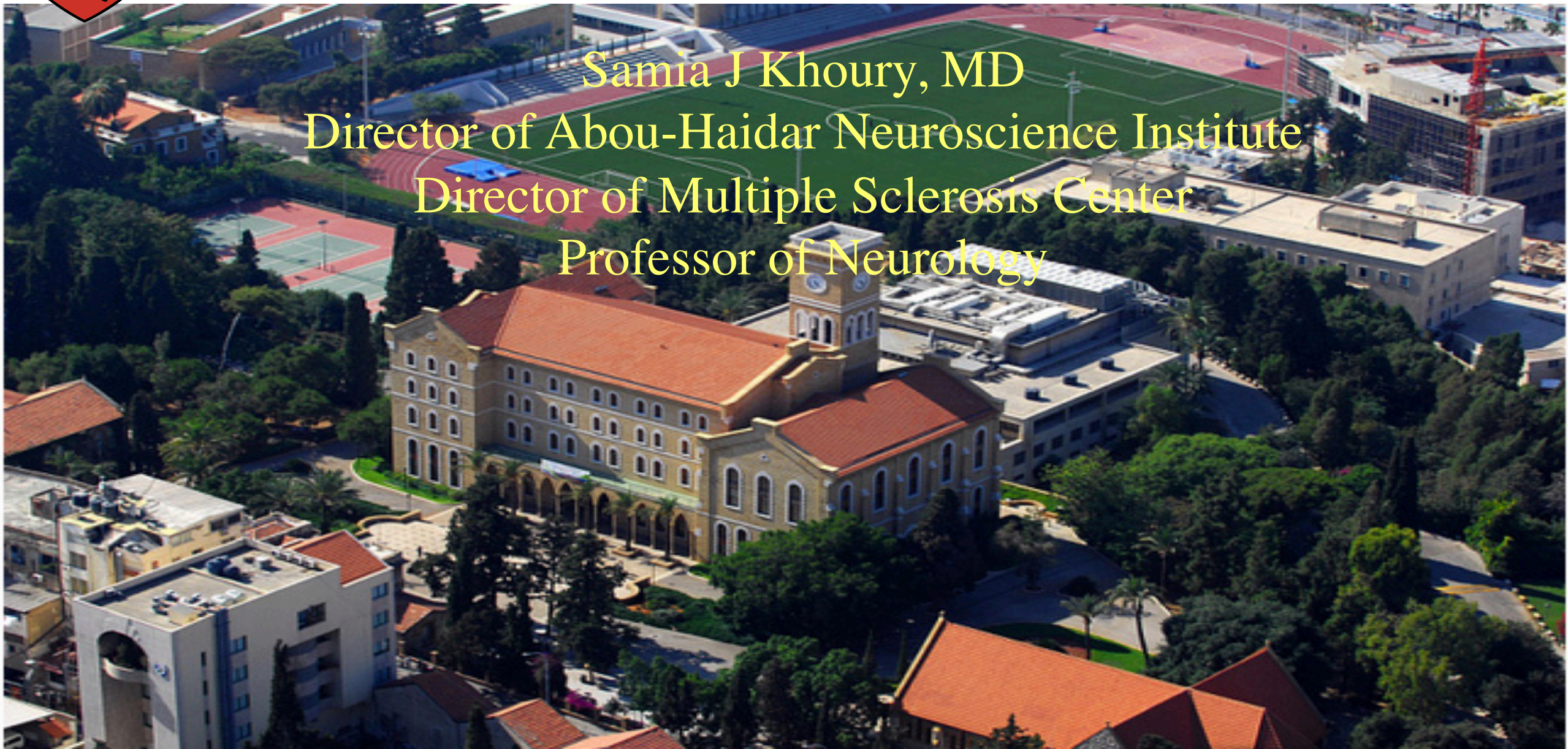
Progressive MS



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Disclosures

None

Learning Objectives

Phenotypic studies on progression

Pathology and mechanisms

Imaging correlates

Treatments

Key Messages

There is a ‘window of opportunity’ for anti-inflammatory/anti-immune therapies for MS to affect progression

