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Miscellaneous

Variation in worldwide incidence of amyotrophic lateral sclerosis: a meta-analysis

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Abstract

Background: To assess the worldwide variation of amyotrophic lateral sclerosis (ALS) incidence, we performed a systematic review and meta-analysis of population-based data published to date.

Methods: We reviewed Medline and Embase up to June 2015 and included all population-based studies of newly diagnosed ALS cases, using multiple sources for case ascertainment. ALS crude and standardized incidence (on age and sex using the US 2010 population) were calculated. Random effect meta-analysis and meta-regression were performed using the subcontinent as the main study level covariate. Sources of heterogeneity related to the characteristics of the study population and the study methodology were investigated.

Results: Among 3216 records, 44 studies were selected, covering 45 geographical areas in 11 sub-continents. A total of 13 146 ALS cases and 825 million person-years of follow-up (PYFU) were co-nsidered. The overall pooled worldwide crude ALS incidence was at 1.75 (1.55–1.96)/100 000 PYFU; 1.68 (1.50–1.85)/100 000 PYFU after standardization. Heterogeneity was identified in ALS standardized incidence between North Europe [1.89 (1.46–2.32)/100 000 PYFU] and East Asia [0.83 (0.42–1.24)/100 000 PYFU, China and Japan $P = 0.001$] or South Asia [0.73 (0.58–0.89)/100 000/PYFU Iran, $P = 0.02$]. Conversely, homogeneous rates have been reported in populations from Europe, North America and

New Zealand [pooled ALS standardized incidence of 1.81 (1.66-1.97)/100 000 PYFU for those areas].
Conclusion: This review confirms a heterogeneous distribution worldwide of ALS, and sets the scene to sustain a collaborative study involving a wide international consortium to investigate the link between ancestry, environment and ALS incidence.

Key words: Amyotrophic lateral sclerosis, epidemiology, incidence, ethnic groups

Key Messages

- Variation of ALS incidence between subcontinents might be related to population ancestries.
- Homogeneous incidence rates have been reported in populations from Europe, North America and New Zealand (pooled ALS standardized incidence: 1.81 (1.66-1.97)/100 000 PYFU
- Differences were identified in ALS standardized incidence between North Europe [1.89 (1.46-2.32)/100 000 PYFU] and East Asia [0.83 (0.42-1.24)/100 000 PYFU, China and Japan, $P = 0.001$] and South Asia [0.73 (0.58-0.89)/100 000/PYFU, Iran, $P = 0.02$].
- It is not possible in our study to disentangle the real impact of ancestral origin from lifestyle or environmental factors.
- An international consortium to perform, with homogeneous methodology, an investigation of the link between ancestry, environment and ALS, is needed.

Introduction

Variation in the incidence of amyotrophic lateral sclerosis (ALS) between geographical areas could support the notion that genetic factors, especially populations' ancestries, along with environmental and lifestyle factors, play a dominant role in the occurrence of the disease.

In 2007, a systematic review argued for a uniform occurrence of ALS across populations of European origin and, by contrast, a lower incidence of ALS among populations of African, Asian and Amerindian origin.[1] It was nevertheless difficult to draw firm conclusions, as there was methodological heterogeneity among studies in non-European populations. Also, both the population-based and the clinic-based studies were lumped together, rendering conclusions even more challenging. These results were consistent with those of a subsequent systematic review.[2]

Since then, numerous new incidence or mortality data have been reported from various parts of the world.[3–14] In addition, considering that in some settings ALS mortality rates can be considered as valid proxy for ALS incidence rates,[15] lower mortality rates of ALS in a mixed population in Cuba raised the hypothesis that a much wider variety of and different combinations of at-risk alleles lower the overall risk of developing the disease.[16] Finally, no formal meta-analyses of ALS incidence have been performed.

An analysis of worldwide incidence rates may provide new clues into the role of ancestry and environment in the occurrence of ALS. We performed a systematic review and meta-analysis of published data concerning the incidence of ALS in relation to subcontinents.

Methods

We applied the guidelines for Meta-Analyses and Systematic Reviews of Observational Studies (MOOSE)[17] and followed other specific recommendations for systematic reviews and meta-analyses.[18] As this review of literature/meta-analysis did not include ALS patients but only publications on ALS, informed consent of patients was not applicable. Approval of an ethics committee was not applicable.

Definitions

In this study, the disease under consideration was motor neurone disease (MND), which includes ALS and ALS subtypes.[19] We included only population-based studies. A population-based study implies using an appropriate methodology, an epidemiological investigation of a sample or the entire population, within defined geographical and time boundaries.[20] To investigate the worldwide

heterogeneity of ALS incidence, we considered sub-continent as our main study-level covariate. Sub-continent classification was based on the United Nations Statistics Division.[21]

Search strategy

Medline and Embase were searched. Period of publication (until June 2015) and language were unlimited. We did not use filters as regards species or type of article. Keywords, defined with a medical librarian, are described in eTable 1 (available as Supplementary data at *IJE* online). We also performed hand-searching (reference lists of articles). All references identified were imported into Endnote X7 and duplicates were deleted.

Inclusion criteria

Systematic reviews were not included but their references were examined. Proceedings of conferences were not included. We included population-based studies of newly diagnosed ALS cases, using multiple types of sources to ensure the highest level of completeness for case ascertainment: (i) ALS referral centres; (ii) hospital discharge data; (iii) neurologists; (iv) other specialists; (v) health insurance data; (vi) death certificates; (vii) patients' associations; and (viii) primary care physicians. For each study, the number and type of sources were collected. Appropriate methodology was mandatory in terms of definition of the geographical coverage, study population, investigated period and diagnostic criteria for ALS cases. Only studies with a neurological confirmation of the diagnosis were included.

All population-based studies of newly diagnosed ALS cases were included; nevertheless: (i) when more than one article was available for the same geographical area, the one with the longest follow-up and most person-years was prioritized; (ii) in case of overlap of geographical areas, the article with the widest geographical coverage was prioritized; (iii) and studies from historical ALS foci (Guam ALS-PDC focus and Wakayama prefecture) were not included in order to avoid gathering ALS with variants unrelated to sporadic ALS and potentially implying differing aetiological mechanisms such as toxic exposures, specific nutritional habits and food and water supplies associated with toxins.[22] Full texts were examined by one author, who assessed their eligibility. Decision about inclusion was confirmed by a second author.

