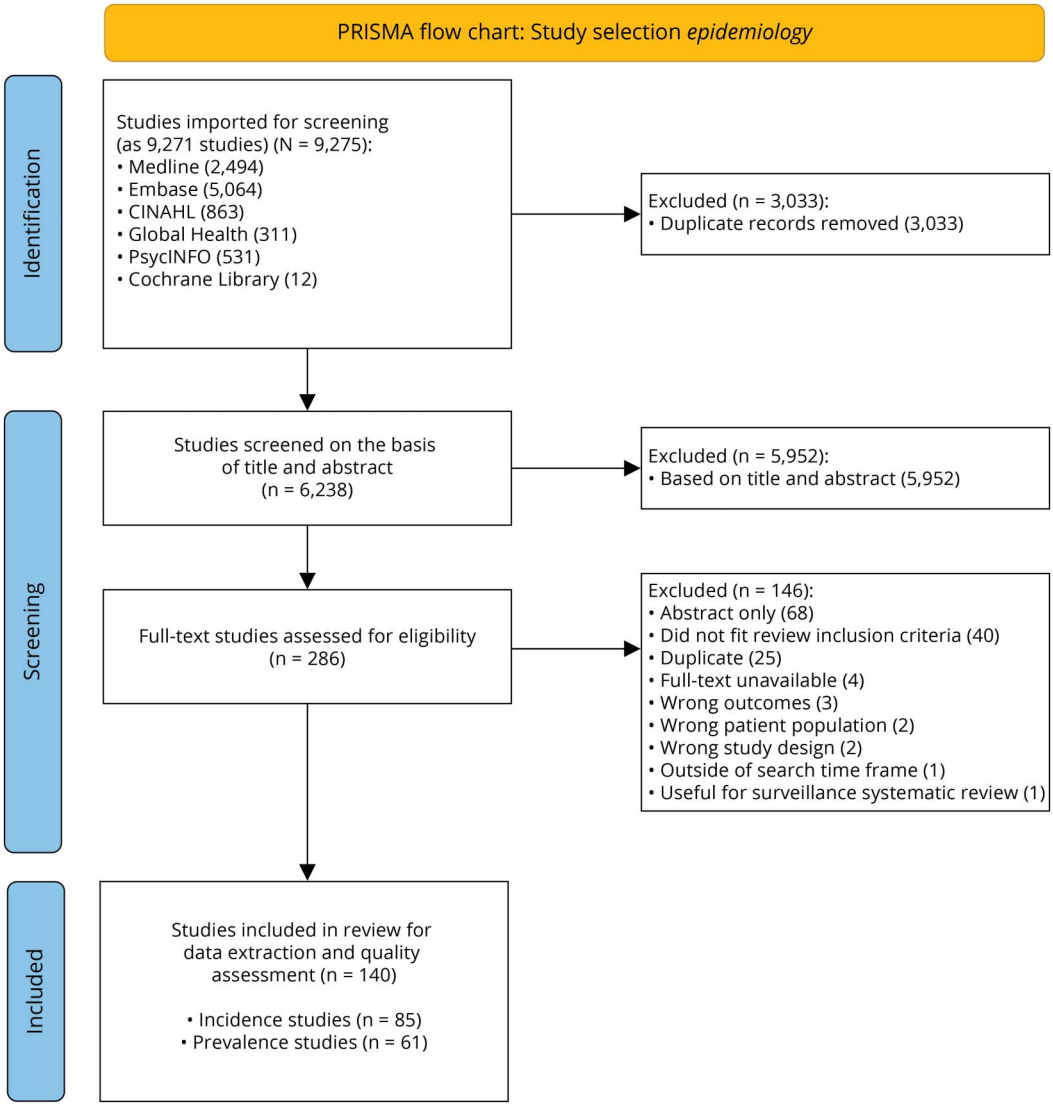
Quality Assessment

Each publication selected for data extraction was independently reviewed using a quality assessment (QA) tool that included the evaluation of methodology relevant to epidemiologic research. This tool was developed based on those used in previous systematic reviews of prevalence and incidence of neurologic conditions and on general guidelines for assessing epidemiologic studies.[7-9] The QA tool consisted of modules assessing sample representativeness, assessment of ALS, and statistical analysis (eAppendix 2, links.lww.com/WNL/C896). Recent standards in ALS diagnostic criteria were reviewed by a neurologist (M.O.) and incorporated into both the data extraction and QA forms. The QA tool was piloted on 1 published study by each team member and curated to grade the quality of each study. The denominator of the QA score varied depending on the number of parameters estimated (i.e., incidence, prevalence, survival, and/or mortality) and consisted of 9 questions with the following response options: yes, no, unclear, not reported, or not applicable. If the answer to a question was not applicable, it was not included in the denominator total. QA scores were obtained by dividing the numerator (i.e., number of questions answered "yes") by the denominator (i.e., total number of applicable questions for the study). The first 7 questions addressed issues of study design, and questions 8 and 9 assessed the information provided in the results.

