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META-ANALYSIS

Clinical and demographic factors and outcome of amyotrophic lateral sclerosis in relation to population ancestral origin

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Abstract
Background To review how the phenotype and outcome of amyotrophic lateral sclerosis (ALS) change with variations in population ancestral origin (PAO). Knowledge of how PAO modifies ALS phenotype may provide important insight into the risk factors and pathogenic mechanisms of the disease.
Methods We performed a systematic review and meta-analysis of the literature concerning differences in phenotype and outcome of ALS that relate to PAO.
Results A review of 3111 records identified 78 population-based studies. The 40 that were included covered 40 geographical areas in 10 subcontinents. Around 12,700 ALS cases were considered. The results highlight the phenotypic heterogeneity of ALS at time of onset [age, sex ratio (SR), bulbar onset], age at diagnosis, occurrence of comorbidities in the first year after diagnosis, and outcome (survival). Subcontinent is a major explanatory factor for the variability of the ALS phenotype in population-based studies. Some markers of ALS phenotype were homogeneously distributed in western countries (SR, mean age at onset/diagnosis) but their distributions in other subcontinents were remarkably different. Other markers presented variations in European subcontinents (familial ALS, bulbar onset) and in other continents. As a consequence, ALS outcome strongly varied, with a median survival time from onset ranging from 24 months (Northern Europe) to 48 months (Central Asia).
Discussion This review sets the scene for a collaborative study involving a wide international consortium to investigate, using a standard methodology, the link between ancestry, environment, and ALS phenotype.

Keywords Amyotrophic lateral sclerosis · Phenotype · Epidemiology · Ethnic groups · Continental population groups

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Introduction

Phenotypic diversity of amyotrophic lateral sclerosis (ALS) has received increasing attention in recent years [1–3]. Age at onset, combination of upper motor neuron (UMN) and lower motor neuron (LMN) signs, disease duration, and association with other conditions are major contributors to the variation [2].

There is evidence from mixed populations that phenotypic features diverge between populations of different ancestral origin. The data suggest possible variations in sex ratio, age at diagnosis, clinical manifestations, and survival [4–8]. Population ancestral origin (PAO) might modulate the disease via genetic background. The environment may also have an effect, as PAO is associated with geographic, behavioral and demographic differences [9]. Knowledge about how ancestry modifies ALS phenotype may provide important insight into risk factors and pathogenic mechanisms. Against this background, we performed a systematic review and meta-analysis of data concerning the differences in phenotype and outcome of ALS in relation to variations in PAO.

Methods

MOOSE statements [10] and other recommendations for systematic reviews and meta-analyses in neuro-epidemiology [11] were applied.

Definitions

The disease under consideration was ALS, which includes ALS subset, Progressive Bulbar Palsy (PBP), Progressive Muscular Atrophy (PMA), and Primary Lateral Sclerosis (PLS) [12]. Hence ALS was considered here to be synonymous with Motor Neuron Disease. Only population-based studies were included, i.e. epidemiological investigations of a sample or the entirety of well-defined populations [13]. Ancestral origin defines "a group of individuals, who are more or less isolated geographically or culturally, who share a common genetic pool, whose allele frequencies at some loci differ from those of the other populations" [14]. As genetic differentiation is greatest when defined on a continental basis [15], "subcontinent" was used as a proxy for ancestral origin. Continent and subcontinent classification was obtained from the United Nations Statistics Division [16]. Phenotype was defined by age at onset and at time of diagnosis, sex ratio (SR), site of onset (bulbar/spinal), delay between first symptoms and diagnosis, and presence of comorbidities. The outcome was represented by survival time from onset and from diagnosis.

Search strategy

We searched in Medline and Embase to June 2014 without language limitations. Key-words, defined with the help of a medical librarian, are described in eTable 1. Reference lists of selected articles were hand searched.

Inclusion criteria

Systematic reviews wee not included, but their references were screened. Proceedings of conferences were not included. We included population-based studies of newly-diagnosed ALS cases with multiple sources of cases to ensure the highest level of completeness for case ascertainment. Sound methodology was mandatory in terms of definition of geographical coverage, study population, period investigated, and accuracy of ALS diagnosis (i.e. based on neurological confirmation). We did not use a "score of quality" for eligibility examination or for included articles as their use has been criticized for being inaccurate in some cases [11]. Instead, an ad-hoc checklist formulated on the basic principles of descriptive epidemiology was used and focused on all aspects of study design that can influence the quality of case ascertainment and of the results presented. We collected data on variability between studies to adjust, during statistical analysis, on objective criteria reflecting each study's characteristics and quality. It was not possible to collect information on access to health systems within and between populations (not available in the original contributions). When more than one article was available for the same geographical area, the one with the widest follow-up was accorded higher priority. In cases of overlapping geographical areas, we retained the article with the widest geographical coverage.

Data extraction

Reports were examined by the first author, who assessed eligibility and extracted data. Decisions about inclusion/exclusion were confirmed by the last author. The following data were recorded: Authors, publication year, period of study, setting, design, sources of case ascertainment, diagnostic criteria, number of ALS cases (male, female), underlying population, mean age at onset and at time of diagnosis, site of onset (bulbar/spinal; generalized onset was considered as bulbar onset), proportion of familial ALS cases (fALS), definition of fALS in the original study—a limitation on this topic is the variability of fALS definition among studies, comorbidities (fronto-temporal dementia (FTD), dementia, parkinsonism), median survival time from onset and from diagnosis. Where not available in the published material, authors (or their collaborators) of the articles retained in the review were contacted to seek

more information about the ALS phenotypic aspects. For each population, life expectancy at 50 years for men and women (both indicators used as proxy for the pool of subjects at risk to develop ALS in each area) were retrieved from the demographic yearbook published by the United Nations at the time of the mid-point period [17]. Life expectancy in Egypt was used as a proxy for Libya due to missing data.

Data-analysis

Graphical descriptive analysis

Box whisker plots displaying median, interquartile range, minimum and maximum of each variable of interest were created.

Crude incidence by site of onset

Crude incidence for bulbar onset (per 100,000 inhabitants per year of follow-up) was recalculated based on number of cases, duration of case ascertainment and study population extracted from each article.

Meta-analysis

Random effect meta-analyses allowed us to produce forest plots for (1) proportion of fALS cases, proportion of bulbar onset, (2) SR, (3) crude incidence of bulbar onset. In each case the estimates (ES) are given in the figures. Pooled estimates were calculated. For SR, first coefficients and pooled estimates were calculated for proportions of men and then transformed as SR. Weights were based on the precision of the estimates for each study, i.e. standard error of the distribution. For proportions, 95 % confidence interval (CI) and standard error are based on exact method; the logit transformation was used to stabilize variances. Standard error of incidence assumed a Poisson distribution for the calculation of 95 % CI. The I^2 value was also calculated [18]. Stratified estimates according to subcontinent were calculated.

