



Global variation in prevalence and incidence of amyotrophic lateral sclerosis: a systematic review and meta-analysis

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Abstract

Background Amyotrophic lateral sclerosis (ALS) is a global disease, which adversely affects the life quality of patients and significantly increases the burden of families and society. We aimed to assess the changing incidence, prevalence of ALS around the world.

Methods We searched Medline, Embase, Web of Science, and Cochrane library to identify articles published until September 9, 2018. Each included study was independently reviewed for methodological quality by two reviewers. We used a random-effects model to summarize individual studies and assessed heterogeneity (I^2) with the χ^2 test on Cochrane's Q statistic.

Results We identified 124 studies that were eligible for final inclusion, including 110 studies of incidence and 58 studies of prevalence. The overall crude worldwide ALS prevalence and incidence were 4.42 (95% CI 3.92–4.96) per 1,00,000 population and 1.59 (95% CI 1.39–1.81) per 1,00,000 person-years, respectively. ALS prevalence and incidence increased by age until the age of 70–79. Since 1957, incidence has been significantly rising year by year, and this upward trend was weakened after standardization. The longest survival time were in Asia (ranging from 3.74 years in South Asia to 9.23 years in West Asia).

Conclusions With the aggravation of population aging and the rapid growth of economy, developing regions following the development pattern of the developed regions may suffer rising ALS prevalence and incidence which may increase their disease burden as well. These data highlight the need for research into underlying mechanism and innovations in health-care systems.

Keywords Amyotrophic lateral sclerosis · Incidence · Prevalence · Meta-analysis

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Background

Amyotrophic lateral sclerosis (ALS) is a rare neurodegenerative disease. ALS starts in a single part and then spreads to most muscles including the diaphragm of body, rendering the majority of patients dead from respiratory failure eventually [1]. Patients with ALS may suffer from cognitive impairments, such as frontotemporal dementia (ALS-FTD), executive cognitive impairment (ALS-ECI), non-executive cognitive impairment (ALS-NECI), etc. [2, 3]. As a public challenge, 3,30,918 people suffered from motor neuron disease, causing 9,26,090 disability-adjusted life years (DALYs) and 34,325 deaths in 2016 [4]. In Google and Bing/Yahoo, ALS was one of the most frequently searched neurological diseases [5].

The existing epidemiological studies of ALS indicated variation in ALS prevalence and incidence across different populations, especially in terms of age and sex. Furthermore,

a number of studies revealed regional and temporal variations as well. Taking Norway as an example, the ALS prevalence climbed from 3.67 per 1,00,000 population in 1988 [6] to 4.10 per 1,00,000 population in 2015 [7]. Meanwhile, the incidence rose from 1.60 per 1,00,000 person-years between 1978 and 1988 [6] to 2.10 person-years between 2000 and 2015 [7]. While the ALS prevalence and incidence of Taiwan in 2008 were 2.07 per 100 000 population and 0.53 per 1,00,000 person-years, respectively [8].

Considering the particularity of rare diseases, most related studies only collected data within a certain region or limited years, making it difficult to assess the geographical variation and temporal trend in a single study. However, systematic review and meta-analysis, as powerful statistical methods, could provide quantitative approaches for pooling the results of different studies on the same topic and estimating the diversity among different regions and years [9]. To date, a couple of systematic reviews have summarized the worldwide prevalence and incidence of ALS. The results of the sex and age variation of ALS were consistent with single studies: prevalence and incidence were higher in males than females, and ascending by age [4, 10, 11]. Two systematic reviews have explored the ALS geographical variation [4, 10], and found that the incidence was higher in Europe and America than in Africa and Asia. One of those meta-analysis published in 2017 [10], which included all articles published before June 2015, failed to detect temporal trend of the standardized ALS incidence. However, since 2016 a great many high-quality studies with sample size larger than 1,00,000 [12–15] have added into this field. For instance, after 2015, two studies based on larger sample size in West Asia [16, 17] suggested the incidence was 1.3–1.8 per 1,00,000 person-years, which was nearly three times the result from a meta-analysis published in 2017 [18].

Given that all above systematic reviews were based on articles before 2016, we proposed to update the geographical characteristics and temporal trend of ALS incidence and prevalence. Therefore, we did a systematic review of population-based studies reporting the incidence and prevalence of ALS across the world from inception to September 2018 to update the geographical variation and temporal trends of ALS prevalence and incidence. This study is registered in the PROSPERO, number CRD42019119168, and followed the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines (Online Resource 1).