Data Extraction

This systematic review was managed using Covidence.[10] Screening of titles and abstracts for eligibility was completed by 3 reviewers (D.E.G., F.I., and C.W.) independently. Articles at each stage of the review process required 2 reviewers to vote, while the third adjudicated disagreement(s). After this initial screen, full-text versions of the articles selected were retrieved and further reviewed to confirm eligibility and

Figure 1 Study Selection Flowchart



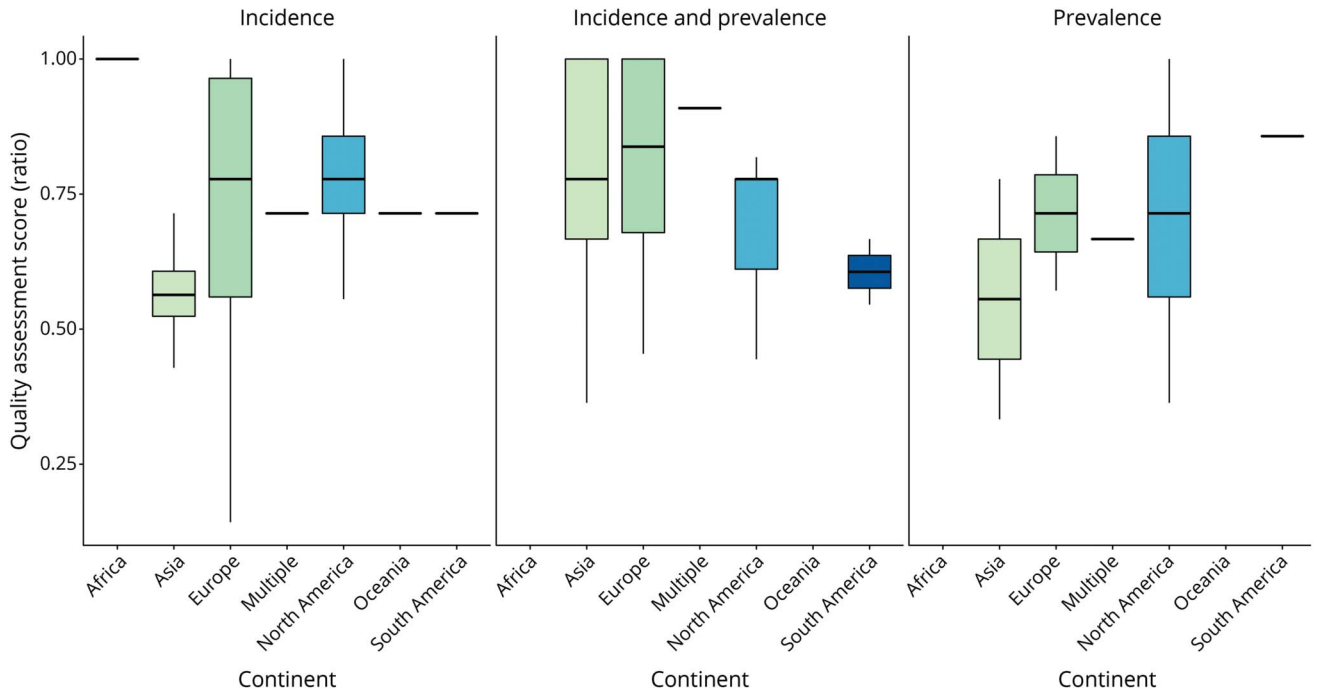
These totals include studies that reported on ALS mortality/survival. ALS = amyotrophic lateral sclerosis; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

inclusion in the systematic review. This step was performed independently by 2 of the 3 reviewers, with disagreements adjudicated by the third reviewer. Two reviewers then independently assessed all eligible studies and compiled selected information in a data extraction form. The following information was sought: publication and study characteristics (publication year, author, study period, and study region), study population characteristics, case definition of ALS, and reported outcomes (incidence, prevalence, mortality, and/or survival) with corresponding CIs and statistical approaches (e.g., age adjustment, reference population, etc). Data extraction form was piloted on select studies by all team members.

Statistical Analysis

We present the results per study along with the median (and Q1, Q3) crude incidence and prevalence for each continent and overall. Age-adjusted and sex-adjusted values were not reported for all studies. To have the most coverage and make the most of our included studies, we opted to report only crude estimates in the body of the article. eTables 1 and 2 (links.lww.com/WNL/C896) include adjusted incidence and prevalence estimates per study, respectively, where available. Given the variation in methodology and results from the individual studies, it is our view that the creation of pooled estimates through meta-analysis would likely obfuscate the findings. We present ranges in estimates in the body of the article, and additional study-specific information is available in eTables 1 and 2. Countries were grouped by continent per the United Nations classification of geographical regions.[11] The Americas were further subdivided into North and South America. When several articles reported on the same cohort, the most recent/comprehensive study was retained in the

Figure 2 Distribution of QA Scores for Studies Reporting Incidence Only, Prevalence Only, or Both, Stratified by Continent



QA scores were obtained by dividing the numerator (i.e., number of questions answered "yes") by the denominator (i.e., total number of applicable questions for the study). The maximum attainable score for a study that assessed 1 parameter (incidence, prevalence or mortality/survival) was 9. If the study assessed 2 parameters, the maximum attainable score was 11, and if all 3 parameters were assessed the maximum attainable score was 13. The greater the score (i.e., the closer the ratio of the numerator and denominator is to 1), the greater the quality of the study based on the parameters evaluated in the QA tool. QA = quality assessment.

figures/country estimates. For readability, outliers (i.e., large estimates of incidence/prevalence) were excluded from figures and indicated in the footnotes of relevant figure(s). All data visualization and descriptive analyses were performed using R version 4.1.0.[12]

Data Availability

Requests for access to the data reported in this article will be considered by the corresponding author.

