Amyotrophic lateral sclerosis mortality rates in Latin America and the Caribbean: a meta-analysis

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Abstract

Background: Recent studies have described a low occurrence of Amyotrophic Lateral Sclerosis (ALS) in Latin America. Significant differences in ALS risk have been reported among ethnic populations in the region. We conducted a meta-analysis using population-based data to describe ALS mortality rates in Latin America. We explored sources of heterogeneity among key covariates.

Methods: National mortality registries from Latin American countries were searched to identify ALS deaths according to the International Classification of Diseases (ICD-9: code 335.2 and ICD-10: code G12.2). Crude and standardized mortality rates were calculated. A random-effect meta-analysis was conducted to estimate pooled mortality rates. Subgroup analysis was performed as a means of investigating heterogeneity.

Results: Overall, 28,548 ALS deaths and 819 million person-years of follow-up (PYFU) from ten Latin American countries were considered. Standardized mortality varied among countries. The highest mortality rates were observed in Uruguay and Costa Rica at 1.3 and 1.2 per 100,000 PYFU, respectively. The pooled crude mortality rate was 0.38 (95%CI: 0.28–0.53) and the pooled standardized mortality was 0.62 (95%CI: 0.49–0.77) per 100,000 PYFU. Heterogeneity was high (I²: 99.9%, Cochran’s Q p < 0.001). Subgroup analysis showed a higher mortality rate among countries with a higher proportion of Caucasian populations and higher income levels.

Conclusion: There is a lower ALS occurrence in Latin America compared to Europe and North America. This meta-analysis supports the hypothesis of a higher ALS risk among the Caucasian population. Further studies are needed to investigate the role of ancestral origins in ALS, taking socioeconomic status into consideration.

Keywords: Amyotrophic lateral sclerosis, epidemiology, mortality, Latin America, heterogeneity

Introduction

Amyotrophic Lateral Sclerosis (ALS) is a rare neurodegenerative disease with a poor prognosis due to respiratory insufficiency, with a median survival time from diagnosis of around 15–20 months (1). Recent studies have suggested heterogeneity of ALS epidemiology among geographical areas and populations (2–5). Lower incidence and mortality rates of ALS have been described in Latin America compared to Europe and North America (6).

A lower ALS occurrence has been observed in Hispanic populations compared to Non-Hispanic populations in studies performed in the United States (5,7). In Latin America, studies from Cuba and Ecuador have shown significant differences among ethnic groups (3,4). Furthermore, the results described in Latin American countries were consistent with those observed in Hispanic populations in the United States.

This could imply that ancestral origin could play an important role in ALS occurrence, as
higher risks of developing ALS have been observed between ethnic groups (3–5). Variations of ALS occurrence could also be explained, by methodological heterogeneity and differences of socioeconomic status.

There is a major lack of information in some regions of the world, including Latin America. Population-based registries have played a key role in understanding descriptive ALS epidemiology (8). In countries where ALS registries are not available, mortality data has been a valuable source of information as it can be expected to identify all ALS cases due to the fatal outcome of the disease (9). Hence, mortality data could be considered as a proxy of ALS incidence if high-quality methodology is followed (10).

Latin America is an interesting region for ALS studies because of the diversity among ethnic groups. To improve our understanding of the role of ancestral origins in ALS occurrence, there is a need for high-quality studies using standardized methodology. In this context, we conducted a meta-analysis using general population data to describe ALS mortality rates in Latin America. Sources of heterogeneity were also explored.

**Methods**

We followed the guidelines for Meta-analyses and Systematic Reviews of Observational Studies (MOOSE) (11). We followed specific epidemiological criteria for ALS mortality studies (10). The Moose checklist is shown in Supplementary etable 1.

**Source of information**

We performed an online search of registries of annual mortality causes from all Latin American countries. Available information for each country was collected from 1990 to 2019. Mortality registries from the National Institutes of Statistics of eight countries were available online: Argentina (12), Chile (13), Colombia (14), Costa Rica (15), Ecuador (16), Guatemala (17), Mexico (18), and Uruguay (19).

We identified mortality studies using data from national registries in Brazil and Cuba, through a previous systematic review of ALS in Latin America (6). The authors were contacted to obtain the mortality data of their countries (Brazil (20) and Cuba (4)).

**Case ascertainment**

All death records in the mortality registries were searched. National registries collect causes of death from standard death certificates. Health professionals fill in these certificates. Registries in Latin American countries follow guidelines for mortality coding according to the recommendations provided by the World Health Organization (21).

