Supplementary Online Content

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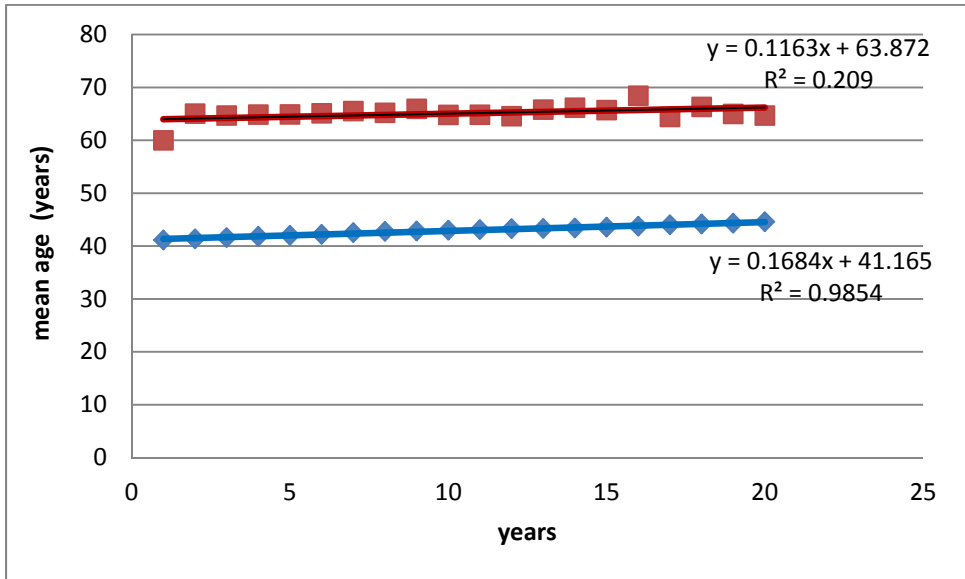
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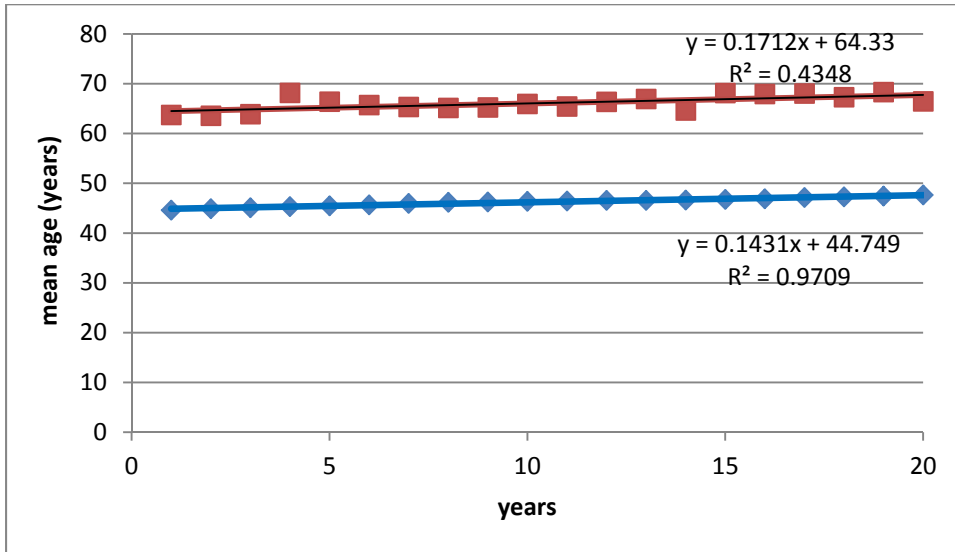
This supplementary material has been provided by the authors to give readers additional information about their work.

eFigure 1. Trend of Mean Age at Onset Compared to the Mean Age of the Piemonte and

