La sclerosi multipla: orientarsi opportunità e rischi.

10 giugno 2015

Markers clinici di malattia

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Centro Sclerosi Multipla

Ospedale Papa Giovanni XXIII di Bergamo

Markers clinico di malattia

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indicatore prognostico

importante per:

- Dare risposte al paziente (disabilità, futuro familiare, necessità di terapia)
- Sostenere le decisioni terapeutiche
- Migliorare il disegno e l'analisi degli studi clinici

Indicatori clinici all'esordio indicativi di prognosi sfavorevole

- **sesso maschile :** *Confavreux et al., 1980; Detels et al.; 1982, Wolfson and Confavreux 1987; Weinshenker et al., 1991; Lauer et al., 1992; Runmarker and Andersen, 1993; Trojano et al., 1995; Kantarci et al. 1998; Bergamaschi et al., 2001; Confavreux et al., 2003; Debouverie 2009*
- **esordio tardivo :** *Confavreux et al., 1980; Detels et al., 1982; Visscher et al., 1984; Weinshenker et al., 1989; Phadke et al., 1990; Weinshenker et al., 1991; Riise et al., 1992; Runmarker and Andersen, 1993; Citterio et al., 1996; Weinshenker et al., 1996; Trojano et al., 2002; Bergamaschi et al., 2005; Debouverie 2009*
- **esordio polisintomatico:** *Kraft et al., 1981, Wolfson and Confavreux, 1987; Phadke 1990; Runmarker and Andersen, 1993; Amato et al., 1999; Bergamaschi et al., 2001; Mikaeloff et al., 2004*
- **esordio cerebellare:** *Poser et al., 1982; Phadke, 1990; Lauer et al., 1992; Riise et al., 1992; Weinshenker et al., 1996; Amato et al., 1999*
- **esordio motorio:** *Weinshenker et al., 1991; Riise et al., 1992; Trojano et al., 1995; Kantarci et al., 1998; Amato et al., 1999; Simone et al., 2002; Pittock et al., 2004*
- **esordio sfinterico:** *Citterio et al., 1989; Phadke, 1990, Kantarci et al., 1998; Amato et al., 1999; Simone et al., 2002*
- **esordio con sequele:** *Phadke, 1990; Weinshenker et al., 1991; Runmarker and Andersen, 1993; Trojano et al., 1995; Amato et al., 1999; Bergamaschi et al, 2991; Mikaeloff et al., 2004*
- **breve intervallo esordio-ricaduta:** *Confavreux 1980; Thompson et al., 1986; Phadke 1990; Weinshenker et al., 1991; Trojano et al., 1995; Amato et al., 1999; Simone et al., 2002; Confavreux et al., 2003, Ghezzi 2005*
- **elevato numero di ricadute nel I anno**: *Trojano 1995; Kantarci 1998; Confavreux et al., 2003; Weinshenker et al., 1989; Bergamaschi et al., 2001; Ebers 2005; Mikaeloff et al., 2004; Ghezzi 2005*

evoluzione progressiva: *Noseworthy et al., 1983; Citterio et al., 1989; Phadke 1990; Runmarker and Andersen, 1993; Weinshenker et al., 1991; Lauer et al., 1992; Amato et al., 1999; Mikaeloff et al., 2004; Bergamaschi et al., 2005; Tremlett et al., 2006*

Arch Neurol, 2006

NEUROLOGICAL REVIEW

Clinical and Demographic Predictors of Long-term Disability in Patients With Relapsing-Remitting Multiple Sclerosis

A Systematic Review

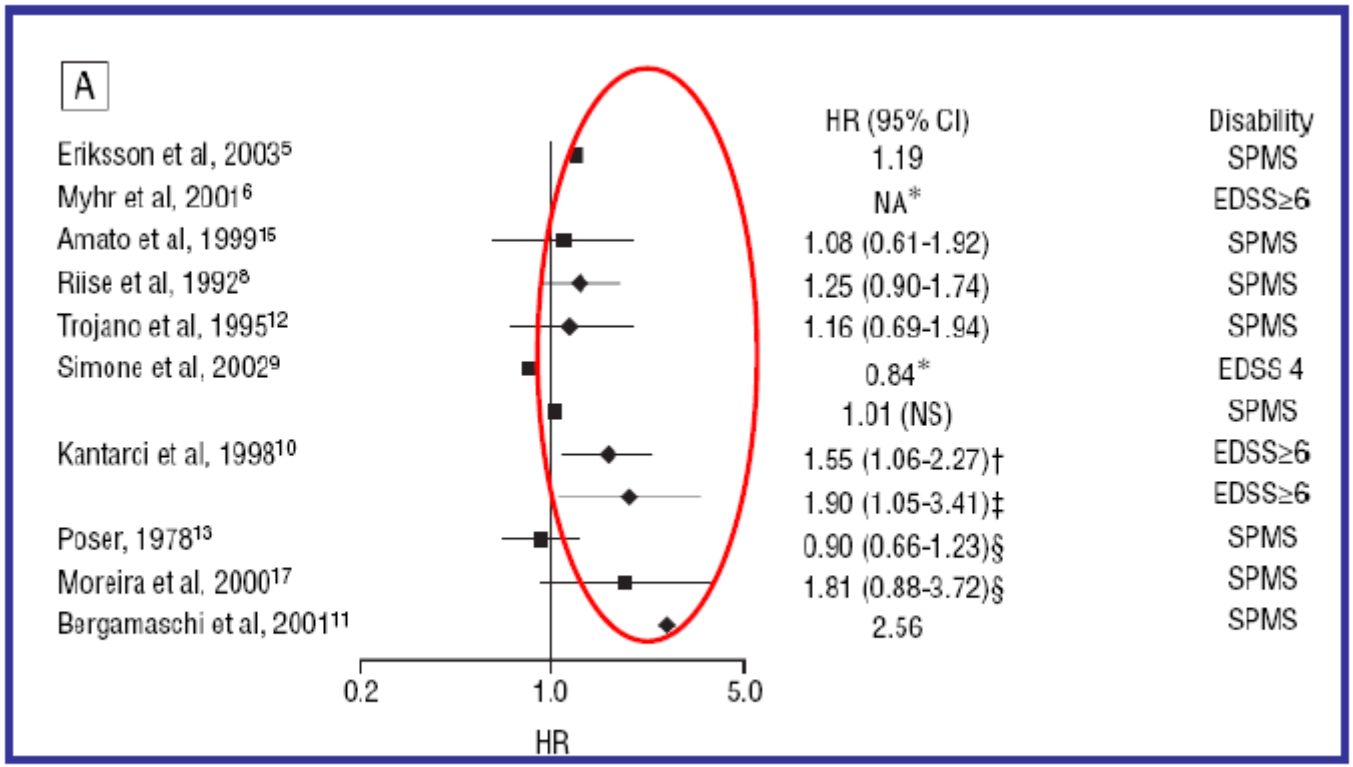
Annette Langer-Gould, MS, MD; Rita A. Popat, PhD; Stella M. Huang, MS; Kristin Cobb, PhD; Paulo Fontoura, MD; Michael K. Gould, MS, MD; Lorene M. Nelson, PhD