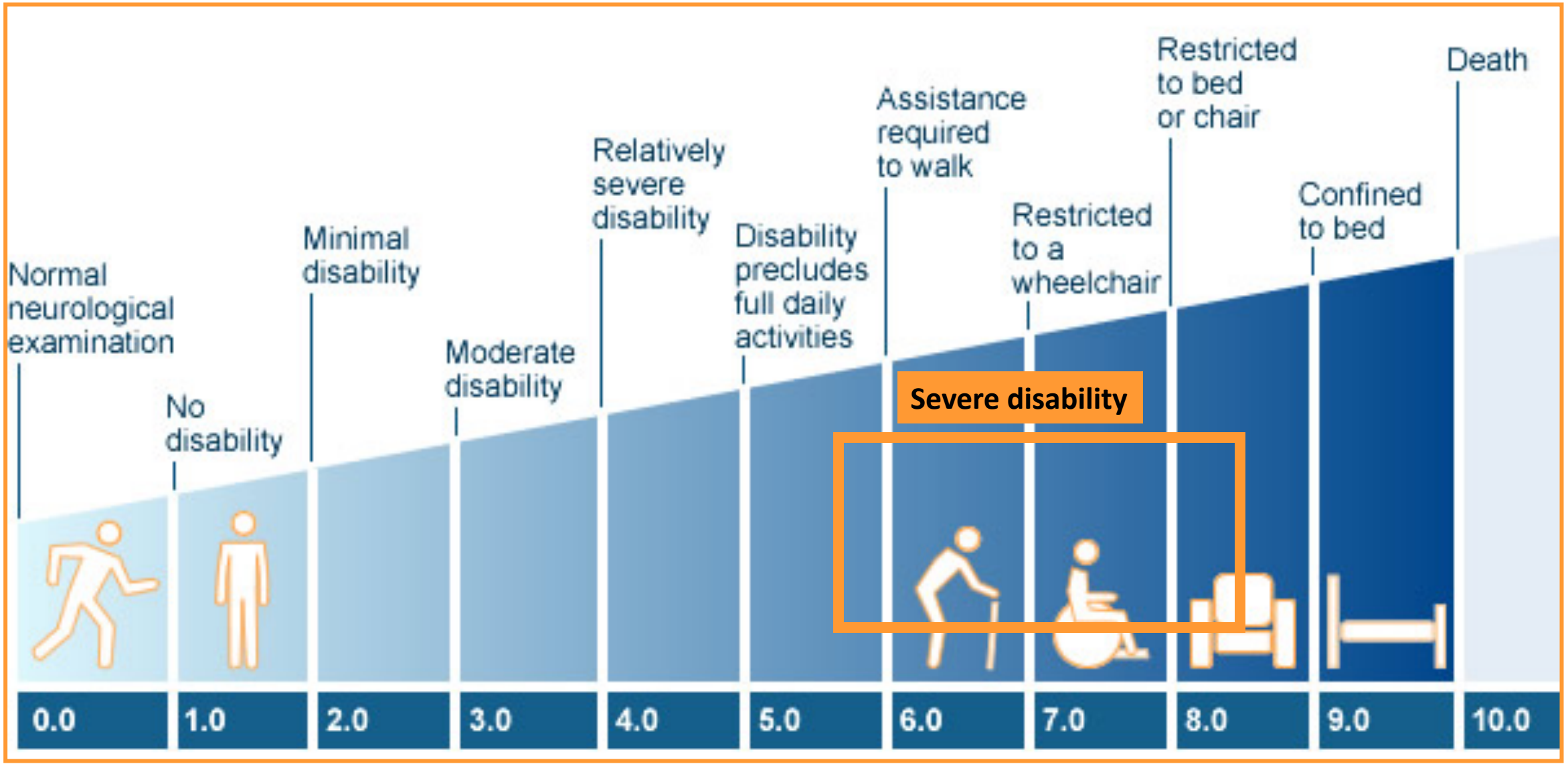
In early disease peripheral adaptive immune system activation predominates, while in late disease innate immune system activation within the CNS predominates

Number of cortical lesions and deep gray matter volume on brain MRI as well as spinal cord volume correlate with disability progression

