IL DECORSO PROGRESSIVO: DIVERSA FASE O DIVERSA MALATTIA?

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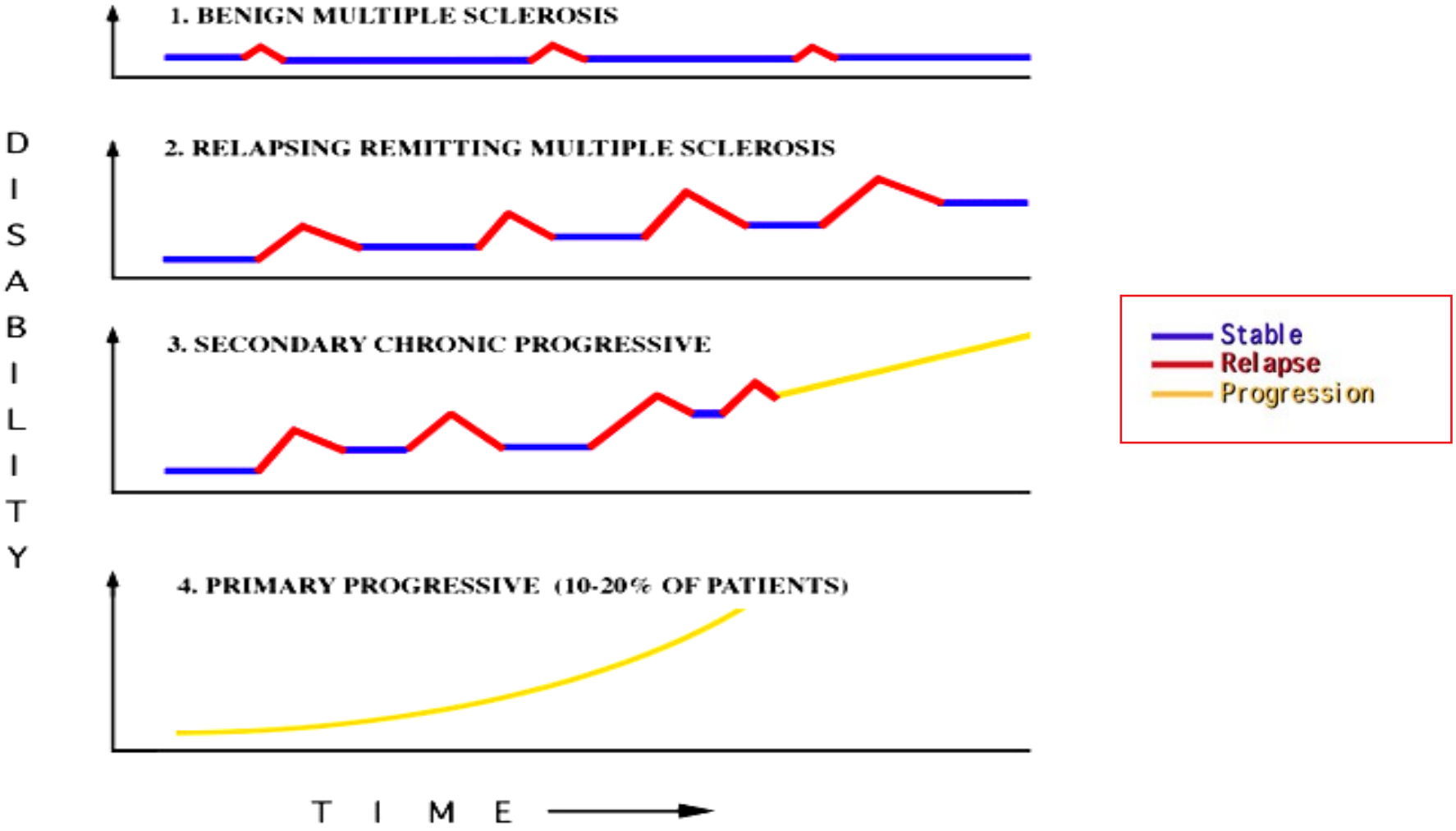
Fondazione Don Gnocchi - Milano

SCLEROSI MULTIPLA PROGRESSIVA



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Diversa fase o diversa malattia?

Spunti di riflessione:

- Epidemiologia
- Fisiopatologia e patogenesi
- Trattamento

SCLEROSI MULTIPLA PROGRESSIVA

	Multiple sclerosis with an exacerbating–remitting initial course† n = 1562	Multiple sclerosis with a progressive initial course# n = 282	P-value
Gender: no. (%)			
Males	536 (34)	121 (43)	0.006*
Females	1026 (66)	161 (57)	
Age at onset of multiple sclerosis: no. (%)			
Mean ± SD	29.6 ± 9.5	39.3 ± 11.3	<0.001***
Median	29.0	40.1	
Range	5–62	11–67	
Initial symptoms of multiple sclerosis: no. (%)			
Isolated optic neuritis	330 (21)	5 (2)	<0.001*
Isolated brainstem dysfunction	158 (10)	1 (0)	
Isolated dysfunction of long tracts	727 (47)	236 (84)	
Combination of symptoms	347 (22)	40 (14)	
Kaplan–Meier estimates of the time (median [95% CI]): (years)			
From onset of multiple sclerosis to assignment of			
DSS 4	11.4 [10.5–12.3]	0.0	<0.001**
DSS 6	23.1 [20.1–26.1]	7.1 [6.3–7.9]	<0.001**
DSS 7	33.1 [29.2–37.0]	13.4 [11.0–15.9]	<0.001**
From assignment of DSS 4 to assignment of			
DSS 6	5.7 [4.9–6.4]	5.4 [4.3–6.6]	0.74**
DSS 7	12.1 [10.0–14.2]	12.0 [10.1–13.9]	0.70**
From assignment of DSS 6 to assignment of			
DSS 7	3.3 [2.8–3.9]	4.0 [2.9–5.1]	0.48**
Kaplan–Meier estimates of the age (median [95% CI]) at the time of assigning DSS (years)			
DSS 4	44.8 [43.8–45.9]	42.1 [40.2–44.0]	<0.001**
DSS 6	55.3 [54.2–56.7]	53.0 [51.1–54.9]	0.002**
DSS 7	62.8 [60.3–65.4]	63.1 [60.0–66.2]	0.24**
Duration of multiple sclerosis: (years)			
Mean ± SD	11.5 ± 9.9	10.1 ± 8.0	0.02***
Median	10.0	9.0	
Range	0–52	0–62	

Confavreux and Vukusic, Brain 2006

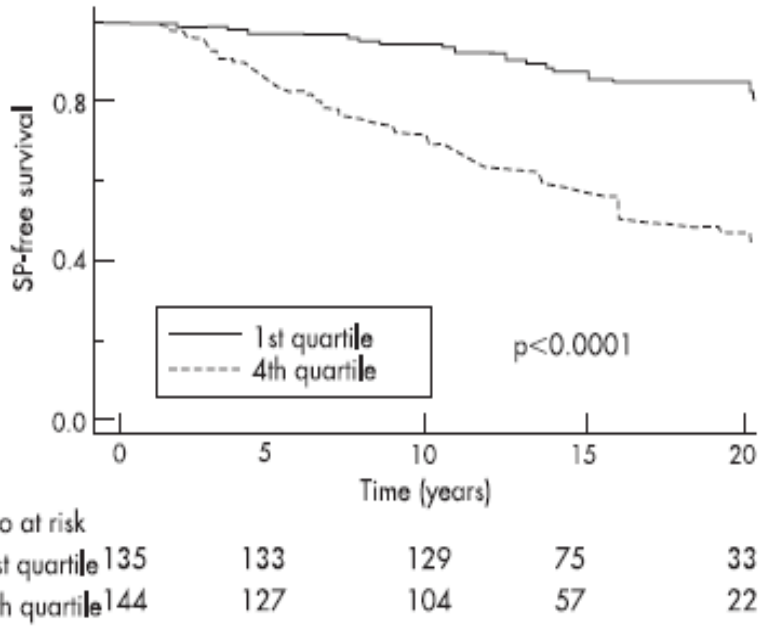
SHORT REPORT

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

Table 1 Estimates of the Bayesian risk associated with early clinical predictors observed within 1 year of disease onset

	Mean LRR	Mean log LRR	95% CI
Age at onset (in decades)	1.05	0.05	1.02 to 1.09
Female sex	0.39	−1.07	0.17 to 0.78
Sphincter onset	2.98	0.93	1.10 to 6.10
Pure motor onset	2.11	0.62	0.90 to 4.20
Motor–sensory onset	2.40	0.81	1.15 to 4.41
Sequel after onset	1.76	0.52	1.04 to 2.88
Functional systems involved at onset	1.39	0.32	1.16 to 1.64
Sphincter plus motor relapses	2.10	0.71	1.56 to 2.89
EDSS ≥4 outside relapse	2.28	0.44	0.40 to 6.50

EDSS, Expanded Disability Status Scale; LRR, local relative risk; 95% CI, 95% Bayesian credible interval for the local relative risk.