Data extraction from included studies

During the collection of data from articles included in the review, we did not calculate a 'quality score' as its use has been criticized for being inaccurate in some cases.[18] Instead we used a checklist, whose components are described below, based on the basic principles of descriptive epidemiology and focused on all aspects of the study design that can influence the quality of case ascertainment and results. The following data were recorded: investigators, year of publication, period, location, design, sources of case ascertainment, diagnosis criteria, number of patients (male, female), population understudy (male, female, age structure) and number of cases by age group and sex. Where not available in the published material, authors (or their collaborators) were contacted in order to obtain more information regarding the variables included in the review. When the attempt to contact the author failed and the article displayed age and sex-specific incidence in a figure, we performed a graphical reading of the figure to obtain numerical rates. For each geographical area, life expectancy at 50 years for men and for women was retrieved from the demographic yearbook published by the United Nations at the mid point of the study period.[23] For Libya, we used Egypt life expectancy as proxy due to missing data, and for Hawaii, data were extracted from the United States Census Bureau.[24] With the help of a geographer, we accurately identified the geographical area for each study. We collected Global Positioning System (GPS) coordinates of the areas in order to create worldwide maps of crude and standardized incidence.

Data analysis

Crude incidence [number of cases per 100 000 person-years of follow-up (PYFU)] was re-calculated based on number of ALS cases, duration of case ascertainment and study population extracted from each article. Direct standardizations were performed on age and sex on the US 2010 populations.[25,26] This reference population was chosen for congruence with usual practices in this field because this is the most frequently used standard population in ALS. To allow homogeneity of reports, we did not exclude any part of the population (when authors considered only subjects older than 15 or 18 years of age, we re-included the youngest subjects in the population under study); 95% confidence intervals (95% CI) were calculated based on the Poisson distribution.

Meta-analysis was conducted and forest plots were obtained.[27] Stratification by subcontinents was performed. Pooled incidence rates were calculated. Weights were based on the precision of the incidence estimates for each study, i.e. the inverse of their standard error assuming a Poisson distribution. The I^2 value was also calculated.[28] Because the heterogeneity was statistically significant, random effects models were used.

Random effects meta-regression with the DerSimonian and Laird method[29,30] was used to assess sources of

Table 1. Population-based studies of ALS incidence included in the review

Continent	Subcontinent	Country	Area	References ($n = 44$)	Period	Duration	Number of ALS cases	PYFU	Design	Diagnostic method	Types of sources for case ascertainment								Duplicates ($n = 35$)
											Ref	Hosp	Neuro	Spe	HI	DC	Asso	PCP	
Europe	North Europe	Sweden	Varmland	Gunnarson (1984)	1970-81	12	89	3.41E+06	R	Neurologist		x	x			x			
			Vasterbotten, Norbotten, Angermanland	Forsgren (1983)	1969-80	12	128	7.60E+06	R	Neurologist		x				x		x	
		Finland	Middle Finland	Murros (1983)	1976-81	6	36	1.45E+06	R	Neurologist		x				x			
		Denmark	North Jutland and Aarhus	Hojer Pedersen (1989)	1974-86	13	186	1.37E+07	P	Neurologist	x	x							Christensen (1990)
		Faroe Islands	Countrywide	Joensen (2012)	1987-2009	22	28	1.04E+06	P	EEDC		x	x						
		Scotland	Countrywide	Forbes (2007)	1989-98	10	1226	5.13E+07	P	EEDC		x	x	x			x		Forbes (2004), Chancellor (1993), Chancellor (1993)
		England	Devon and Cornwall	Imam (2010)	2002-07	6	243	9.75E+06	R	EEDC		x	x	x					
			Lancashire and South Cumbria	Logroscino (2010)	1998-99	2	54	3.25E+06	P	EEDC	x	x	x	x					
		England	South-East England	Abhinav (2007)	2002-06	4.5	138	1.60E+07	P	EEDC	x	x	x	x			x		Johnston (2006, sub-region), Scott (2009), Scott (2010), Manjaly (2010), Rojas-Garcia (2012, sub-region)
		Ireland	Countrywide	O'Toole (2008)	1995-97/ 2002-04	6	465	2.28E+07	P	EEDC	x		x	x			x	x	Rooney (2013), Phukan (2011), Donaghy (2010), Donaghy (2009), Traynor (2000), Traynor (1999)
		Estonia	South Estonia	Gross-Paju (1998)	1986-95	10	50	3.92E+06	R	Neurologist		x	x						
	West Europe	France	Limousin	Marin (2014)	2000-11	12	279	8.76E+06	R	EEDC	x	x			x				
		The Netherlands	Countrywide	Huisman (2011)	2006-09	4	1217	6.59E+07	P	EEDC	x	x	x				x		
		Germany	Rhineland-Palatinate	Wolf (2014)	2010-11	2	146	8.01E+06	P	EEDC	x	x	x	x		x	x	x	
			Swabia	Uenal (2014)	2008-10	2	438	1.68E+07	R	EEDC	x	x	x						
	South Europe	Italy	Lombardy	Beghi (2007)	1998-2002	5	517	2.47E+07	P	EEDC	x	x	x	x			x		Pupillo (2014), Millul (2005)
			Piemonte and Vallée Aosta	Chio (2009)	1995-2004	10	1260	4.40E+07	P	EEDC	x	x	x	x		x			Chio (2011), Chio (2002), Parals (2001), Chio (1999)
			Friuli-Venezia Giulia	Drigo (2013)	2002-09	8	262	9.65E+06	R	EEDC		x	x	x			x		
			Emilia Romagna	Mandrioli (2014)	2009-11	3	347	1.32E+07	P	EEDC	x	x	x			x			Mandrioli (2012), Mandrioli (2006), Guidetti (1996), Georgoloupou (2011, sub-region) Bonvicini (2008, sub-region), Mandrioli (2003, sub-region), Govoni

(continued)