The International Classification of Diseases (ICD) was used to identify ALS deaths: ICD-9 code 335.5 from 1990 to 1996 and ICD-10 code G12.2 from 1997 to 2019. The underlying cause of death was used to identify ALS cases. Cases younger than 15 years of age were excluded to reduce the risk of false positives.

**Data collection**

Demographic information was collected from each mortality registry including sex and age group at the time of death. The population at risk in each country was obtained from the Annual Demographic Yearbook published by the United Nations Statistics Division (22). The mid-year population per year was considered to calculate the mortality rates.

Subcontinent classification was performed according to the United Nations Statistics Division (23). Country classification by income was obtained from the World Bank’s classification by income level. As we include large periods among countries, we took into consideration the middle year of the period for each country as the reference for the income classification (24). The proportion of ethnic groups was obtained from a nonprofit private corporation “Latino Barómetro,” which carries out an annual public opinion survey using a standardized methodology among Latin American countries (25). Self-reported ethnicity is categorized into Caucasian, Admixed, Black, Asians, Indigenous, Mulatto, other race, or no answer. Information for ethnic groups was available from 2007 to 2018. To obtain the proportion of each ethnic group from each country, we collected the crude data for each year and then we calculated the proportion for the overall period. The Latino Barómetro database and methodology are published elsewhere (25).

**Statistical analyses**

Qualitative variables were described as frequencies and percentages. The frequency counts of ALS deaths were categorized in 5-year age increments. Crude mortality rates per 100,000 person-years of follow-up (PYFU) were calculated along with 95% confidence intervals (95%CI) based on the Poisson distribution. Direct age and sex standardization was performed using the US 2010 population.

A meta-analysis was performed using a random-effect model and Forest plots were generated. Pooled mortality rates were calculated. The Cochran’s Q-test (p < 0.1) and I² statistics were used to assess statistical
We defined heterogeneity as high if greater than 75% (I² statistics).

We performed stratified analyses as a means of investigating heterogeneity with respect to a number of key covariates: (i) Proportion of Caucasian population, (ii) Income level and (iii) Geographic localization (Subcontinent). We categorized geographic localization into two subcontinent groups: (a) Central America and The Caribbean, and (b) South America. The proportion of Caucasian population was categorized (<25%, 25–50%, 50–75%, >75%). Mortality data from nine countries were used for the proportion of Caucasian population subgroup analysis, as this information was not available for Cuba in Latino Barómetro.

Analyses were conducted using R statistical software version 3.6.1 (The R project for statistical computing) and Stata version 11.1 (Stata Corporation, College Station, TX).

Results

Overall, 28,548 ALS deaths were identified considering a population of 819 million PYFU covering 10 Latin American countries. Fifty-five percent of ALS cases were males (15,717 cases) and 45% were female (12,831 cases). The total male/female sex ratio was 1.22. The characteristics of ALS mortality data are described in Table 1.

Crude and standardized ALS mortality among Latin American countries

Crude ALS mortality ranged from 0.07 to 1.24 per 100,000 PYFU. Mortality remained variable after standardization (Figure 1), showing the highest standardized mortality rates per 100,000 PYFU in Uruguay (1.30, 95%CI: 1.22–1.38), Costa Rica (1.16, 95%CI: 1.08–1.25) and Chile (0.98, 95%CI: 0.95 – 1.02). While the lowest rates were observed in Guatemala (0.19, 95%CI: 0.15-0.23), Ecuador (0.35, 95%CI: 0.33-0.38) and Mexico (0.44, 95%CI: 0.43–0.45).

Age-related profile and sex ratio of ALS mortality in Latin America

The peak age of crude mortality was between 75 and 79 years followed by a decrease after 80 years. A similar pattern was observed for standardized mortality (Figure 2). The crude mortality sex ratio was 1.30, while the standardized mortality sex ratio was 1.27. The crude and standardized mortalities by sex in each country are shown in Table 2.

Meta-analysis

Crude and standardized ALS mortality are reported in Figure 3. The overall pooled crude mortality of ALS per 100,000 PYFU was 0.38 (95%CI: 0.28–0.53), with high heterogeneity (Cochran’s Q p < 0.001; I²=99.9%). The pooled standardized mortality per 100,000 PYFU was 0.62 (95%CI: 0.49–0.77). A high level of heterogeneity was also observed (Cochran’s Q p < 0.001; I²=99.7%). Male and female pooled standardized mortality was 0.69 (95%CI: 0.55–0.88) and 0.54 (95%CI: 0.44–0.68), respectively.