Analizzati 2812 studi

Selezionati 16 studi 8626 pazienti

Sesso maschile

Paradosso: M meno esposti, ma malattia più severa

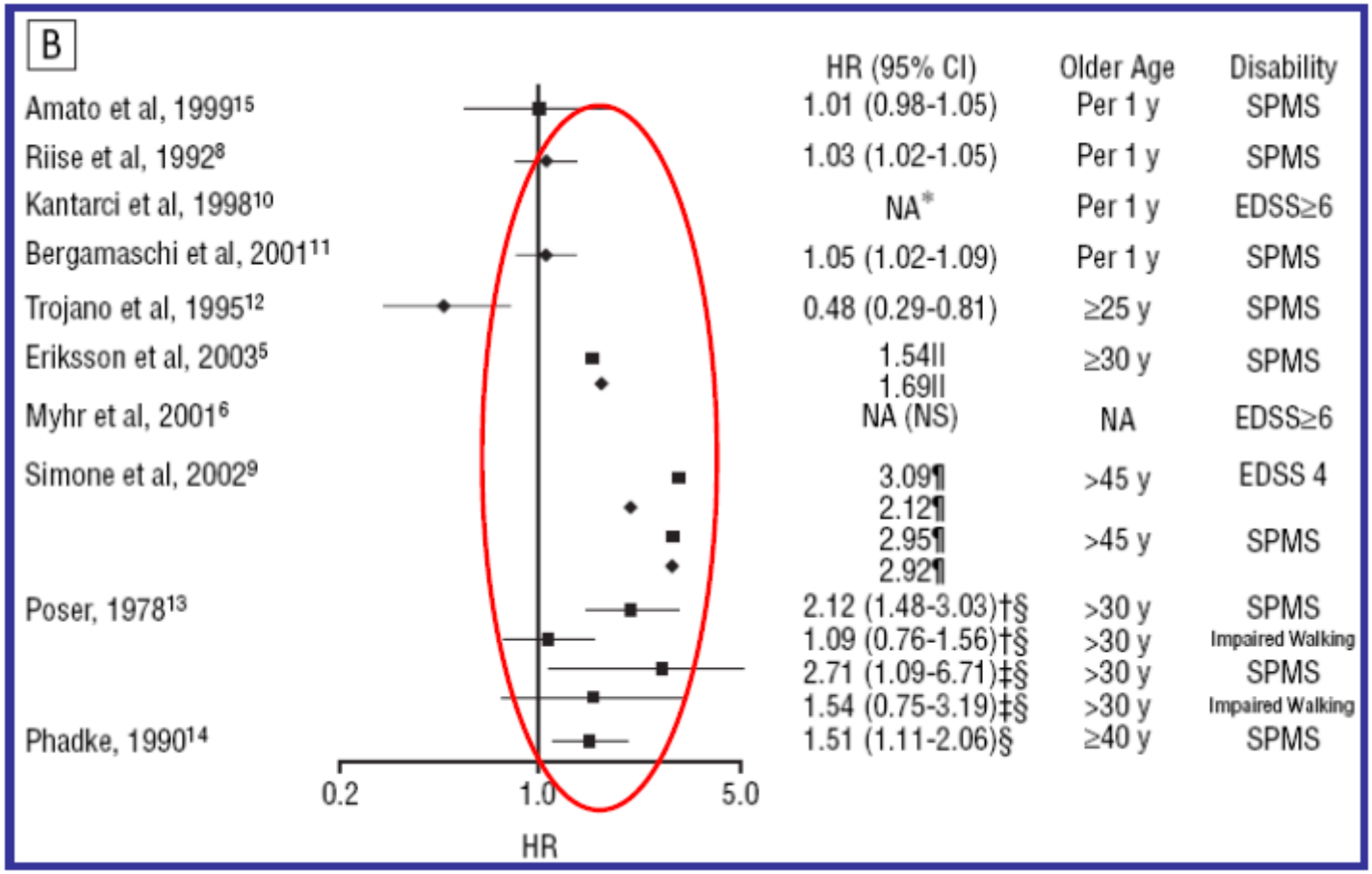


Langer-Gould et al, Arch Neurol, 2006

Sesso maschile

- Forma «benigna»: rapporto F/M 4/1 (Hawkins SA 1999)
- Decorso recidivante remittente >F (Hawkins SA 1999)
- Progressione della disabilità più lenta in F
  (Duquette P 1998, Confavreux C 2003)
- F presentano più facilmente ricadute visive e sensitive, M ricadute piramidali, tronco e cerebellari (Kalincik 2014)