Valle d'Aosta Population, 1995-2014, Males

The linear regression is shown. The two trends are significantly correlated (Pearson's correlation coefficient 0.504, p=0.024). Read: mean age at onset of ALS; Blue, mean age of the Piemonte and Valle d'Aosta population

eFigure 2. Trend of Mean Age at Onset Compared to the Mean Age of the Piemonte and Valle d'Aosta Population, 1995-2014, Females
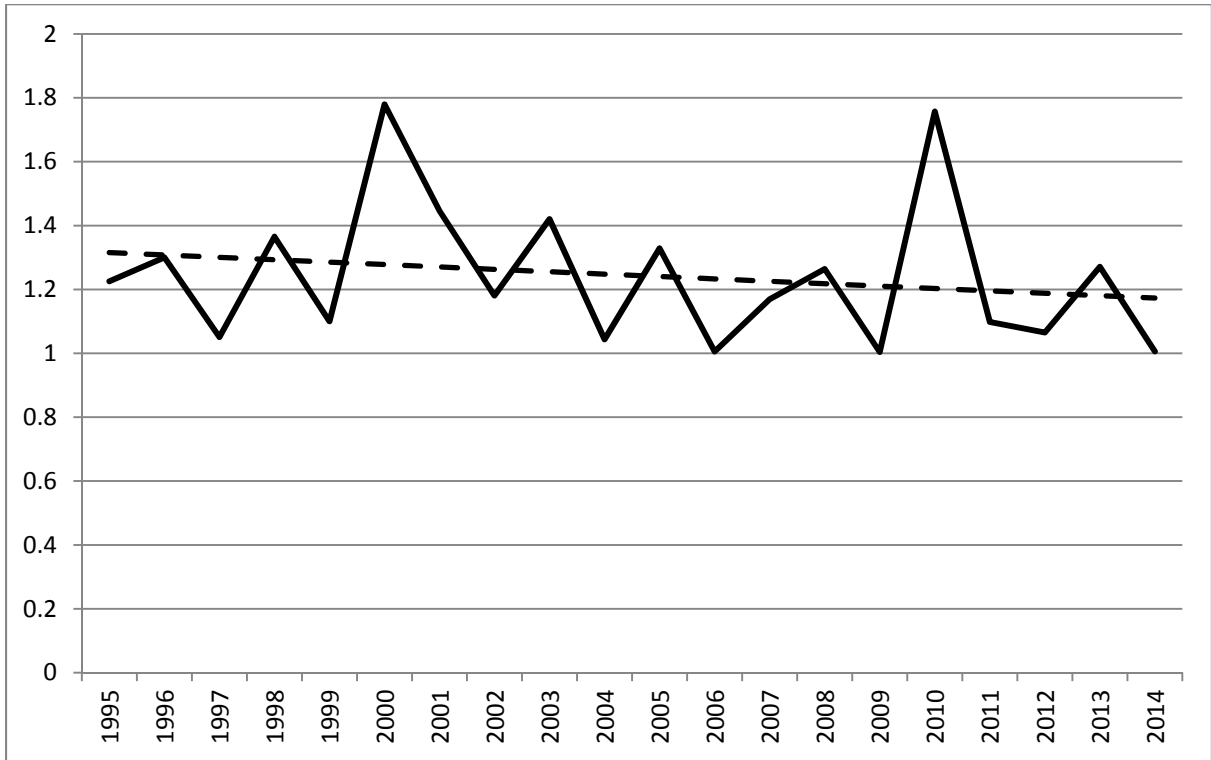

The linear regression is shown. The two trends are significantly correlated (Pearson's correlation coefficient 0.504, p=0.002). Read: mean age at onset of ALS; Blue, mean age of the Piemonte and Valle d'Aosta population

eFigure 3. Progressive Decline of Men to Women Rate Ratio During the 20 Years of the Study.