Stratified analysis. A higher mortality rate was observed among countries with a higher proportion of Caucasian population. The crude mortality rate for countries with a proportion of Caucasian population less than 25% was 0.15 (95%CI: 0.10–0.21), 0.42 (95%CI: 0.26–0.70) for countries with 25–50%, and 0.76 (95%CI: 0.51–1.13) for countries with 50–75%. Heterogeneity was high.

Table 1. Characteristics of ALS mortality data by countries.

| Country             | Period            | ICD code | Duration of study | Total | Male  | Female | Sex ratioa | PYFU          |
|---------------------|-------------------|----------|-------------------|-------|-------|--------|------------|---------------|
| South America       |                   |          |                   |       |       |        |            |               |
| Argentina           | 1995–2018         | G12.2    | 24                | 4936  | 2708  | 2228   | 1.21       | 942,326,443   |
| Brazil              | 2004–2013         | G12.2    | 10                | 8036  | 4348  | 3688   | 1.17       | 1,904,851,795 |
| Chile               | 1990–1996         | 335.2    | 28                | 3003  | 1663  | 1340   | 1.24       | 443,327,868   |
|                     | 1997–2017         | G12.2    |                   |       |       |        |            |               |
| Colombia            | 1992–1996         | 335.2    | 24                | 2478  | 1370  | 1108   | 1.23       | 1,012,372,492 |
|                     | 1997–2015         | G12.2    |                   |       |       |        |            |               |
| Ecuador             | 1990–1996         | 335.2    | 30                | 722   | 388   | 334    | 1.16       | 404,321,939   |
|                     | 1997–2019         | G12.2    |                   |       |       |        |            |               |
| Uruguay             | 1997–2019         | G12.2    | 22                | 962   | 533   | 429    | 1.24       | 77,536,023    |
| Central America and the Caribbean | |          |                   |       |       |        |            |               |
| Costa Rica          | 1999–2019         | G12.2    | 21                | 711   | 430   | 281    | 1.53       | 93,679,955    |
| Cuba                | 2001–2006         | G12.2    | 6                 | 427   | 222   | 205    | 1.08       | 67,403,216    |
| Guatemala           | 2009–2016         | G12.2    | 8                 | 88    | 56    | 32     | 1.75       | 122,197,136   |
| Mexico              | 1990–1997         | 335.2    | 30                | 7185  | 3999  | 3186   | 1.25       | 3,125,274,168 |
|                     | 1998–2019         | G12.2    |                   |       |       |        |            |               |

ICD: international classification of diseases; PYFU: person years follow up.

*Sex ratio number: number of ALS male deaths over the number of ALS female deaths.
As shown in Figure 4, this finding remained consistent after standardization. Countries with a proportion of Caucasian population less than 25% showed a remarkably low estimate (0.32, 95%CI: 0.24–0.42), while the mortality rate was higher in countries that had 50–75% Caucasian population (0.95, 95%CI: 0.67–1.35).

Upper-middle-income countries displayed higher mortality compared to lower-middle-income countries. The crude mortality was 0.56 (95%CI: 0.37–0.84) for upper middle-income countries and 0.21 (95%CI: 0.12–0.37) for lower-middle-income countries. When comparing standardized estimates, upper-middle-income countries showed a higher rate (0.82, 95%CI: 0.62–1.09) compared to lower-middle-income countries (0.40, 95%CI: 0.28–0.56) per 100,000 PYFU (Figure 5).

Regarding geographic localization, crude and standardized mortality in South America was 0.45 (95%CI: 0.31–0.65) and 0.68 (95%CI: 0.53–0.88), respectively. In Central America and the Caribbean countries, the crude and standardized mortality was 0.30 (95%CI: 0.14–0.65) and 0.53 (95%CI: 0.29–0.95) per 100,000 PYFU (Supplementary eFigure 1).

Discussion

The present meta-analysis reports ALS crude and standardized mortality rates using population-based data from Latin America. Our findings support the evidence of a lower occurrence of ALS in this geographic region compared to Europe and North America. A higher mortality rate was observed among countries describing a higher proportion of Caucasian population and higher income level.

Age pattern and sex ratio of ALS mortality in Latin America

ALS mortality in Latin America exhibits a specific age-related pattern, characterized by low mortality rates in younger ages (before 40 years of age), and a sudden decrease in older ages (70 years of age), similar to reports from Europe, North America and East Asia (26). Recent studies have suggested a younger age at onset in Latin America compared to Europe and New Zealand (6). Age peaks for ALS incidence in European populations ranged between 71.6 and 77.4 years and around 75 years in East Asia (26). In Latin America, the highest peak of ALS standardized mortality was in the 60–69 year age group. This differences could be related to life expectancy, under ascertainment of cases and difficulties in access to healthcare (27).