Età di esordio



Età di esordio

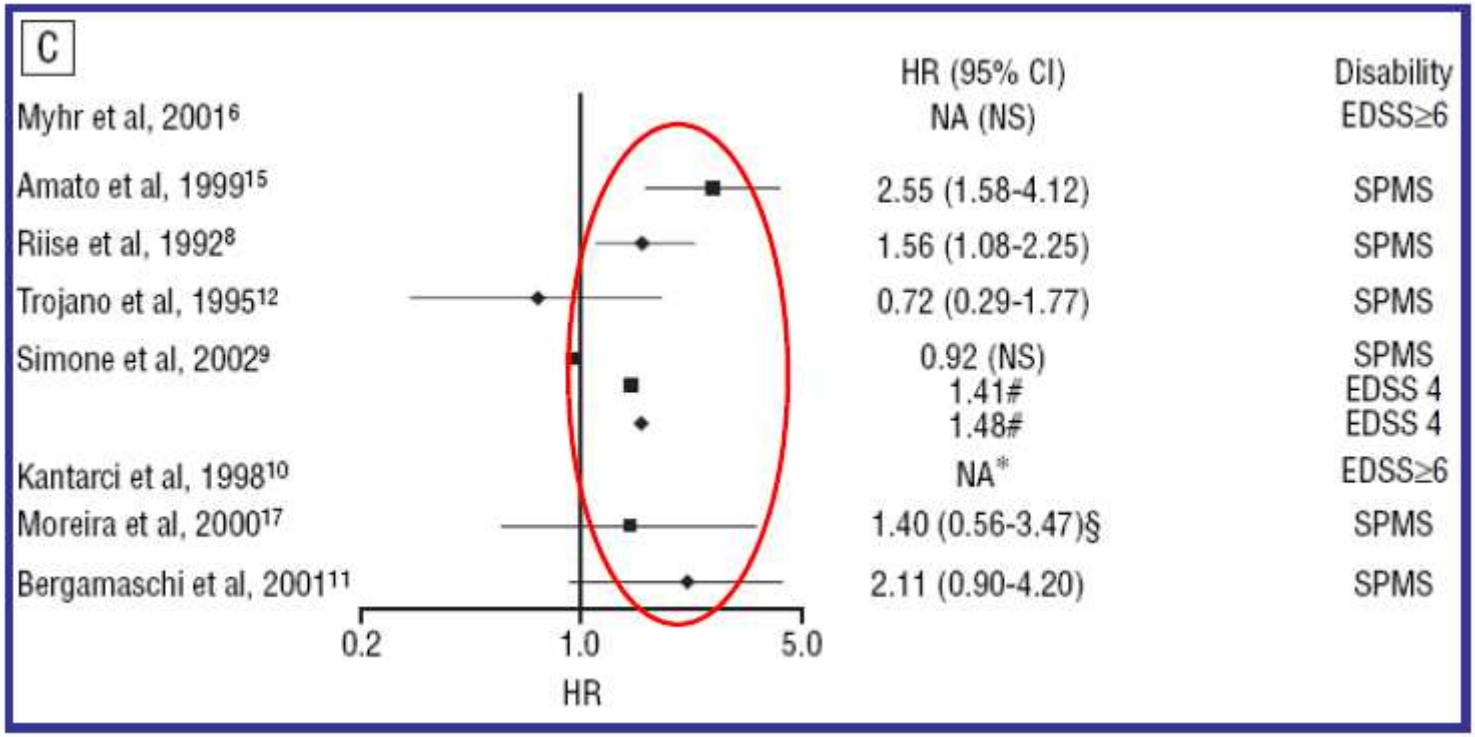
I pazienti con esordio precoce (<16 anni) raggiungono i vari livelli di disabilità in tempi medi paragonabili a quelli dei pazienti con esordio in età adulta.

(Deryck 2006)

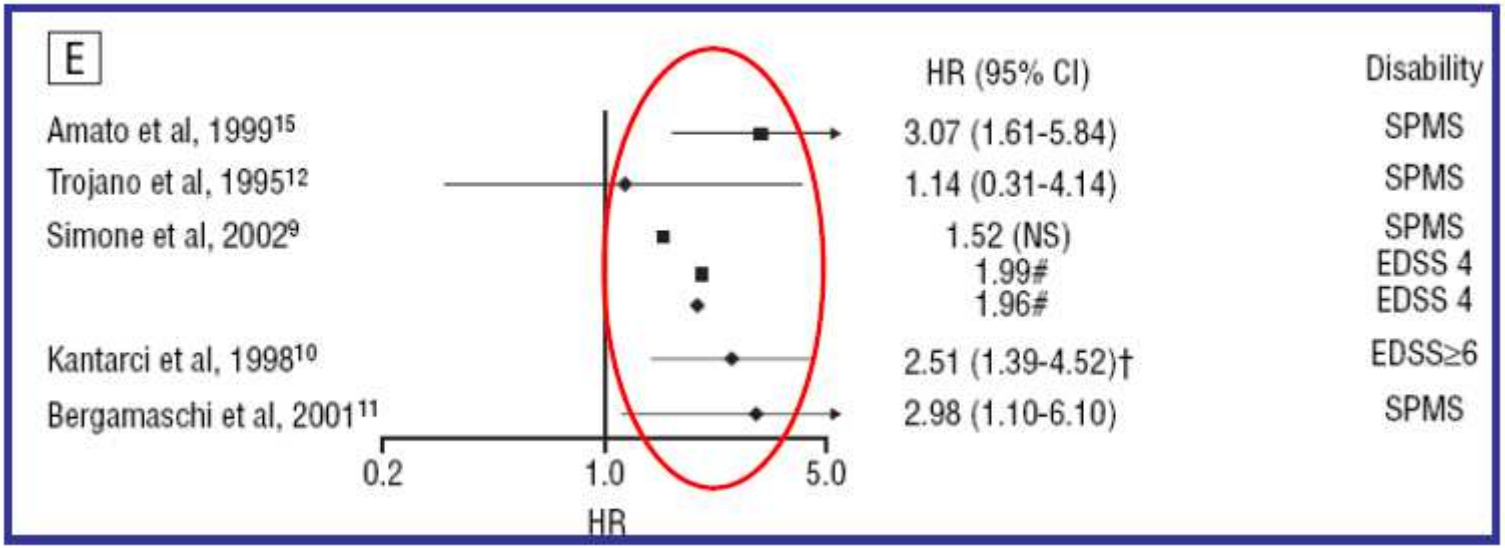
I pazienti con esordio tardivo (>50 anni) raggiungono EDSS 6.0 in età più avanzata rispetto a quelli con esordio in età adulta (16-50), 71.2 aa vs 58.4 aa.

(Tremleu 2006)