Methods

Search strategy

In this systematic review and meta-analysis, we searched Medline, Embase, Web of Science, and Cochrane library

to identify all relevant studies focusing on the global population with ALS, published up to September 9, 2018. The search strategy was made by consulting the librarians in Peking University Health Science Center (Online Resource 2). To supplement these database searches, references of all relevant studies were also screened to identify additional potential data sources. This study is registered with PROSPERO, number CRD42019119168.

Inclusion and exclusion criteria

Inclusion criteria were: (1) population-based studies, reporting the prevalence or incidence of ALS or providing the data to compute these estimates; (2) The diagnosis of ALS was based on neurological experts, self-reports, disease codes or neurological examinations according to pre-defined criteria. Exclusion criteria were: (1) duplicates, reviews, conference proceedings, case reports, experiments and clinical trials; (2) Studies reporting prevalence or incidence for specific population not for general population; (3) studies from ALS foci [10, 19] including Papua, Guam ALS-PDC focus and Wakayama prefecture; (4) non-English studies; (5) no full text.

Data extraction and quality evaluation

Two reviewers (TXL and YXY) assessed all studies independent from each other and filled the following items in a data extraction form: (1) publication year, author, study region, study period, (2) case definition criteria, number of patients, size of study population, (3) prevalence, incidence and corresponding 95% CIs, and (4) the year-specific, age-specific, region-specific, and sex-specific results.

A quality assessment tool was applied (Online Resource 3) consistent with published guidelines [20, 21] and previous relevant meta-analysis [22], which involved three aspects including sample representativeness, condition assessment, and statistical methods.

In the event of disagreement on extracted data, the article was assessed by 2 other authors (LX and SFW) independently from each other and discussed between the four authors until agreement was achieved.

Statistical analysis

To minimize the influence from studies with extreme estimates on the combined values, we first stabilized the variance of study-specific rate using the Freeman-Tukey double arcsine transformation before pooling analysis [23, 24]. Unadjusted pooled rate was calculated on the basis of the information of crude rates and corresponding standard errors provided by individual studies or estimated from statistics in

individual studies. We only used crude rates, not adjusted for age or sex in the quantitative synthesis [25].

First, we did subgroup meta-analysis by sex and age to assess the variations in different populations. Age was classified into seven groups: 0–29, 30–39, 40–49, 50–59, 60–69, 70–79, and over 80 years. Second, the incidence and prevalence data were grouped by geographical region and economic level using the United Nations classification of economic regions (<https://unstats.un.org/unsd/methodology/m49/>, retrieved April 1, 2019), which is based on geographical proximity and economic similarities. If an author reported multiple time periods for a region, we used the most recent one. When data were reported for only one region within a subcontinent, the region was used to represent the subcontinent. Third, the temporal trends in prevalence and incidence were calculated by fitting a linear regression to the square root of the annual rates with the year as the predictor variable. Age-adjusted pooled rates were also utilized to analyze temporal trends. Age-adjusted pooled rates were calculated by direct standardization according to WHO 2000–2025 populations. We used the median year if the time points reported were longer than one year but no longer than 10 years [26] and the prevalence or incidence with time points longer than 10 years were excluded. The *P* values of coefficients from these regressions less than 0.05 were considered statistically significant. Furthermore, we also tried to estimate the survival time by formula: Survival

time (years) = Prevalence/Incidence [27]. Meta-regression was performed to explore the sources of heterogeneity by including the proportion of males, subcontinent, proportion of population over 60 years old, study period and study quality. Heterogeneity between studies was assessed with Cochran's *Q*, *I*². The *I*² statistic estimates the percentage of total variation across studies due to true between-study differences rather than chance. Generally, *I*² values greater than 60–70% indicate the presence of substantial heterogeneity [28]. Funnel plots and Egger's test were used to detect publication bias. Asymmetric funnel plots or *P* value less than 0.10 on Egger's test implicates the existence of statistically significant publication bias [29]. This meta-analysis was done with metan, metareg, metafunnel and metabias packages in Stata 14.0.