Table 1. Continued

Continent	Subcontinent	Country	Area	References ($n = 44$)	Period	Duration	Number of ALS cases	PYFU	Design	Diagnostic method	Types of sources for case ascertainment								Duplicates ($n = 35$)
											Ref	Hosp	Neuro	Spe	HI	DC	Asso	PCP	
																			(2012, sub-region), Govoni (2003, sub-region), Granieri (1988, sub-region)
			Liguria	Bandettini (2013)	2009-10	2	104	3.23E+06	P	EEDC		x	x		x		x		
			Puglia	Logroscino (2005)	1998-99	2	130	8.16E+06	P	EEDC	x	x	x				x		Zoccolella (2008), Zoccolella (2008), Zocolella (2006)
			Sardinia (Sassari and Nuoro)	Pugliatti (2013)	2005-09	5	89	3.55E+06	R	EEDC	x	x			x	x	x		
			Sicily (Agrigento, Catania, Caltanissetta, Palermo, Trapani)	Ragonese (2012)	2005-06	2	97	6.93E+06	R	EEDC		x	x		x				
		Spain	Catalognia	Pradas (2013)	1999-2001	3	215	1.87E+07	P	EEDC	x	x	x		x	x			
America	North America	Canada	Ontario	Hudson (1986)	1978-82	5	139	8.54E+06	R	Neurologist	x	x							
			Nova Scotia	Bonaparte (2007)	2003	1	21	9.36E+05	P	EEDC			x	x					
		USA	Olmsted County	Sorenson (2002)	1925-98	74	77	5.15E+06	P	EEDC	x	x	x	x	x			x	Mateen (2010), Mulder (1991), Yoshida (1986)
			Washington State	McGuire (1996)	1990-95	5	235	1.28E+07	P	Neurologist			x	x			x		Del Aguila (2003)
			Harris County	Annegers (1991)	1985-88	4	97	1.18E+07	R	Neurologist		x	x			x	x		
			Los Angeles County	Valle (2015)	2009-11	3	330	2.95E+07	R	EEDC		x	x			x			
			San Francisco Bay Area	Valle (2015)	2009-11	3	289	1.35E+07	R	EEDC		x	x			x			
			New Jersey	Jordan (2014)	2009-11	3	493	2.64E+07	R	EEDC		x	x			x			
			Florida	Freer (2015)	2009-11	3	1021	5.64E+07	R	EEDC		x	x			x			
			Baltimore and Philadelphia	Jordan (2015)	2009-11	3	142	9.72E+06	R	EEDC		x	x			x			
	South America	Argentina	Buenos Aires	Bettini (2013)	2003-10	8	63	1.01E+06	R	EEDC		x	x	x					
		Uruguay	Countrywide	Vazquez (2008)	2002-03	2	89	6.48E+06	P	EEDC			x	x	x	x			
	Hawaii	USA	Hawaii	Matsumoto (1972)	1952-69	18	118	1.14E+07	R	Neurologist		x	x						
Latin America and the Caribbean	Caribbean	France	Guadeloupe Islands	Lannuzel (2015)	1996-2011	15	32	5.90E+06	R	EEDC		x	x						
Africa	North Africa	Libya	Benghazi	Radhakrishnan (1988)	1980-85	5	23	2.59E+06	P	Neurologist		x		x					
	East Asia	Japan	Hokkaido Island	Okumura (2003)	1980-89	10	389	5.67E+07	P	Neurologist			x	x	x				
		China	Taiwan	Lai (2008)	2000-05	5	1187	1.14E+08	R	Neurologist		x			x				Lee (2013)
		China	Hong Kong	Fong (2005)	1997-2002	5.1	98	1.64E+07	R	EEDC		x	x						Fong (1996)
Asia	West Asia	Israel	Countrywide	Kahana (1984)	1959-74	16	246	3.73E+07	R	Neurologist		x	x			x			Gubbay (1985)
	South Asia	Iran	Isfahan	Sajjadi (2010)	2002-06	5	98	2.28E+07	R	EEDC		x	x						
Oceania	Australia and New Zealand	New Zealand	Canterbury	Murphy (2008)	1985-2006	22	215	9.21E+06	R	EEDC		x	x						

PYFU, person-years of follow-up; Ref, ALS referral centres; Hosp, hospital discharge data; Neuro, neurologist; Spe, other specialist; HI, Health insurance data; DC, death certificates; Asso, patients' association; PCP, primary care physicians; R, retrospective; P , prospective; Neurologist, diagnostic method based on neurological diagnosis without the use of El Escorial criteria; EEDC, diagnostic method based on neurological diagnosis using El Escorial criteria (original or revised version). For some articles, 'sub-region' is mentioned, indicating that those references considered a restricted area included in the main reference selected.

Hawaii and Carribbean included in North American subcontinent for United Nations is presented separately in this table.

heterogeneity. We used sub-continents as the study level covariate candidate to be the most important source of heterogeneity. The referent sub-continent was the one with the highest number of articles. We considered the following study level covariates as further sources of heterogeneity: (i) characteristics of the study population—life expectancy after 50 years in men and women and sex-ratio (SR) of the study population; and (ii) methods—study design (prospective/retrospective), diagnostic criteria [clinical assessment vs El Escorial original (EEDC)[31] or revised (EEDC-R) classification],[32] duration of the study period, number of PYFU and period of study. Bubble plots were produced for continuous study-level covariates. R-squared of the models were given. Analyses were done using the statistical software Stata v11.1 (Stata Corporation, College Station, TX, USA).

Results

Included studies

Of 3254 articles identified in the literature search, 70 were duplicates. After screening (title, abstract), 291 full-text articles were considered. After a comprehensive examination of the full texts, 44 articleswere finally included, covering 45 geographical areas and 11 sub-continents[3,4,6,8–14,33–36] (Figure 1, Table 1). Types of sources used for case ascertainment are given for each included study; 40 other papers were considered as duplicate material because they described an investigation performed in the same population or in a subset of a population already included.[67–106] Reasons for non-inclusion of articles are described in the flowchart (Figure 1).

Geographical coverage

Of the 45 geographical areas investigated (Figure 2), 24 (53.3%) were from Europe: [11 in North Europe, 4 in West Europe, 9 in South Europe (8 from Italy)], and 14 (31.1%) from the American continent: 10 in North America (Canada and the USA), 2 in South America (Uruguay and Argentina), 1 in Hawaii and 1 in the Caribbean (Guadeloupe Island). East Asia was represented by three studies (6.6%). South Asia was represented by only one study (Iran), as was the case for West