Meta-regression

Adjusted associations between subcontinents and phenotypic characteristics were assessed using weighted random effects meta-regression using the DerSimonian and Laird method [19]. The Freeman-Tukey arcsin transformation were used for proportions [20]. Reference category for subcontinents was the one with the highest number of studies. The following adjusting variables were considered: (1) characteristics of the study population: life expectancy after 50 years in men, life expectancy after 50 years in women, SR, (2) methods: study design (prospective/retrospective), method of diagnosis (clinical assessment vs. El Escorial original (EEDC) [21] or revised criteria (EEDC-R) [22]), duration of the study period, number of person-years of follow-up (PYFU), period of study (the midtime point was used to categorize studies performed: (1) before 1990, (2) between 1990 and 2000, (3) after 2000).

To minimize the number of adjustment variables, for each phenotypic aspect, a multivariable model was used retaining variables with a p value < 0.20 in univariable analysis. The model was simplified using a backward stepwise procedure allowing for identification of adjustment variables with p value < 0.05. Analyses were made using statistical software Stata v11.1 (Stata Corporation, College Station, TX, USA).

Results

Included studies

Our search strategy identified 3085 reports after removal of duplicates (n = 70). Twenty-six other articles were identified through hand searching, giving a total of 3111 reports to be examined. After removal of articles based on title and abstract (n = 2831) and examination of 280 full texts, we identified 78 population-based studies, and included 40 studies, covering 40 geographical areas [3, 8, 23–60]. Other references were considered as duplicated reports for the same area [61–98]. eFigure 1 shows the flowchart of the studies selected for analysis.

Geographical coverage of population-based studies

eFigure 2 and eTable 2 show the contribution of each subcontinent and country to the ALS phenotype. Twenty-three reports (57.5 %) were from Europe and nine (22.5 %) from the American continent. East Asia was represented by four studies (10 %). North Africa was represented by only one study (Libya), as was the case for Central Asia (Iran), West Asia (Israel) and Oceania (New Zealand). For the atypical aspects of the disease, data from the ALS-Parkinson-Dementia foci (Wakayama prefecture [50] and Guam [56]) are not included but are considered in the Discussion section.

Familial ALS

The overall pooled estimate (29 studies) of the proportion of fALS was 4.7 % (95 % CI 3.9–5.7), Fig. 1. There was a tendency for a lower proportion of familial cases in Southern Europe ($p = 0.09$) as compared to Northern Europe (Table 1), ($p = 0.04$ as compared to Western

Europe, $p = 0.02$ as compared to North America). The proportion was at 0.0 % in Libya, 1.2 % in Hong Kong and 0.6 % in Israel and was unaffected by study design or period of publication.

Mean age at ALS onset and diagnosis

The mean age at onset of ALS was available for 28 studies, Fig. 2. As expected, mean age at onset/diagnosis varied between subcontinents in parallel to life expectancy in men or women. The median value of the reported mean age at onset in the original articles was between 63 and 65 years for Europe and New Zealand. For North America and East Asia the medians were around 59 years. Mean age at onset was even lower for Israel, Iran, and Libya. A similar pattern was shown when the mean age at diagnosis was considered (n = 25).

Diagnostic delay

The median value of the mean diagnostic delay in European studies was around 12 months. The mean delay in New Zealand was 10 months. For North America, the diagnostic delay appeared longer (between 13.2 and 17.5 months, median 17 months). While the delay in Uruguay appeared consistent with North American data, it was 42 months in Libya.

Sex ratio of ALS cases

The SR (male/female ratio) appeared stable in European populations, with pooled estimates at 1.29 (95 % CI 1.15–1.45), 1.27 (95 % CI 1.08–1.48) and 1.24 (95 % CI 1.15–1.34) in Northern, Western and Southern Europe, respectively (Fig. 3). The pooled estimate was 1.33 (95 % CI 1.19–1.49) in North America and 1.22 (95 % CI 0.94–1.58) in New Zealand. Conversely, the SR was 1.53 (95 % CI 1.39–1.67) in East and 1.72 (95 % CI 1.36–2.18) in West Asia while it was higher than 2 for Iran, Uruguay, Libya and Hawaii. In meta-regression for SR, the univariable p value was <0.20 for life expectancy in women after 50 years of age and SR in the study population, hence we considered these variables for adjustment. After rejection of life expectancy in a first multivariable model, we adjusted our estimates on SR ($p = 0.002$). SR in Northern Europe was significantly different from Uruguay, $p = 0.04$, East Asia ($p = 0.035$) and Hawaii ($p < 0.0001$). R^2 of this multivariable model was 97 % (Table 1).

Bulbar form at onset

The pooled estimate for bulbar onset ALS from Northern Europe (45.4 %, 95 % CI 38.1–52.8) was significantly higher than that from other European subcontinents (34.9 % (95 % CI 32.5–37.3) and 34.2 % (95 % CI 31.3–37.3) in Western and Southern Europe (Fig. 4). As compared to Northern Europe, bulbar onset was also different for North America, East Asia, Israel and Iran where the proportions were reduced by at least 15 %.

For 27 areas, the crude incidence of bulbar onset ALS is presented (Fig. 5). It was 0.86 (95 % CI 0.81–0.91)/100,000 PYFU in Northern Europe, 0.73 (95 % CI 0.49–0.96) in Eastern Europe and 0.68 (95 % CI 0.48–0.88) in Southern Europe. Incidence in the American continent appeared reduced by 50 % (pooled estimate of 0.43 (95 % CI 0.21–0.66) for North America, $p = 0.006$; 0.46 (95 % CI 0.31–0.66) in Uruguay, $p = 0.08$). Incidence of bulbar onset ALS was at 0.15 (95 % CI 0.12–0.18) in East Asia and 0.11 (95 % CI 0.07–0.17) in Iran. When considering the characteristics of the (1) study population (life expectancy and SR) and (2) study methodology, the data were substantially unchanged.

Comorbidities

Information about dementia, fronto-temporal dementia (FTD), and PD-associated ALS was available in less than one in four reports (eTable 3). In most studies, co-morbidities were reported either at the time of diagnosis or within a window of less than 1 year after diagnosis.

Median survival time

The median survival time after ALS onset was available for 24 geographical regions (Fig. 2).

Median survival time since onset was around 25 months in Northern Europe (range 23.0–34.0, n = 6), but around 30 months in Western (range 25.4–34.8, n = 3) and Southern Europe (range 26.6–49.0, n = 9). In North America, survival was 32.0 [45] and 39.5 months [46]. Data from Asia varied from 28 months in East Asia (Japan, n = 1) to 36 months in Israel and 48 months in Iran, n = 1. No information was available for Libya and Uruguay.