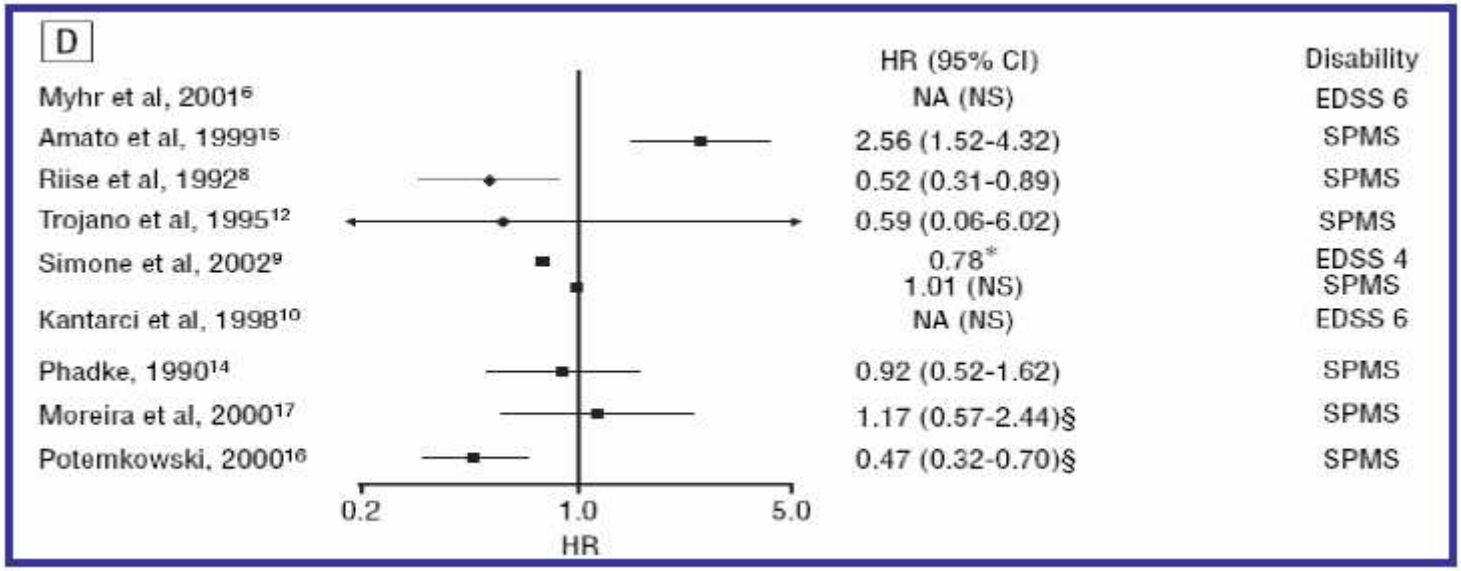
Esordio motorio



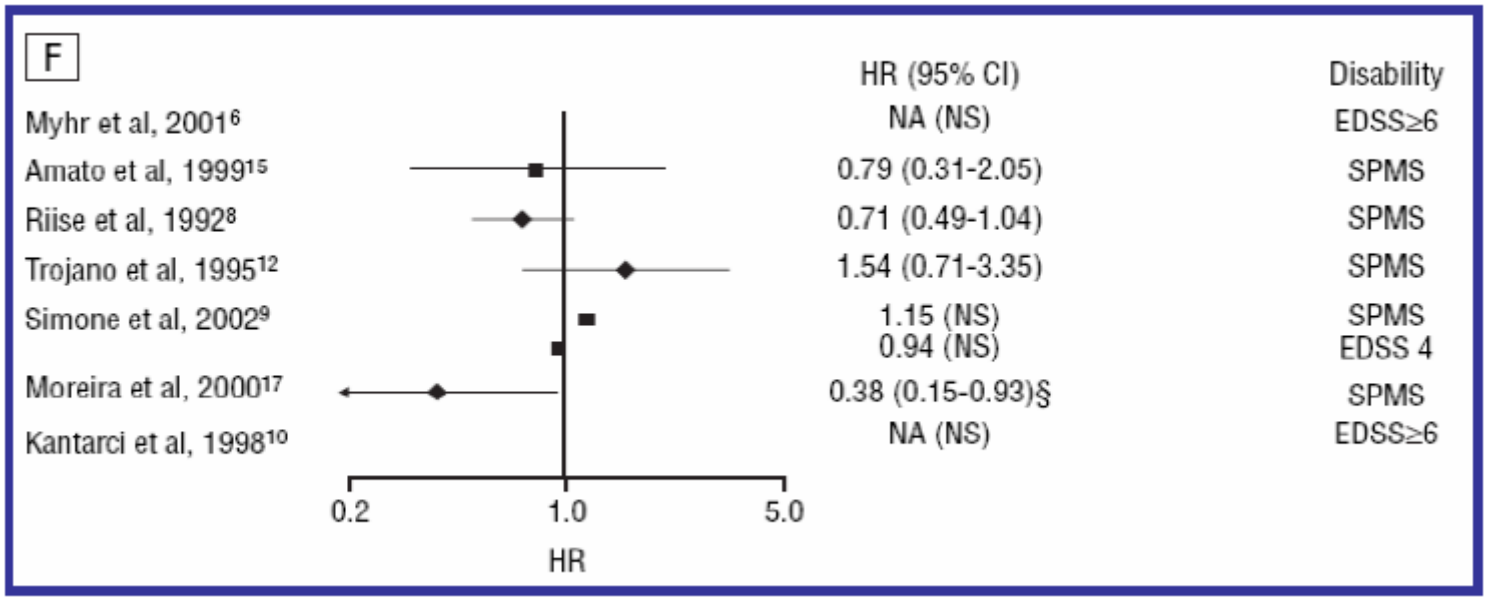
Esordio sfinterico



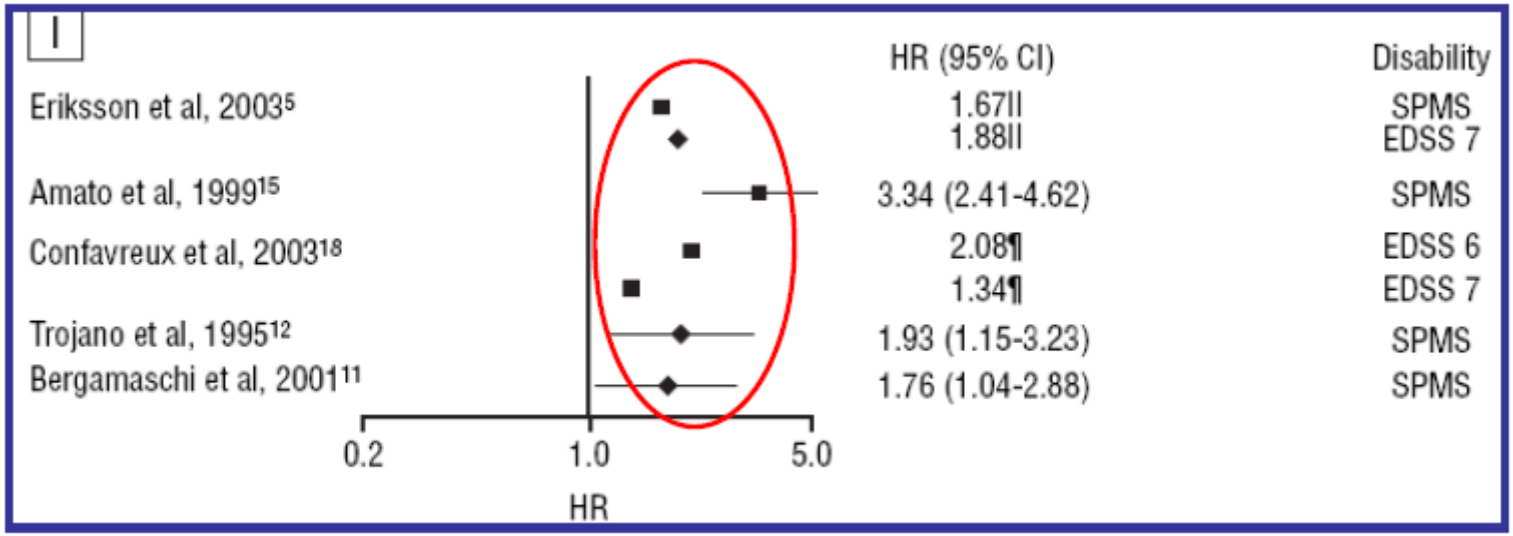
Esordio NORB



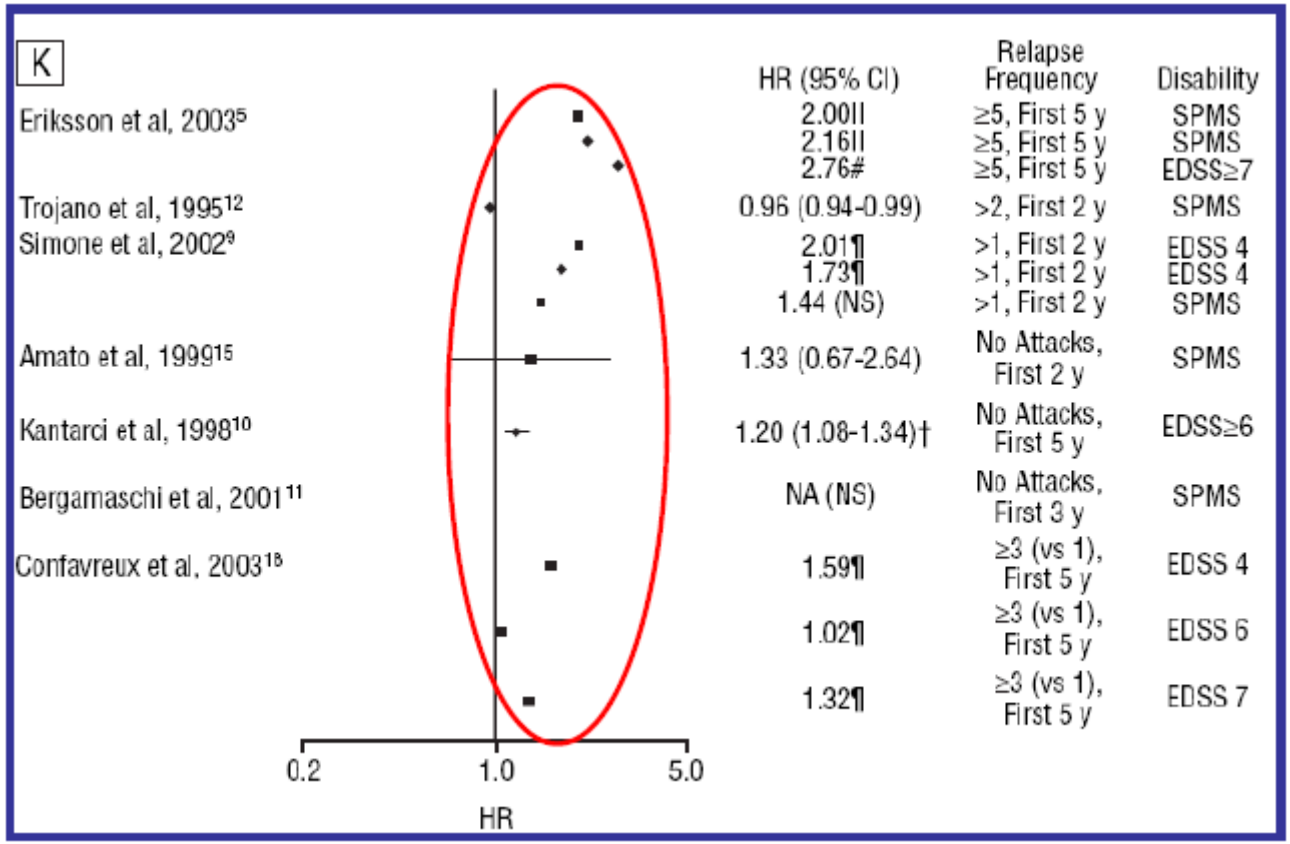
Esordio sensitivo



Esordio con sequele



Breve intervallo esordio-ricaduta



Cognitive impairment

Mult Scler. 2010 Jan;16(1):62-7. doi: 10.1177/1352458509350311. Epub 2009 Dec 7.

Cognitive impairment predicts conversion to multiple sclerosis in clinically isolated syndromes.

Zipoli V[1], Goretti B, Hakiki B, Siracusa G, Sorbi S, Portaccio E, Amato MP.