Result

Characteristics of included studies

After removal of duplications and initial screening, 522 articles were eligible for full-text review (Fig. 1). On full-text review of 522 articles, 398 were excluded. Overall, 124 studies were eligible for final inclusion in the systematic review, including 110 studies of incidence and 58 studies of prevalence. Characteristics of the 110 incidence studies

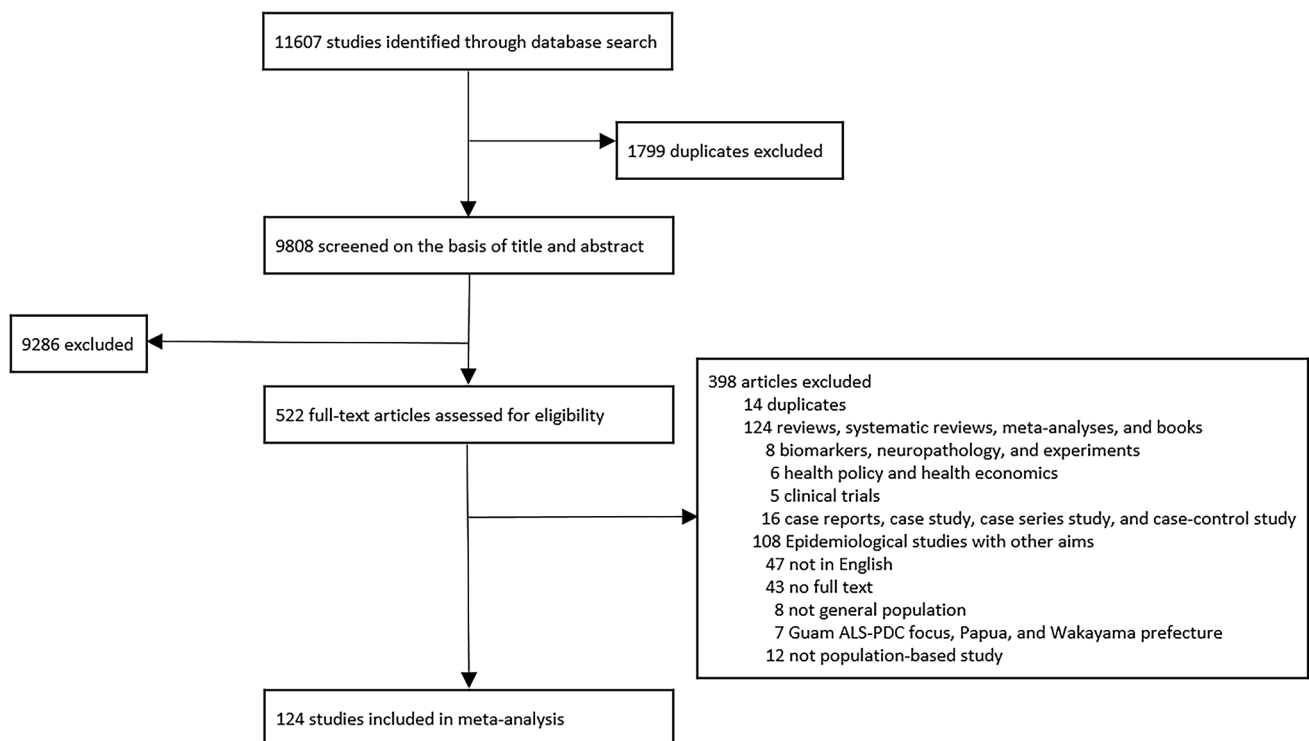


Fig. 1 Study selection

and 58 prevalence studies, including quality assessment, are available in Online Resource 4. Prevalence was reported for North Africa (one study), North America (13 studies), South America (three studies), Australia and New Zealand (one study), East Asia (five studies), South Asia (one study), West Asia (two studies), North Europe (13 studies), South Europe (17 studies), and West Europe (two studies). Of the 110 incidence studies, one study was in North Africa, 16 in North America, three in South America, one in Australia and New Zealand, eight in East Asia, one in South Asia, four in West Asia, 25 in North Europe, 43 in South Europe, six in West Europe, one in Caribbean, and one in Hawaii.

Sex and age distribution of prevalence and incidence

The crude worldwide ALS prevalence and incidence were 4.42 (95% CI 3.92–4.96) per 1,00,000 population and 1.59 (95% CI 1.39–1.81) per 1,00,000 person-years, respectively. Both ALS incidence and prevalence of males (incidence: 1.91, 95% CI 1.65–2.19; prevalence: 5.96, 95% CI 5.14–6.85) were higher than the corresponding values of females (incidence: 1.36, 95% CI 1.14–1.59; prevalence: 3.90, 95% CI 3.30–4.56). Figure 2 shows that prevalence and incidence increased by age before the age of 70–79, followed by a decrease.