Treatment with DMTs delays progression

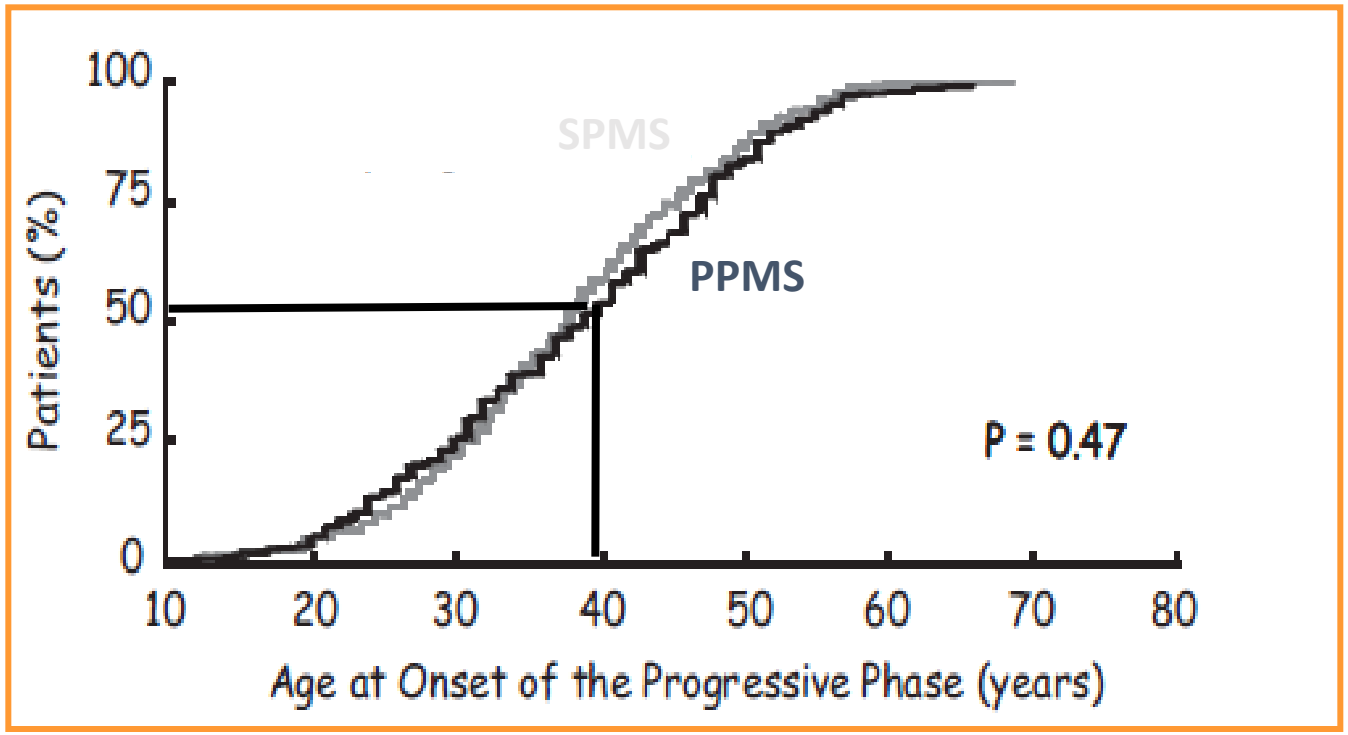
There are new treatments available that affect disability progression