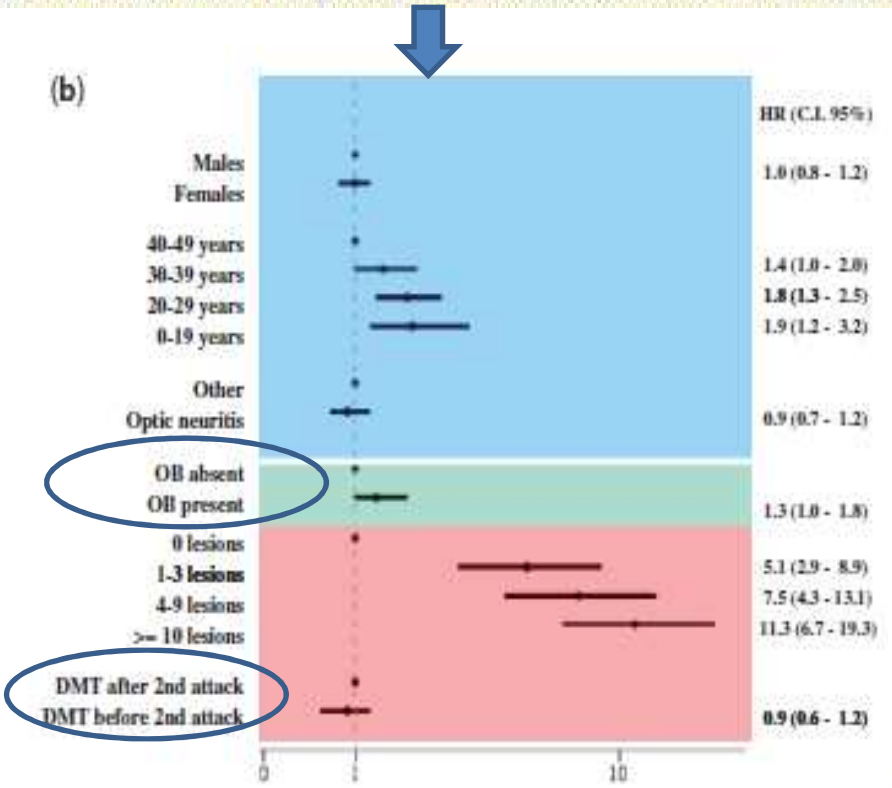
Author information

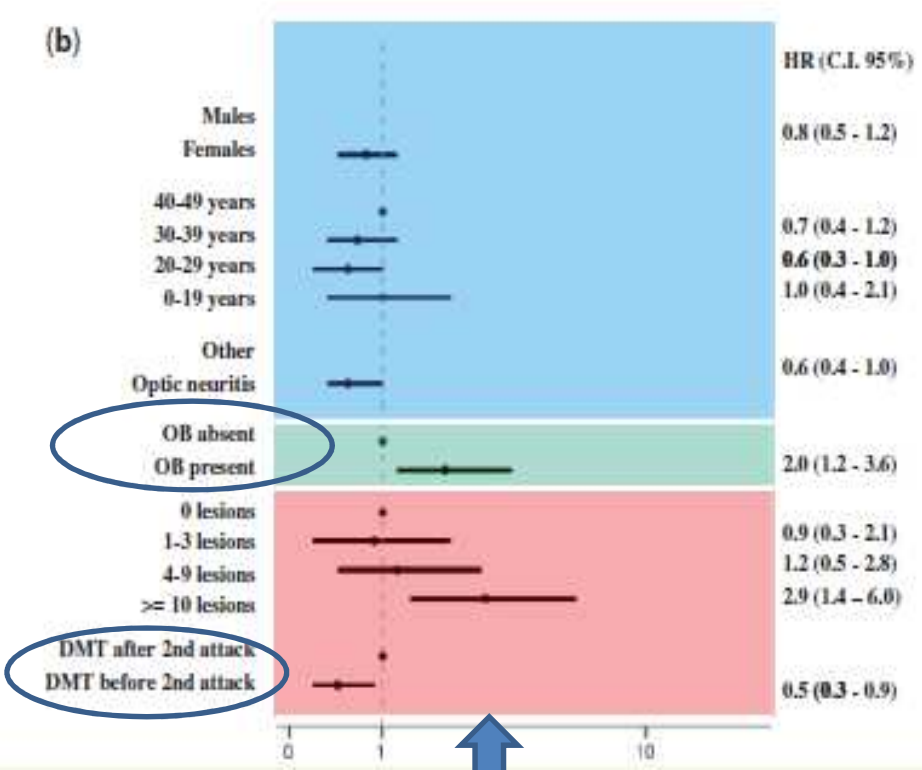
Abstract

Significant cognitive impairment has been found in 20-30% of patients with clinically isolated syndromes suggestive of multiple sclerosis. In this study we aimed to assess the prognostic value of the presence of cognitive impairment for the conversion to multiple sclerosis in patients with clinically isolated syndromes. All patients with clinically isolated syndromes consecutively referred to our centre since 2002 and who had been followed-up for at least one year underwent cognitive assessment through the Rao's Battery and the Stroop test. Possible predictors of conversion to clinically definite multiple sclerosis were evaluated through the Kaplan Meier curves and Cox regression analysis. A total of 56 patients (41 women; age 33.2 +/- 8.5 years; expanded disability scale score 1.2 +/- 0.7) were recruited. At baseline, 32 patients (57%) fulfilled McDonald's criteria for dissemination in space. During the follow-up (3.5 +/- 2.3 years), 26 patients (46%) converted to a diagnosis of multiple sclerosis. In particular, 64% of patients failing >or= 2 tests and 88% of patients failing >or= 3 tests converted to multiple sclerosis. In the Cox regression model, the failure of at least three tests (HR 3.3; 95% CI 1.4-8.1; p = 0.003) and the presence of McDonald's dissemination in space at baseline (HR 3.8; 95% CI 1.5-9.7; p = 0.005), were found to be predictors for conversion to multiple sclerosis. We conclude that cognitive impairment is detectable in a sizable proportion of patients with clinically isolated syndromes. In these subjects cognitive impairment has a prognostic value in predicting conversion to multiple sclerosis and may therefore play a role in therapeutic decision making.

Trattamento immunomodulante (Tintorè 2015)

Effect of baseline clinical, biological and MRI characteristics on the conversion to CDMS.





Effect of baseline clinical, biological and MRI characteristics on the risk of attaining an EDSS score of 3.0.

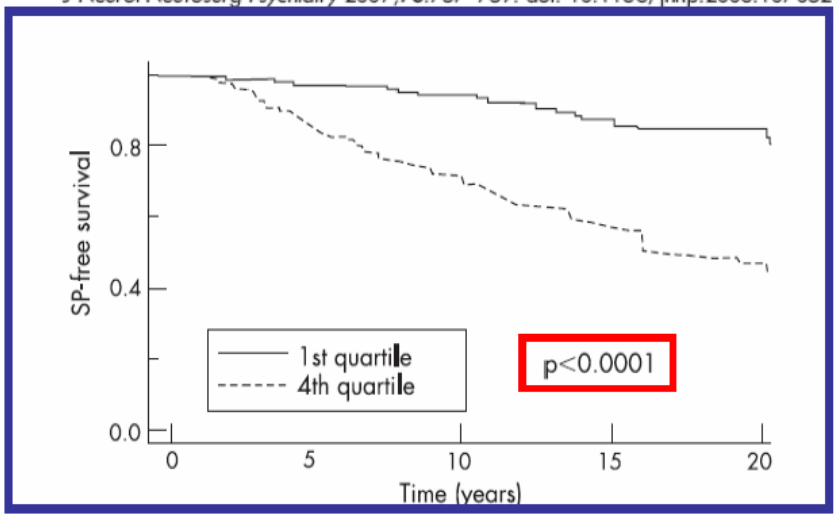
SHORT REPORT

Early prediction of the long term evolution of multiple sclerosis: the Bayesian Risk Estimate for Multiple Sclerosis (BREMS) score