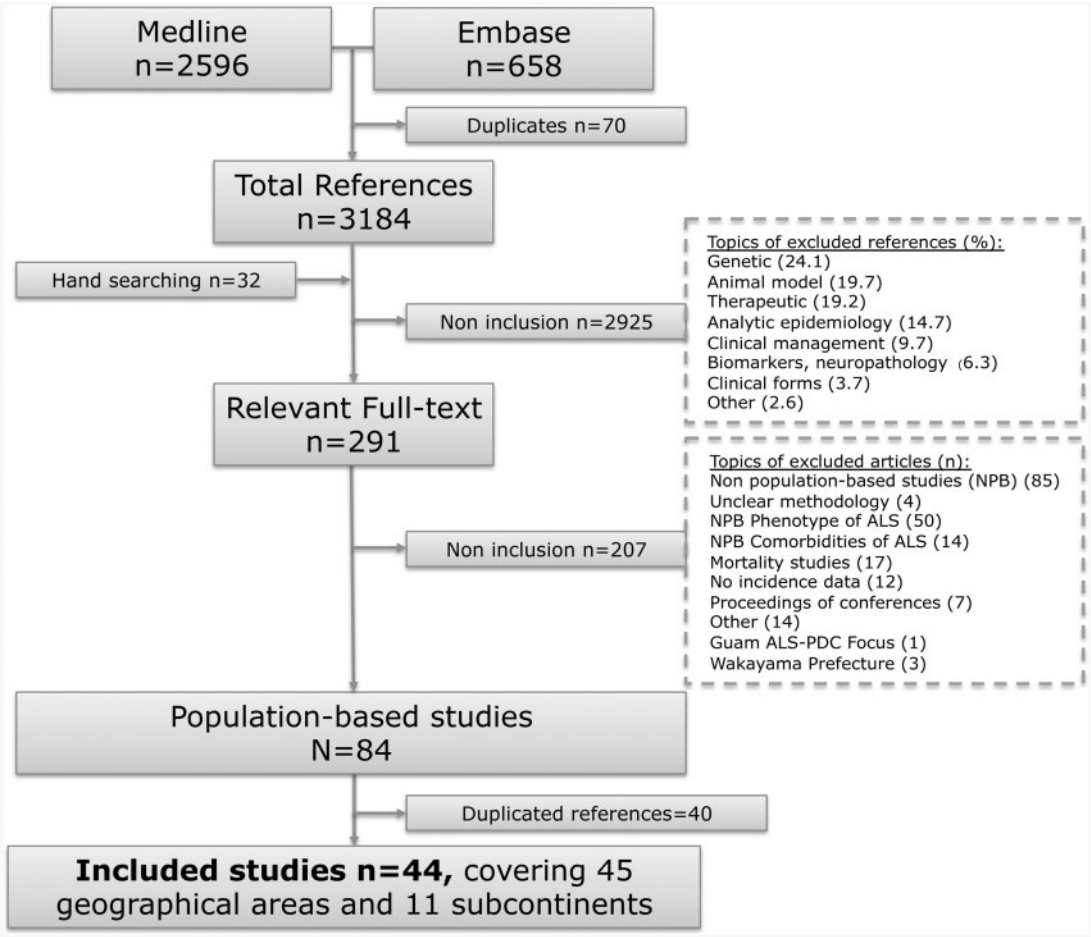

Figure 1. Flow chart eligibility criteria of articles on ALS incidence.

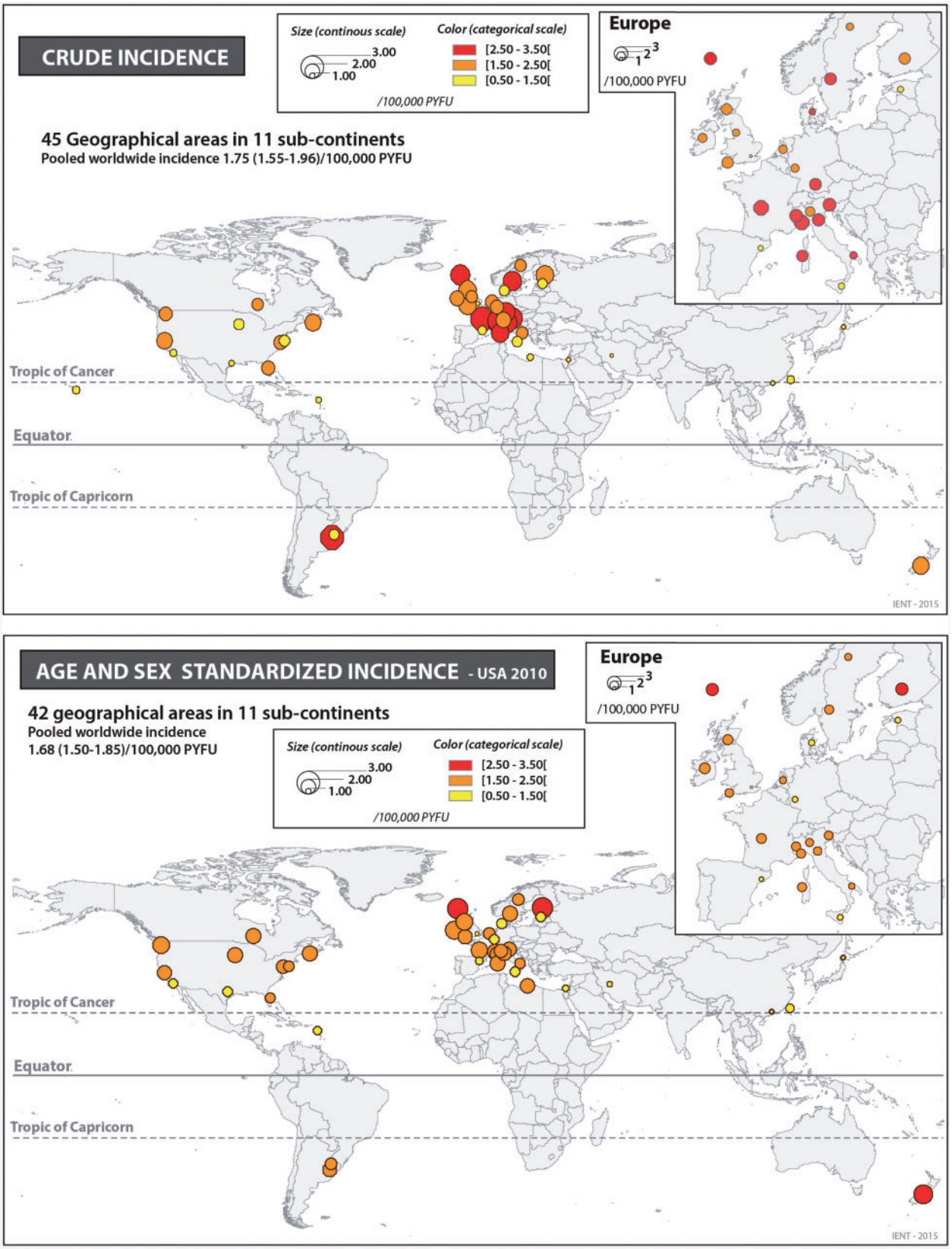

Figure 2. Distribution of ALS worldwide: crude incidence and age- and sex-standardized incidence on USA 2010 population.

Asia (Israel), North Africa (Libya) and Oceania (New Zealand).

Crude incidence

A total of 13 146 ALS cases and 825 million PYFU were considered. The overall pooled worldwide crude incidence of ALS was at 1.75 (1.55-1.96)/100 000 PYFU (Figure 3, Table 2), 2.03 (1.79-2.37) in men and 1.45 (1.25-1.64) in women. Whereas pooled incidence from European sub-continents ranged from 1.92 (1.49-2.34) in North Europe, number of studies = 11) to 2.22 (1.72-2.73) in South Europe ($n = 9$) and 2.35 (1.79-2.92) in West Europe ($n = 4$) per 100 000 PYFU, incidence was at 1.59 (1.32-1.87) for North America ($n = 10$) and 0.78 (0.50-1.05) for East Asia ($n = 3$). Incidence rates from studies performed in South America varied between 1.37 and 3.17/100 000 PYFU, leading to a pooled estimate of 2.19 (0.44-3.94)/100,000 PYFU. Among studies from the Caribbean (Guadeloupe Island), North Africa (Libya), West Asia (Israel) and South Asia (Iran), ALS incidence appeared remarkably low [1.02 (0.76-1.27), 0.89 (0.52-1.25), 0.66 (0.58-0.74) and 0.43 (0.34-0.52), respectively]. Pooled crude incidence for populations of European origin (Europe, North America and New Zealand) was at 1.96 (1.76-2.17)/100 000. There was heterogeneity in ALS crude incidence (Table 2, first column) in East Asia, South Asia (Iran) and Israel as compared with North Europe ($P = 0.006$, 0.02 and 0.049, respectively).