Bergamaschi et al., JNNP 2007

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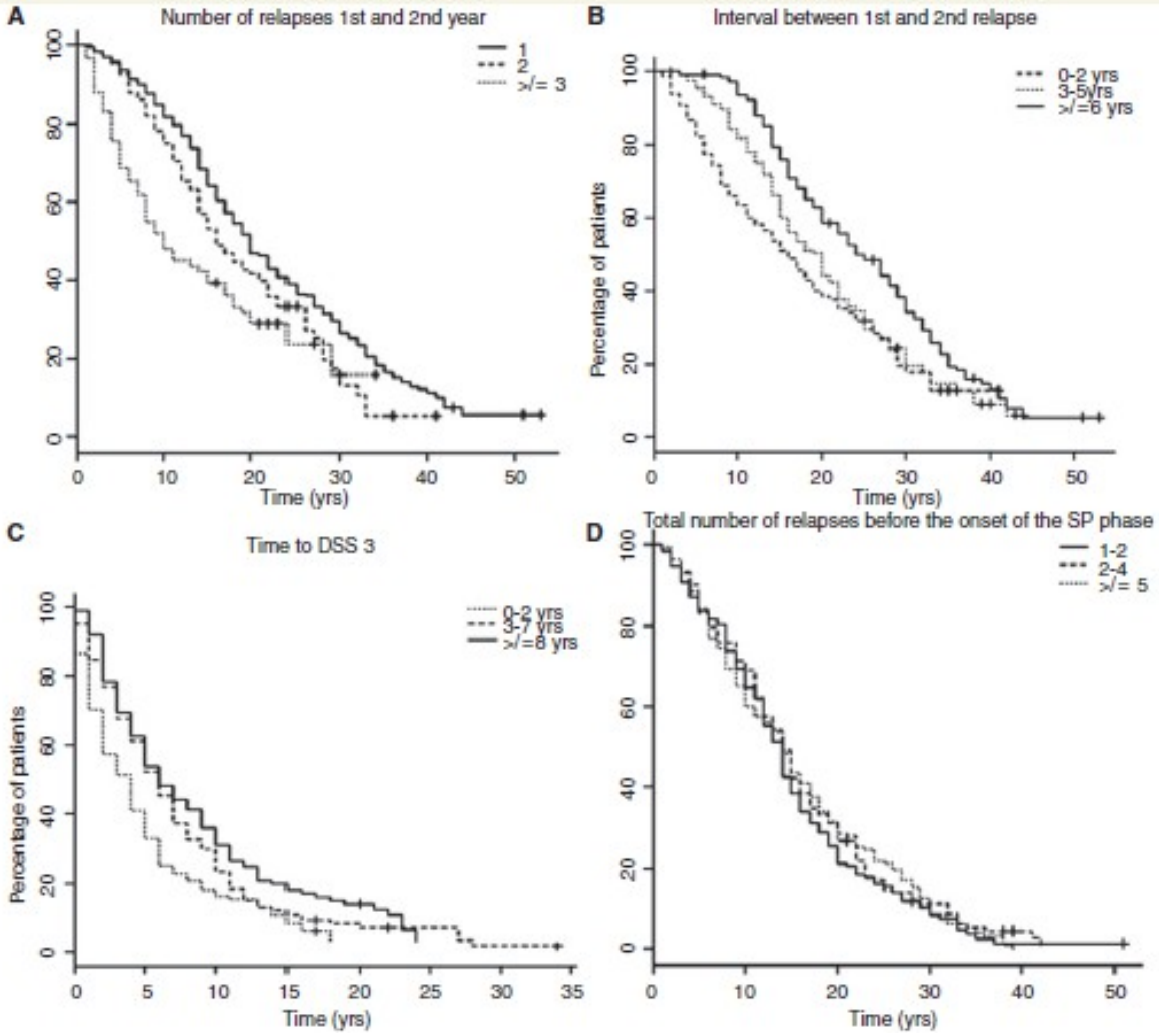

Outcome: tempo di evoluzione a EDSS 6

Scalfari et al., Brain 2010

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2000 – Tension headaches MRI at RIS diagnosis :	2002 through 2004 – MRIs at RIS follow-up:	2009 – Progressive myelopathy MRI at MS diagnosis:

	Nonconverters	All Converters	RIS to CIS/MS (15 yr)	RIS to PPMS (15 yr)	*P* (CIS/MS vs PPMS)
N	324	128	113	15	NA
F%	81	71	75	40	0.005[a]
Median (yr) age at RIS (range)	38.6 (14–74)	32.5 (11–70)	32.0 (11–70)	43.3 (20–66)	<0.001[b]
Median (yr) follow-up (range)	2.0 (0–20)	5.2 (0.2–21.1)	5.2 (0.2–21.1)	5.8 (1.1–18.0)	0.66[b]
Median (yr) time to symptomatic MS[c] (range)	NA	2.4 (2.0–2.8)	2.3 (1.7–2.9)	3.5 (1.6–5.4)	0.21[d]
CSF + (%)	61	75	73	85	0.37[a]
Spinal cord lesions at the time of RIS (%)	23	69	64	100	0.005[a]
(Gd+) spinal cord lesions at the time of RIS (% of all spinal cord lesions)	3.1	17.4	19	27	0.48[a]

Kantarci et al., Ann Neurol 2016

SCLEROSI MULTIPLA PROGRESSIVA

un mondo libero dalla SM

Contents lists available at ScienceDirect

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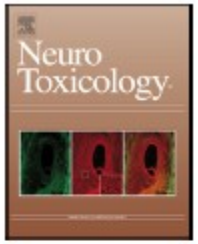

Full length article

Factors associated with onset, relapses or progression in multiple sclerosis: A systematic review

Kyla A. McKay[a], Shayesteh Jahanfar[b], Tom Duggan[a], Stacey Tkachuk[a], Helen Tremlett[a,*]

[a] Division of Neurology, Faculty of Medicine, Djavad Mowafaghian Centre for Brain Health, University of British Columbia, Vancouver, Canada
[b] School of Population and Public Health, Faculty of Medicine, University of British Columbia, Vancouver, Canada

Fattori associati con aumentato rischio di sviluppo SM o aumentato tasso di recidive:

- Bassi livelli vitamina D
- Infezione da EBV
- Infezioni alte vie respiratorie
- Obesità nell'adolescenza

Fattori associati con aumentato rischio di evoluzione a SM SP:

- Fumo di sigaretta

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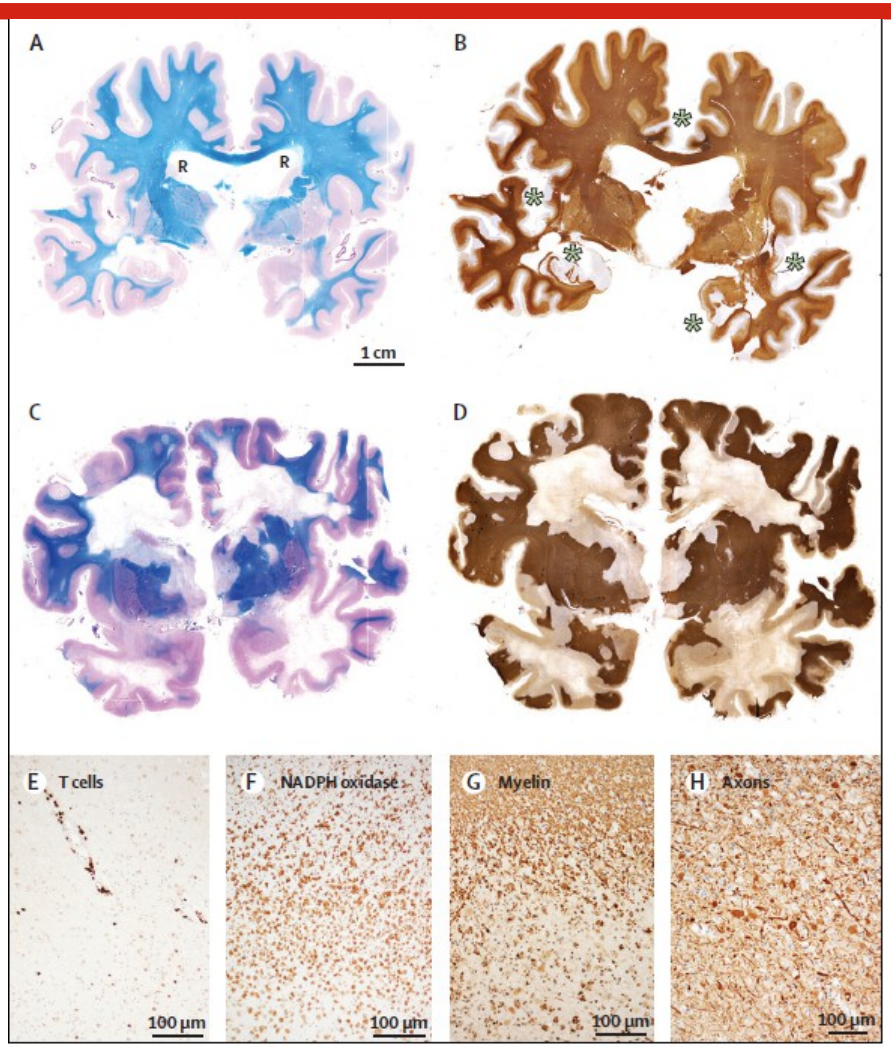
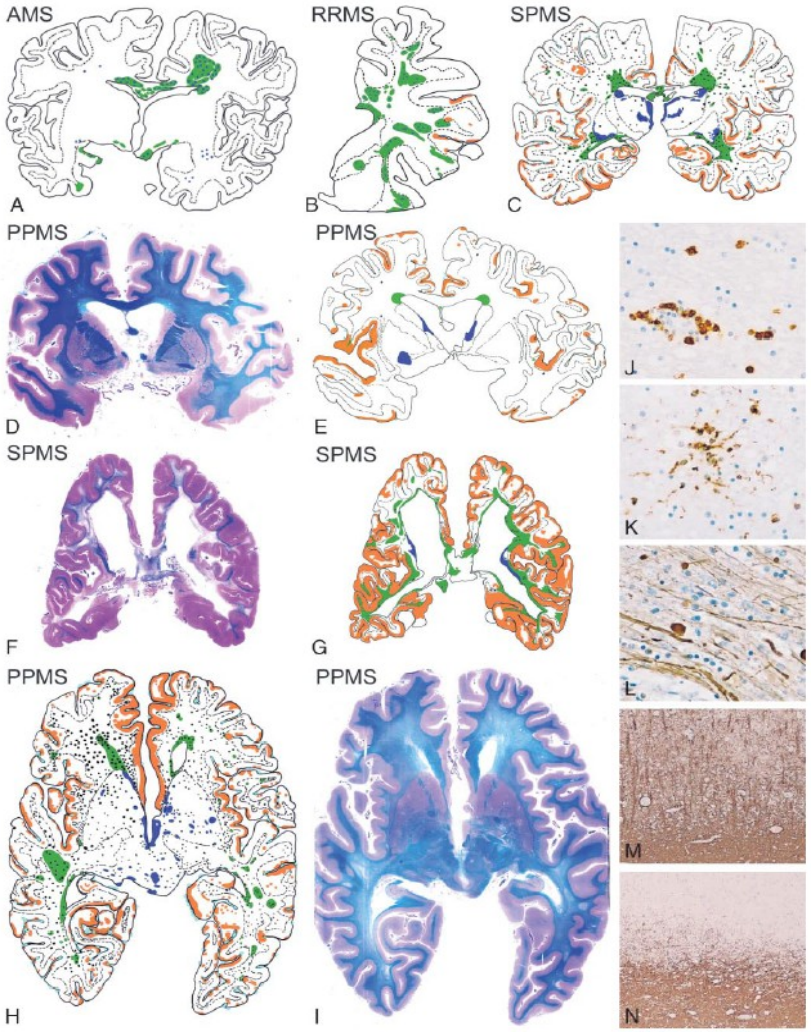
un mondo libero dalla SM