A male predominance was observed in Latin America, similar to reports in Europe, North America and New Zealand (28). A recent dose–response meta-analysis of population-based studies reported a pooled male to female ratio of 1.28, a crude incidence sex ratio of 1.33 and a sex ratio of
standardized incidence of 1.35, which is consistent with our findings (29).

**ALS variability in Latin American countries**

Recent evidence supports a low ALS occurrence in Latin America. A recent systematic review, found that methodological issues, make it difficult to draw firm conclusions of ALS epidemiology in this region (6). In this meta-analysis, we confirm a low occurrence of ALS in Latin America. This approach provides reliable epidemiological data to gain important insights into ALS heterogeneity among geographical areas.

ALS mortality rates were heterogeneous among Latin American countries. Geographic regions with a similar ancestral origin population (Europe, North America and New Zealand) have shown homogenous incidence rates, while significant differences were found between Europe and Asia (2). A recent study in South Africa described a significant difference in ALS occurrence among populations, with a lower incidence rate among the population of African ancestry compared to those of European ancestry (30). Epidemiological studies performed in the United States showed that incidence rates were lower in Hispanic populations compared to Non-Hispanic White populations (5,7). Differences among ethnic population groups

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**Figure 2. ALS crude and standardized mortality by age group and sex.**
 Researchers have proposed that ALS risk variability could be associated with ancestral origin, as studies have shown a higher ALS occurrence among European populations which could share common "at risk" alleles, increasing ALS susceptibility (4). In contrast, admixed populations could show a lower risk for ALS because of the combinations of this alleles (4). Latin American populations reflect a continuous admixture of Native American, European and African ancestries shaped by the interaction of migrants and Native American indigenous peoples, due to historical events such as colonization and the slave trade (31,32). Ancestral origin is heterogeneous in Latin American and the Caribbean countries. A genome-wide pattern investigation of population structures showed that individuals from Mexico and Ecuador have the highest levels of Native American ancestry (31). Colombia and Brazil have shown widespread genetic patterns, which vary between geographical regions within the country. In Colombia, for instance, the highest levels of African ancestry have been shown to be in the coastal regions, with a higher level of European ancestry in central areas (33). In Brazil, a higher level of European ancestry has been evidence in the south, conversely a higher level of African ancestry has been described in the East (33). A higher proportion of European ancestry has been exhibited in Chile, Argentina and Uruguay (32,34,35). Ethnic identification has been used as a proxy of ancestral origin. However, this is prone to several limitations including the lack of a standardized definition. For instance, ethnicity is self-reported based on cultural and traditional aspects in Ecuador (36), while ethnic classification is performed using skin color in Cuba (37). To address this issue, we used ethnic data collected from previous studies.

### Table 2. ALS crude and standardized mortality by sex in Latin American countries.

| Country              | Crude mortality (95% CI) per 100,000 PYFU | US 2010 standardized mortality (95% CI) per 100,000 PYFU |
|----------------------|------------------------------------------|---------------------------------------------------------|
|                      | Male                                      | Female                                                  | Overall                                   | Male                                      | Female                                                  | Overall                                   |
| South America        |                                          |                                                        |                                          |                                          |                                                        |                                          |
| Argentina            | 0.59 (0.57-0.61)                          | 0.47 (0.45-0.48)                                         | 0.52 (0.51-0.53)                          | 1.25 (0.76-0.82)                          | 0.58 (0.56-0.61)                                         | 0.68 (0.66-0.70)                          | 1.36|
| Brazil               | 0.46 (0.45-0.48)                          | 0.38 (0.37-0.40)                                         | 0.42 (0.41 – 0.43)                        | 1.21 (0.74-0.80)                          | 0.76 (0.62-0.64)                                         | 0.70 (0.68-0.72)                          | 1.18|
| Chile                | 0.75 (0.71-0.79)                          | 0.60 (0.56-0.63)                                         | 0.67 (0.65 – 0.69)                        | 1.25 (1.04-1.15)                          | 1.10 (0.82-0.91)                                         | 0.98 (0.95-1.02)                          | 1.26|
| Colombia             | 0.27 (0.25-0.28)                          | 0.21 (0.20-0.22)                                         | 0.24 (0.23-0.25)                         | 1.29 (0.48-0.54)                          | 0.51 (0.39-0.42)                                         | 0.46 (0.44-0.48)                          | 1.24|
| Ecuador              | 0.19 (0.17-0.21)                          | 0.15 (0.14-0.18)                                         | 0.18 (0.17-0.19)                        | 1.27 (0.32-0.39)                          | 0.36 (0.29-0.37)                                         | 0.35 (0.33-0.38)                          | 1.09|
| Uruguay              | 1.42 (1.30-1.54)                          | 1.07 (0.97-1.17)                                         | 1.24 (1.16-1.32)                        | 1.32 (1.42-1.69)                          | 1.08 (0.97-1.18)                                         | 1.30 (1.22-1.38)                          | 1.44|
| Central America and the Caribbean |                                          |                                                        |                                          |                                          |                                                        |                                          |
| Costa Rica           | 0.93 (0.84-1.02)                          | 0.59 (0.52-0.65)                                         | 0.76 (0.71-0.82)                        | 1.57 (1.27-1.54)                          | 0.93 (0.82-1.04)                                         | 1.16 (1.08-1.25)                          | 1.50|
| Cuba                 | 0.65 (0.57-0.74)                          | 0.60 (0.52-0.69)                                         | 0.63 (0.57-0.69)                        | 1.08 (0.66-0.86)                          | 0.78 (0.67-0.89)                                         | 0.77 (0.70-0.85)                          | 0.97|
| Guatemala            | 0.09 (0.06-0.11)                          | 0.05 (0.03-0.06)                                         | 0.07 (0.06-0.09)                        | 1.80 (0.17-0.30)                          | 0.24 (0.08-0.18)                                         | 0.19 (0.15-0.23)                          | 1.84|
| Mexico               | 0.26 (0.25-0.27)                          | 0.20 (0.19-0.21)                                         | 0.23 (0.22-0.25)                        | 1.30 (0.47-0.50)                          | 0.40 (0.38-0.41)                                         | 0.44 (0.43-0.45)                          | 1.22|