Data are based on age-adjusted incidence rates. The dotted line represents the linear regression.

eTable 1. Frequency of El Escorial Criteria Revised Levels of Diagnosis, 1995-2004 vs

2005-2014

El Escorial revised level	1995-2004	2005-2014
Definite	618 (49.7%)	687 (47.1%)
Probable	398 (32.0%)	446 (30.6%)
Probable - Laboratory Supported *	59 (4.7%)	83 (5.7%)
Possible	120 (9.7%)	178 (12.2%)
Suspected	48 (3.9%)	65 (4.4%)
Overall	1243	1459

* ALS cases diagnosed before 2000 were re-classified according to the El Escorial

Criteria revised

eTable 2. Site of Onset of ALS Cases According to Sex, 1995-2004 vs 2005-2014

	1995-2004		2005-2014		p value *	
	Male	Female	Male	Female	Male	Female
Bulbar	219 (32.3%)	246 (43.5%)	213 (27.4%)	294 (43.2%)	0.05	0.94
Spinal	459 (67.7%)	319 (56.5%)	565 (72.6%)	387 (56.8%)		

*Comparison between 1995-2004 and 2005-2014 periods for each gender

eTable 3. Age-Period-Cohort Rates and Relative Risks (RRs)

TOTAL			
Age	Rate	2.5%	97.5%
40	8.57821E-06	6.27734E-06	1.17224E-05
45	1.47701E-05	1.17923E-05	1.84999E-05
50	2.54314E-05	2.17917E-05	2.9679E-05
55	4.30422E-05	3.80598E-05	4.86767E-05
60	6.57116E-05	5.97517E-05	7.22661E-05
65	8.83721E-05	8.06833E-05	9.67937E-05
70	0.000114501	0.000105812	0.000123903
75	9.65964E-05	8.92904E-05	0.0001045
80	7.26953E-05	6.3838E-05	8.27815E-05
85	5.47081E-05	4.42927E-05	6.75726E-05
Period	RR	2.5%	97.5%
1995	1.0262124	0.9800675	1.07453
2000	0.977959	0.9155164	1.04466
2005	0.9732843	0.9129617	1.037593
2010	1.0225646	0.9847657	1.061814
Cohort	RR	2.5%	97.5%
1910	0.6894939	0.5072607	0.9371942
1915	0.7556151	0.6075019	0.9398392
1920	0.8280771	0.7232734	0.9480671
1925	0.9074882	0.8380418	0.9826894
1930	0.9920089	0.9186836	1.0711868
1935	1.0599011	0.9919121	1.1325504
1940	1.0694754	0.9997358	1.1440798
1945	1.0558446	0.9576561	1.1641003
1950	1.0645744	0.9425007	1.2024592
1955	1.0911962	0.9330209	1.2761871
1960	1.1215573	0.8985478	1.3999154
1965	1.1527632	0.8543439	1.5554195
1970	1.1848374	0.8082156	1.7369619

MEN			
Age	Rate	2.5%	97.5%
40	1.01605E-05	6.92148E-06	1.49154E-05
45	1.77709E-05	1.36339E-05	2.31633E-05
50	3.10816E-05	2.62461E-05	3.6808E-05
55	5.3108E-05	4.62784E-05	6.09453E-05

Age	Rate	2.5%	97.5%
60	7.88837E-05	7.04041E-05	8.83845E-05
65	0.000101693	8.9427E-05	0.000115642
70	0.000142993	0.000126016	0.000162258
75	0.00012289	0.000106831	0.000141363
80	9.1798E-05	7.40279E-05	0.000113834
85	6.85725E-05	4.93579E-05	9.5267E-05
Period	RR	2.5%	97.5%
1995	0.9963126	0.9338292	1.062977
2000	1.0304725	0.9446551	1.124086
2005	0.9514593	0.8705513	1.039887
2010	1.0205312	0.9697239	1.074001
Cohort	RR	2.5%	97.5%
1910	0.8381515	0.5350442	1.312972
1915	0.8684242	0.622981	1.210567
1920	0.8997902	0.7189384	1.126136
1925	0.9322892	0.8051002	1.079571
1930	0.9672985	0.849627	1.101267
1935	1.0051212	0.9139509	1.105386
1940	1.0194195	0.9208907	1.12849
1945	0.9998173	0.8971033	1.114292
1950	1.0084918	0.8795429	1.156346
1955	1.0430031	0.8816904	1.233829
1960	1.083201	0.8388689	1.398698
1965	1.1249483	0.7810477	1.620271
1970	1.1683044	0.7220531	1.890353