Results

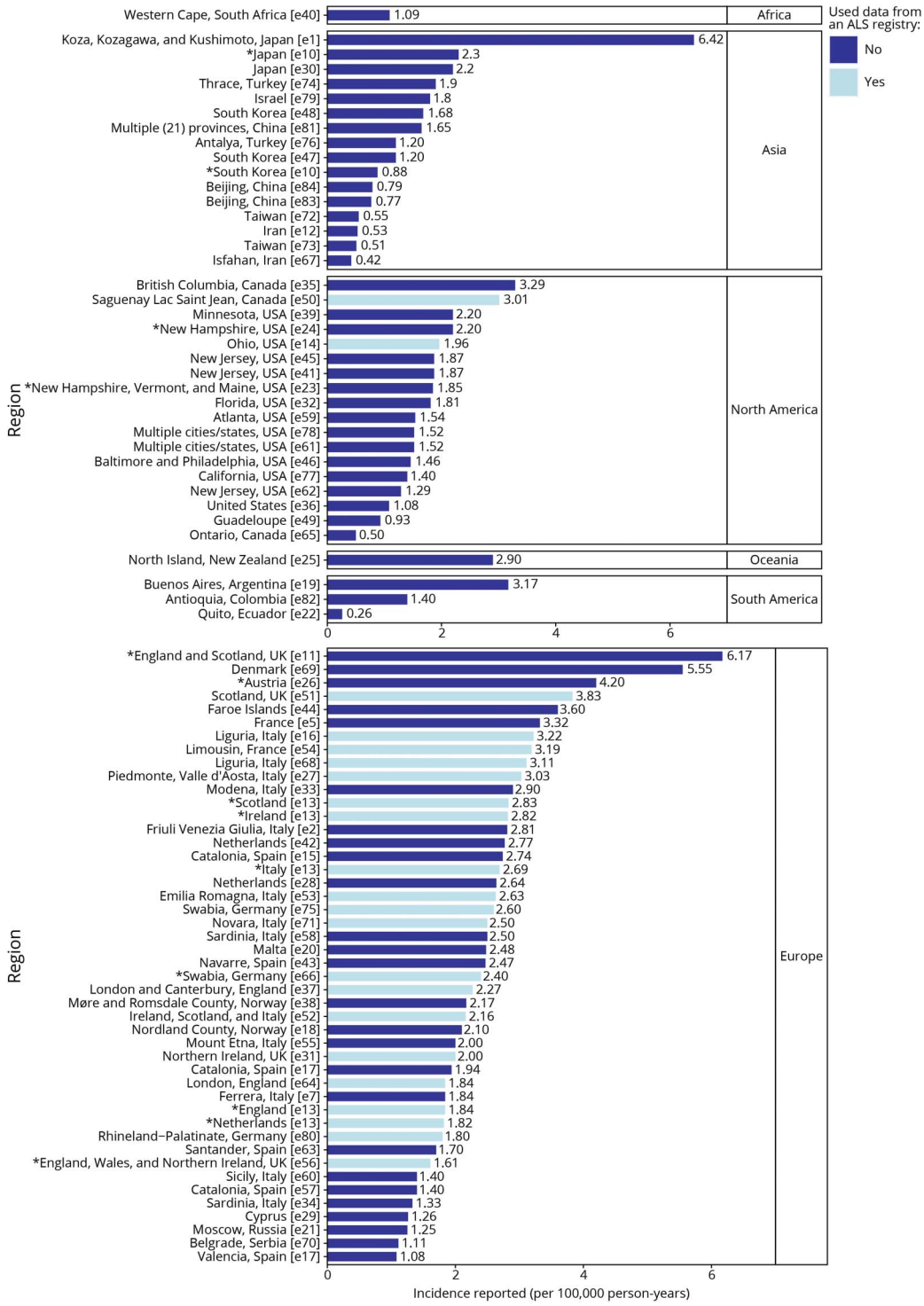
From the database searches (Figure 1), 6,238 articles were included for title and abstract screening. After screening, 286 articles were retained for a full-text review, and 4 articles where English translation was not possible or full text was not available were excluded. After a full-text review, 140 articles (this total includes mortality/survival) were selected for data extraction and QA. Of these, 44 articles reported on both incidence and prevalence, 41 on incidence only, and 17 on prevalence only. The 38 articles focusing on mortality/survival were not included in the results presented in this study. Boxplots of the QA score distributions stratified by continent are presented in Figure 2. The median (Q1, Q3) QA score was 0.78 (0.57, 0.89). Overall, 39 (38.24%) of the studies attained a quality score of at least 0.85, indicating a high degree of rigor. There were no obvious patterns in QA scores by continent or whether the articles reported only incidence, only prevalence, or both. eTables 1 and 2 (links.lww.com/WNL/C896) provide detailed information extracted from the studies.

Incidence and Prevalence of ALS by Continent

An overview of results from studies reporting incidence per 100,000 person-years (for most recent year reported) by continent and city (when applicable) are presented in Figure 3. Of the 85 studies reporting estimates of ALS incidence, more than half (48) were conducted in Europe, 17 in North America, 13 in Asia, 3 in South America, 1 in Africa, and 1 in Oceania, and 2 reported estimates from multiple continents. Time frames for which incidence estimates were reported ranged from 1960 to 2018. The few studies for which only adjusted estimates were available are noted by an asterisk in Figure 3. Bars shown in pale blue identify studies that included registries as a source of cases. The median incidence by continent and overall is summarized in Figure 4, showing similar crude incidence estimates across continents.