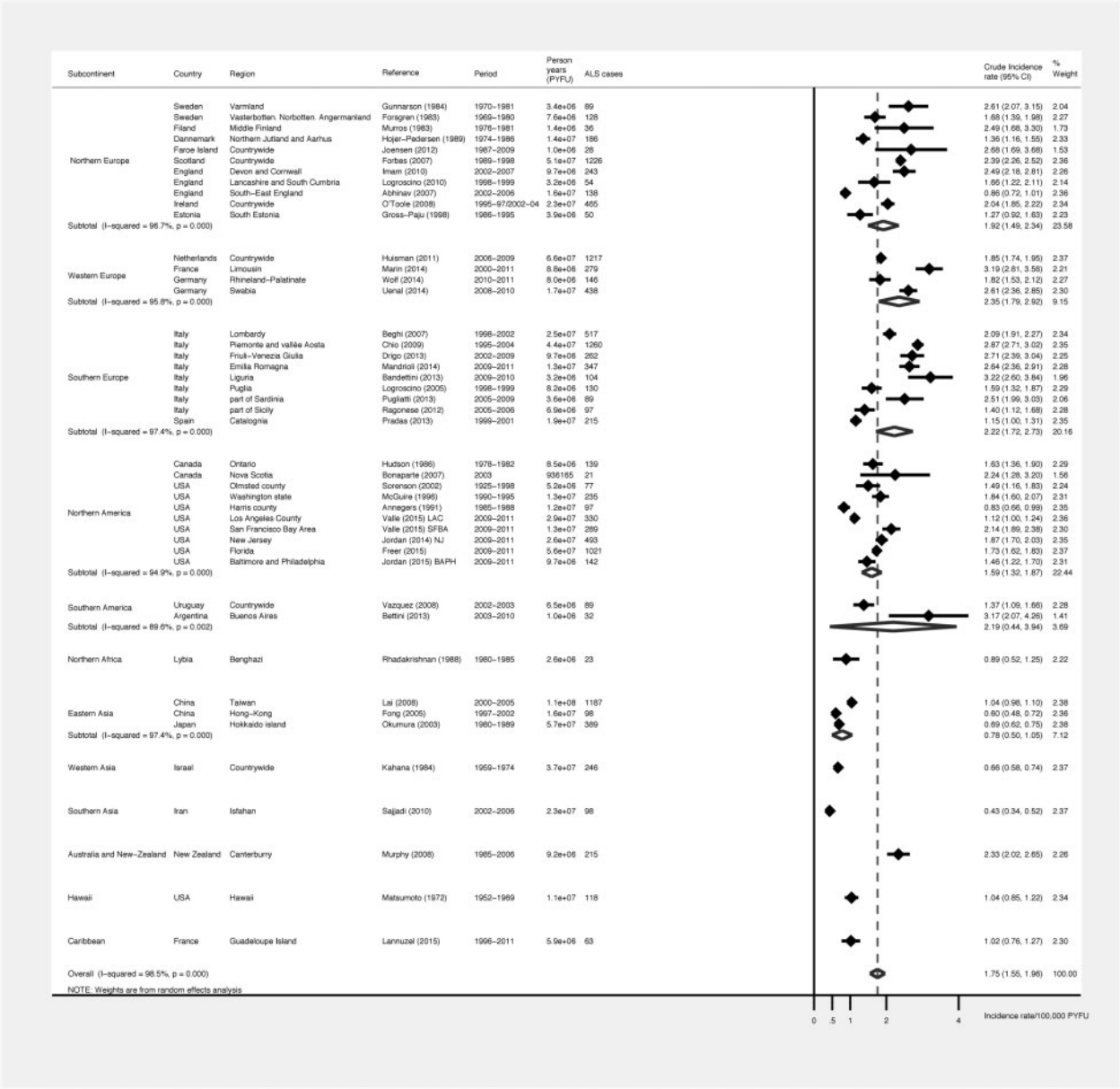

Figure 3. Meta-analysis: forests plots and pooled estimates for ALS crude incidence by sub-continents.

Table 2. Meta-regression of ALS crude and standardized incidence (2010 USA population)

Study level covariates		Cruce incidence				Standardized incidence (2010 USA population)			
		Incidence rate or intercept[a]	Coefficient[b]	*P*-value	R^2	Incidence rate or intercept[a]	Coefficient[b]	*P*-value	R^2
Subcontinent					37.8				32.2
	North Europe (Reference, $n = 11$)	1.92					1.89		
	West Europe ($n = 4$)	2.35		0.21			1.71	0.68	
	South Europe ($n = 9$)	2.22		0.27			1.75	0.66	
	North America ($n = 10$)	1.59		0.27			1.79	0.84	
	South America ($n = 2$)	2.19		0.85			1.59	0.64	
	Hawaii ($n = 1$)	1.04		0.17			–	–	
	Carribean ($n = 1$)	1.02		0.16			1.15	0.16	
	North Africa ($n = 1$)	0.89		0.11			2.03	0.77	
	East Asia ($n = 3$)	0.78		**0.006**			0.83	**0.001**	
	West Asia ($n = 1$)	0.66		**0.049**			0.94	0.057	
	South Asia ($n = 1$)	0.43		**0.02**			0.73	**0.02**	
	Oceania ($n = 1$)	2.33		0.50			2.56	0.15	
Design	Prospective ($n = 26$)	1.81		0.40	0.0	1.75		0.43	0.0
	Retrospective ($n = 19$)	1.70				1.61			
Diagnostic method	El Escorial ($n = 32$)	1.93		**0.018**	11.4	1.71		0.51	0.9
	Neurologist only ($n = 13$)	1.29				1.55			
Mid-point study period	< 1990 ($n = 11$)	1.35			7.3	1.60			0.0
	1990-00 ($n = 12$)	1.76		0.19		1.71		0.71	
	>= 2000 ($n = 22$)	1.96		**0.03**		1.68		0.71	
Life expectancy after 50 years	In men (/5 years)	−0.71	0.45	0.057	7.8	1.74	−0.01	0.95	0.0
Life expectancy after 50 years	In women (/5 years)	−2.35	0.64	**0.005**	18.5	1.11	0.09	0.63	0.0
Sex ratio of the underlying population	(/1 unit)	5.43	−3.82	**0.04**	8.1	1.29	0.41	0.80	0.0
Duration of the study	(/5 years)	1.77	−0.010	0.85	0.0	1.59	0.05	0.23	1.2
Person-years of follow-up	(/1000000)	1.89	−0.007	0.17	1.4	1.80	−0.006	0.09	3.5

Hawaii included in North American subcontinent for United Nations is presented separately in this table. p values less than 0.05 appear bold.

[a]Incidence rates are calculated for categorical study-levelcovariates, intercept is given for continuous study-level covariate.

[b]Coefficients are calculated for continuous study-level covariates. *P*-value refers (i) to difference between reference categories and other categories or (ii) to significance of coefficient.