EDSS



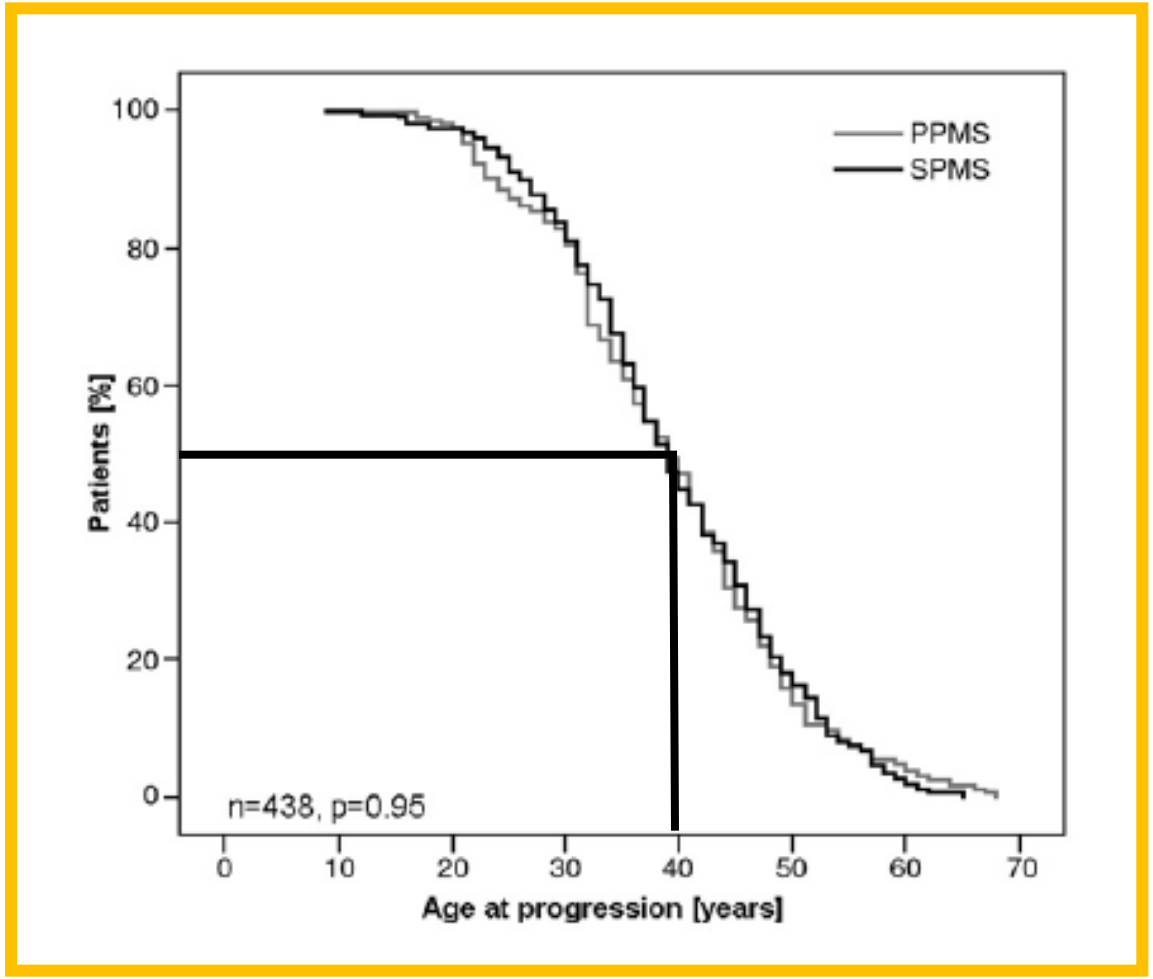
 Adapted from Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology. 1983; 33: 1444-52.

Onset of progressive MS is age-sensitive & independent of pre-progression disease course



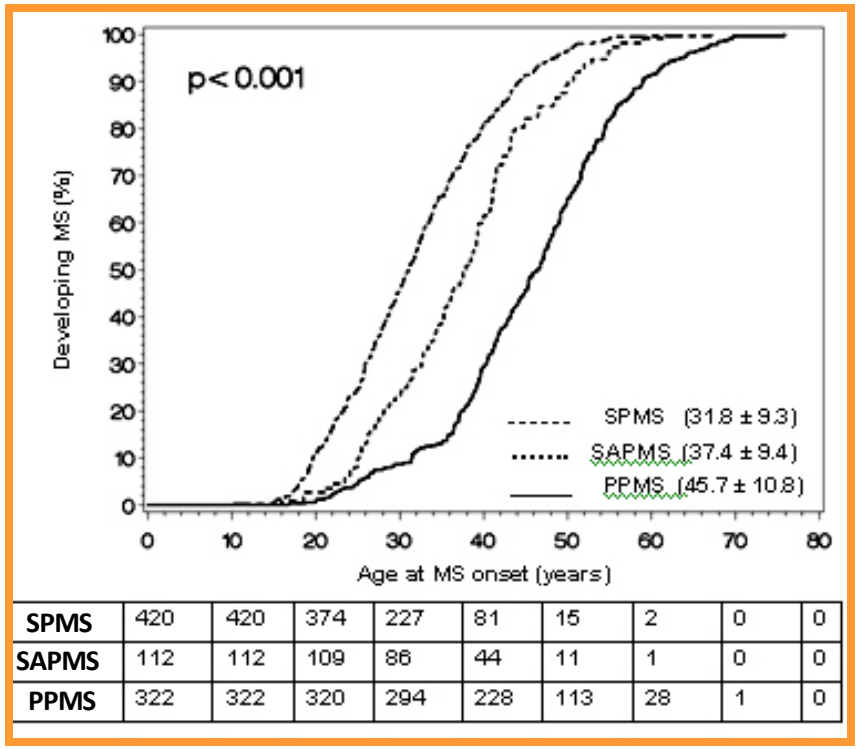
Confavreux & Vukusic. Brain 2006.