Mahad et al., Lanc Neurol 2015



Kutzelnigg et al., Brain 2005

SCLEROSI MULTIPLA PROGRESSIVA

Some recent studies sug
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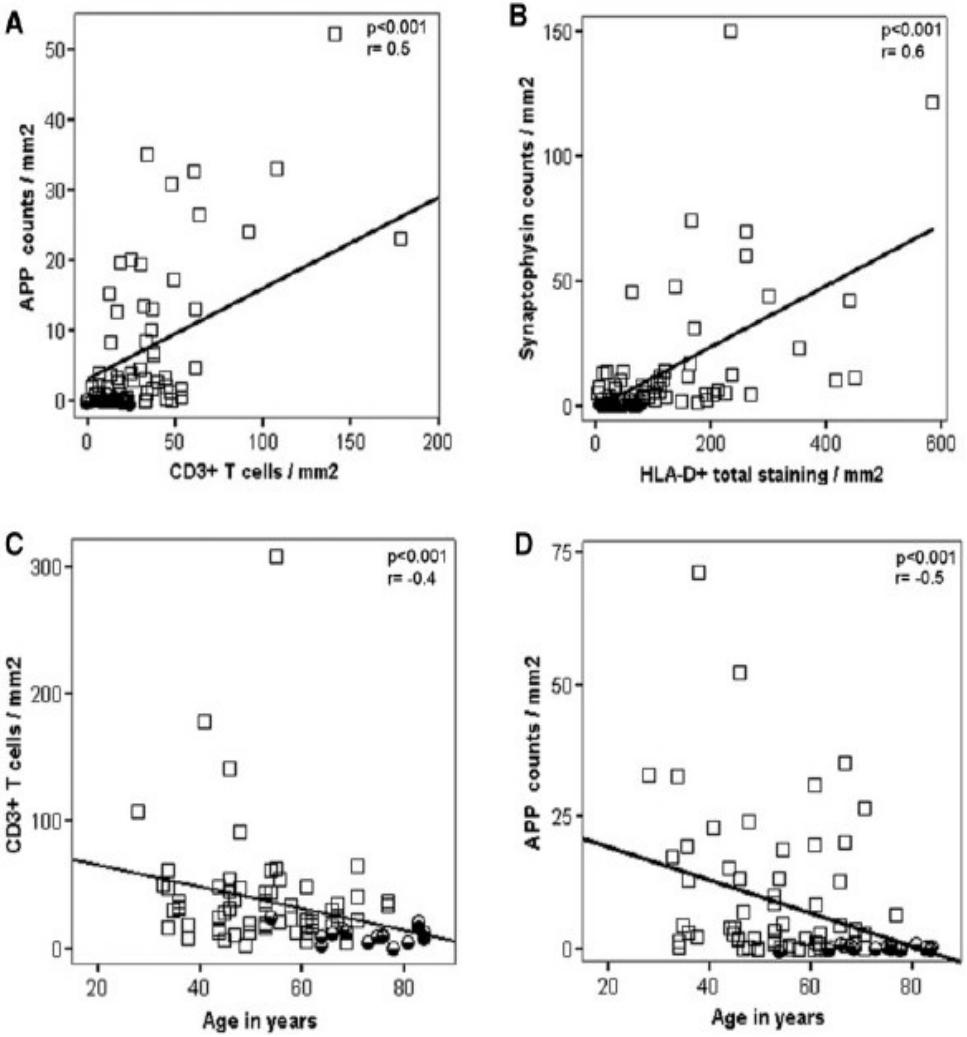

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Frischer et al., Brain 2009

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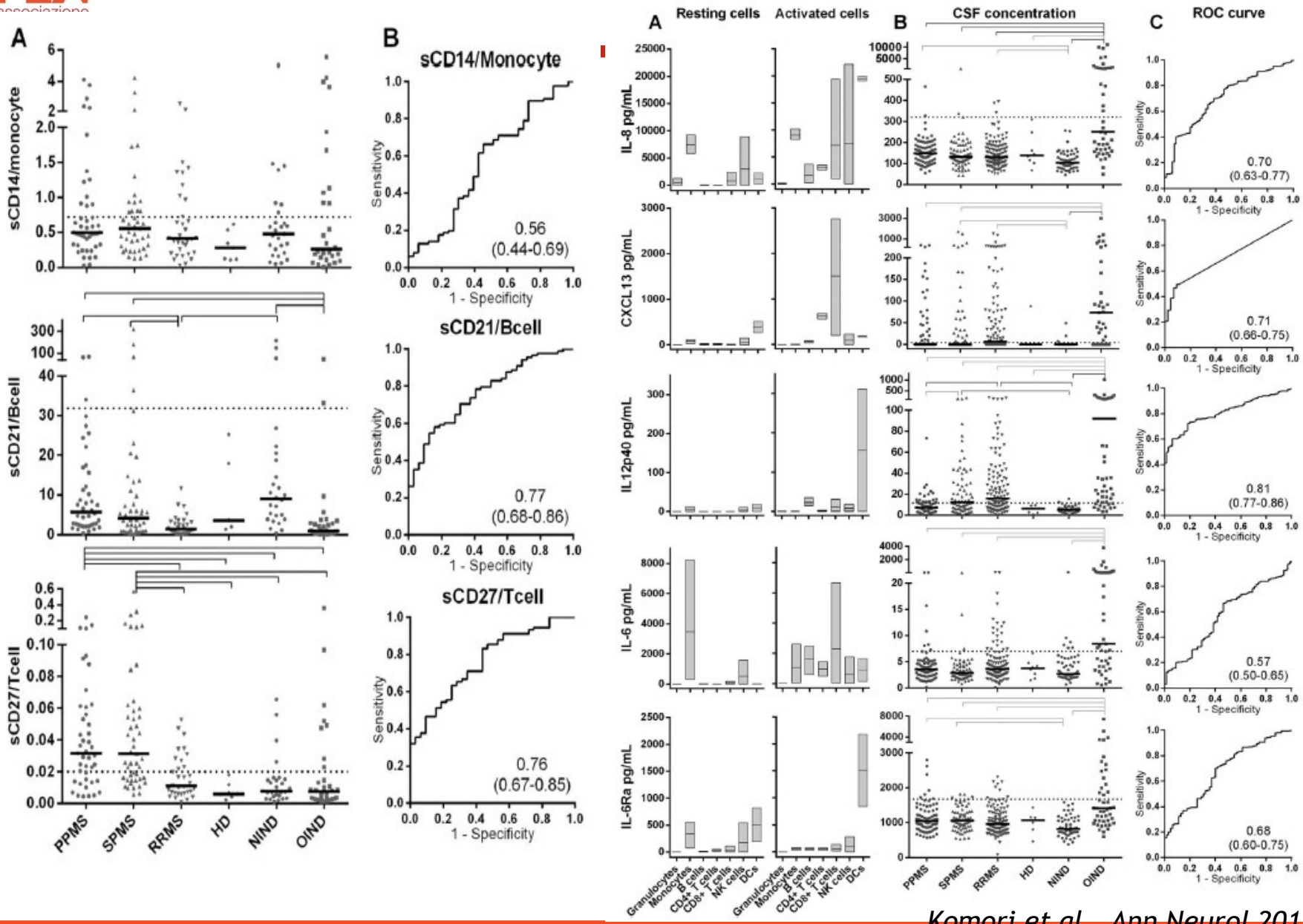
un mondo libero dalla SM



Komori et al., Ann Neurol 2015

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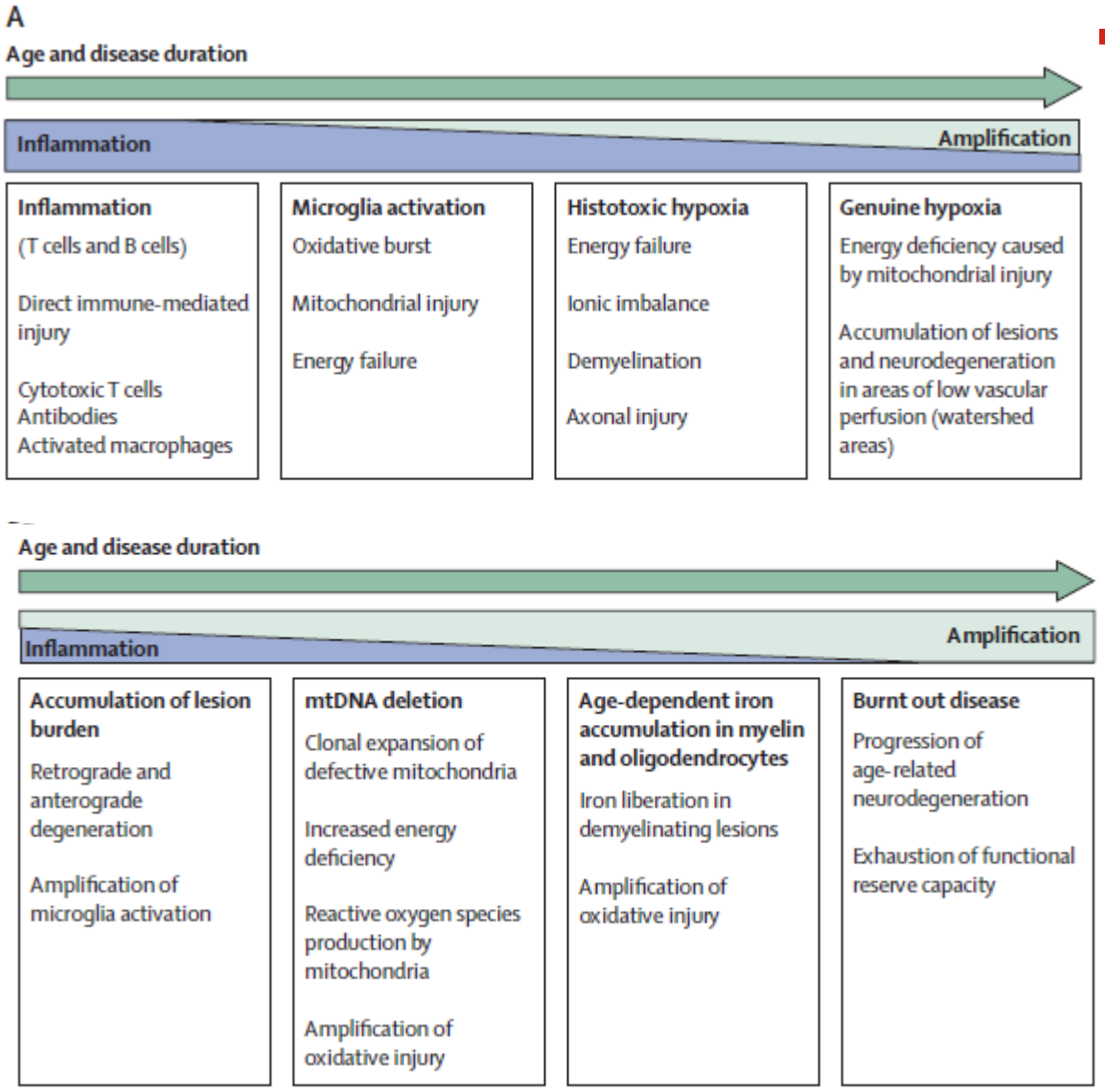