Discussion

Main results

This work highlights the phenotypic heterogeneity of ALS in terms of onset (age, SR, ratio between bulbar and spinal-onset ALS and incidence by type of onset), diagnosis (age), occurrence of comorbidities within 1 year of diagnosis, and outcome (survival after| first symptoms and after diagnosis).

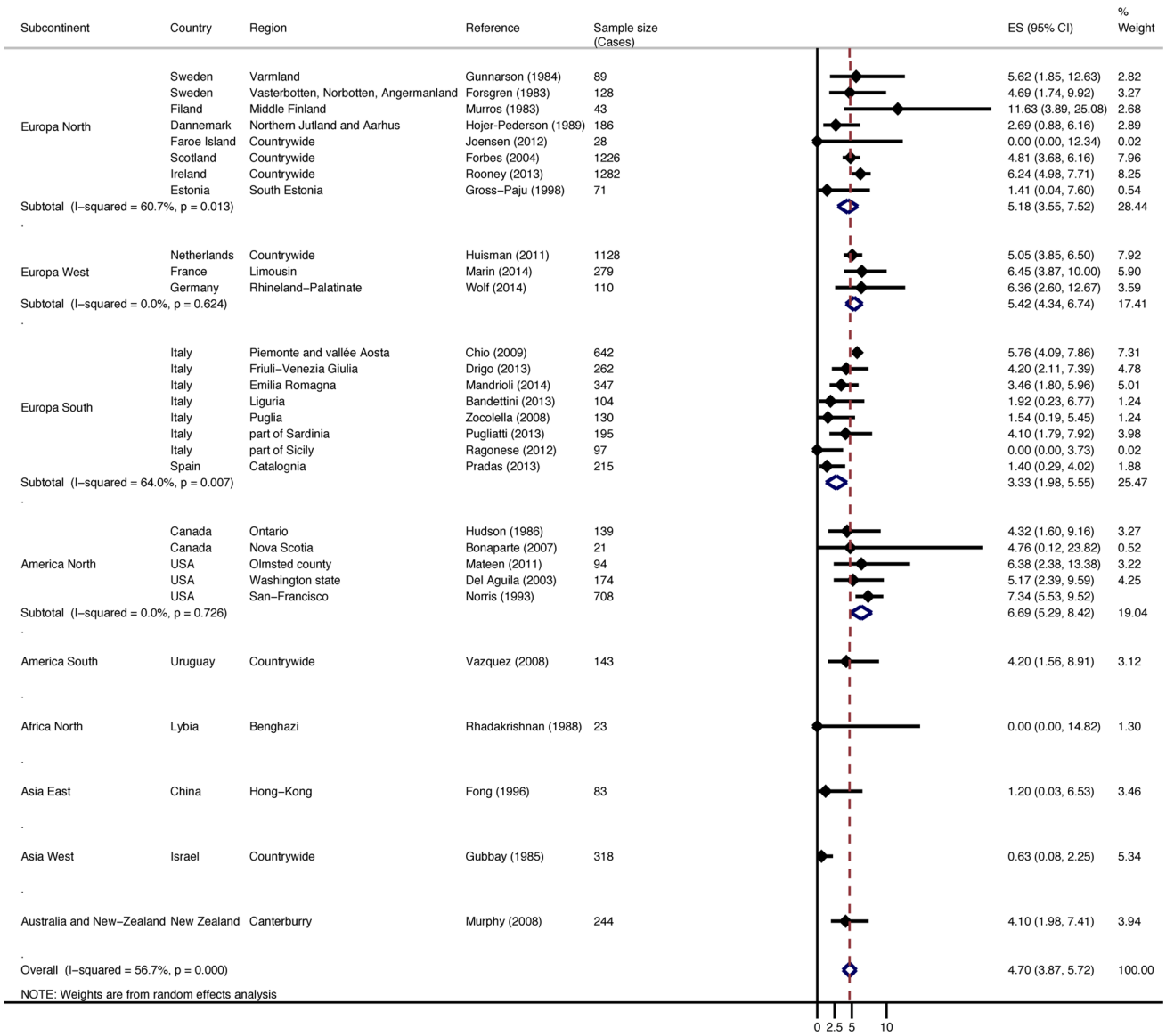

Fig. 1 Meta-analysis: forests plots and pooled estimates for proportion of familial ALS cases. "ES": Estimate of proportion of familial ALS cases; "sample size (cases)" is the total number of ALS cases in each original study

A major explanation of the variability of the ALS phenotype in population-based studies is subcontinent. For example, 83 % of the variability (R^2) in SR was explained by subcontinent (R^2 was 40 and 53 % for the proportion of bulbar onset cases and for the incidence of bulbar-onset ALS, and 56 % for fALS). In critically appraising these results, we considered the possible concurrent impact of population characteristics (life expectancy and SR) and study characteristics (type of design, methods of diagnosis), which were, however, uneventful. Diagnostic delay has been found to be heterogeneous, but few studies reported those data. This may reflect the rate of progression of the disease as well as its local management and the organization of health care for diagnosis.

Some markers of ALS phenotype were found to have homogeneous distribution within western countries (SR, mean age at onset/diagnosis) but their distributions in other subcontinents were remarkably different. Some other markers presented variations even in the European subcontinents (for example, fALS, bulbar onset between Northern, Western and Southern Europe) and strong variability in the other continents. As a consequence, outcome strongly varied between subcontinents, with a median survival time from onset of around 25 months in Northern