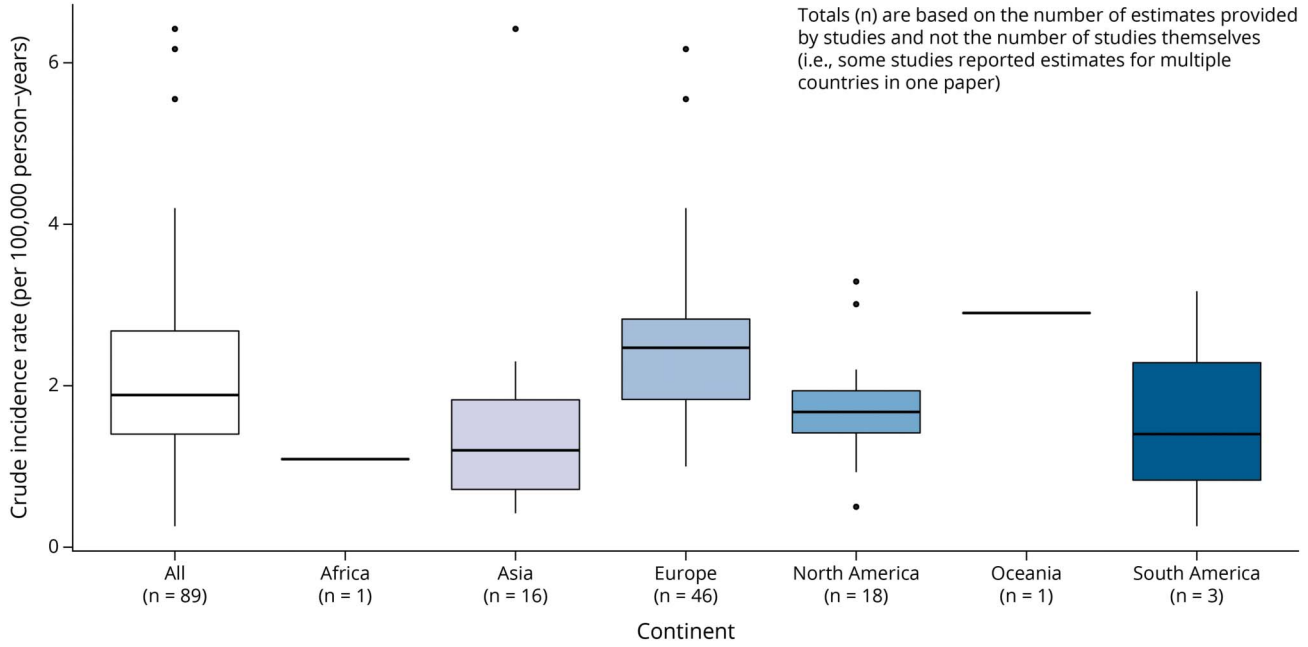
Of 61 studies reporting the prevalence of ALS, close to half (29) were conducted in Europe, 16 in North America, 11 in Asia, and 3 in South America, and 2 reported estimates of prevalence from multiple continents. Results from studies reporting prevalence by continent are displayed in Figure 5.

Figure 3 Crude Incidence Reported per Study, Stratified by Continent



*Adjusted incidence estimate. Excluded studies: Incidence of 23.46 per 100,000 person-years in Oshima, Japan (Kihira et al., 2012).[e1] Study conducted by Palese et al. (2019) is a continuation (extended study period, same methods) of a study conducted by Drigo et al. (2013), and we included only the most recent study by Palese et al. (2019) in Figures 3 and 4.[e2,e3] Similarly, Kab et al. (2017) and Ahmadzai et al. (2018) presented identical ALS incidence estimates in France, with overlapping study periods and identical data sources; thus, we included only the study conducted by Ahmadzai et al. (2018) in Figures 3 and 4.[e4,e5] Govoni et al. (2012 and 2015) presented updated estimates in their most recent study (inclusion of 1 additional incident case over the same study period); for this reason, only study conducted by Govoni et al. (2015) is included in Figures 3 and 4.[e6,e7] Two studies from Ireland (Rooney et al., 2014; Tobin et al., 2016) were omitted from Figures 3 and 4 because they did not report incidence rates (they reported measures of relative risk of ALS); these 2 studies are nevertheless summarized in eTable 1 (links.lww.com/WNL/C896).[e8,e9] One study (Vucic et al., 2020) reported incidence rates for Japan, South Korea, and Australia; however, the incidence of ALS in Australia was derived from mortality data and not estimated directly, so it was not included in Figures 3 and 4 for Oceania.[e10] One study from the United Kingdom used data from the UK Million Women Study, and the estimate provided in Figure 3 is an incidence rate per 100,000 women-years (originally presented per 1,000).[e11] ALS = amyotrophic lateral sclerosis.

Figure 4 Overall Median Incidence and per Continent



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Across studies, the period in which estimates of prevalence were reported ranged from 1990 to 2018. Studies for which only adjusted estimates were presented are noted by an asterisk in Figure 5. Bars shown in dark green identify period prevalence studies, while bars in light green represent point prevalence studies. The median period and point prevalence varied across continents (Figure 6).