Onset of progressive MS is age-sensitive & independent of pre-progression disease course

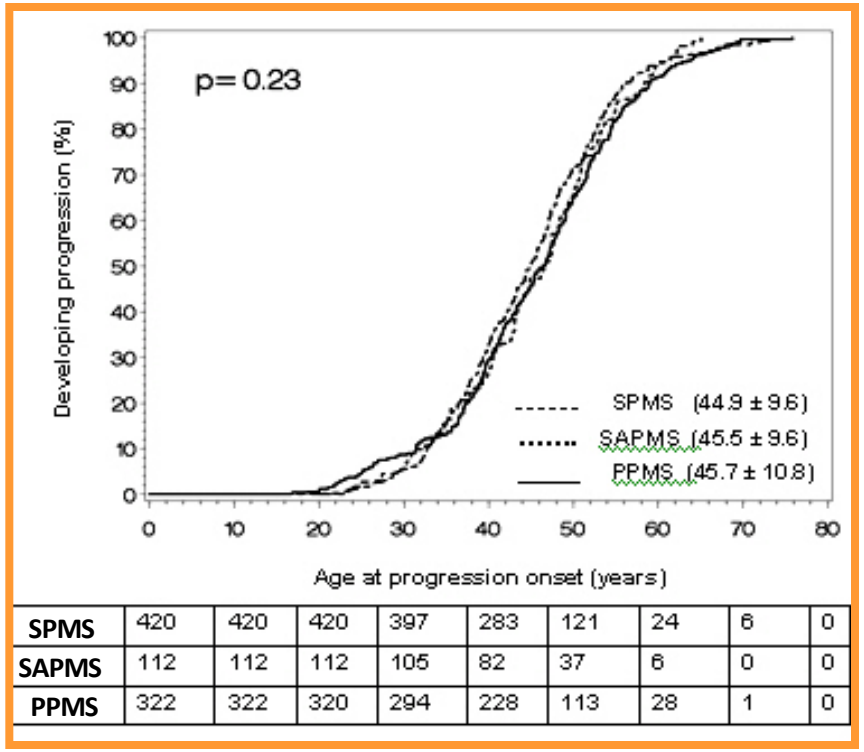


Koch et al. J Neurol Sci. 2007

Onset of progressive MS is age-sensitive & independent of pre-progression disease course



SPMS	420	420	374	227	81	15	2	0	0
SAPMS	112	112	109	86	44	11	1	0	0
PPMS	322	322	320	294	228	113	28	1	0



SPMS	420	420	420	397	283	121	24	6	0
SAPMS	112	112	112	105	82	37	6	0	0
PPMS	322	322	320	294	228	113	28	1	0

- SPMS (420); SAPMS (112); PPMS (322)
- Mean age at progressive MS onset: 45 ± 10 yrs
- 99% of conversion to progressive MS < 75 yrs age

Tutuncu et al, MSJ 2013.