Sex ratio\(^a\) for crude mortality: male crude mortality by female crude mortality.

Sex ratio\(^b\) for standardized mortality: male standardized mortality by female standardized mortality.

PYFU: person years follow up.
using a homogenous methodological framework among countries (Latino Barometro). Further studies using objective assessments of ancestral origin are needed in ALS research.

Socioeconomic factors have been considered an important determinant to take into consideration for ALS variations. The Global Burden of Disease Study of motor neuron diseases reported a higher age-standardized prevalence and incidence in countries with a higher socio-demographic index (SDI) compared to low and middle SDIs. Age-standardized prevalence, however, was lower in certain geographic regions with high SDIs (38). A population-based study suggests that ALS incidence could be associated with socioeconomic status (SES) and race. After using adjustment models for age, sex and race they showed that the participants in the highest-income quartile had a higher relative risk for ALS compared to the lowest-income quartile. The relative risk of having ALS was significantly lower among Blacks and Asians than among Whites (39). On the contrary, another study in the United States, after using adjusted models to control socioeconomic

| Country  | Period       | Years | Cases | PYFU | ALS mortality per 100,000 PYFU (95%CI) | % Weight |
|----------|--------------|-------|-------|------|-------------------------------------|----------|
| Chile    | 1990-2017    | 28    | 3003  | 4.433e+08 | 0.67 (0.65, 0.69) | 10.05 |
| Ecuador  | 1990-2019    | 30    | 722   | 4.043e+08 | 0.18 (0.17, 0.19) | 10.02 |
| Mexico   | 1990-2019    | 30    | 7165  | 3.125e+09 | 0.23 (0.22, 0.24) | 10.06 |
| Colombia | 1992-2015    | 24    | 2478  | 1.012e+09 | 0.24 (0.23, 0.25) | 10.05 |
| Argentina| 1995-2018    | 24    | 4936  | 9.423e+08 | 0.52 (0.51, 0.53) | 10.06 |
| Uruguay  | 1997-2019    | 22    | 962   | 77536023 | 1.24 (1.16, 1.32) | 10.03 |
| Costa Rica| 1999-2019   | 21    | 711   | 93679955 | 0.76 (0.71, 0.82) | 10.02 |
| Cuba     | 2001-2006    | 6     | 427   | 67403216 | 0.83 (0.57, 0.69) | 9.98 |
| Brazil   | 2004-2013    | 10    | 8036  | 1.905e+09 | 0.42 (0.41, 0.43) | 10.06 |
| Guatemala| 2009-2016    | 8     | 88    | 1.222e+08 | 0.07 (0.06, 0.09) | 9.67 |
| Overall  | (I-squared = 99.9%, p < 0.001) |       |       |      | 0.38 (0.28, 0.53) | 100.00 |

NOTE: Weights are from random effects analysis

Figure 3. Meta-analysis: forests plots and pooled estimates of ALS mortality in Latin America. Crude and age- and sex-standardized based on the 2010 US population.
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Figure 4. Meta-analysis: forests plots and pooled estimates of ALS mortality in Latin America. Crude and age- and sex-standardized based on the 2010 US population by proportion of Caucasian population.