Africa

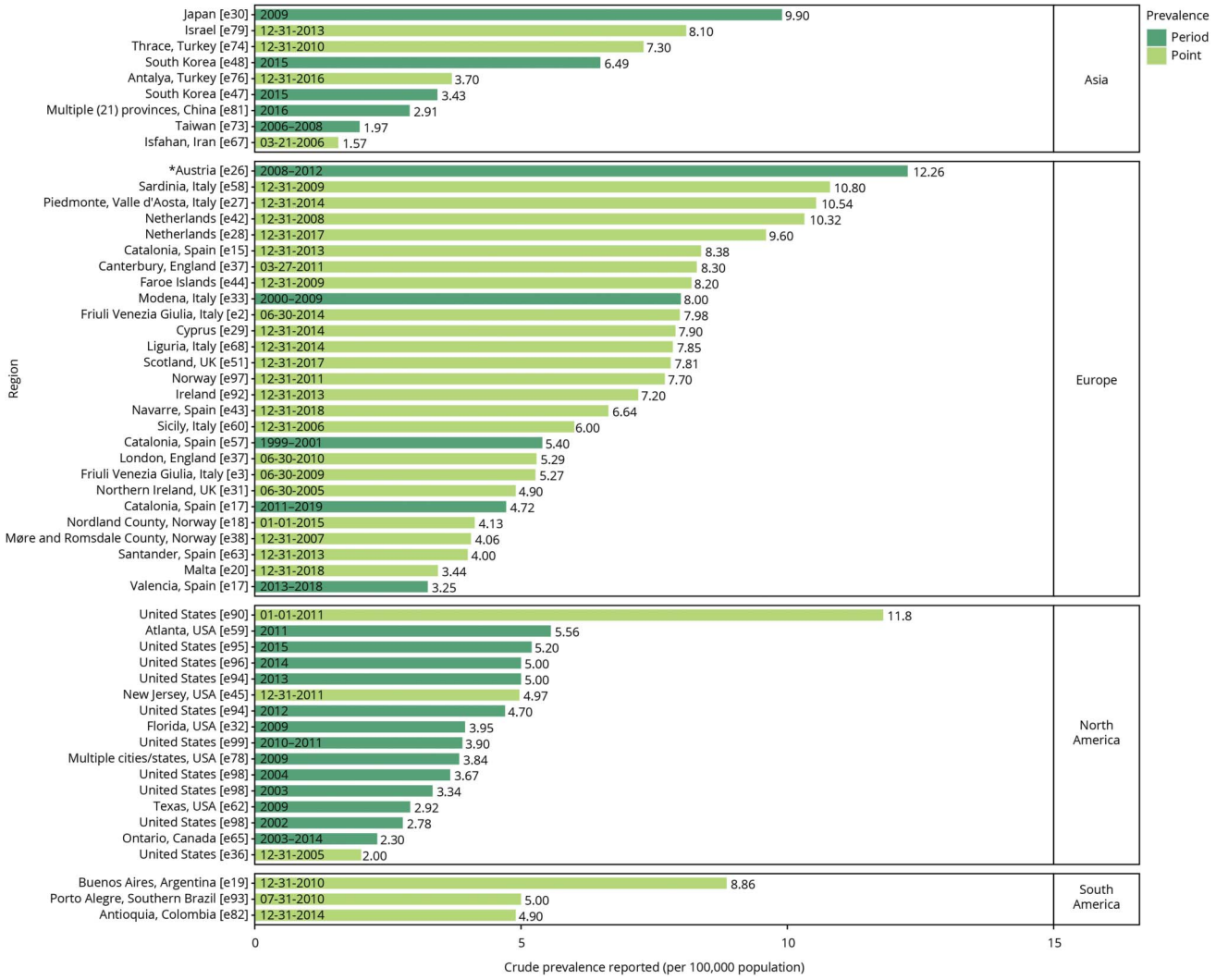
There was only 1 ALS incidence study from Africa (Western Cape, South Africa) included in this review.[13] The study period spanned from 2014 to 2018, and 203 incident cases (per El Escorial criteria) were identified. Multiple sources of cases were used, including ALS clinics, neurology clinics, and the MND/ALS Association of South Africa. Two source capture-recapture analysis was used to estimate the number of cases not included in the sources used. The authors report a crude average annual incidence rate of 1.09 (95% CI 0.94–1.24) per 100,000 person-years and an adjusted (capture-recapture) estimate of 1.11 (1.01–1.22) per 100,000 person years. There were no ALS prevalence studies in Africa identified as part of this review.

Asia

There were 16 publications that reported on the incidence and/or prevalence of ALS in Asia. These studies identified cases from several sources including insurance records, hospital records, government financial aid records, and door-to-door surveys, and 1 study used data from Global Health Data Exchange. Most studies used the Revised EI Escorial criteria, others used (*International Classification of Diseases, Ninth/Tenth Revision*), and neurologist/physician diagnosis. The average annual crude incidence in Asia ranged from 0.42 per 100,000 person-years in Iran[14] (no CI) to 2.20 per 100,000 person-years (95% CI 2.10–2.30) in Japan.[15] Markedly higher incidence rates of 6.42 per 100,000 person-years were reported in the Kii Peninsula and 23.46 per 100,000 person-years in Oshima, Japan (no CI).[16]