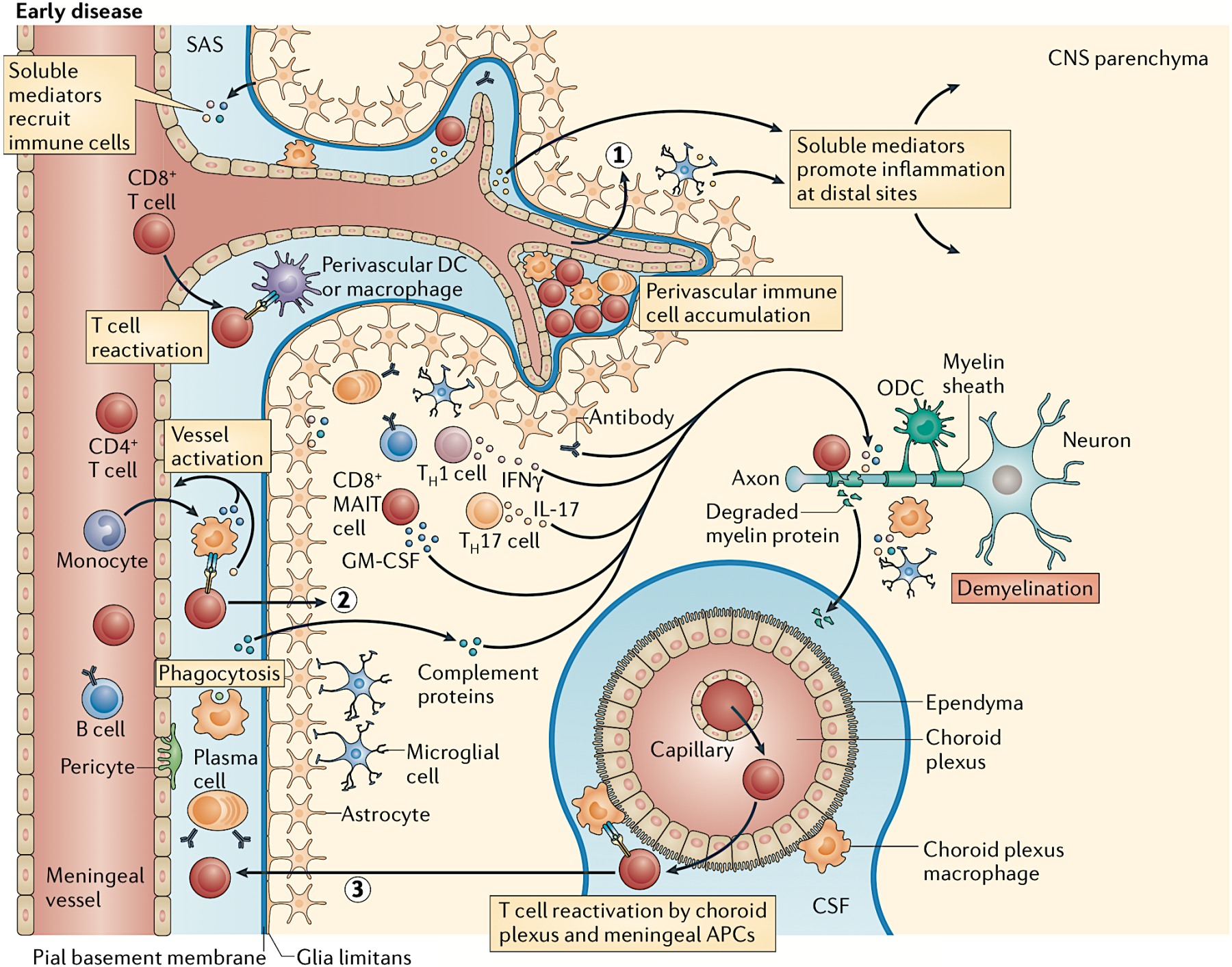
What does this tell us

- Once a certain threshold of disability has been reached disease progression is uninfluenced by relapses, either those that have occurred previously or those which have occurred subsequently
- Almost complete suppression of relapses with Alemtuzumab in patients that have already entered the progressive phase of MS had little effect on subsequent disease progression
- Use of Alemtuzumab at earlier disease stages (before onset of progressive disease) has demonstrated that the drug may have effects on preventing or delaying onset of disease progression
- These observations suggest a ‘window of opportunity’ for anti-inflammatory/anti-immune therapies for MS and that once a clinical level of disability has been reached these therapies become less effective.