Global variation of prevalence and incidence

The results by subcontinent and economic level are displayed in Fig. 3. Both prevalence and incidence were lowest in South Asia (prevalence: 1.57, 95% CI 0.17–4.39; incidence: 0.42, 95% CI 0.06–1.11) and highest in West Europe (prevalence: 9.62, 95% CI 4.80–16.10; incidence: 2.76, 95% CI 2.00–3.64). Divided by economic levels, developed

regions were higher than developing regions in both prevalence (4.94, 95% CI 4.46–5.45 vs 1.79, 95% CI 1.58–2.02) and incidence 2.15, 95% CI 1.34–3.16 vs 0.63, 95% CI 0.44–0.85).

Temporal trend for prevalence and incidence

No significant temporal trend was detected for crude prevalence since 1959 (coefficient = -0.000 , $t = -0.00$, $P = 0.997$) (Fig. 4). However, incidence was significantly rising by 0.00013 per year ($t = 7.21$, $P < 0.001$), and this upward trend was weakened after standardization with WHO 2000–2025 populations.

Survival time of ALS

The survival time of West Asia (9.23 years) and East Asia (4.32 years) was longer than other subcontinents. The European survival time ranged from 2.00 years in North Europe to 3.70 years in South Europe (Fig. 5).

Heterogeneity and publication bias

Heterogeneity was identified for proportion of population aged 60 or over (Table 1) and study period in univariate meta-regression. Using multivariate meta-regression, the heterogeneity for proportion of population aged 60 or over was still statistically significant. The funnel plot and the Egger test (Online Resource 5) suggested that no publication bias existed in the studies on prevalence, but might exist in studies on incidence.

Discussion

This meta-analysis summarizes available evidence on the worldwide ALS prevalence and incidence. There were several key findings: ALS prevalence varied from 1.57 per 1,00,000 population to 9.62 per 1,00,000 population and ALS incidence varied from 0.42 per 1,00,000 person-years to 2.76 per 1,00,000 person-years by subcontinent; both ALS prevalence and incidence were higher in developed regions and a slight positive temporal trend was found in crude incidence.

Compared with the meta-analysis of ALS incidence in 2017 [10], we included 66 more original studies by combining the rates using only the rates and corresponding standard errors. The sex and age variations in ALS prevalence and incidence were consistent with previous results [4, 10]. It is interesting to note that, consistent with previous studies, this study also observed a decline in ALS incidence in the older age group. This phenomenon was possibly due to the underdiagnosis of the oldest old, since the oldest old usually suffer

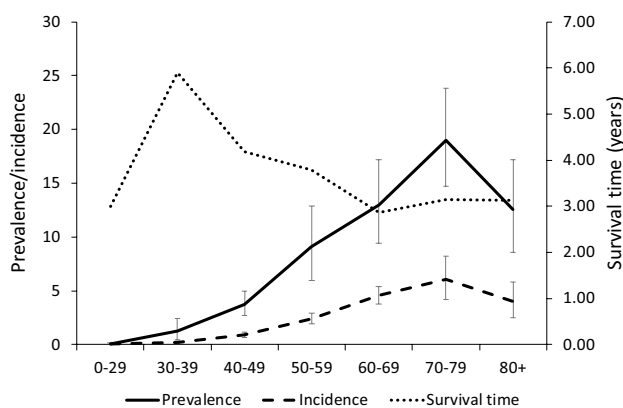


Fig. 2 Crude prevalence, crude incidence and survival time of ALS by age. Vertical lines at each point show 95% confidence intervals. The unit of prevalence is per 1,00,000 population and the unit of incidence is per 1,00,000 person-years