Mahad et al., Lanc Neurol 2015

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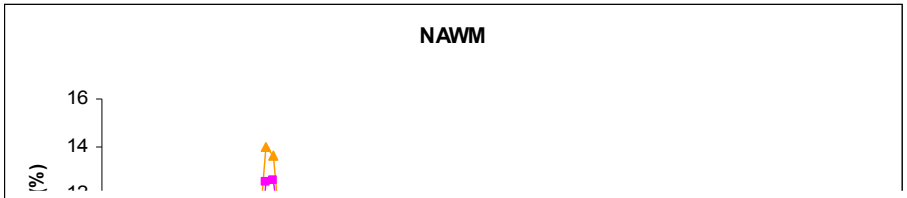
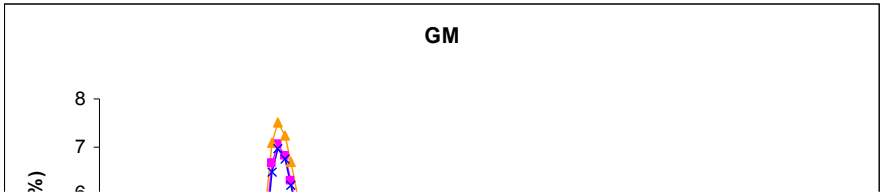
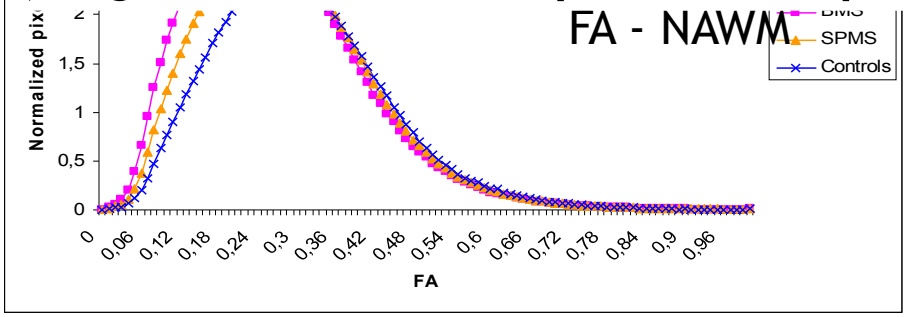




Parametri degli istogrammi di DM e AF tutti alterati rispetto a controlli sani (p: 0.007, 0.002 e <0.001); nessuna differenza tra pazienti e controlli per volume cerebrale normalizzato

Pazienti con SM benigna cognitivamente integri rispetto a pazienti con SM SM: minor carico lesionale T2 (p=0.03), minore atrofia cerebrale (p=0.006) and minore alterazione DM sostanza grigia (p=0.03)

<u>Nessuna differenza significativa tra pazienti con SM benigna cognitivamente compromessi e pazienti con SM SP</u>



SPMS

Controls

Rovaris et al., Neurology 2008

241 soggetti con SM RR (68% in trattamento)

Conversione a SM SP: 42 soggetti
Soggetti trattati con 2 o più farmaci: prognosi peggiore

Volume SG basale predittore di:

conversione a SM SP (-1% GMf = +20% rischio)
progressione EDSS (-1% GMf = +15% rischio)

raggiungimento EDSS 4.0
tempo a EDSS 4.0

Lavorgna et al., MS Journal 2013

13-y outcome	Yes/no	Predictors[a]	OR (95% CI)	p	C-index
EDSS deterioration	48 (14 CIS, 18 RRMS, 16 SPMS)/25 (6 CIS, 16 RRMS, 3 SPMS)	Baseline GMF	0.79 (0.65–0.96)	0.01	0.69
Evolution to benign MS	15 (2 CIS, 12 RRMS)/39 (17 CIS, 22 RRMS)	Baseline disease duration	1.27 (1.03–1.57)	0.02	0.82
		Baseline GMF	1.26 (0.97–1.65)	0.08	
		12-mo percentage change of average lesion MTR	0.90 (0.80–0.99)	0.04	
Evolution to secondary progressive MS	15 (2 CIS, 13 RRMS)/37[b] (16 CIS, 21 RRMS)	Baseline GMF	0.71 (0.51–1.00)	0.04	0.84
		Baseline T2 LV	1.13 (1.04–1.24)	0.005	
Evolution to a more severe stage	33 (15 CIS, 13 RRMS, 5 SPMS)/40 (5 CIS, 21 RRMS, 14 SPMS)	Baseline GMF	0.81 (0.66–1.00)	0.05	0.78
		12-mo percentage change of T2 LV	0.85 (0.74–0.98)	0.02	
Cognitive deterioration	15 (1 CIS, 11 RRMS, 3 SPMS)/25 (12 CIS, 9 RRMS, 4 SPMS)	Baseline disease duration	1.50 (0.94–2.39)	0.08	0.97
		Baseline average GM MTR	0.87 (0.77–0.99)	0.03	

Filippi et al., Neurology 2013

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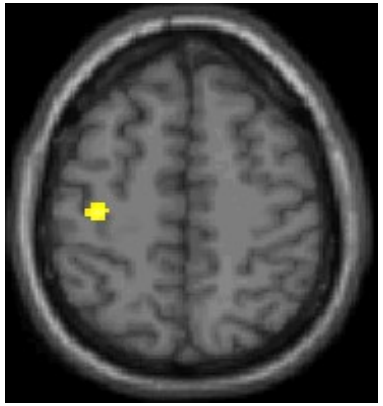
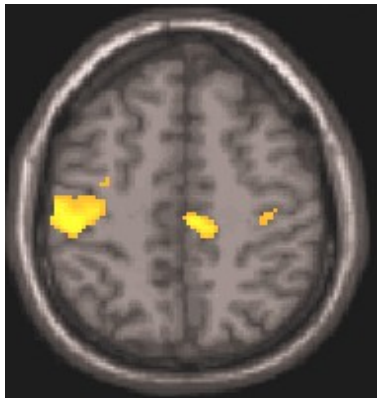
CIS *vs*. SMRR non disabili