Roberto Bergamaschi, Silvana Quaglini, Maria Trojano, Maria Pia Amato, Eleonora Tavazzi, Damiano Paolicelli, Valentina Zipoli, Alfredo Romani, Aurora Fuiani, Emilio Portaccio, Carlo Berzuini, Cristina Montomoli, Stefano Bastianello, Vittorio Cosi

J Neurol Neurosurg Psychiatry 2007;**78**:757–759. doi: 10.1136/jnnp.2006.107052

535 pazienti con forma iniziale RR e storia naturale di malattia



+ 0.05 x età *(in decadi)*
+ (-1.07) *(se ♀)*
+ 0.93 *(se esordio sfinterico)*
+ 0.82 *(se esordio motorio puro)*
+ 0.81 *(se esordio sensitivo-motorio)*
+ 0.32 x n°FS all'esordio
+ 0.52 *(se sequele dopo l'esordio)*
+ 0.71 *(se ricadute sfinteriche o motorie)*
+ 0.44 *(se EDSS 4.0 non in ricaduta entro 1° anno)*

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BREMS

(Bayesian Risk Estimate for Multiple Sclerosis)

BREMSO score

Bayesian Risk Estimate for Multiple Score at Onset

da MSBase registry (14211 pz: 10262 trattati con DMTs)

0.05 x età (decadi)

- 1.07 (se F)

+ 0.93 (se esordio sfinterico)

+ 0.62 (se esordio motorio puro)

+ 0.81 (se esordio motorio+sensitivo)

+ 0.32 x n° di sistemi funzionali coinvolti all'esordio

+ 0.52 (se recupero incompleto dopo l'esordio)

(Bergamaschi R 2015)

Specificità 79% come strumento predittivo dell'impatto clinico della SM

Dei 3445 pz con BREMSO <1°quartile→ solo 15% avrà forma severa (MSSS>3°quartile)

Dei 3535 pz con BREMSO>3° quartile→ solo16% avrà MSSS <1° quartile

Altri markers

Systematic Review

Neuro
epidemiology

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Multiple Sclerosis Relapses: Epidemiology, Outcomes and Management. A Systematic Review

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Department of Medicine, University of Melbourne; Department of Neurology, Royal Melbourne Hospital, Melbourne, Vic., Australia

Altri markers

Table 1. Factors predisposing to MS relapses

	Diagnosis	Cohort	Effect size	Reference
Female sex				
	CIS, CDMS	11,570	HR 1.08 (CI 1.06–1.11)	Kalincik et al. [42]
	CIS*	4,732 (from 33 studies)	RR 1.20 (CI 0.98–1.50)	Dobson et al. [43]
	CDMS	2,477	RR 1.14 (CI 1.06–1.23)	Tremtlett et al. [44]
Young age				
	CDMS	11,570	HR 1.22 (CI 1.16–1.20) per 10 years	Kalincik et al. [42]
	CIS	1,047	HR 1.22 (CI 1.10–1.22) per 10 years	Kuhle et al. [59]
	CIS	330	HR 1.5 (CI 1.3–1.8) per 10 years	Mowry et al. [45]
	CIS	186	HR 1.76 (CI 1.07–2.89) for age <30 years	West et al. [48]
	CIS	131	RR 2.81 (CI 2.07–3.81) pediatric versus adult MS	Gorman et al. [46]
Short MS duration				
	CDMS	2,477	RR 1.20 per 5 years	Tremtlett et al. [44]
	CDMS	921 (from 22 trials)	RR 1.02 per year	Held et al. [47]
Ethnicity				
Non-white	CIS	330	HR 2.4 (CI 1.6–3.6)	Mowry et al. [45]
Non-white	CIS	186	HR 2.54 (CI 1.48–4.36)	West et al. [48]
Hispanic	CIS, CDMS	469	HR 1.2 (CI 0.7–2.1)	Mowry et al. [36]
Season				
	CDMS	9,811	spring peak, RR 1.08	Spelman et al. [25]
	CDMS	199	mid-late summer peak, RR 2.2	Tremlett et al. [73]
	CDMS	96	spring peak, RR 1.12	Salvi et al. [26]
	CDMS	336	summer peak, RR 1.61	Goodkin et al. [28]
	CDMS	178	spring-summer peak, RR 1.11	Bamford et al. [27]
	CDMS*	(from 10 studies)	spring peak, RR 1.1	Jin et al. [24]
Low serum vitamin D levels				
	CIS	465	RR 2.3 (CI 1.1–5) per 50 nmol/l decrement	Ascherio et al. [37]
	CDMS	267	RR 1.96 per 10 nmol/l decrement	Smolders et al. [30]
	CDMS	73	RR 1.36 (CI 1.08–1.72) per halving serum concentration	Runia et al. [31]
	CDMS	145	HR 1.10 (CI 1.03–1.18) per 10 nmol/l decrement	Simpson et al. [34]
	pediatric onset CIS/CDMS	110	RR 1.52 (CI 1.05–2.17) per 10 nmol/l decrement	Mowry et al. [35]
Smoking				
	CIS	1,047	HR 0.95 (CI 0.79–1.14) – serum cotinine levels	Kuhle et al. [59]
	CIS, CDMS	469	HR 1.43 (CI 1.01–2.03)	Mowry et al. [36]
	CIS	129	HR 1.8 (CI 1.2–2.8)	Di Pauli et al. [183]
	CDMS	183	HR 0.94 (CI 0.41–1.58)	Pittas et al. [58]
Stress				
	CDMS*	1,082 (from 14 studies)	Cohen's d +0.53 (CI 0.40–0.65)	Mohr et al. [60]
	CDMS	101	OR 1.52 (CI 1.01–2.29)	Brown et al. [184]
	CDMS	73	HR 2.2 (CI 1.2–4.0)	Buljevac et al. [185]
	CDMS	156	increased relapse activity during war	Golan et al. [62]
	CDMS	32	decreased relapse activity during war	Nisipeanu and Korczyn [61]
Vaccination				
Multiple vaccines	CDMS	643	HR 0.7 (CI 0.4–1.3)	Confavreux et al. [65]
Hepatitis B, tetanus	pediatric CIS	356	hepatitis B: HR 0.8 (CI 0.3–1.9), tetanus: HR 1.0 (CI 0.6–1.7)	Mikaeloff et al. [66]