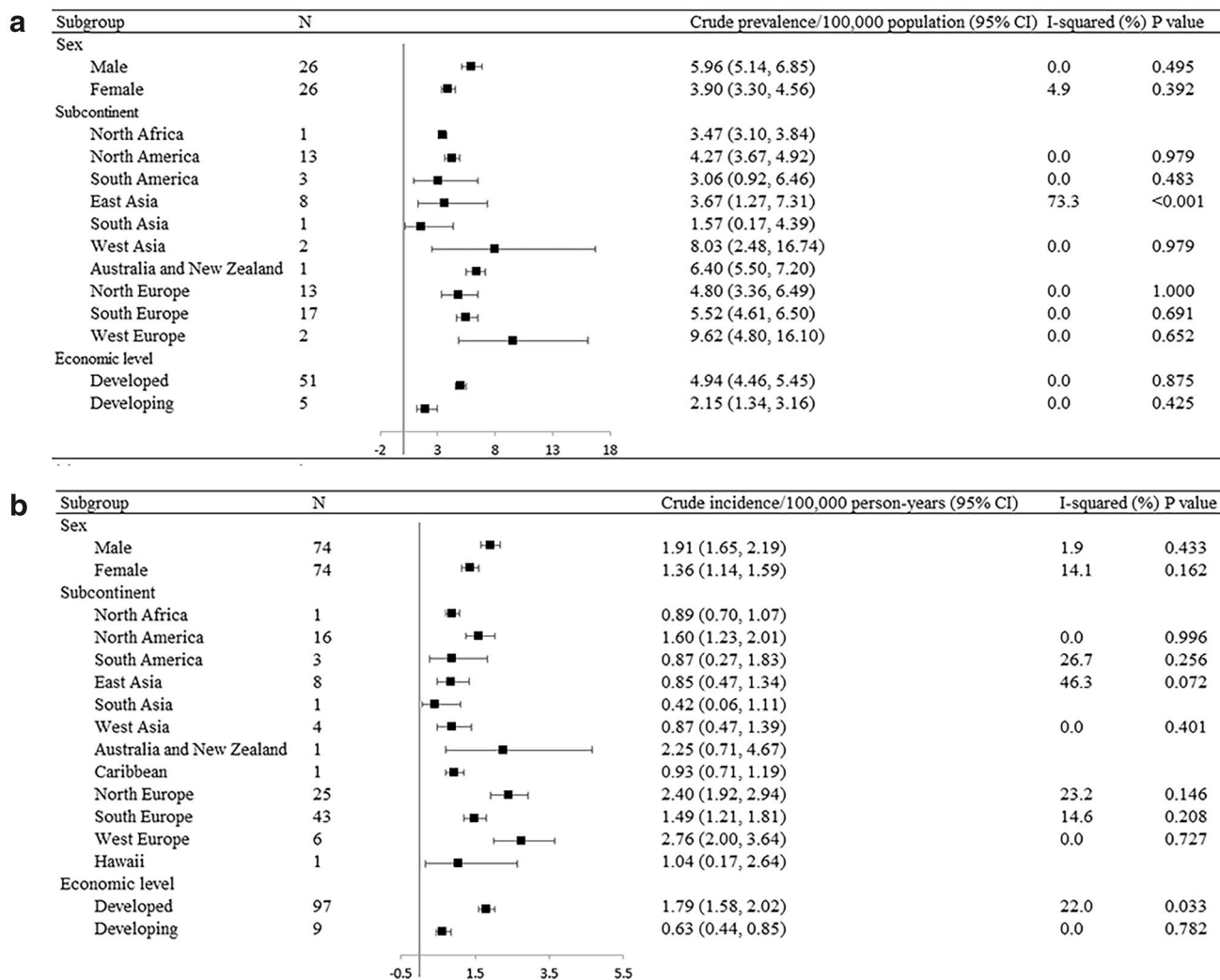


Fig. 3 Pooled prevalence and incidence of ALS in different sexes, subcontinents, and regions of different economic levels

from comorbidity, have difficulties in seeking for medical service and may die from other diseases before the diagnosis of ALS [30].

The worldwide ALS incidence in our study was similar to the result of the aforementioned meta-analysis [10], in which the incidence in European regions was higher and that in Asian regions was lower. Our study adopted the same regional classification standard as a previous meta-analysis [10], however, we first found that the prevalence in West Asia was much higher, only second to that of West Europe. This may be due to the fact that West Asia is adjacent to Europe and there may be an ancestry association between them [31]. The modern humans who replaced Neanderthals in Europe probably originated in West Asia, and the genetic distances between West Asia and Europe was also shorter than other Asian regions [32, 33]. Actually, a hexanucleotide GGGGCC repeat expansion in the *C9orf72* gene (9p21.2 region) has been identified as the most frequent genetic

cause of ALS in Caucasian population [34–40], which happens relatively rare in Asia and might be a potential explanation [40]. Therefore, the prevalence of West Asia was higher than other Asian regions, similar to European regions. Furthermore, the overall incidence in our study was higher than that of the Global Burden of Disease (GBD 2016), possibly because of the inclusion of articles after 2015 in our study, which might reflect the rise of ALS incidence during recent years in another perspective.