Table 1 Metaregression of ALS phenotype

Variables	Familial ALS % (n = 29) Univariate					Sex-ratio (n = 38)							
						Univariate					Multivariate		
	Coeff (arcsin)*	FALS (%)[b]	*p* value	n	R^2	Coeff (arcsin)[a]	Sex-ratio[b]	*p* value	n	R^2	*p* value	n	R^2
Subcontinent			**0.04**	29	55.9			**0.0006**	38	82.9	**0.0007**	37	97.1
Europe North (reference, n = 10)	0.45	4.9		8		1.70	1.29		10			10	
Europe West (n = 4)	0.04	0.9	0.50	3		−0.003	−0.009	0.93	4		0.33	3	
Europe South (n = 9)	−0.09	−1.7	0.09	8		−0.02	−0.04	0.65	9		0.86	9	
America North (n = 6)	0.06	1.4	0.31	5		0.0006	0.002	0.99	6		0.44	6	
America South (n = 1)	−0.02	−0.4	0.87	1		0.25	0.86	**0.047**	1		**0.04**	1	
Hawaii (n = 1)						0.56	3.24	**<0.0001**	1		**<0.0001**	1	
Africa North (n = 1)	−0.24	−3.8	0.29	1		0.26	0.91	0.25	1		0.32	1	
Asia East (n = 3)	−0.18	−3.2	0.19	1		0.08	0.25	0.065	3		**0.035**	3	
Asia West (n = 1)	−0.27	−4.1	**0.008**	1		0.14	0.42	0.075	1			1	
Asia Central (n = 1)						0.22	0.75	0.06	1		0.10	1	
Oceania (n = 1)	−0.03	−0.6	0.76	1		−0.03	−0.08	0.70	1		0.75	1	
Design								0.31					
Retrospectif (reference, n = 19)	0.40	4.0		13		1.75	1.44		18				
Prospectif (n = 19)	0.01	0.2	0.83	16		−0.04	−0.12		20				
Diagnostic								0.25					
Neurologist (reference, n = 14)	0.41	4.0		10		1.76	1.47		14				
El Escorial (n = 24)	−0.007	0.04	0.89	19		−0.05	−0.14		24				
Midtime			0.58										
≤1990 (reference, n = 12)	0.43	4.5		9		1.76	1.45	0.67	12				
≤2000 (n = 11)	−0.05	−1.1		9		−0.05	−0.14		11				
>2000 (n = 15)	−0.005	−0.1		11		−0.02	−0.07		15				
Duration study (constant)	0.38			29		1.72			38				
For 5 years	0.01		0.25			0.001		0.91					
PYFU (constant)	0.38			29		1.72			38				
For 1,000,000	0.001		0.15			0.0004		0.62					
Life exp 50 men (constant)		–				1.87			38				
For 5 years						−0.03		0.39					
Life exp 50 women (constant)		–				2.09			38				
For 5 years						−0.05		0.085					
SR population (constant)		–				0.46			38			38	
For 1 unit						1.31		**0.002**			0.47		

Variables	Bulbar onset								
	Proportion % (n = 29) Univariate					incidence (/100,000 PYFU, n = 27) Univariate			
	Coeff (arcsin)[a]	Bulbar (%)[b]	*p* value	n	R^2	Coeff	*p* value	n	R^2
Subcontinent			**0.03**	29	39.5		**0.004**	27	53.4
Europe North (reference, n = 10)	1.48	45.3		8		0.88		8	
Europe West (n = 4)	−0.23	−11.5	**0.03**	3		−0.15	0.32	3	
Europe South (n = 9)	−0.24	−11.6	**0.007**	9		−0.21	0.08	8	
America North (n = 6)	−0.33	−15.8	**0.006**	3		−0.45	**0.006**	3	

Table 1 continued

Variables	Bulbar onset								
	Proportion % (n = 29) Univariate					incidence (/100,000 PYFU, n = 27) Univariate			
	Coeff (arcsin)[a]	Bulbar (%)[b]	*p* value	n	R^2	Coeff	*p* value	n	R^2
America South (n = 1)	−0.23	−11.4	0.21	1		−0.42	0.08	1	
Hawaii (n = 1)									
Africa North (n = 1)									
Asia East (n = 3)	−0.36	−23.2	**0.01**	2		−0.72	**<0.0001**	2	
Asia West (n = 1)	−0.50	−18.5	**0.005**	1					
Asia Central (n = 1)	−0.39	−13.6	**0.042**	1		−0.77	**0.002**	1	
Oceania (n = 1)	−0.28	−13.6	0.10	1		−0.07	0.77	1	
Design									
Retrospectif (reference, n = 19)	1.25	33.8	0.71	12		0.60		10	
Prospectif (n = 19)	0.03	−1.3		17		0.06	0.60	17	
Diagnostic									
Neurologist (reference, n = 14)	1.31	37.1		8		0.64		7	
El Escorial (n = 24)	−0.06	−3.0	0.45	21		0.007	0.96	20	
Midtime							0.95		
≤1990 (reference, n = 12)	1.25	34.3		7		0.60		6	
≤2000 (n = 11)	0.04	1.7		11		0.05		11	
>2000 (n = 15)	−0.001	−0.04	0.89	11		0.05		10	
Duration study (constant)	1.27			29		0.63	0.85	27	
For 5 years	−0.001		0.92			0.004			
PYFU (constant)	1.31			29		0.70	0.31	27	
For 1,000,000	−0.002		0.21			−0.003			
Life exp 50 men (constant)	1.66			29		0.39	0.69	27	
For 5 years	−0.07		0.31			0.05			
Life exp 50 women (constant)	1.40			29		−0.08	0.35	27	
For 5 years	−0.02		0.77			0.11			
SR population (constant)	1.05			29		0.71	0.97	27	
For 1 unit	0.25		0.77			−0.05			

Approach by Sub-continents

p-value < 0.05 appear in bold

Coefficients of the model using arcsin transformated data are displayed for each explanatory variable[a] and re-transformed in the original unit for qualitative explanatory variables only [b]

Coeff: coefficient, arcsin: Freeman-Tukey arcsinus transformation, fALS: familial ALS

Europe, 30 months in Southern and Western Europe, 35 months in North America, and 48 months in Iran.

Discussion of results and examination of data from mixed populations

.Some differences in phenotype might be related to differences in environmental exposures, an influence that was impossible to disentangle from PAO in our work. Hence we will consider in the following sections data from mixed populations, to investigate the level of agreement between the results of our meta-analyses and previous reports of ALS phenotype stratified by what is reported as "ethnic group" (eTable 4).

fALS and high-risk genes

We identified an overall pooled fALS estimate of 4.7 %. This result, based on 29 population-based studies, is in agreement with Byrne et al. [99] who identified a pooled estimate of 4.5 % of fALS in a previous meta-analysis (22 population-based studies). We identified variations in the distribution of fALS among European subcontinents (highest estimates in Western and Northern Europe as compared to Southern Europe). Such variability was previously related to the variability in the genetic structure of the European population [99]. Founders' effects could also be implicated. fALS in North America was even higher. Nevertheless, the definition of