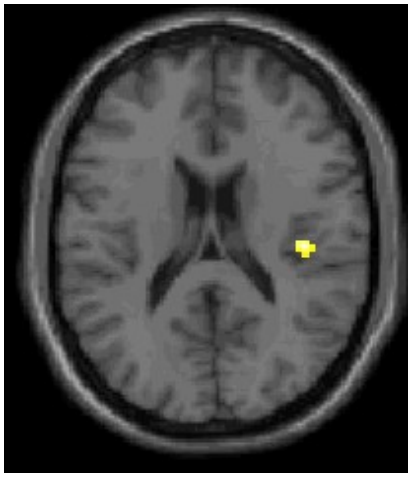
SMC

SMRR non disabili *vs*. SMRR con lieve disabilità

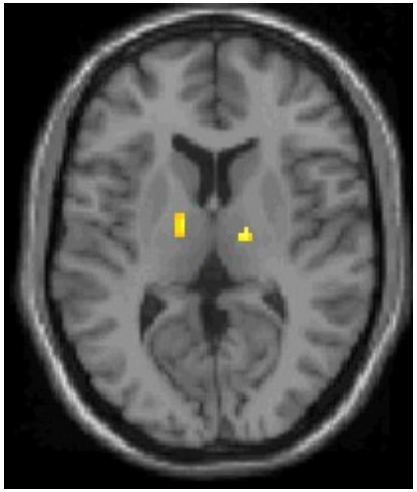


SMC, SMA

SMRR con lieve disabilità *vs*. SMSP

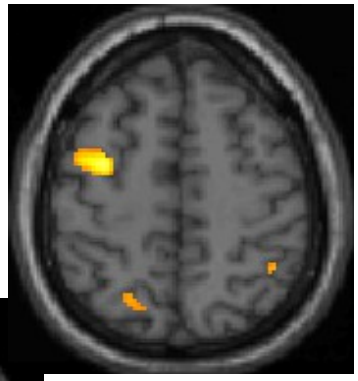


SII

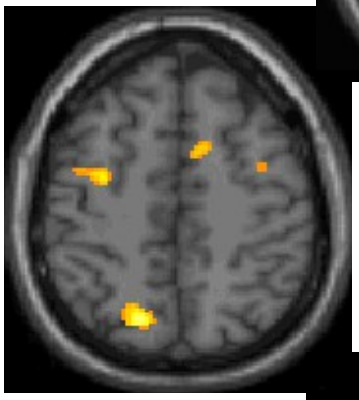


Thalamus

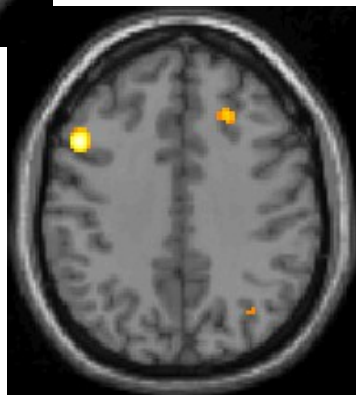
SMSP *vs*. SMRR con lieve disabilità



Precuneus, IPL, MFG



Precuneus, CMA, MFG



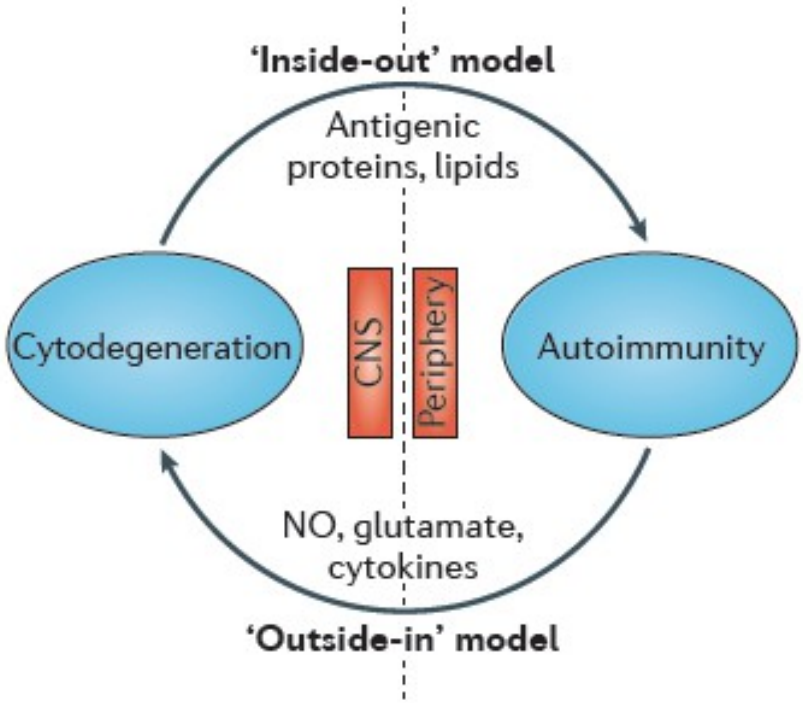
MFG, IPL

Rocca et al., Lancet Neurol 2005

OPINION

Will the real multiple sclerosis please stand up?

Peter K. Stys, Gerald W. Zamponi, Jan van Minnen and Jeroen J. G. Geurts



Nature Reviews - Neuroscience, 2012

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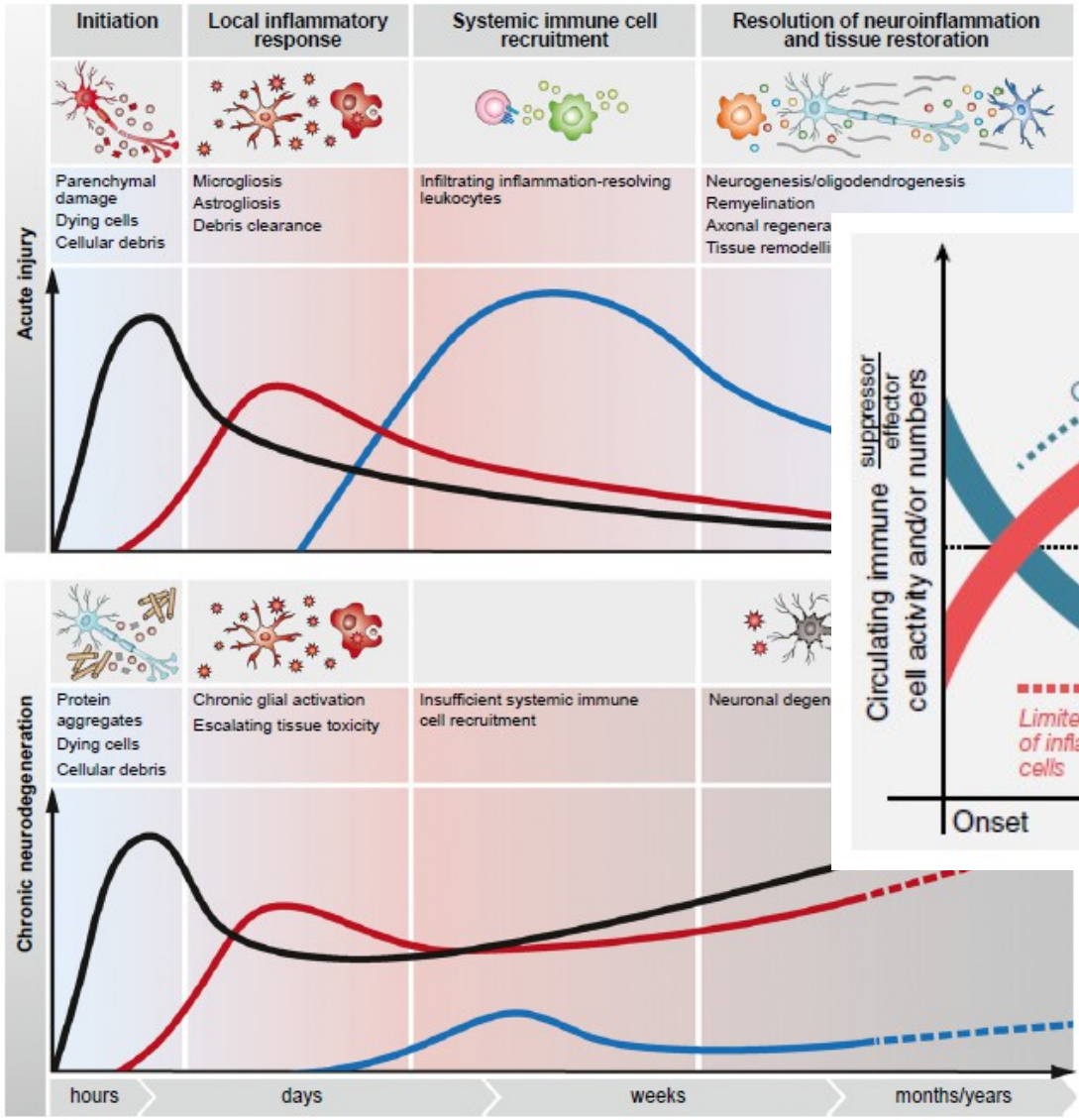
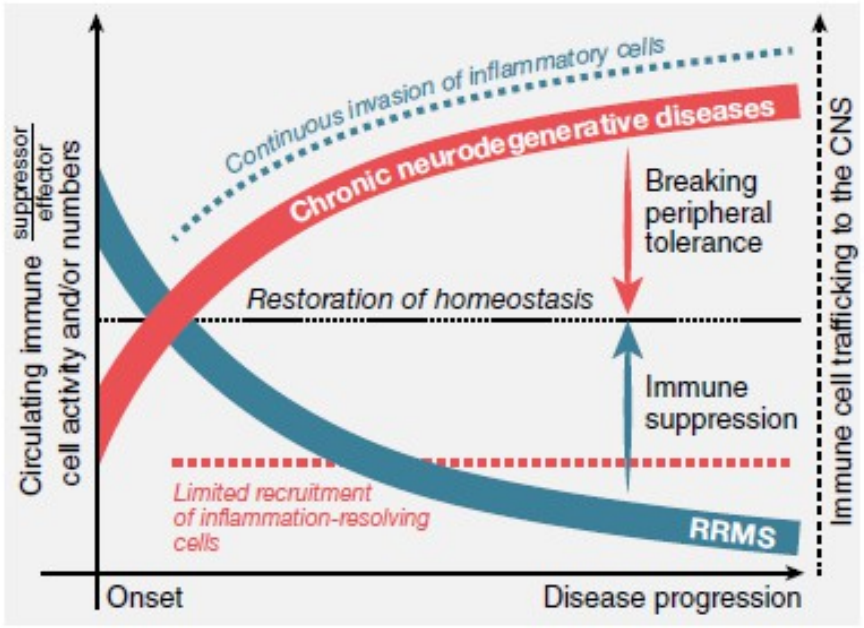