Altri markers

	Diagnosis	Cohort	Effect size	Reference
Influenza, H1N1	CDMS (RCT)	61	incidence: vaccination 12% vs. placebo 14%	Bamford et al. [67]
Influenza, H1N1	CDMS (RCT)	88	incidence: vaccination 3% vs. placebo 6.5%	Myers et al. [68]
Yellow fever	CDMS	7	RR 12.8 (CI 4.3–38)	Farez et al. [69]
Infections				
Influenza A, EBV	CDMS	407	influenza A: OR 6.5 (CI 1.8–24), EBV: OR 4.4 (CI 1.3–15)	Oikonen et al. [186]
	CDMS	73	RR 2.1 (CI 1.4–3.0)	Buljevac et al. [70]
Chlamydia	CDMS	73	RR 3.1 (CI 1.3–6.7)	Buljevac et al. [71]
URTI	CDMS	41	RR 2.0 (CI 1.3–3.2)	Edwards et al. [72]
URTI	CDMS	199	r (Pearson) 0.39	Tremlett et al. [73]
	CDMS	170	RR 2.8	Sibley et al. [74]
	CDMS	60	RR 1.3	Andersen et al. [75]
Pregnancy				
	CDMS	365 (269 pregnancies)	3rd trimester RR 0.4; postpartum RR 2.4	Confavreux et al. [77]
	CDMS	227	3rd trimester RR 0.3; postpartum RR 1.7	Vukusic et al. [78]
	CDMS	674 (893 pregnancies)	3rd trimester RR 0.4; postpartum RR 1.9	Hughes et al. [81]
	CDMS	33 (49 pregnancies)	postpartum RR 1.6	Roullet et al. [187]
	CDMS	111 (191 pregnancies)	postpartum versus pregnancy RR 3.4	Nelson et al. [79]
	CDMS	70 (98 pregnancies)	pregnancy RR 0.6; postpartum RR not significant	Salemi et al. [80]
Assisted reproduction				
	CDMS	32 (70 IVF cycles)	RR 2.0	Michel et al. [90]
	CDMS	16 (26 IVF cycles)	RR 6.9 (CI 3.4–14)	Correale et al. [93]
	CDMS	10	RR 4.8	Laplaud et al. [91]
	CDMS	23 (78 IVF cycles)	RR 1.5	Hellwig et al. [92]

Studio pilota:

Fattori neuropsicologici e clinici predittivi di progressione di disabilità a due anni in una popolazione di soggetti con nuova diagnosi di Sclerosi Multipla Relapsing Remitting

Popolazione in studio:

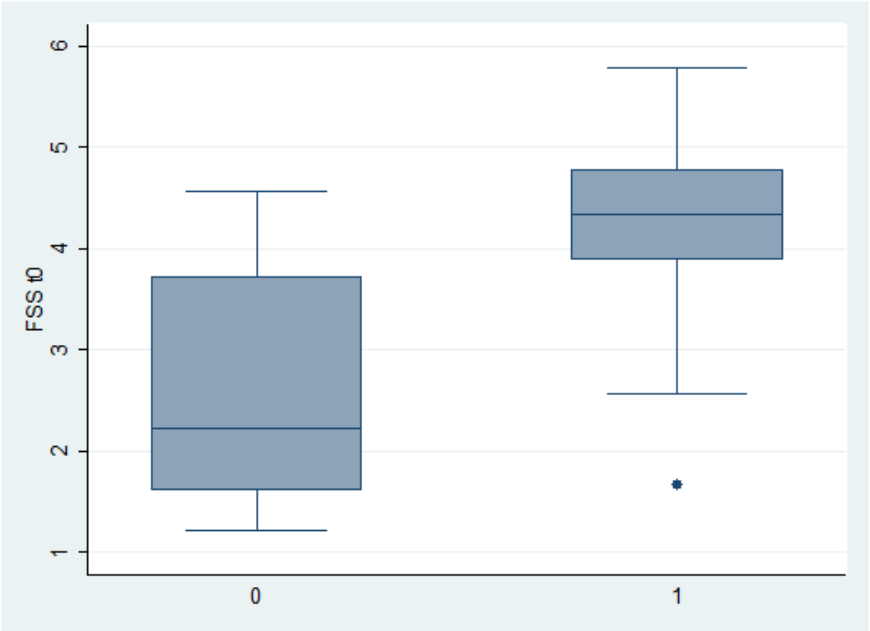
- Soggetti con nuova diagnosi di Sclerosi Multipla RR secondo i criteri McDonald 2010 dal Maggio 2012 ad oggi

Materiali e Metodi:

- Valutazione delle funzioni cognitive entro sei mesi dalla diagnosi con batteria neuropsicologica estesa e standardizzata (BRB ed altri test, in particolare esploranti le funzioni esecutive)
- Valutazione del grado di disabilità (EDSS) e dei sintomi motori (deambulazione - TWT; destrezza manuale - 9-HPT)
- Valutazione dei sintomi non motori (fatica - FSS), dei sintomi comportamentali (ansia- STAI, depressione - BDI, disturbi del sonno – PSQI, ESS) e della qualità di vita (MSQOL-54)

La fatica ha uno score maggiore nel gruppo di pazienti con progressione di disabilità a due anni.

	MS-STABILI N° 12			MS-PROGREDITI N°10			
	median	mean	sd	median	mean	sd	p value
BDI	5.0	6.8	6.2	10.5	13.6	12.5	0.115
STAI-y Trait	59	40.9	11.7	45.5	45.4	12.9	0.401
STAI-y State	39.5	41.2	13.0	52.0	47.9	12.7	0.236
PSQI	4.5	5.0	2.7	5.0	6.5	4.0	0.306
ESS	5.5	5.9	3.9	6.0	7.2	4.1	0.469
MSQOL-54f	78.7	76.0	15.6	60.9	62.8	21.0	0.105
MSQOL-54m	83.0	75.9	16.1	62.7	62.1	22.4	0.11
FSS	2.2	2.6	1.2	4.3	4.2	1.2	0.015



Un’aumentata percezione soggettiva della fatica, soprattutto se in assenza di disturbi della sfera ansioso-depressiva e del sonno, potrebbe rappresentare un fattore da considerare come possibile fattore predittivo in studi futuri.

Grazie per l’attenzione…