Factors, type of health insurance and birthplace, a lower risk for ALS was observed in Non-Hispanics Blacks and Hispanics versus Non-Hispanic White populations (40).

A lower mortality in lower-middle income countries could be explained by difficulties in health care access, social inequalities, inadequate case ascertainment and scarce medical resources (27). According to the World Health Organization, the median number of neurologists per 100,000 population for lower-middle-income countries was 0.13 and 1.09 for upper-middle-incomes (41). The Pan American Health Organization showed that the ratio of neurologists per 100,000 habitants was 0.92 in Central America, 0.48 in the Caribbean and 1.59 in South America (42).

Regardless of these factors, lifestyle and environmental factors cannot be dismissed as possible sources of epidemiological heterogeneity for ALS. Some authors have propose that ALS could be the...
result of a complex interaction between environmental risks and genetic predisposition (43).

**Mortality data**

Population-based registries are the gold standard methodology for epidemiological studies in ALS. These registries were mostly developed in European countries. The key point for ALS registries is the capacity to identify a reference population in a well-defined geographic area, ensuring case identification among all possible sources, which is possible because of the structured national health systems and specific funding (44). Latin American countries’ health systems face different challenges including a double burden of diseases that makes rare diseases have less or inexistent government funding. In countries where no ALS registries exist and incidence studies are challenging, the use of death certificates can be a key tool in estimating ALS occurrence since they allow a population-based approach and provide standard data collection instruments among countries.

The use of death certificates as a source for descriptive epidemiology has raised different
concerns among researchers as mortality studies present limitations that could lead to an underestimation of cases. Various studies have shown, however, that death certificates have good sensitivity for ALS case identification (45). Mortality studies conducted in Hong Kong and England exhibited mortality rates consistent with incidence rates for similar time intervals (46,47). Mortality data can be used as a proxy of ALS incidence; because of the fatal outcome of the disease; we could assume all ALS cases will be identified (10).

**Limitations and strengths**

Our study had certain intrinsic strengths. First, there was a population-based approach and a homogenous methodology following high standard criteria for reporting mortality studies. Second, we considered the sex and age structure of the population per year in each country to estimate mortality rates. Third, a long period was investigated to include a sufficient number of events. Lastly, we explored ALS heterogeneity considering key covariates through subgroup analysis.

Some limitations need to be acknowledged. Self-reported ethnicity was considered as a proxy of ancestral origin which could lead to bias, as this is not an objective assessment of the ancestral origin of individuals and is normally based on traditional cultural aspects and physical appearance (48). Nevertheless, the results of previous studies of the genomic patterns in Latin America are consistent with the reports of the self-reported Caucasian proportion from the “Latino Barómetro”. Another limitation was that some registries only provided the underlying basic cause of death and not the secondary causes, to assure a homogenous methodology we considered only the basic cause of death, which could lead to an underestimation of cases.

**Conclusion**

This meta-analysis using population-based data confirmed a lower ALS occurrence in Latin America, supporting the hypothesis of a higher risk in developing ALS for populations of Caucasian origin. Furthermore, subgroup analysis showed ALS heterogeneity, with higher mortality among countries with upper-middle income levels. Further studies are needed to investigate the role of ancestral origins in ALS, taking into consideration socioeconomic factors, gene association and environmental interactions.

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**Ethical approval**

No ethical approval was required, as the information is available in open access and anonymized.

**Disclosure statement**

The authors report no conflicts of interest. The authors are responsible for the content and writing of this article.

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**References**

1. Marin B, Couratier P, Arcuti S, Copetti M, Fontana A, Nicol M, et al. Stratification of ALS patients’ survival: a population-based study. J Neurol. 2016;263:100–11.

2. Marin B, Boumédiene F, Logroscino G, Couratier P, Barbron M-C, Leutenegger AL, et al. Variation in worldwide incidence of amyotrophic lateral sclerosis: a meta-analysis. Int J Epidemiol. 2017;46:57–74.

3. Luna J, Preux P-M, Logroscino G, Erazo D, Del Brutto OH, Boumediene F, et al. Amyotrophic lateral sclerosis mortality rates among ethnic groups in a predominant admixed population in Latin America: a population-based study in Ecuador. Amyotroph Later Scler Frontotemporal Degener 2019;20:1–9.