In addition, we found that the developing regions enjoyed lower ALS prevalence and incidence in comparison to developed regions. This may be due to the fact that population aging was more severe in developed regions [41] and the ALS prevalence and incidence of elder population were higher.

Notably, crude incidence was found a statistically significant upward temporal trend, but the annual growth was small and the trend weakened by applying standardized incidence,

Fig. 4 Crude prevalence and crude incidence of ALS by year

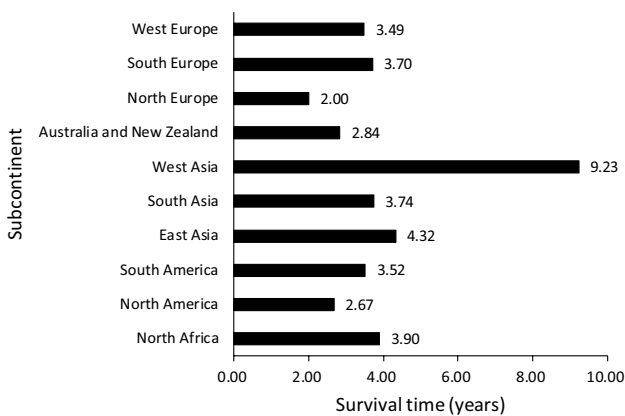
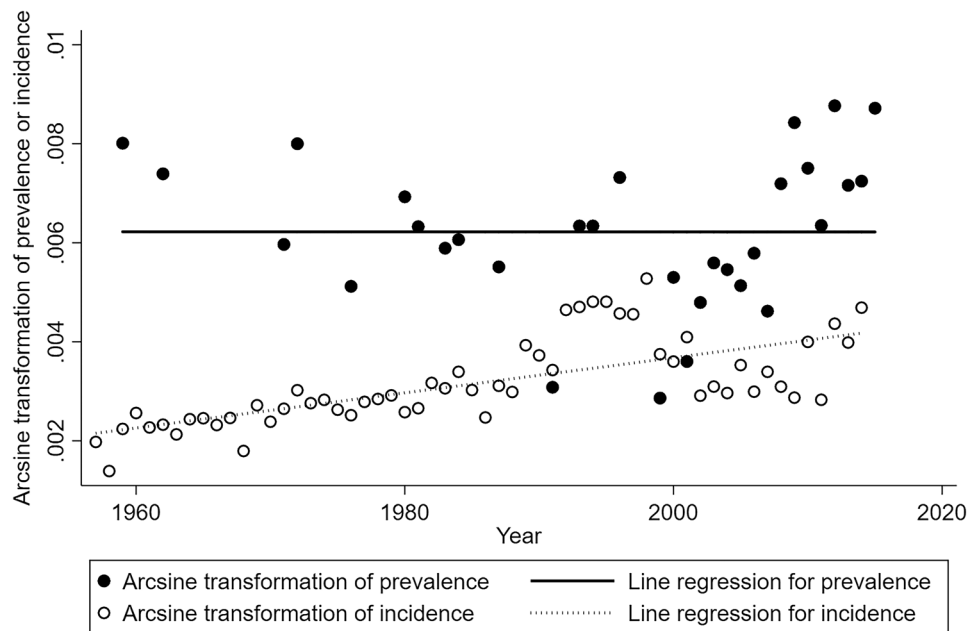


Fig. 5 Survival time of ALS in different subcontinents

which is consistent with the previous meta-analysis [10] and similar to the observation by Chio et al. [42], in which age effect was attenuated by standardization as well. In that study, the standardized incidence of women patients with ALS witnessed a statistically significant increase from 1995 to 2014 and the researchers explained the increase may be due to a birth cohort effect in women. We didn't find similar results due to the limited number of studies reporting sex-age-specific incidence. But taken together, it implied that the temporal trend of crude incidence in our study might be caused by population aging [43]. As aforementioned, several studies including our study discovered that ALS incidence grew by age with a peak in 60–70 years old [4, 30]. The severity of population aging is increasing year by year, which might cause the rise of crude incidence. And we did find that age was significantly associated with the combined

results in heterogeneity analysis for both prevalence and incidence. The upward temporal trend of incidence weakened after age standardization, and the *P* value even turned to be not significant. But we should note that the number of studies used to calculate the standardized incidence was reduced to 41 and the time range was reduced to 1970–2014 instead of the 1957–2014 in crude pooled incidence. It still cannot be excluded for the possibility of rising trend for crude incidence.