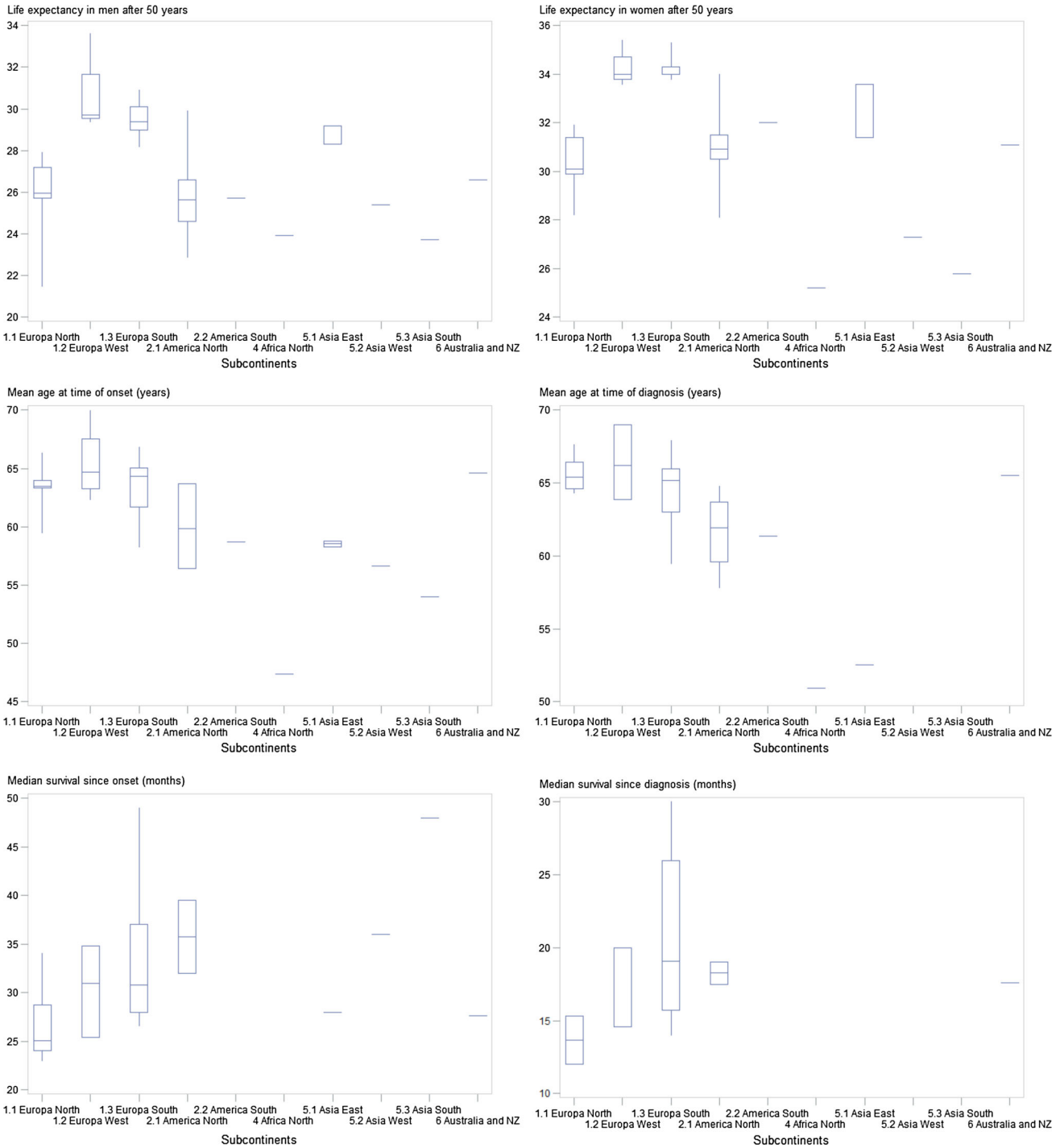

Fig. 2 Distribution of characteristics of (i) populations under study and (ii) ALS patients by subcontinent. *Boxplot* represents median, interquartile range, minimum and maximun of the distributions. Life expectancy at 50 years for men and women was retrieved from the demographic yearbook published at the time of the mid-point period by the United Nation. The demographic yearbooks are available online at https://unstats.un.org/unsd/demographic/products/dyb/dyb2.htm. Mean age at onset was available for 28 cohorts. It was given in the original papers [24, 32–35, 40–42, 45, 46, 48, 49, 51, 53–55, 57–59, 66] or obtained through personal communication with the authors [26, 27, 31, 36–39, 60]. Mean diagnostic delay was available for 22 cohorts. It was given either in the original reports [3, 27, 30, 32, 33, 35, 38–42, 46, 48, 49, 55, 57, 59] or obtained through personal communication [31, 36, 37, 45] or through a duplicated Ref. [81]. Survival pattern of the cohorts was available for 24 cohorts. It was given in the original papers [23–25, 27, 31–33, 35, 38, 39, 42, 46, 51, 54, 55, 57, 58, 60], or obtained through personal communication [36, 37, 40, 41, 45] or based on a duplicated Ref. [66]