WOMEN				
Age	Rate	2.5%	97.5%	
40	7.24184E-06	4.50588E-06	1.16391E-05	
45	1.23191E-05	8.75718E-06	1.73299E-05	
50	2.09562E-05	1.66171E-05	2.64283E-05	
55	3.52779E-05	2.93973E-05	4.23347E-05	
60	5.57757E-05	4.84354E-05	6.42283E-05	
65	7.8507E-05	6.89694E-05	8.93635E-05	
70	9.33303E-05	8.38903E-05	0.000103833	
75	8.30378E-05	7.33641E-05	9.39871E-05	
80	6.18055E-05	5.15767E-05	7.4063E-05	
85	4.46541E-05	3.26175E-05	6.11325E-05	
Period	RR	2.5%	97.5%	
1995	1.0563313	0.989605	1.127557	

2000	0.9186126	0.8302646	1.016362	
2005	0.999419	0.911395	1.095944	
2010	1.0225813	0.9670544	1.081297	
Cohort	**RR**	**2.5%**	**97.5%**	
1910	0.6217821	0.4045547	0.9556508	
1915	0.6982723	0.5143956	0.9478777	
1920	0.784172	0.6482287	0.9486247	
1925	0.880639	0.7848339	0.9881391	
1930	0.986919	0.8825682	1.1036076	
1935	1.079626	0.9784231	1.1912969	
1940	1.1001848	0.9961025	1.2151427	
1945	1.0849129	0.9395811	1.2527241	
1950	1.0877061	0.909024	1.3015109	
1955	1.1066358	0.8753174	1.3990843	
1960	1.1286535	0.8066084	1.5792777	
1965	1.1511092	0.7294861	1.816419	
1970	1.1740117	0.6549537	2.1044287	

eTable 4. Case Ascertainment by Year Using Two Source Capture-Recapture Methods,

Piemonte and Valle d'Aosta Register for ALS, 1994-2004

Year	Observed	Unobserved*	Coverage (%) §	Crude incidence #	Corrected crude incidence (95% c.i.) **
1995	114	3	97.7	2.59	2.65 (2.20-3.20)
1996	105	2	98.3	2.38	2.42 (1.99-2.95)
1997	129	3	98.2	2.92	2.98 (2.50-3.55)
1998	134	2	98.6	3.04	3.09 (2.60-3.67)
1999	127	2	98.3	2.88	2.93 (2.45-3.50)
2000	126	2	98.7	2.86	2.90 (2.43-3.45)
2001	144	4	97.2	3.32	3.42 (2.90-4-03)
2002	131	5	96.5	3.01	3.12 (2.63-3.70)
2003	112	2	98.2	2.55	2.60 (2.16-3.14)
2004	121	1	98.8	2.72	2.81 (2.34-3.37
1995-2004	**1243**	**26**	**98.0**	**2.89**	**2.95 (2.77-3.14)**
2005	146	4	96,9	3.27	3.36 (2.85-3.95)
2006	137	2	98.3	3.06	3.11 (2.62-3.68)
2007	153	4	97.3	3.41	3.50 (2.98-4.11)
2008	107	2	98.1	3.35	2.39 (1.97-2.89)
2009	146	5	96.7	3.20	3.31 (2.81-3.89)
2010	144	3	98.1	3.15	3.21 (2.72-3.77)

2011	160	4	97.6	3.57	3.66 (3.13-4.27)
2012	170	4	97.6	3.78	3.87 (3.32-4.50)
2013	141	2	98.5	3.09	3.14 (2.66-3.71)
2014	154	5	97.0	3.39	3.50 (2.99-4.10)
2005-2014	**1459**	**35**	**97.6**	**3.23**	**3.31 (3.11-3.52)**

Incidence is reported per 100,000 population. 95% c.i. = 95% confidence interval.

* Maximum likelihood estimator = (cases unique to source x cases not present in source)/cases common to both sources;

§ Coverage = observed cases/(observed cases + unobserved cases) %;

Observed cases / Piemonte and Valle d'Aosta population for the corresponding year;

** (Observed + unobserved cases)/ Piemonte and Valle d'Aosta population for the corresponding year.