4. Zaldívar T, Gutiérrez J, Lara G, Carbonara M, Logroscino G, Hardiman O. Reduced frequency of ALS in an ethnically mixed population: a population-based mortality study. Neurology 2009;72:1640–5.

5. Rechtman L, Jordan H, Wagner L, Horton DK, Kaye W. Racial and ethnic differences among amyotrophic lateral sclerosis cases in the United States. Amyotroph Later Scler Frontotemporal Degener. 2015;16:65–71.

6. Erazo D, Luna J, Preux P-M, Boumediene F, Couratier P. Epidemiological and genetic features of amyotrophic lateral sclerosis in Latin America and the Caribbean: a systematic review. Amyotroph Later Scler Frontotemporal Degener 2021;23:1–13.

7. Larson TC, Kaye W, Mehta P, Horton DK. Amyotrophic Lateral Sclerosis Mortality in the United States, 2011–2014. Neuroepidemiology 2018;51:96–103.

8. Logroscino G, Traynor BJ, Hardiman O, Chio’ A, Couratier P, Mitchell JD, et al. Descriptive epidemiology of amyotrophic lateral sclerosis: new evidence and unsolved issues. J Neurol Neurosurg Psychiatry. 2008;79:6–11.
9. Luna J, Logroscino G, Couratier P, Marin B. Current issues in ALS epidemiology: variation of ALS occurrence between populations and physical activity as a risk factor. Rev Neurol (Paris). 2017;173:244–53.

10. Marin B, Couratier P, Preux P-M, Logroscino G. Can mortality data be used to estimate amyotrophic lateral sclerosis incidence? Neuroepidemiology 2011;36:29–38.

11. Stroup DF, Berlin JA, Morton SC, Olin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000;283:2008–12.

12. Dirección de Estadísticas e Información Argentina de la Salud. Available at: https://www.argentina.gob.ar/salud/destatis/2015/.

13. Instituto Nacional de Estadísticas y Censos Costa Rica. Available at: https://www.inec.cr/.

14. Departamento Administrativo Nacional de Estadística. Available at: https://www.dane.gov.co.

15. Instituto Nacional de Estadística y Censos Costa Rica. Available at: https://www.inecn.cr/.

16. Instituto Nacional de Estadística y Censos Ecuador. Available at: https://www.ecuadorencifras.gob.ec/institucional/home/.

17. Instituto Nacional de Estadística Guatemala. Available at: https://www.ine.gub.gt/ine/.

18. Instituto Nacional de Estadística y Geografía Informática Mexico. Instituto Nacional de Estadística y Geografía. INEGI. Available at: https://www.inegi.org.mx/.

19. Instituto Nacional de Estadística Uruguay. Available at: https://www.ine.gub.uy/.

20. Moura MC, Casulari LA, Carvalho Garbi Novaes MR. Ethnic and demographic incidence of amyotrophic lateral sclerosis (ALS) in Brazil: A population based study. Amyotroph Lateral Scler Frontotemporal Degener. 2016;17:275–81.

21. World Health Organization. ICD-10: international statistical classification of diseases and related health problems. 10th ed., Vol. 2. Geneva: World Health Organization; 2010.

22. The United Nations Statistics Division. Demographic and Social Statistics [Internet]. Available at: https://unstats.un.org/unsd/demographic-social/products/dyb/#statistics

23. United Nations. UNSD — Geographic regions [Internet]. Available at: https://unstats.un.org/unsd/methodology/m49/

24. Income per capita in Latin America & Caribbean countries 2020 [Internet]. Statista. Available at: https://www.statista.com/statistics/1066610/gross-national-income-per-capita-latin-america-caribbean/.

25. Latinobarómetro Database [Internet]. Available at: https://www.latinobarometro.org/latContents.jsp. Accessed September 27, 2021.

26. Marin B, Fontana A, Arcuti S, Copetti M, Boumédiene F, Couratier P, et al. Age-specific ALS incidence: a dose-response meta-analysis. Eur J Epidemiol. 2018;33:621–34.

27. Boumediene F, Marin B, Preux P-M. Chapter 1 - methodological challenges of neuroepidemiological studies in low- and middle-income countries. In: Preux P, Dumas M, ed. Neuroepidemiology in tropical health. San Diego, CA: Academic Press; 2018. p. 3–12. Available from: https://www.sciencedirect.com/science/article/pii/B9780128046074000100

28. Marin B, Logroscino G, Boumédiene F, Labrunie A, Couratier P, Babron M-G, et al. Clinical and demographic factors and outcome of amyotrophic lateral sclerosis in relation to population ancestral origin. Eur J Epidemiol. 2016;31:229–45.