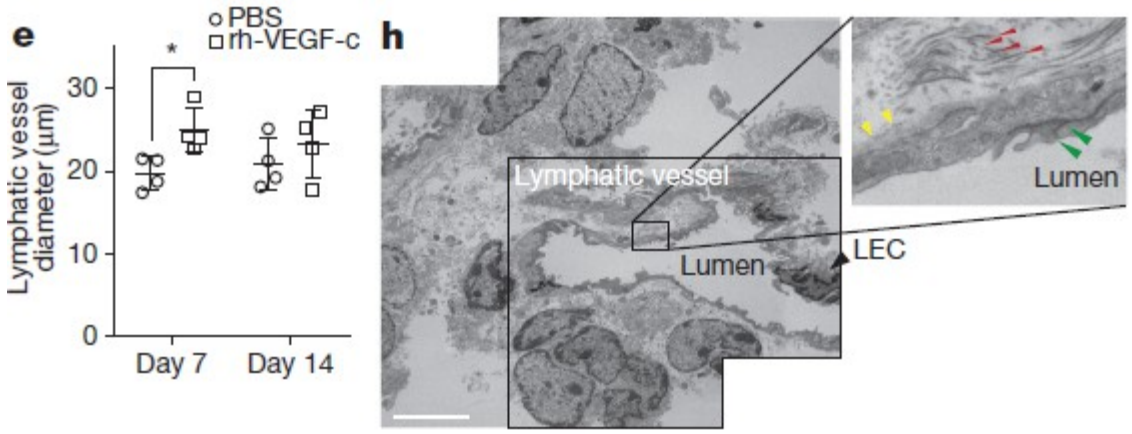


Schwartz and Baruch, EMBO Journal 2014

LETTER

doi:10.1038/nature14432

Structural and functional features of central nervous system lymphatic vessels



Louveau et al., Nature 2015

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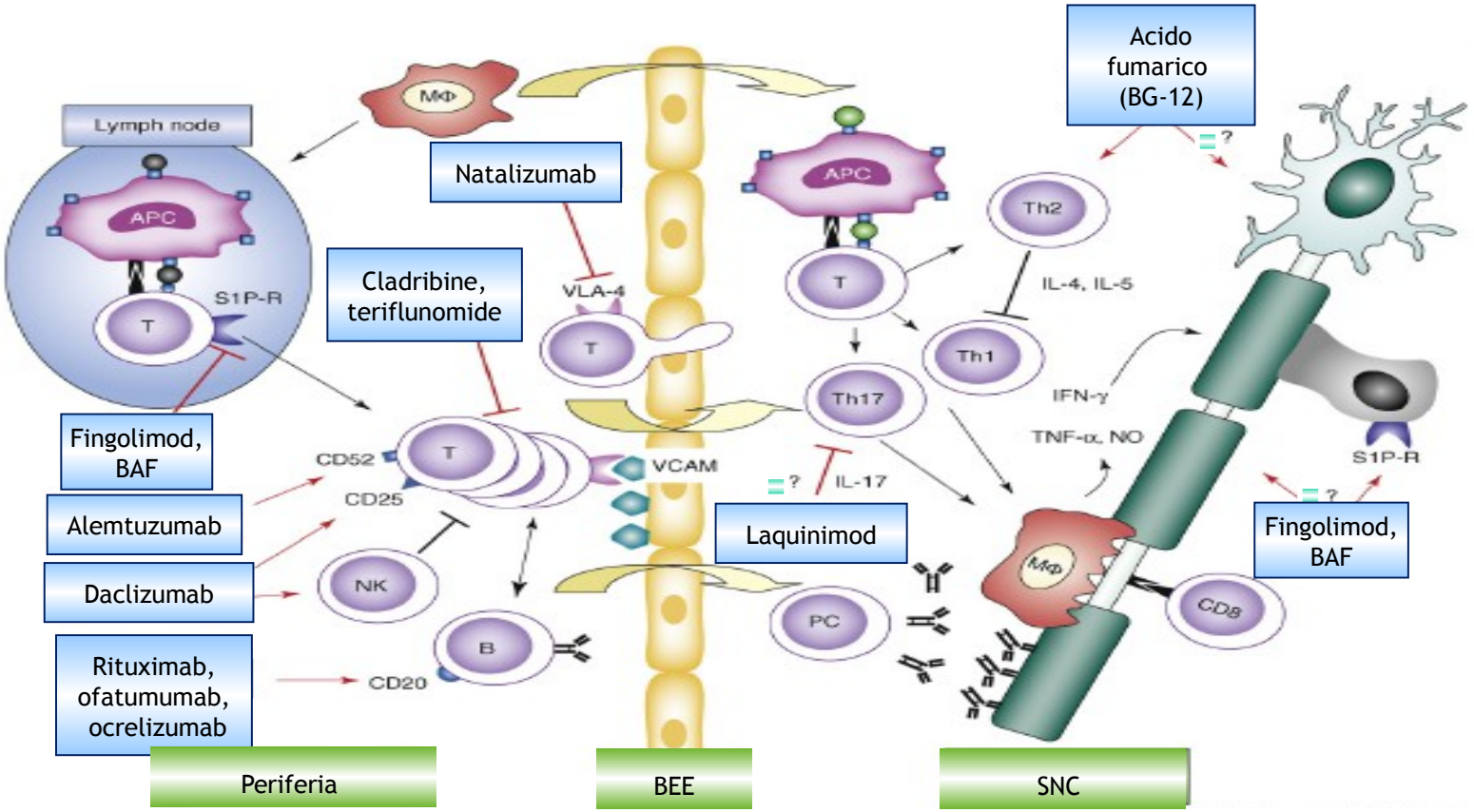

Linker et al. Trends Pharmacol Sci 2008

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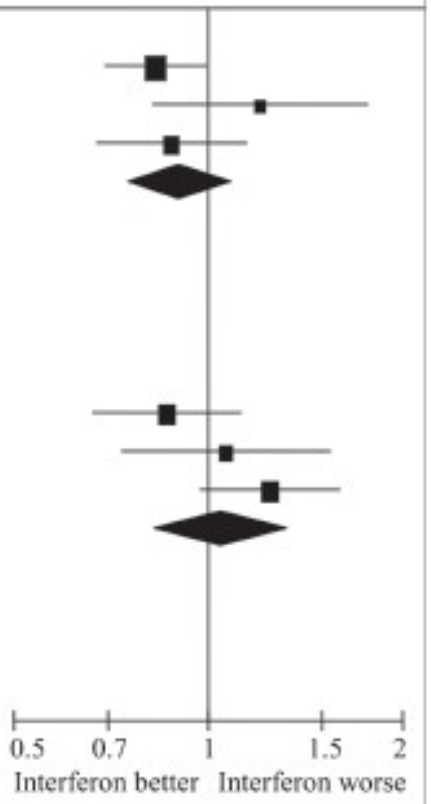
Study	Interferon n	Interferon N	Placebo n	Placebo N	RR (95% CI)
In patients with pre-study relapses					
European SG 1998*	109	245	138	257	0.83 (0.69 to 0.99)
Nordic 2004	47	111	25	71	1.20 (0.82 to 1.76)
North American SG 2004	98	288	52	134	0.88 (0.67 to 1.14)
Total	254	**644**	215	**462**	**0.90 (0.75 to 1.09)**
Heterogeneity: $\tau^2 = 0.01$; $\chi^2 = 2.99$, df = 2 (p=0.22); $I^2 = 33\%$					
Test for overall effect: Z=1.08 (p=0.28)					
In patients without pre-study relapses					
European SG 1998*	54	115	55	101	0.86 (0.66 to 1.12)
Nordic 2004	27	64	42	106	1.06 (0.73 to 1.54)
North American SG 2004	140	343	57	174	1.25 (0.97 to 1.60)
Total	221	**522**	154	**381**	**1.05 (0.83 to 1.33)**
Heterogeneity: $\tau^2 = 0.02$; $\chi^2 = 4.05$, df = 2 (p=0.13); $I^2 = 51\%$					
Test for overall effect: Z=0.38 (p=0.70)					



Lamantia et al., JNNP 2013

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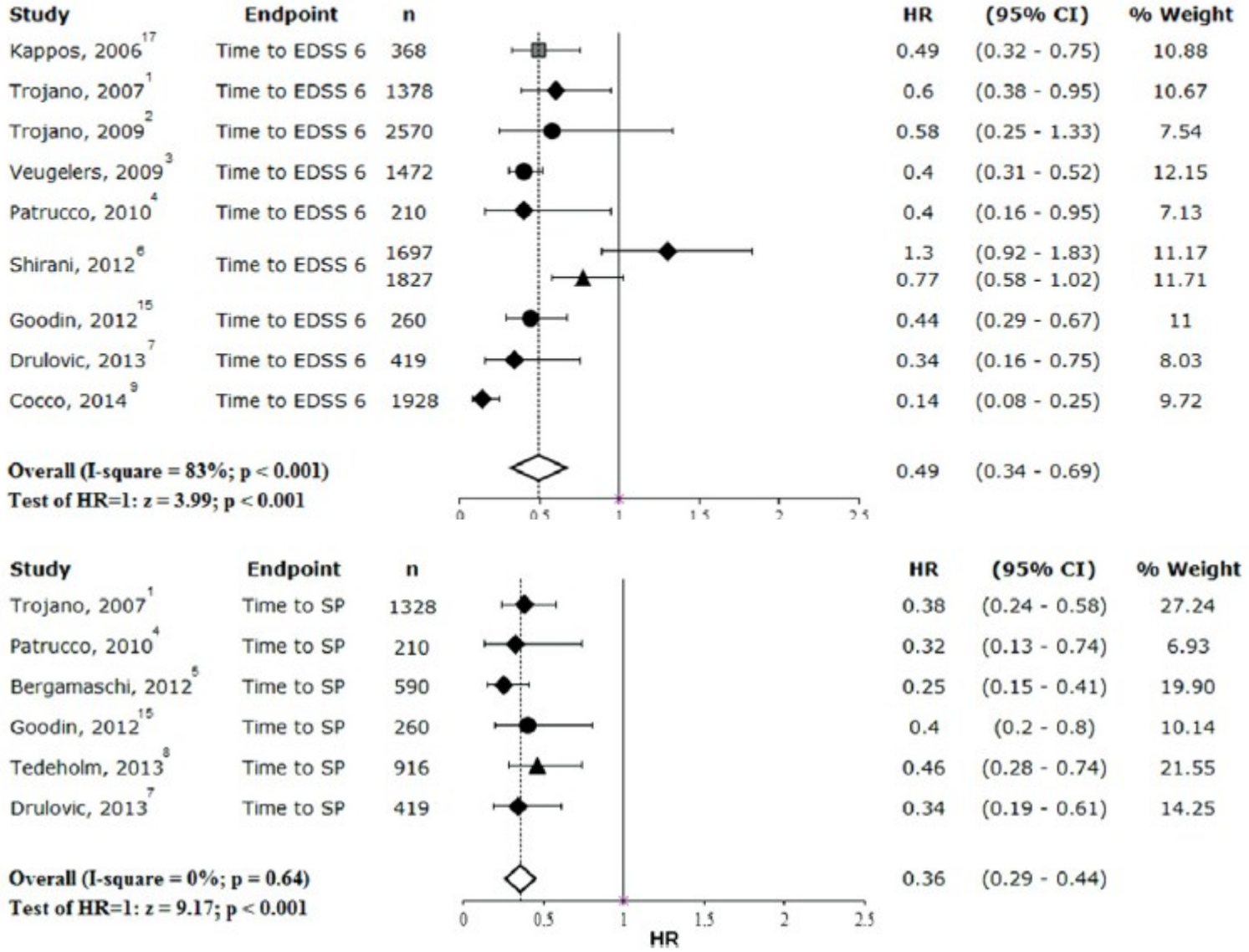