The point prevalence of ALS was reported in 11 studies from Asia with estimates ranging from 1.57 per 100,000 in Iran[14] to 8.10 per 100,000 in Israel.[17] Point prevalence from a study conducted in Indonesia reported extreme values with point estimates of 73.00 (95% CI 0–156) per 100,000 and 133.00 (95% CI 27–240) per 100,000.[18] This study was conducted in the southern coastal regions of Papua, Indonesia, with relatively few study participants (population of 4,100 and 4,500 people). Similarly, a study conducted by Mansukhani et al.[19] (2018) in Gujarat, India, reported a prevalence of 109.53 (no CI) per 100,000 for upper MND and 1,010.10 per 100,000 for lower MND. Period prevalence estimates over various time frames ranged from an average annual prevalence of 1.97 per

Figure 5 Crude Prevalence Reported per study, Stratified by Continent



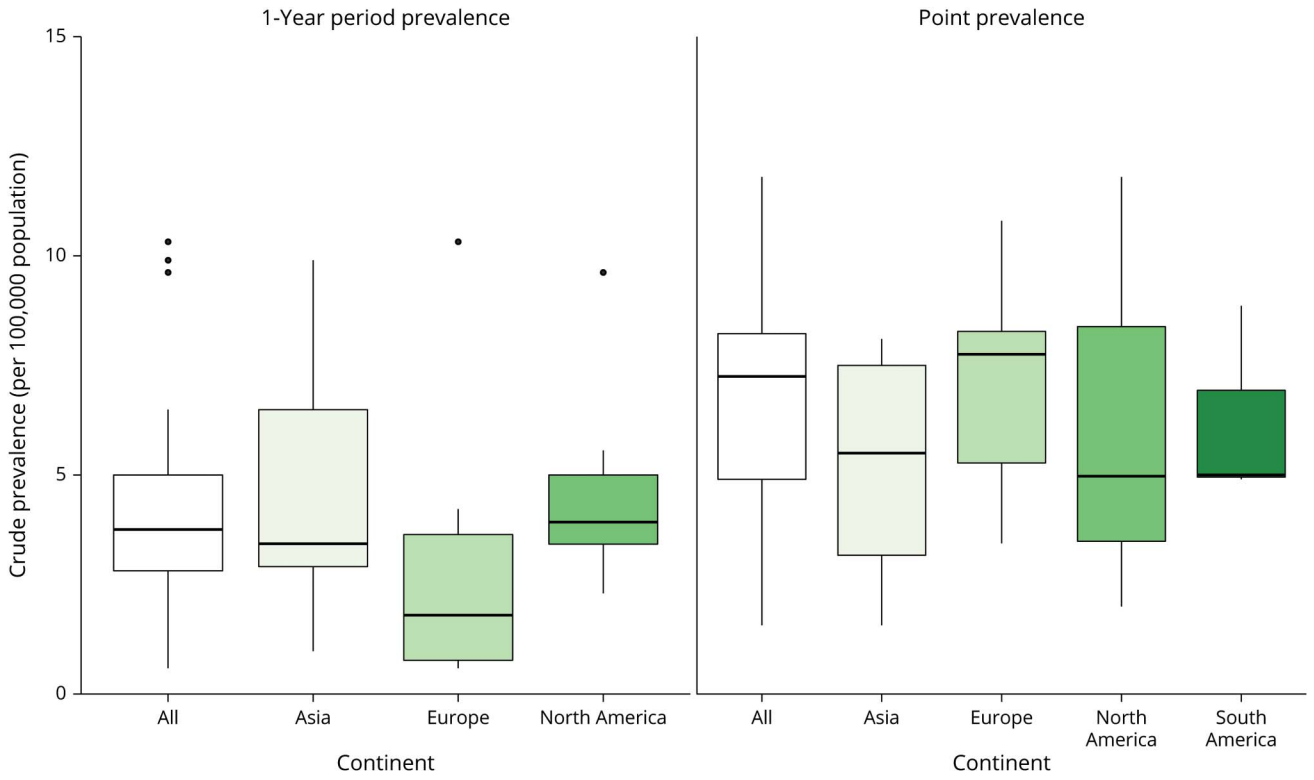
Point prevalence date/ period is noted in each study's respective bar. *Adjusted prevalence estimate. Excluded studies: Point prevalence for a study from Indonesia (Okumiya et al., 2014) reported extreme values with point estimates of 73.00 (95% CI 0–156) per 100,000 and 133.00 (95% CI 27–240) per 100,000.[e85] Mansukhani et al. (2018) in Gujarat, India (8,537 individuals from 1,464 households across 3 villages) reported a prevalence of 109.53 (no CI included) per 100,000 for upper motor neuron disease and 1,010.10 per 100,000 for lower motor neuron disease.[e86] One study from the Faroe Islands (Johansen et al., 2020) reported a period prevalence over a 20-year period (1987–2016) of 122.50 per 100,000 inhabitants (original estimate was presented per 1,000).[e87] Rosenbohm et al. (2017) did not estimate prevalence directly but used estimated mean survival and estimated incidence to derive an estimate of prevalence.[e66] Conde et al. (2019) used riluzole consumption as a proxy for ALS diagnosis (with no other measures of validation); this study was also excluded.[e88] Wittie et al. (2014) reported a period prevalence of 38.50 per 100,000 over a 5-year period, 2001–2005, in Georgia, United States.[e89] Bhattacharya et al. (2019) reported a 5-year (2007–2011) period prevalence of 20.50 per 100,000.[e90] Sagiraju et al. (2020) reported a prevalence of 19.70 per 100,000 over a period of more than a decade (2001–2015) among the post-9/11 Veteran population in the United States.[e91] ALS = amyotrophic lateral sclerosis.