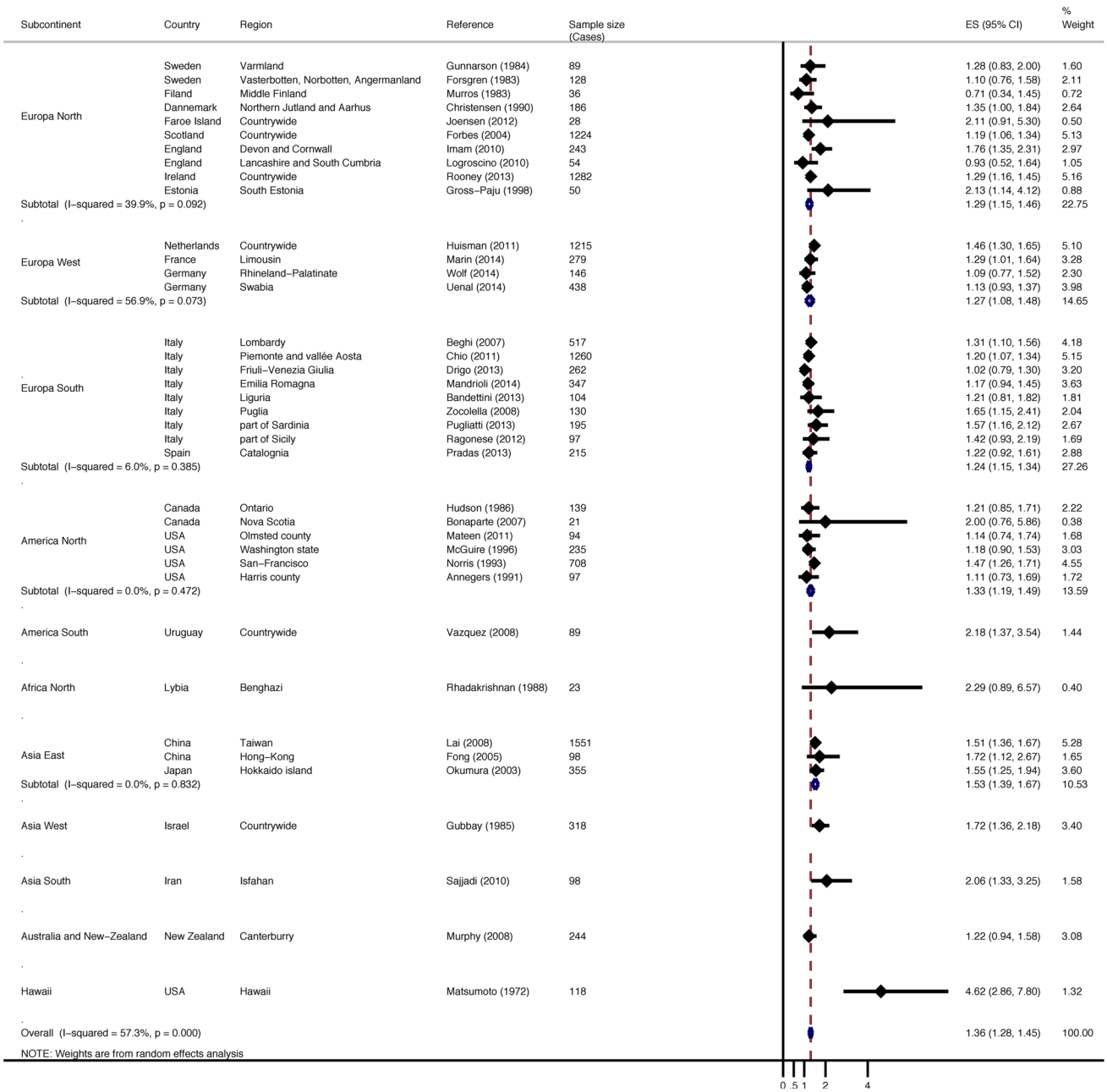

Fig. 3 Meta-analysis: forest plots and pooled estimates for Sex Ratio. ES: Estimate of sex ratio (male/female); "sample size (cases)" is the total number of ALS cases in each original study

fALS among publications is frequently imprecise, which may have led to underestimation of the real proportion of fALS. Systematic high-risk gene screening in ALS cases in a population-based setting found much higher percentages [100]. This difference is related to the penetrance of genes, to the degree of relatedness and to the size of the extended kindred considered while investigating fALS.

There is evidence of significant differences in the frequency of known ALS-associated genetic variants across European populations (e.g. SOD1, C9ORF, TARDBP) [101, 102]. For example, variants in SOD1 account for around 12 % of familial ALS cases in Italy [100] but are rare in Ireland [103] and the Netherlands [104]. Local founder effects cannot be discounted in some areas. Rates of C9ORF72 and TARDBP variants are high in genetically isolated populations such as Finland or Sardinia [105–107]; while ANG mutations seem relatively common in Scotland, Italy and Ireland, they are very rare in England, the Netherlands, France, Germany and Sweden [108]. The frequency of the C9ORF72 repeat expansion is far lower in

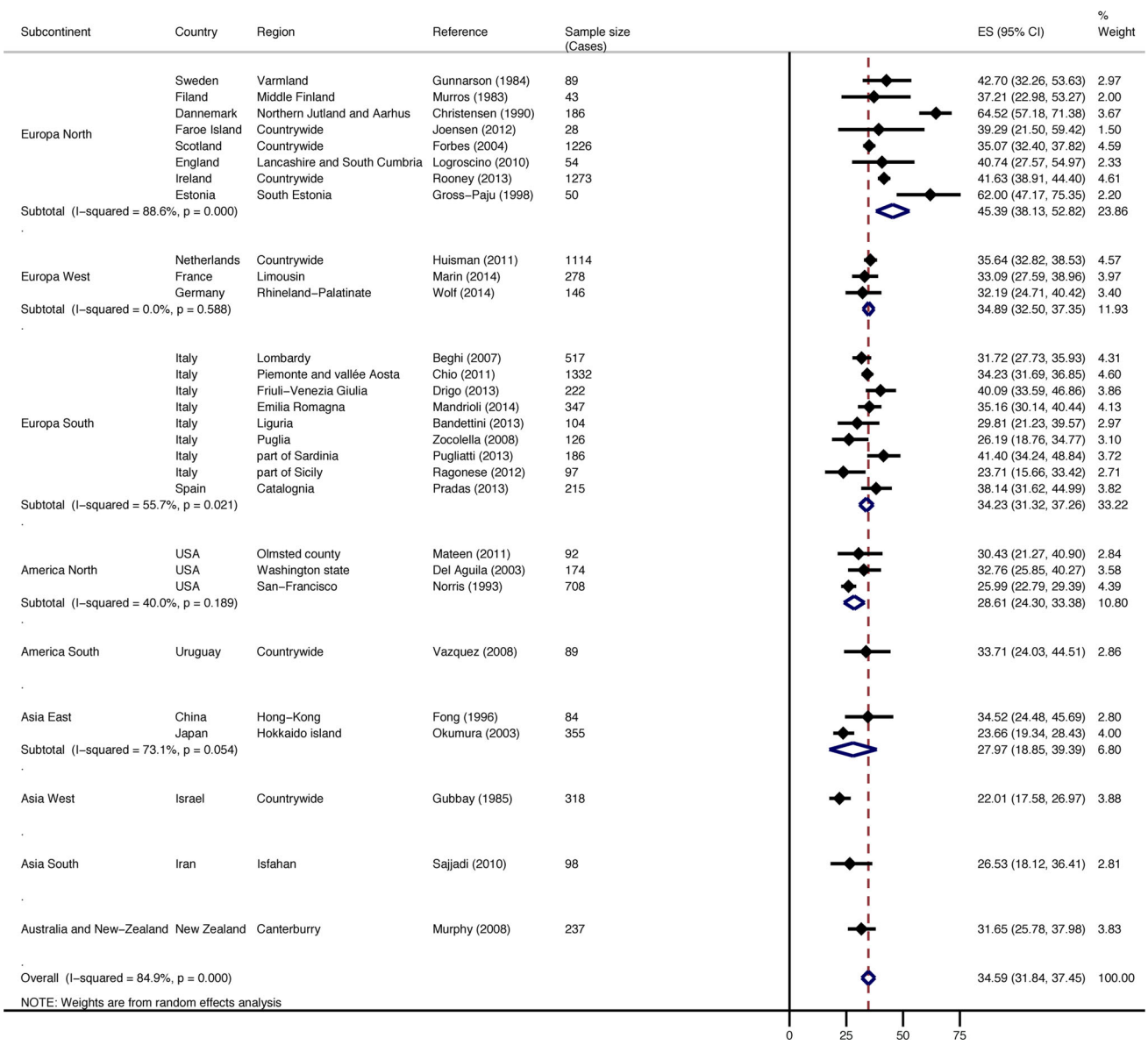

Fig. 4 Meta-analysis: forest plots and pooled estimates for proportion of bulbar onset. ES: Estimate of proportion of bulbar onset; "sample size (cases)" is the total number of ALS cases in each original study

China and Japan [109] than among Europeans in whom the frequency is around 7 % [110, 111], whereas the inverse pattern is observed for OPTN mutations [101]. Differences in distribution could be correlated with ALS phenotype [101, 110, 112]. For example, the mutations in C9ORF72 seem to be associated with a specific phenotype of ALS, with earlier age of onset, more malignant course of disease, a bulbar onset, comorbid FTD and frequent occurrence of psychotic symptoms [111].