Signori et al., MS Rel Dis 2016

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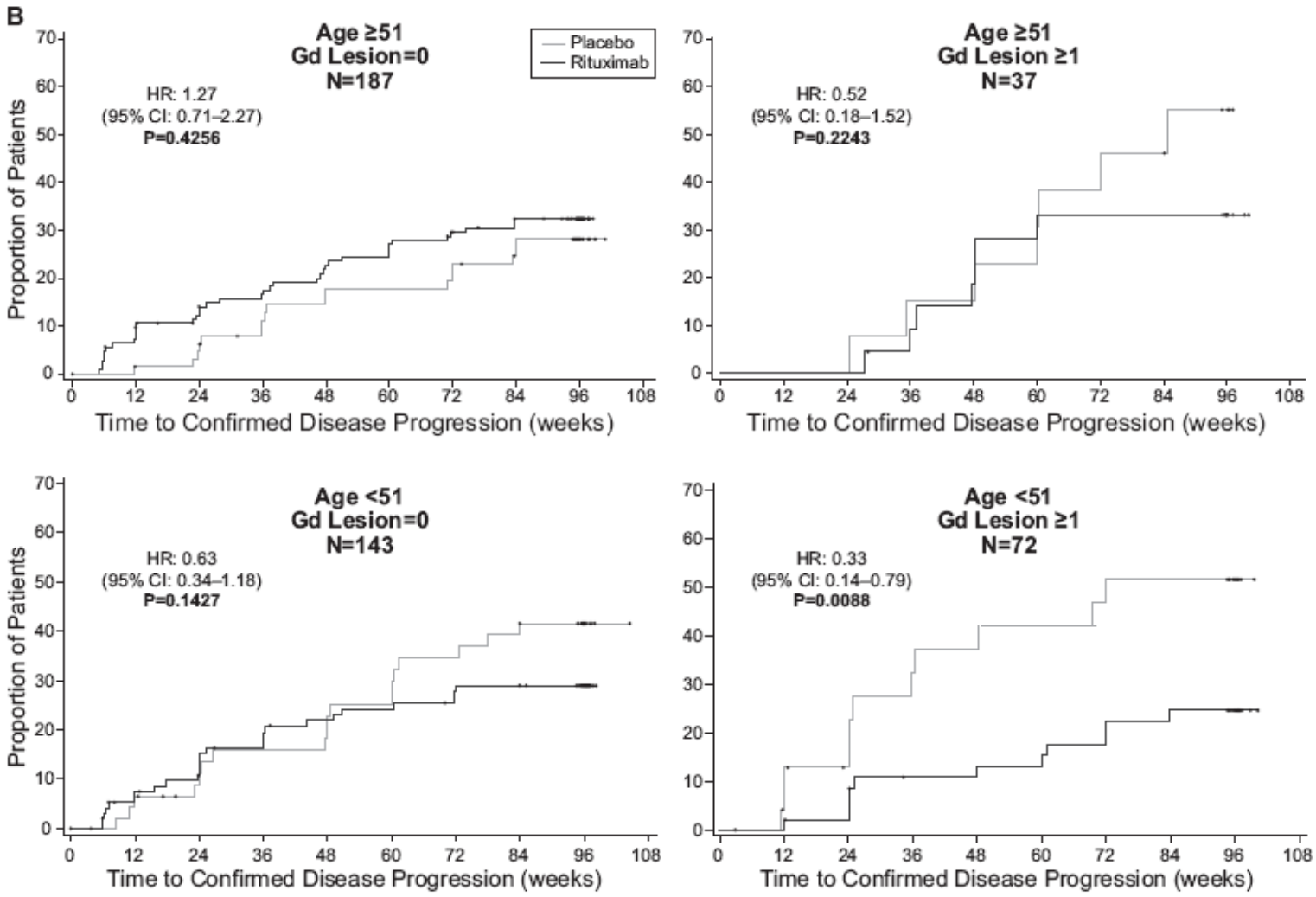

Hawker et al., Ann Neurol 2009

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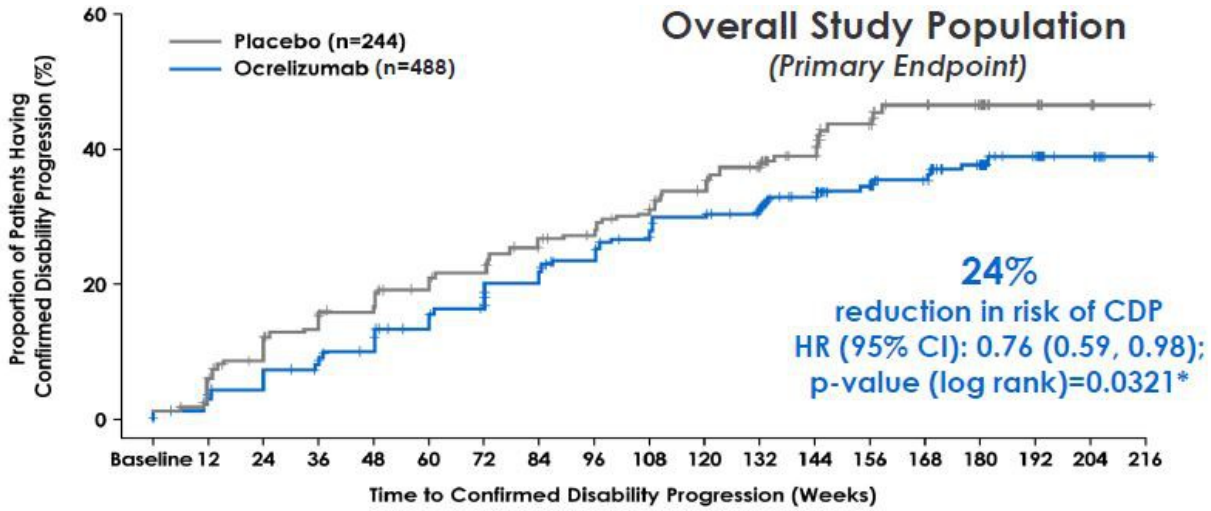


	Total	Placebo (N=244)		Ocrelizumab (N=488)		Hazard Ratio	95% CI
	n	n	Events	n	Events		
Overall population	731	244	96	487	160	0.76	(0.59, 0.98)
T1 Gd+ lesions	193	60	27	133	43	0.65	(0.40, 1.06)
No T1 Gd+ lesions	533	183	68	350	115	0.84	(0.62, 1.13)

*Analysis based on ITT population; p-value based on log-rank test stratified by geographic region and age. Patients with initial disability progression who discontinued treatment early with no confirmatory EDSS assessment were considered as having confirmed disability progression.
CDP, confirmed disability progression; Gd+, gadolinium-enhancing; EDSS, Expanded Disability Status Scale; HR, hazard ratio; ITT, intent to treat.

Wolinsky et al., ACTRIMS 2016

SCLEROSI MULTIPLA PROGRESSIVA

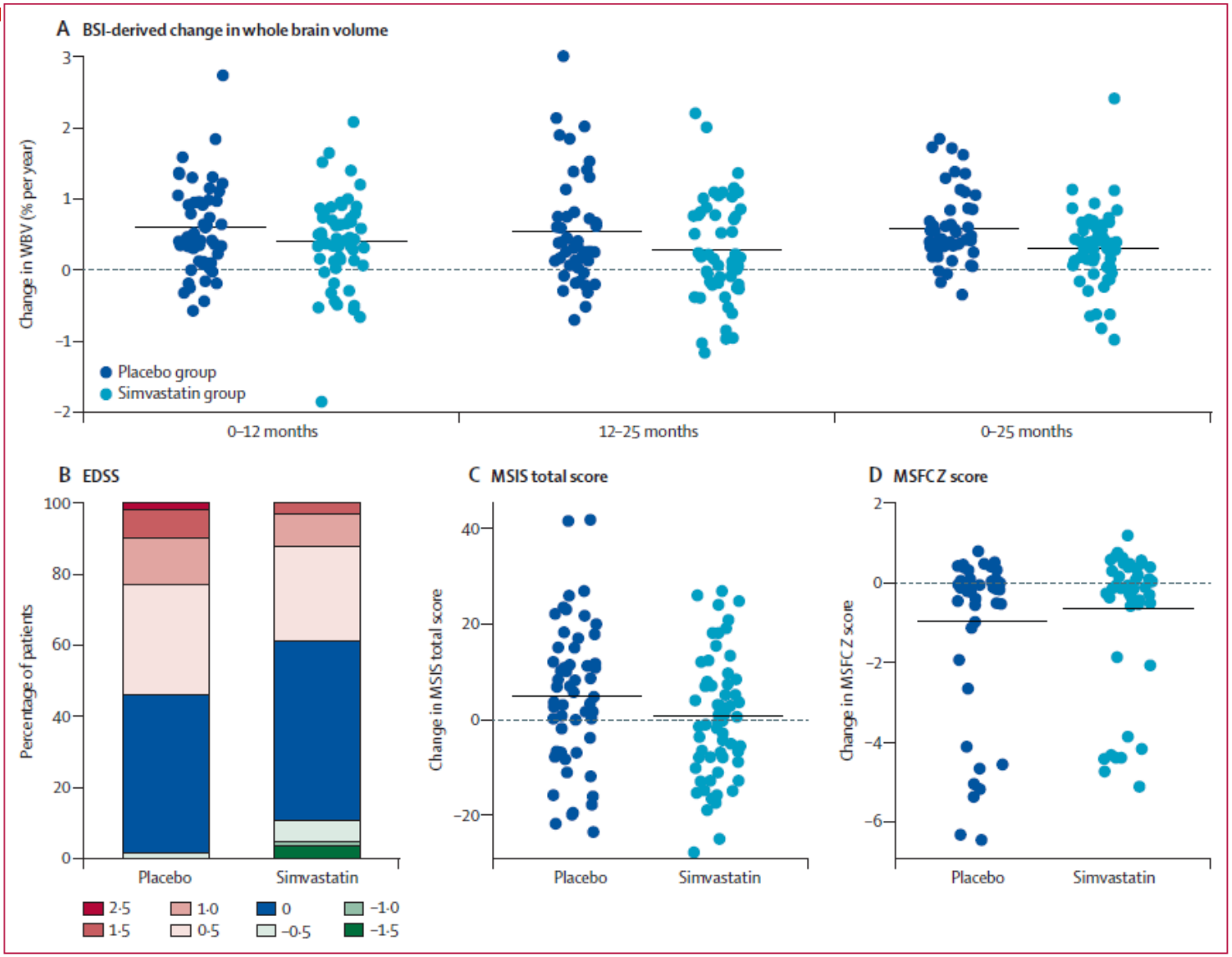
Baseline characteristic	PROMiSe[1] N=943	OLYMPUS[2] N=439	INFORMS[3] N=970	ORATORIO[4] N=732
Age, years, mean (±SD)	50.4±8.3	49.9±8.9	48.5±8.4	44.6±8.0
Male, %	48.8	49.7	51.6	50.7
Time since MS symptom onset, years, mean (±SD)	11.0±7.3	9.1±6.6	5.8±2.4	6.48±3.89
EDSS score, mean (±SD)	4.9±1.2	4.8±1.4	4.67±1.03	4.7±1.2
Patients with T1 Gd+ lesions, %	14.1	24.5	13.4	26.4

Gd+, gadolinium-enhancing; SD; standard deviation.