29. Fontana A, Marin B, Lena J, Beghi E, Logroscino G, Boumédiene F, et al. Time-trend evolution and determinants of sex ratio in Amyotrophic Lateral Sclerosis: a dose-response meta-analysis. J Neurol. 2021;268:2873–84.

30. Henning F, Heckmann JM, Naidu K, Vlok L, Cross HM, Marin B. The incidence of motor neuron disease/amyotrophic lateral sclerosis in South Africa: a 4-year prospective study. Eur J Neurol. 2021;28:81–9.

31. Bryc K, Velez C, Karafet T, Moreno-Estrada A, Reynolds A, Auton A, et al. Genome-wide patterns of population structure and admixture among Hispanic/Latino populations. PNAS 2010;107:8954–61.

32. Hombrebur J, Moreno-Estrada A, Gignoux CR, Nelson D, Sanchez E, Ortiz-Tello P, et al. Genomic insights into the ancestry and demographic history of South America. PLoS Genet. 2015;11:e1005602.

33. Ruiz-Linares A, Adhikari K, Acuña-Alonzo V, Quinto-Sanchez M, Jaramillo C, Arias W, et al. Admixture in Latin America: geographic structure, phenotypic diversity and self-perception of ancestry based on 7,342 individuals. PLoS Genet. 2014;10:e1004572.

34. Seldin MF, Tian C, Shigeta R, Scherbarth HR, Silva G, Belmont JW, et al. Argentine population genetic structure: large variance in Amerindian contribution. Am J Phys Anthropol. 2007;132:455–62.

35. Sans M, Salzano FM, Chakraborty R. Historical genetics in Uruguay: estimates of biological origins and their problems. Hum Biol. 1997;69:161–70.

36. Villacis B., Carrillo D. Estadística demográfica en el Ecuador: diagnóstico y propuestas [Internet]. Quito-Ecuador: Instituto Nacional de Estadística y Censos (INEC); 2011. Available at: https://www.ecuadorencifras.gob.ec/wp-content/descargas/Libros/Demografia/documentofinal1.pdf

37. Oficina Nacional de Estadística e Información República de Cuba. Informe Nacional Censo de población y viviendas Cuba 2012 [Internet]. CUBA; 2012. Available at: http://www.onei.gob.cu/sites/default/files/informe_nacional_censo_0.pdf

38. Logroscino G, Piccininni M, Marin B, Nichols E, Abd-Allah F, Abdelalim A, et al. Global, regional, and national burden of motor neuron diseases 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2018;17:1083–97.

39. Henry KA, Pagliano J, Jordan HM, Rechtman L, Kaye WE. Geographic variation of amyotrophic lateral sclerosis incidence in New Jersey, 2009–2011. Am J Epidemiol. 2015;182:512–9.

40. Roberts AL, Johnson NJ, Chen JT, Cudkowicz ME, Weisskopf MG. Race/ethnicity, socioeconomic status, and ALS mortality in the United States. Neurology 2016;87:2300–8.

41. World Health Organization. Atlas: country resources for neurological disorders. 2nd ed. Geneva: World Health Organization; 2017.

42. Pan America Health Organization PAHO. Report on Epilepsy in Latin America and the Caribbean [Internet]. 2013. Available at: https://iris.paho.org/handle/10665.2/53836

43. Al-Chalabi A, Hardiman O. The epidemiology of ALS: a conspiracy of genes, environment and time. Nat Rev Neurol. 2013;9:617–28.

44. Logroscino G, Piccininni M. Amyotrophic lateral sclerosis descriptive epidemiology: the origin of geographic difference. Neuroepidemiology 2019;52:93–103.

45. Baldin E, Preux P-M, Couratier P, Pugliatti M, Marin B, FRALIM CONSORTIUM. Validity of death certificates in the identification of cases of amyotrophic lateral sclerosis (ALS) in the Limousin region, France. A population-based study. Amyotroph Lateral Scler Frontotemporal Degener 2020;21:228–34.
46. Fong KY, Yu YL, Chan YW, Kay R, Chan J, Yang Z, et al. Motor neuron disease in Hong Kong Chinese: epidemiology and clinical picture. Neuroepidemiology 1996;15:239–45.
47. Dean G, Quigley M, Goldacre M. Motor neuron disease in a defined English population: estimates of incidence and mortality. J Neurol Neurosurg Psychiatry. 1994;57:450–4.
48. Shraga R, Yarnall S, Elango S, Manoharan A, Rodriguez SA, Bristow SL, et al. Evaluating genetic ancestry and self-reported ethnicity in the context of carrier screening. BMC Genet. 2017;18:99.