Surprisingly, the survival time in Asia regions were consistently longer than other regions. This finding was in accordance with Shahrizaila's study published in 2016, [44] which has also reported that the median survival time in Japan, Taiwan and India was longer than that in western countries.

It is certain that the younger median age of onset in these population contributed to the longer survival in Asian and other non-European population, with age as the strongest factor influencing prognosis in ALS [45]. However, there are still other possible explanations for those differences. First, the disease progression of European patients with ALS might be faster, which might result in worse prognosis [46]. Dorst J. et al. [46] discovered that the proportion of patients with bulbar onset (patients with bulbar onset have a worse prognosis) was smaller in China than that in German, therefore the different proportions of disease subtypes might be responsible for the phenomenon as well. Second, the use of tracheostomy positive pressure ventilation (TPPV) might play a role in this phenomenon. More than 20% of ALS patients used TPPV in Japan and Taiwan [47, 48], however, the utility in West countries was fewer than 10% [48]. In addition, it implies that perhaps Asia residents may possess

Table 1 Meta-regression of ALS crude prevalence and incidence

Study level covariates	Prevalence			Incidence		
	Coefficient		<i>P</i>	Coefficient		<i>P</i>
Univariate meta-regression						
Proportion of the male	0.0031	0.98	0.335	−0.0002	−0.07	0.948
Subcontinent (reference = North Europe)						
North Africa	−0.0011	−0.71	0.491	−0.0019	−1.55	0.134
North America	−0.0004	−0.61	0.549	−0.0009	−2.39	0.022
South America	−0.0014	−1.01	0.331	−0.0019	−2.62	0.015
East Asia	−0.0008	−0.65	0.526	−0.0020	−4.16	<0.001
South Asia	−0.0030	−2.02	0.068	−0.0028	−2.84	0.009
West Asia	0.0020	0.95	0.362	−0.0019	−3.19	0.004
Australia and New Zealand	0.0010	0.48	0.639	−0.0002	−0.12	0.909
South Europe	0.0005	0.70	0.489	−0.0010	−2.94	0.004
West Europe	0.0029	1.80	0.096	0.0003	0.50	0.621
Proportion of population aged 60 or over	0.0146	4.17	0.001	0.0067	3.03	0.005
Study period	0.0007	2.02	0.050	0.0006	3.53	0.001
Quality score	0.0012	0.64	0.526	−0.0004	−0.39	0.699
Multivariate meta-regression						
Proportion of population aged 60 or over	0.0161	2.97	0.013	0.0086	2.74	0.011
Study period	0.0001	0.09	0.934	0.0006	1.81	0.083

Study period was classified as 1925–1954, 1955–1969, 1970–1984, 1985–1999, and after 1999

an inherent protective factor to ensure longer survival [44]. And the aforementioned *C9orf72* gene (9p21.2 region) which is rare in Asian population was just statistically associated with inferior survival [40, 49, 50].

To the best of our knowledge, this paper is the latest meta-analysis that focuses on the ALS prevalence and incidence with 124 population-based studies included [26, 51]. Nevertheless, the findings of this study should be interpreted with caution. First, as in previous meta-analysis exploring the geographical variation [10, 30], the prevalence or incidence in certain subcontinents were represented by only few countries or regions due to lack of relevant original studies, possibly making the estimation biased. Second, the subgroups considered in this study may be not enough, limited by the number of original studies. Subgroups including occupations [52, 53], ethnicity [54] may also be meaningful to be explored. Third, publication bias in studies on incidence owing to small-sampled studies could affect the precision of our estimates [24]. This may be due to the fact that we only included the published studies.

Conclusion

This systematic review provides a comprehensive global overview of the incidence, prevalence, and survival time of ALS. The findings suggest that the ancestral origin of population in West Asia is awaited to be explored, because of its characteristics of low incidence but long survival time.

Furthermore, developing regions may face increasing ALS prevalence and incidence in decades to come, since developing countries, like developed countries decades ago, are accelerating their economic development. The rising global burden of ALS requires more studies to identify plausible determinants for ALS and more innovations in health-care system to manage and control this costly disease.

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The manuscript does not contain clinical studies or patient data.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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