1. Wolinsky JS, *et al. Ann Neurol* 2007; **2.** Hawker K, *et al. Ann Neurol* 2009;66:460–71;
3. Lublin FD, *et al. Lancet* 2016; in press; 61:14–24; **4.** Montalban X, *et al. ECTRIMS* 2015;Abstract 228.

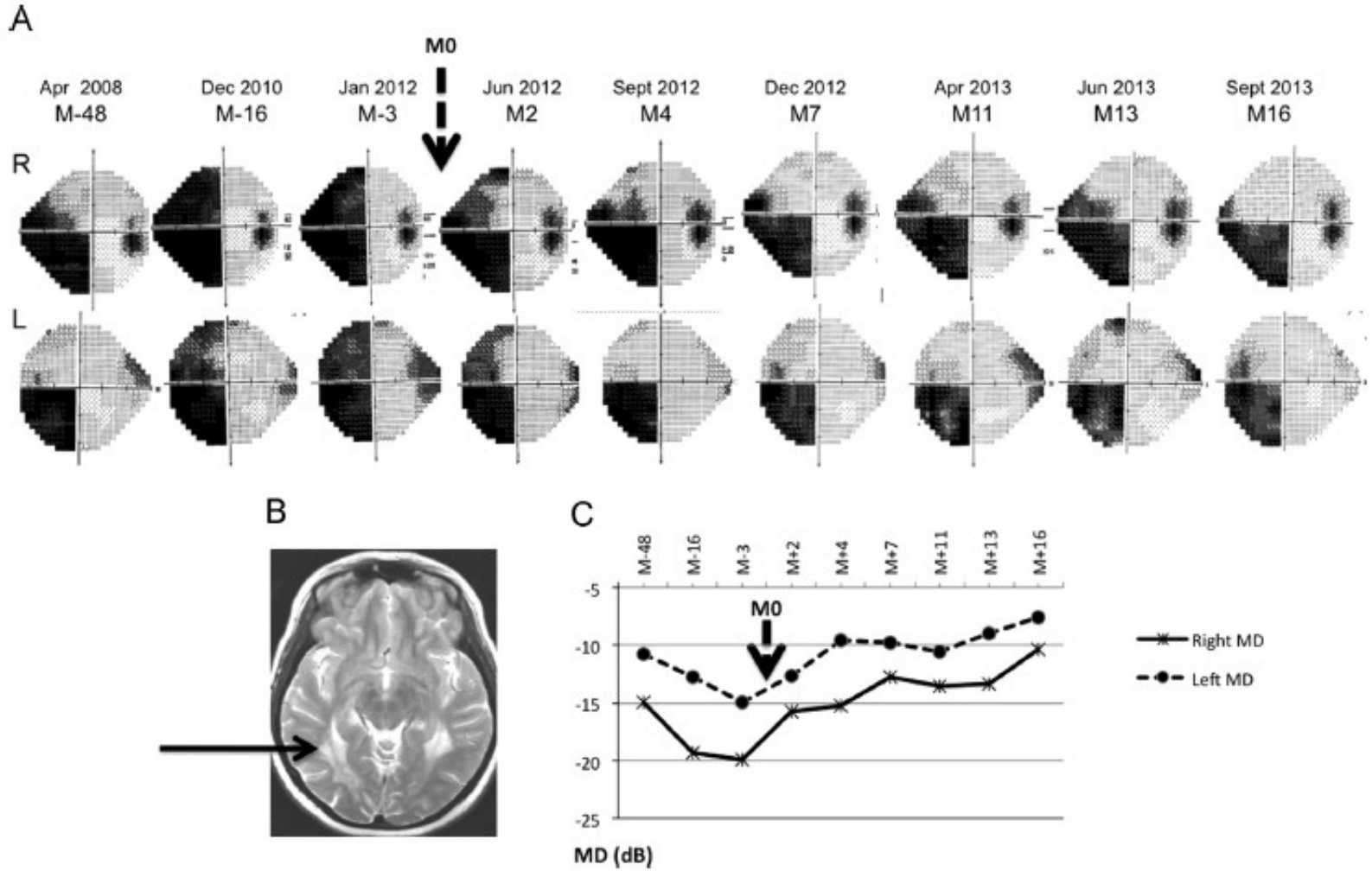
SCLEROSI MULTIPLA PROGRESSIVA

un mondo libero dalla SM



Chataway et al., Lancet 2014

SCLEROSI MULTIPLA PROGRESSIVA



Sedel et al., MS Rel Dis 2015

SPECIAL ARTICLE

AMERICAN ACADEMY OF NEUROLOGY.

Summary of comprehensive systematic review: Rehabilitation in multiple sclerosis

Results: This systematic review highlights the paucity of well-designed studies, which are needed to evaluate the available MS rehabilitative therapies.

REVIEW ARTICLE

Physiotherapy Rehabilitation for People With Progressive Multiple Sclerosis: A Systematic Review

Evan Campbell, MRes,[a] Elaine H. Coulter, PhD,[a] Paul G. Mattison, MD,[b] Linda Miller, MPhil,[b,c] Angus McFadyen, PhD,[d] Lorna Paul, PhD[a]

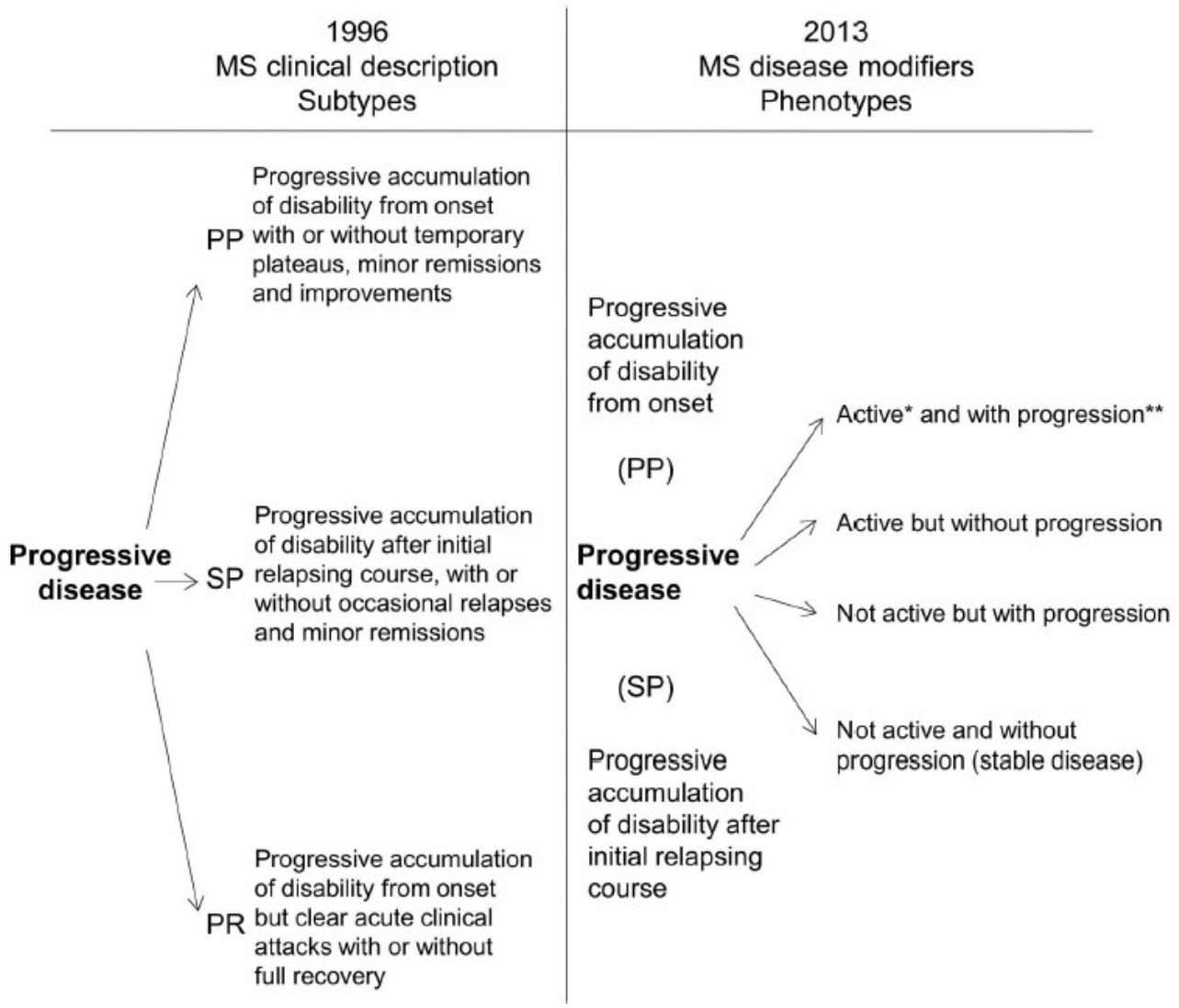
Conclusions: This review suggests that physiotherapy may be effective for the rehabilitation of people with progressive multiple sclerosis. However, further appropriately powered studies are required.

SCLEROSI MULTIPLA PROGRESSIVA

un mondo libero dalla SM

VIEWS & REV

Fred D. Lublin



Lublin et al., Neurology 2014

SCLEROSI MULTIPLA PROGRESSIVA

Singola malattia con diverse declinazioni

Multifattorialità

Complessità e non eterogeneità

Terapie combinate e complementari

INTERNATIONAL
PROGRESSIVE MS ALLIANCE

CONNECT TO END PROGRESSIVE MS