100,000 over 3 years (2006–2008) in Taiwan[20] to a 1-year period prevalence (2009) of 9.90 per 100,000 in Japan.[15] Prevalence in South Korea over a 1-year period ranged from 3.43 per 100,000 to 6.49 per 100,000.[21,22]

Europe

We identified 51 studies that reported the incidence and/or prevalence of ALS in Europe. Three studies reported prevalence alone, 22 studies reported only incidence, and 26 studies reported both incidence and prevalence. Several studies used data from European population–based ALS registers. Many studies used multiple sources of data, which in addition to ALS registries included health databases (e.g., hospital discharge, death, and pharmacy records), membership lists from regional ALS patient associations, neurology departments, and ALS clinics. In Europe, overall, the average annual crude incidence ranged from 1.11 per 100,000 person-years in Serbia[23] to 5.55 per 100,000 person-years in Denmark.[24] Most studies reported incidence rates higher in men than in women with a peak incidence at 70–79 years of age, declining thereafter. Fourteen of the studies were from Italy. Crude average annual incidence rates in Italy ranged from 1.33 per 100,000 person-years in Sardinia[25] to 3.22 per 100,000 person-years in Liguria.[26] The lowest incidence rates in all the European studies were reported for Serbia,[23] Russia,[27] and Cyprus.[28] The highest incidence rates reported were for

Figure 6 Overall Median (1-Year Period and Point) Prevalence and per Continent



For studies reporting a period prevalence of greater than 1-year interval (n = 11), 1-year prevalence was computed. Excluded studies: point prevalence for a study from Indonesia (Okumiya et al., 2014) reported extreme values with point estimates of 73.00 (95% CI 0–156) per 100,000 and 133.00 (95% CI 27–240) per 100,000.[e85] Mansukhani et al. (2018) in Gujarat, India (8,537 individuals from 1,464 households across 3 villages) reported a prevalence of 109.53 (no CI included) per 100,000 for upper motor neuron disease and 1,010.10 per 100,000 for lower motor neuron disease.[e86] Rosenbohm et al. (2017) did not estimate prevalence directly but used estimated mean survival and estimated incidence to derive an estimate of prevalence.[e66] Conde et al. (2019) used riluzole consumption as a proxy for ALS diagnosis (with no other measures of validation); this study was also excluded.[e88] ALS = amyotrophic lateral sclerosis.

Scotland,[29] Austria,[30] and Denmark.[24] The median crude incidence by continent (Figure 4) was highest in Europe (and Oceania).

Of the 29 prevalence studies in Europe, overall, point prevalence ranged from a 3.44 per 100,000 population in Malta[31] to 10.80 per 100,000 population in Italy.[32]

North America

In North America, 11 studies reported on incidence alone (8 from the United States, 2 from Canada, and 1 from Guadeloupe), 10 reported on prevalence alone (all from the United States), and 6 studies reported both incidence and prevalence (5 from the United States and 1 from Canada). The average annual crude incidence ranged from 0.50 to 3.29 per 100,000 person-years; these upper and lower ranges were from studies conducted in Canada.[33,34] Crude average annual incidence rates in the United States ranged from 1.08 per 100,000 person-years to 2.20 per 100,000 person-years.[35-37] Cases were ascertained from multiple sources, including the Ontario Health Administrative Database, ALS clinics and organizations, hospital inpatient databases, the ALS Society of BC patient database, and the US National ALS Registry. There was 1 study conducted in Guadeloupe, which reported an average annual crude incidence of 0.93 per 100,000 person-years.[38]

The point prevalence of ALS in North America ranged from 2.00 per 100,000 to 11.80 per 100,000 in the United States.[35,39] Most 1-year period prevalence studies of ALS in North America were from the United States and used data from the National ALS Registry (United States), with estimates ranging from 2.78 to 5.56 per 100,000.[40,41] We identified 1 period prevalence study of ALS in Canada, reporting an averaged period prevalence of 2.30 per 100,000 over nearly a decade (2003–2014).[33]

South America

In South America, there were 3 incidence studies, 1 each, from Argentina, Colombia, and Ecuador. Average annual crude incidences reported were 0.26 per 100,000 person-years in Ecuador,[42] to 1.40 per 100,000 person-years in Colombia,[43] and 3.17 per 100,000 person-years in Argentina.[44] There were 3 prevalence studies, 1 each, from Argentina, Colombia, and Brazil. Point prevalence was 4.90 per 100,000 in Colombia,[43] 5.00 per 100,000 in Brazil,[45] to 8.86 per 100,000 in Argentina.[44] Studies used records from hospitals, clinics, neurologists, and ALS organizations.

Oceania

Only 1 study was identified that included estimates of the incidence of ALS in Oceania. This study was conducted in

New Zealand and included 25 cases identified through clinical coding data at a hospital in Palmerston North, New Zealand.[46] Incidence was estimated at 2.90 per 100,000/year.