Age- and sex-standardized incidence

We were able to perform a standardization of ALS incidence rates on US 2010 population for 42 geographical areas: for 41 areas on age and sex[3,4,6,8–14,22,33–64,66–101,107–111] and, on age only, in one area.[65] For the three remaining areas (Swabia, Lancashire, Hawaii) this was not possible; in these latter cases, we did not have access to the number of ALS cases by age and sex groups.[9,39,60] Number of cases or incidence rates of ALS by sex and age groups were available (present in the article or in supplementary material or provided on request by authors) for 36 areas.[6,8,11–14,35–38,40–51,54–58,61,63,63,66,100,108,112] For the remaining six articles, a graphical reading of the figure of age-specific incidence was performed to obtain rates.[4,33,35,52,53,59] The demographic structure of the study population was fully available in 25 cases,[6,8,10–14,37,38,40,41,43–50,55,57,58,61,64,65] and in four

additional studies the number of subjects for the youngest age groups (0-18) was re-calculated based on national census data.[3,42,51,66] For the other studies ($n = 12$), the structure of the population under study was retrieved from national demographic databases.[4,33–36,52–54,56,59,62,63]

The pooled worldwide US 2010-standardized incidence of ALS was 1.68 (1.50-1.85)/100 000 PYFU (Figure 4, Table 2), 1.96 (1.75-2.18) for men and 1.39 (1.21-1.56) for women, giving a standardized sex ratio of 1.41. As compared with crude incidence, standardization on the US population reduced the pooled estimates for Europe [1.89 (1.46-2.32), 1.71 (1.33-2.10) and 1.75 (1.44-2.06)/100000 PYFU, respectively in North, South and West Europe]. Conversely, there was an increase in the point estimates and pooled estimates for North America [1.79 (1.56-2.01)], Oceania [New-Zealand: 2.56 (2.22-2.90)], North Africa [Libya: 2.03 (1.16-2.91)], East Asia [0.83 (0.42-1.24)], South Asia [Iran: 0.73 (0.58-0.89)] and the Caribbean [Guadeloupe Island: 1.15 (0.86-1.45)]. The point estimate of standardized incidence in Southern America was at 1.59 (1.30-1.88)/100 000 PYFU and there was no heterogeneity between the two studies published in this area ($P = 0.41$). We identified heterogeneity in standardized ALS incidence in East Asia and South Asia as compared with North Europe (*P*-value 0.001 and 0.02, respectively). Pooled ALS standardized incidence for populations of European origin (Europe, North America and New Zealand) was at 1.81 (1.66-1.97)/100 000 PYFU.

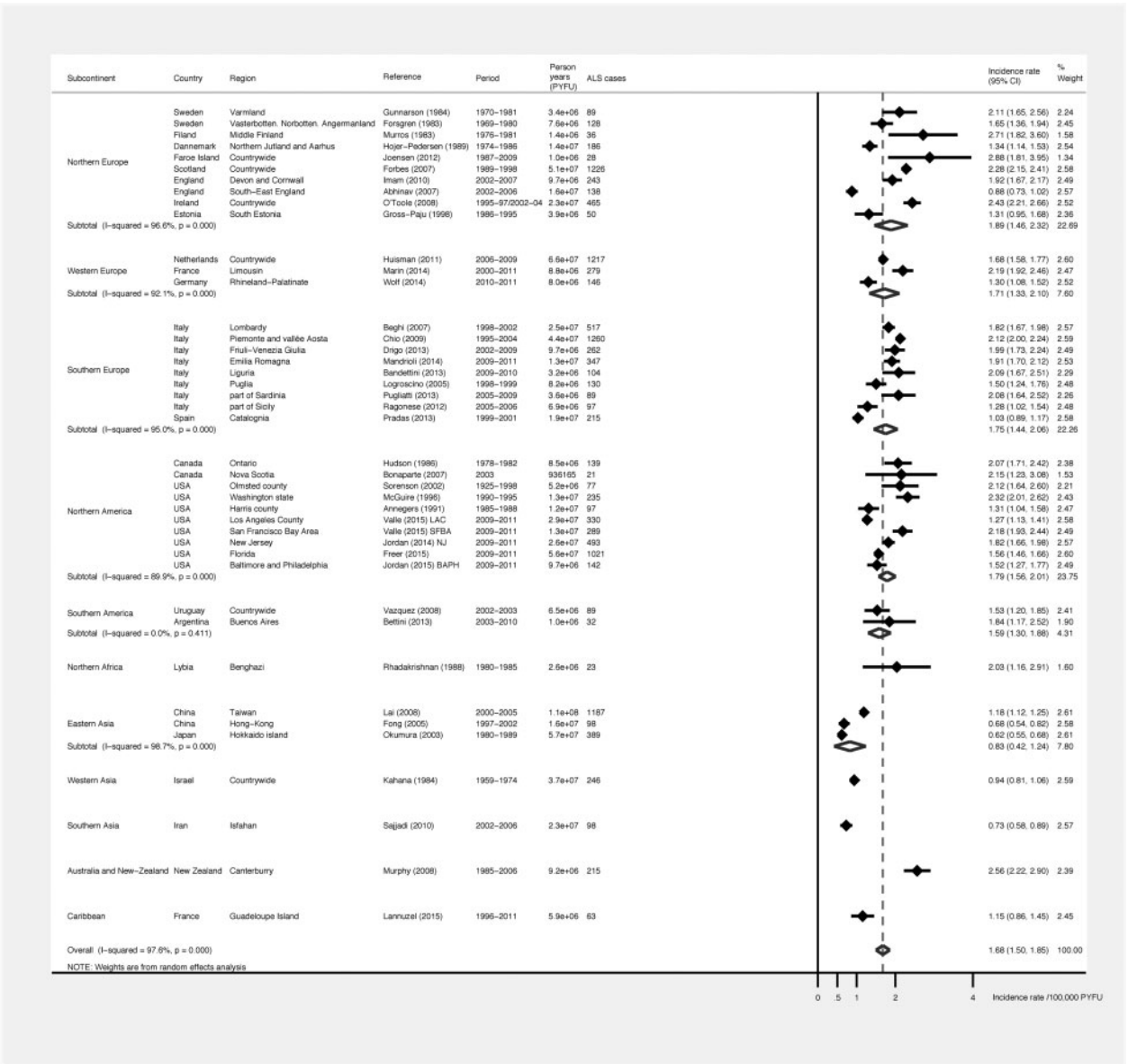

Figure 4. Meta-analysis: forests plots and pooled estimates for ALS age- and sex-standardized incidence on USA 2010 population, by subcontinents.

Robustness analysis

An additional analysis was performed to explore sources of heterogeneity related to (i) the characteristics of the study population and (ii) the study methodology.

Crude incidence.