Understanding sex ratio variations

There is still a male predominance of ALS, which is partly driven by the demographic characteristics of the populations. In meta-regression, SR in ALS cases was found to be positively associated with SR of the underlying population and a tendency was apparent for a negative association with life expectancy in women after 50 years. There is, however, a significant negative correlation between SR in ALS cases and mean age at onset (data not shown), suggesting that while the populations are getting older, there is a progressive increase in the relative number of female ALS cases as compared to men. SR rose to around 1.6 in East Asia and Israel. The pooled estimate SR of 1.6 for East Asia is in line with a recent incidence study performed in Japan based on patients certified as eligible for financial aid for the treatment of ALS which documented an SR of 1.5 [113]. SR reached a value higher than 2 for Uruguay, Libya, Iran and Hawaii.

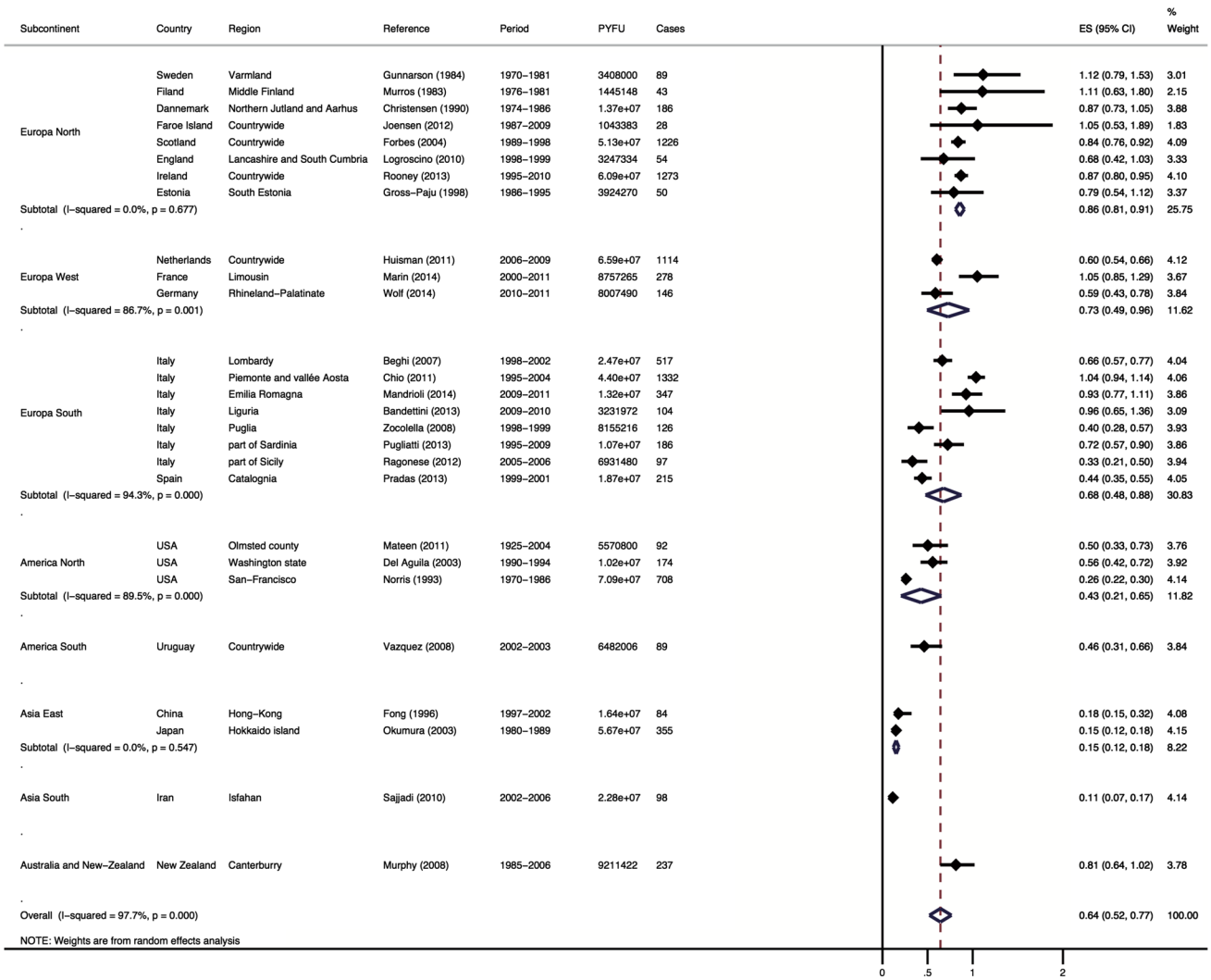

Fig. 5 Meta-analysis: forest plots and pooled estimates for crude incidence of bulbar cases. ES: Estimate of crude incidence of bulbar cases; "Cases" is the number of bulbar onset ALS patients; PYFU: person-years of follow-up

Based on studies in mixed populations (eTable 4), East Asia, Israel and Hawaii experience a high degree of variation of SR between groups of different ancestries [6–8]. Although these data are from small groups, the information is useful to exemplify the variation of SR between different ancestral groups sharing the same environment. Conversely, data from the UK and US do not support differences in SR between patients of African and European origin [4, 114, 115]. Differing case ascertainment between groups with diverse economic status and access to health systems cannot be ruled out. Data from studies with the same methodology in different geographic areas support on one hand the difference between Europe and South America [116] and on the other hand a higher ratio in East Asia as compared to North America [51].

Variability of bulbar onset even between European subcontinents

Bulbar onset ALS is usually considered to account for up to one third of cases. The overall pooled estimate is in agreement with this belief. Nevertheless, stratified meta-analysis highlights an important variation in this proportion across populations. We identified a pooled estimate of 45.4 % in Northern Europe, which is significantly different from Western (34.9 %) and Southern Europe (34.2 %). At the European scale, differences were previously suggested by a pooled analysis of data from EURALS (the Pan European consortium on the epidemiology of ALS) [29]. In that study, bulbar onset ALS was at 45.5 % in Ireland and 40.7 % in England, but ranged from 26.2 to 31.2 % in Italy

(Lombardy, Puglia, Piedmont), suggesting a North–South gradient. Here, the proportion of bulbar onset ALS was 28.6 % in North America and even lower in Asia. Data from mixed populations show close proportions of bulbar onset cases among "ethnic groups", as in Israel, [58] while others report 10 % differences [7, 117]. Two publications from the USA reported slightly lower bulbar onset in subjects of African origin as compared to those of European origin [4, 115].