Global Burden of Disease

Three studies reporting both the incidence and prevalence of ALS in multiple countries used data from the Global Burden of Disease (GBD) Study.[47-49] The GBD is an initiative aimed to systematically quantify the global epidemiology of numerous health conditions. The GBD methodology has been detailed elsewhere.[49] Deuschl et al.[47] (2020) compared the burden of neurologic disorders in Europe (EU28; the 27 member countries of the European Union plus the United Kingdom) between 1990 and 2017. For 2017, they reported an age-standardized incidence rate of 1.00 (95% CI 1.00–2.00) per 100,000 person-years, and the age-standardized prevalence was 6.00 (5.00–7.00) per 100,000. Logroscino et al.[48] (2018) reported on the global, regional, and national burden of MND from 1990 to 2016; the all-age global incidence of MND was 0.78 (95% CI 0.71–0.86) per 100,000 person-years, and the prevalence was 4.50 (95% CI 4.10–5.00) per 100,000 over the study period (1990–2016). Vos et al.[49] (2017) reported on MND incidence and prevalence on a global, regional, and national level. In 2016, the global incidence of ALS was estimated to be 58,000 (95% uncertainty interval [UI] 52,000–63,000), and the prevalence was 331,000 (95% UI 300,000–367,000).

Abbastabar et al.[50] (2019) used GBD data and reported on the incidence of MND in Iran; the incidence for MND was 0.44 per 100,000 person-years in 1990 and 0.53 per 100,000 person-years in 2017. GBD data were also used to estimate incident and prevalent cases of MND in the United States; the crude incident cases were 0.0005 per 100,000 in 1990 and 0.001 per 100,000 in 2017, and the prevalent cases were 0.0025 and 0.0038 per 100,000, respectively.[51]

Discussion

We presented a comprehensive and updated systematic review of the global epidemiologic landscape of ALS. The most recent published systematic review of the global epidemiology of ALS[5] included studies published up until 2018. Marin et al. (2017) included only incidence publications (up until 2015) in their review, while the time frame for the review by Chio et al. (2013) was from 1995 to 2011 (a small window, 2010–2011, of overlap with the current review) (eTable 3, links.lww.com/WNL/C896).

Most studies of the epidemiology of ALS were conducted in Europe (48 reporting incidence, 29 reporting prevalence) and North America (17 reporting incidence, 16 reporting prevalence). Although gaps in reporting remain in some regions (i.e., Africa, Oceania, and South America had few studies), based on the available data, there is variability in the estimated incidence and prevalence reported both within and between countries and continents. The reasons for these differences remain to be fully explored and, in many cases, would require direct contact with authors and exchanging of detailed methodologies. Possible reasons are differences in case ascertainment, coverage and representativeness of target population(s), and genetic and/or environmental factors both within and across geographical regions. It is unlikely that major differences are because of differing diagnostic criteria because most studies used the Original or Revised El Escorial criteria. Regarding sources of cases, the most common were neurology departments, ALS registries, health records, insurance databases, hospital discharge data, death records, and pharmacy records. Many studies identified cases from multiple sources (51 reporting incidence, 32 reporting prevalence). Nearly half of the European studies (22 reporting incidence, 7 reporting prevalence) identified cases from ALS registries. Many prevalence studies (8) in the United States identified cases from the National ALS Registry.

As with all systematic reviews based on published studies, there were several challenges in conducting this work, including in some situations the lack of methodological detail. In future work, direct contact with study authors could permit the clarification of methodological questions and potentially the ability to conduct collaborative individual-level meta-analyses where appropriate and meta-regression to explore the differences due to the characteristics of the studies (continent, population size, case sources, etc). Because of the variation in methodology and results between individual studies, pooling estimates would likely obscure conclusions and reduce the global variation in ALS incidence and prevalence (and the lived experiences of those with ALS) down to 1 number lacking a wider context. Furthermore, while some included studies are dated and may no longer reflect contemporary standards of epidemiologic surveys, in reporting results, we opted to retain all studies that were within our review time frame and that passed our full-text review. Similarly, we did not exclude studies (that passed a full-text review) based on methodology or QA scores for completeness and transparency of reporting. A particular strength of our review lies in the comprehensive reporting of individual studies, painting a broader and more substantial picture of the epidemiologic landscape of ALS globally over the past decade. Comparing estimates across countries and continents allows the identification of gaps in knowledge and resources. In any systematic review, one can never be sure that all relevant studies are identified. Indeed, we excluded studies where a full-text version was not available or translation was not possible. However, this excluded only 4 studies. Our mitigation strategies to identify all eligible published studies included constructing our search strategy in collaboration with a librarian and verifying that our search picked up articles in previous systematic reviews within our review time frame. We did not conduct formal assessment for publication bias, so the potential that published studies were not reflective of all conducted studies on the incidence and prevalence of ALS remains.

There are inherent challenges in studying the epidemiology of ALS that are difficult to overcome without adequate clinical and research resources. Such resources are not readily available everywhere in the world, resulting in gaps in information concerning the epidemiology of ALS in some areas. For example, there were few studies of the epidemiology of ALS in South America, and only 1 study was identified from Africa, a continent with a population of more than 1.2 billion.

With the increasing development of population-based ALS registries and as they grow to include additional cases of ALS over time, new opportunities will arise for collaborative research and more complete ascertainment and follow-up of individuals with ALS using consistent strategies. Accessibility to multiple data sources may help improve case capture and disease surveillance of those living with ALS. This has the potential to greatly strengthen the reliability and validity of estimates of ALS incidence and prevalence worldwide.

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