Using univariable meta-regression, we identified heterogeneity ($P = 0.018$) in ALS crude incidence between studies that used El Escorial criteria (original or revised version) for case definition [incidence estimate: 1.93 (1.65-2.20)/100 000 PYFU] as compared with the neurologist's overall judgment [incidence estimate: 1.29 (1.09-1.49)]. Heterogeneity was also identified depending on the time period of the study, with higher crude incidence rates for a more recent period of investigation (Table 2, eFigure 1). An 'association' between crude incidence and life expectancy after 50 years in women ($P = 0.005$) was identified (eFigure 1 presents the bubble plots of these relations, available as Supplementary data at *IJE* online).

Standardized incidence.

We did not identify any heterogeneity in standardized incidence in relation to (i) characteristics of the study population or (ii) study methodology. Specifically, we did not identify relevant time trends in standardized ALS incidence after controlling for age and sex (eFigure 2, $P = 0.95$, available as Supplementary data at *IJE* online).

Discussion

This review is the first to report pooled estimates of ALS crude and USA-standardized incidence of worldwide population-based studies. It emphasizes the heterogeneity between European ALS incidence and incidence from East Asia (China, Japan), South Asia (Iran) and West Asia (Israel). Conversely, there is homogeneity in incidence among populations from Europe, North America and New Zealand.

Input of mixed populations

It is not possible in our study to disentangle the real impact of ancestral origin from lifestyle or environmental factors, because they are highly associated. In this regard, data from mixed populations might give useful information. Such studies allow comparison of incidence rates between different population subgroups that share, at least partially, the same environment. Table 3 presents ALS incidence data estimated in mixed populations (England,[104] USA,[55,56,113] Hawaii[60] Israel,[65]) or estimated with homogeneous methods in different geographical areas (USA, Japan[62]).

A recent initiative, using a population-based design, investigated the racial variations in ALS incidence in three states (Florida, New Jersey and Texas) and eight metropolitan areas (Atlanta, Baltimore, Chicago, Detroit, Las Vegas, Los Angeles, Philadelphia and San Francisco) of the USA.[113,114] Based on 3819 incident cases identified during the study period (2009-11), higher crude and standardized ALS incidences were found in Whites (USA-standardized incidence 1.48/100 000 PYFU) as compared with African Americans (0.89) and with Asians (0.78). Based on ethnic data, a difference was identified between non-Hispanics (1.36) and Hispanics (0.84). These data are in agreement with most previous reports on this topic, which showed in the USA and in the UK a constantly lower point estimate in non-Whites as compared with Whites.[55,56,104] The consistency of the findings would exclude under-ascertainment of cases as a possible explanation of the differences. Also, a lower access to health systems for some minorities with lower socioeconomic status in the USA needs to be discussed; Whites have traditionally a better access to health care.[115] In this regard in the USA, ALS Asians are less likely to have a federal payer (e.g. 55.2%) as compared with White and African Americans (63.3% and 65.2%, respectively).[113] The use of self-pay was also higher in Asians.

Within a given population, a difference in life expectancy between races or ethnic groups might also be implicated in differences of ALS rates. Indeed, a higher number of old people in some groups (the pool of subjects most likely to develop ALS) will lead to higher rates if these are not standardized on race/ethnicity. For example, Chang *et al.* showed that healthy life expectancy in non-Hispanic Whites was 2.6 years higher than in Hispanics and 7.8 years higher than in non-Hispanic Blacks.[116]

In our review, it was not possible to accurately assess ALS incidence in Africa due to lack of data. Crude incidence in Libya (North Africa) was low [0.89 (0.52-1.25)/100 000], but after adjustment [2.03 (1.16-2.91)/100 000] it was in the same range as data from Europe or North America. Other data from the African continent are needed to understand more about ALS in this continent.[117] Our results comparing incidence data from Europe and from East Asia are in favour of a lower incidence in this latter geographical area. As Eastern Asian studies included in our review are from high-resource areas (Hong Kong, Taiwan, Japan), an under-ascertainment of ALS cases seems unlikely. The report by Okumura *et al.*,[62] comparing incidence between Rochester (USA) and Hokkaido

Table 3. ALS incidence in mixed populations

Continent	Subcontinent	Reference	Period	Country	Diagnostic method	Incident cases by ethnic group, *n* (%)	Crude incidence (95% CI)	Standardized incidence (95 CI%)	Reference population for standardization
Europe	North Europe	Rojas-Garcia (2012)	2002-08	England	EEDC	88			
						74 European origin (84.0)	1.97 (1.55-2.48)		
						14 African origin (16.0)	1.35 (0.72-2.30)		
America	North America	McGuire (1996)	1990-95	USA	Neurologist	235		2.11 (1.27-2.93) m 1.87 (1.08-2.66) w	USA 1990
						225 White (95.7)			
						10 non-White (4.3)		0.74 (0.00-1.96) m 0.53 (0.00-1.91) w	
America	North America	Annegers (1991)	1885-1998	USA	Neurologist	97		1.27 (0.95-1.69) m 1.03 (0.75-1.38) w	USA 1970
						White		1.36 (0.96-1.87) m 1.25 (0.88-1.72) w	
						Black		1.10 (0.48-2.17) m 0.70 (0.28-1.44) w	
						Hispanic		1.27 (0.41-2.96) m 0.10 (0.002-0.46) w	
America	North America	Rechtman (2015)	2009-11	USA	EEDC	3819			USA 2010
						2896 White (75.8)	1.79	1.48 (1.42-1.53)	
						319 African American (8.4)	0.80	0.89 (0.79-0.99)	
						127 Asian (3.3)	0.76	0.78 (0.64-0.92)	
						477 Not reported (12.5)			
						2957 Non-Hispanic (77.4)	1.65	1.36 (1.31-1.41)	
						407 Hispanic (10.6)	0.57	0.84 (0.75-0.92)	
						455 Not reported (12.6)			
America	North America	Matsumoto (1972)	1952-69	Hawaii	Neurologist	118			Hawai 1970
						23 Caucasian (19.5)	0.63	0.82	
						31 Japanese (26.4)	0.85	0.86	
						42 Filipino (35.6)	3.38	1.56	
						7 Part-Hawaian (5.9)	0.82	1.21	
						5 Hawaian (4.2)			
						7 Chinese (5.9)			
						2 Korean (1.7)			
						1 Samoan (0.8)			
Asia	West Asia	Kahana (1976)	1960-70	Israel	Neurologist	142			
						96 European (67.0)		0.72	USA 1970
						38 African Asian (26.8)		0.60	
						7 Israeli (4.9)		0.65	
						1 origin unknown (0.7)			
		Okumura (2003)			Neurologist	401			
America	North America		1952-91	USA		46 USA (Rochester) (11.5)	2.30		
Asia	East Asia		1980-89	Japan		355 Japan (Hokkaido) (88.5)	0.60		

M, men; na, not available; w, women; EEDC: El Escorial Diagnosis Criteria; na: non available; 95%CI: 95% confidence interval.

Island (Japan), was also in agreement with ours: i.e. lower incidence in East Asia as compared with Western populations.