Outcome variation

It is now well recognized that older age and bulbar onset are significant prognostic markers [118]. Differences in survival between studies could be explained at least partially by differences in mean age at onset. Type of onset also appears to be driven by subcontinents, so one might hypothesize an impact of PAO on ALS outcome, at least related to age at onset, and bulbar onset. As it was not possible to perform multivariable analysis of this aspect, we cannot entirely rule out other explanations. Genetic background could also directly influence the progression of ALS. Survival can also be highly influenced by nutritional and respiratory management. For example, tracheostomy is performed in about 30 % of Japanese patients [119], while in the US and Europe proportions range between 0 and 10 % [120]. Conversely, use of non-invasive ventilation (NIV) appears higher in the US (15–35 % of cases) as compared to Japan (around 7 %) and might be even lower in Europe [121].

Data in mixed populations were inconsistent as regards survival times. In the UK, people of African origin presented similar survival times to subjects from European origin, when matched for age and sex [5]. A similar result was found in the US [122]. Conversely, in the study by Del Aguila et al. [86] a population-based study conducted in Washington State, African origin was associated with a 2.2 risk of death after adjustment on age, site of onset, marital status, and county of residence. Differences in terms of adjusting variables between studies render comparisons challenging.

Complexity of the ALS phenotype spectrum

Less than one in four studies considered ALS comorbidities. The proportion of FTD among ALS patients was around 5 % overall, but as high as 13 % in Ireland, while 34.1 % of ALS patients without evidence of dementia fulfilled the criteria for cognitive impairment [82]. Although difficult to assess, behavioral comorbidities, partly associated with cognitive comorbidities, have also been reported (apathy, egocentric or selfish behaviors, irritability) [123]. Hence, the concept of distinct nosological entities (ALS/PD/Dementia/FTD) evolved towards a broader and complex clinical spectrum of neurodegenerative diseases with various outcomes [124]. It is interesting to note that ALS, PD and AD also share some potential risk or protective factors such as age, gender, low education, trauma, pesticide exposure, diet, coffee, smoking, occupation, exercise, family history of neurodegenerative disease, and drug exposure [125, 126]. Some overlap has also been observed in the mutations identified when comparing ALS, PD and AD [2, 127].

ALS foci

We decided a priori not to include data from historical foci of ALS-syndromes (Kii peninsula [50], Guam [56]) in the pooled analyses in order to avoid gathering ALS with variants unrelated to sporadic ALS and potentially implying differing etiologic mechanisms such as toxic exposures, specific nutritional habits, food and water supplies associated with toxins [56].

Limitations

The main body of the literature on ALS epidemiology is large but limited geographically [128]. This is particularly relevant for population-based investigations. Most research has been conducted in Europe or more globally in populations of European origin. Unfortunately, some important areas do not have data on phenotypes (either due to absence of reports or to missing information in the articles). Besides, the few data available for some subcontinents (South America, North Africa, Central Asia) may represent "outliers" of ALS characteristics in those regions and not be truly representative of the real phenotype ALS spectrum. Our literature review identified works from geographic areas (India, Brazil, Africa), which investigated disease variants or selected patient subgroups (e.g., juvenile ALS) and not the classical ALS phenotypes.

We have to recognize the inherent limitation of the geographical approach used here because it is difficult to argue about the homogeneity of ancestral origin within a given subcontinent. Unfortunately to date it is not possible to rely on accurate genotypic information as regards the population under study and to question on this basis the relation between genetic markers and ALS characteristics.

Another important limitation is the variability of study designs, populations at risk and settings. We did our best to exclude studies with low quality methodology and we adjusted our analysis for design, diagnostic method, time period, population size, life expectancy, and study duration. Nevertheless, we cannot exclude that some differences are due to the lack of comparability of some reports, some of them include all MND and others consider only

ALS subtypes. While comparing different studies, appropriate inter-rater reliability in clinical assessment (including EEDC ascertainment) is of major importance [118]. The disease considered here is a syndrome consisting of a number of variants. Different abilities in different studies to make a distinction across variants and heterogeneity in the way these variants were included in the original articles may significantly limit the interpretation of our results.

Various degrees of under-ascertainment of cases could also falsely suggest differences in phenotypes. Differences in health care system organization and access to health care could be also implicated. It is well known that an older age, a bulbar presentation and a poorer prognosis are associated with reduced access to referral centers [129, 130]. Even in population-based settings it is possible that some sub-groups of patients (for example the oldest-old) are missed by the health system [118]. To date, exhaustiveness of recruitment was evaluated only by a sub-group of ALS registers [31, 32, 37, 48, 55, 66, 68]. Lastly, we used data about life expectancy for Egypt as surrogate for unavailable data from Libya because these countries are adjacent. This may have influenced the results and needs to be acknowledged.

Strengths

The main strength of this work relies on the broad literature search and the use of population-based studies using multiple sources of case ascertainment. We systematically contacted the authors or their collaborators in order to seek more information about the characteristics of ALS patients. We also relied on standardized data (mean (for age), median (for survival)). This allowed us to display homogeneous clinical elements for a high number of areas (SR n = 38, mean age at onset n = 28, at diagnosis n = 25, fALS and bulbar onset n = 29, median survival time from onset n = 24). The success of meta-analysis and meta-regression for these main aspects of the ALS phenotype is without antecedents in the epidemiological literature on ALS. We also investigated (and adjusted for) the underlying populations and the study methodology.

Conclusion

There is increasing evidence that the level of clinical and etiological heterogeneity of ALS is far greater than previously assumed [2]. This systematic review shows that differences in ALS phenotype with PAO are not entirely explained by confounding factors. Nevertheless, we cannot exclude that some differences are related to differences in environmental factors in connection with the growing evidence that etiology relies on multifactorial effects resulting from the combination of environmental and genetic factors [102]. Researchers in the field now need to consider the organization of a wide international consortium in order to investigate the link between ancestry, environment (exposomes) and ALS incidence and phenotypes with homogeneous methodology.

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Compliance with ethical standards

Conflicts of interest B Marin and F Boumediene: None declared. G. Logroscino: Dr. Logroscino received personal compensation for educational talks from Novartis, Glaxo and Boerhinger; he is a member of the jury of the "Cohorts" project in biomedicine of the French National Research Agency. Dr Logroscino is neurological editor of nutrition reviews by Karger. F Boumediene: None declared. A Labrunie: None declared. MC Babron: None declared. A Leutenegger: None declared. PM Preux: None declared. Dr E. Beghi received personal compensation from GSK and UCB-Pharma for speaking at an epilepsy congress, and from Viropharma for being part of a steering committee. Dr Beghi received personal compensation from Epilepsia as Associate Editor. Dr Beghi received research support from UCB-Pharma for studies in epilepsy and Parkinson's disease, and from GSK for studies in epilepsy.

Ethics As this review of the literature/meta-analysis does not involve ALS patients but makes use of publications concerning ALS, informed consent of patients is not applicable. Not even approval of an ethics committee is applicable.

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