Additional clues to disentangle genetic and environmental factors can come from studies on migrants. Chio *et al.* 1999[79] raised the issue of ALS incidence among migrants from South Italy who lived in North Italy. Authors identified, in comparison with people born in Piedmont, an increased risk of ALS in migrants from Puglia (South-East Italy) as well as in men migrating from outside Italy. This observation was attributed by the authors to an interaction between environmental and genetic factors or selective migration (people who migrated were of lower socioeconomic status in their native area and most of them were farmers: two characteristics supposed to be associated with an increase in ALS risk).

A clue to a better understanding of ALS incidence variation

The link between the age structure of the population and ALS incidence is well known, as age-specific incidence shows usually a progressive rise with age, with a peak between 65 and 75 years of age followed by a decrease before in men and then in women.[118] We evaluated this link through the meta-regression of crude incidence, using life expectancy after 50 years of age as a proxy for the pool of subjects at risk to develop ALS. This link was identified for crude incidence (*P*-value 0.005 for life expectancy in women). After standardization, this association was not confirmed.

In agreement with others,[2] we did not identify a correlation between incidence and duration of study, even when considering the total PYFU. In contrast with others, we did not identify different incident rates according to the

modalities of data collection (prospective or retrospective). Previous reviews identified lower incidence in retrospective studies.[1,2] However, those reviews considered not only population-based studies with multi-source cases ascertainment but also clinic-based data.

Our data show that, with time, there was an increase in crude incidence but not in standardized incidence. This pattern could be explained, at least partially, by the evolution of the age structure of the populations at risk (which aged especially in the North American continent and in Europe in the past 50 years).

A clue for health care organization

An accurate calculation of synthesized indicators of ALS incidence for various geographical areas allows the estimation of the number of new cases by year with good precision. As the burden of the disease on personal, societal and economic grounds is high, our study can give a better outline of the needs for research and health care organization. Using populations[25] and pooled crude incidences estimates, the numbers of incident cases by year are expected to be around 5500 in the North American continent, 9900 in Europe (summing North, South and West Europe) and 12 300 in East Asia.

Strengths

The main strength of this work relies on the material that was used (population-based studies using multiple sources of case ascertainment). The population-based approach has been consistently shown to be the best suited to describe the entire spectrum of the ALS incidence and phenotype.[118,119] The literature search was broad, without limitations in terms of dates of publication or language, and exhaustive. The ability to perform systematic standardization of ALS incidence with such a wide panel of data, in line with guidelines on meta-analysis of observational studies[17] and recommendations regarding the meta-analysis of incidence studies in neuroepidemiology,[18] is without antecedents. We assessed the impact of study methodology and other characteristics (including markers of study quality, i.e diagnostic method, design) and confirmed the robustness of our results.

Limitations

First, as previously mentioned,[2] the main body of literature on ALS epidemiology is large but limited geographically. This is especially true for population-based investigations. Most research has been conducted in Europe (53.3% of studies) or more globally in populations of Caucasian origin (77.7%, including Europe, North America, New Zealand).

Second, some methodological requirements chosen during the preparation of the study protocol might have influenced our results. The inclusion in four cases, for homogeneity purposes, of the population aged lower than 15 or 18 years might have diluted the ALS rates.[3,42,51,66] The graphical reading of ALS age-specific rates in some cases[4,33,34,52,53,59] might have also influenced the results. Nevertheless: (i) the number of cases given in the article and the total number of cases calculated using age-specific rates were highly concordant and (ii) we were able to verify an excellent agreement between our graphical reading and rates that were available in the supplementary web-only material of one study.[42]

Third, another important limitation is the variability of study designs, populations at risk and settings. We did our best to exclude studies of low quality and we explored sources of heterogeneity related to the design, diagnostic method, time period, population size and life expectancy, and study duration. Nevertheless, we cannot exclude the possibility that some differences are due at least in part to the lack of comparability of the reports included in this review. Differences in health care system organization and access to health care could be also implicated. A differential referral even within the population-based setting cannot be excluded for some categories, i.e. elderly, women and minorities.[119,120]

Fourth, the criteria for the diagnosis of ALS (clinical assessment versus El Escorial criteria), the evolution with time of El Escorial criteria (original vs revised) and the El Escorial categories included might be implicated in the heterogeneity of ALS incidence. The real impact of these methodological differences is difficult to estimate. For example, studies based on the original EEDC included all categories of ALS (Definite, Probable, Possible, Suspected), $n = 12$,[3,39,40,42–45,48,51,53,66] or excluded cases who, during follow-up, remained suspected ALS ($n = 4$)[4,37,38,54] or suspected/possible ALS ($n = 2$).[6,59] Conversely, most papers that used the revised version of EEDC included all types of ALS (Definite, Probable, Probable laboratory supported, Possible) ($n = 13$),[8–14,46,47,50,57,64] and only one excluded cases with possible ALS during follow-up ($n = 1$).[121] However, when looking at standardized rates (i.e when controlling for age and sex distribution of the underlying population), ALS heterogeneity was not explained by the diagnosis ($P = 0.51$). This might suggest that the key driver is the modification in populations demographics, which is related to time.

Fifth, ALS rates were standardized on age and sex only, therefore results are susceptible to unmeasured confounding factors which may vary by subcontinent or country.

Sixth, it would have been of major interest to perform subgroup analyses based on ethnic groups. With the exception of recent data from the US National ALS registry initiative,[113] accurate information on ethnic groups and, consequently, number of cases by ethnic group among ALS patients were not given in the original articles.

Seventh, we attempted to consider subcontinent as a proxy for ancestral origin of the population, but subcontinent does not represent individual population ancestral origin or ethnicity. Also, within a given subcontinent, the ancestral origin of subjects is not homogeneous. Human population groups and level of admixture vary within a given country.

A clue for future research

This work shows the heterogeneity of ALS worldwide incidence between subcontinents. This heterogeneity could be related to the ancestral origin of the populations. Nevertheless, we cannot exclude that some differences are related to differences in environmental factors in connection with the growing evidence that aetiology relies on multifactorial effects resulting from the combination of environmental and genetic factors.[122]

As is the case for Alzheimer disease,[123,124] ALS phenotype and natural history also vary with geographical area. Marin *et al.* showed that a major explanatory variable for the variability of ALS phenotype in population-based studies is subcontinent.[125] Some markers of ALS phenotype have homogeneous distribution in Western countries (male:female sex ratio, mean age at onset or at time diagnosis) but their distributions in other subcontinents are remarkably different. Other markers (familial ALS, bulbar onset) present variations in European and in other subcontinents. As a consequence, ALS outcome markedly varies, with a median survival time since onset ranging from 24 months (North Europe) to 48 months (South Asia).

Considering this important issue, researchers now need to consider the organization of a wide international consortium to perform with homogeneous methodology an investigation of the link between ancestry, environment and ALS incidence and phenotype. Such an initiative might lead to important advances in the knowledge of the mechanisms of ALS.

Supplementary data

Supplementary data are available at *IJE* online.

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