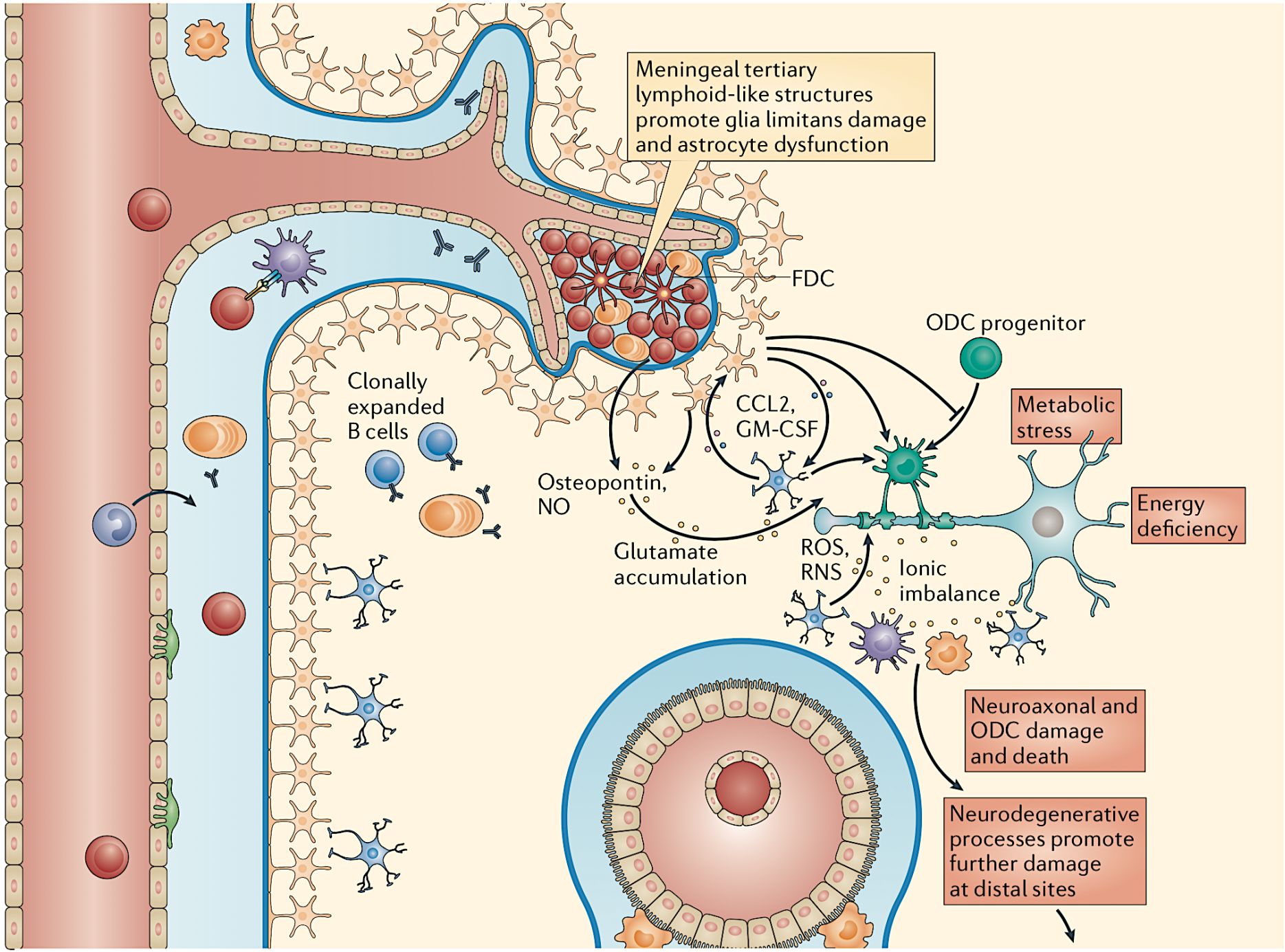
Can we change the natural history of progressive MS ?

- No drug has been proven to prevent progressive MS
  - Sustained moderate to severe disability is due to progressive phase of MS
- Absolute life time risk of SPMS starts dropping after age 45 in a patient that still continues to have RRMS
  - 7% > age 60
- Prevention of relapses can prevent additional disability
  - Most patients stop having relapses after age 59
  - 14% of SPMS patients have ongoing relapses

Absolute risk of SPMS in RRMS			
50% chance of progression at age 45 (odds of no progression = 1.0)	Age (yrs)		
	> 45	> 50	> 60
Chance of SPMS	35%	20%	7%
odds of no progression	2.9	5.1	15.1
	Duration from MS onset (yrs)		
	> 15	>25	>35
Chance of no progression	60%	40%	20%
odds of SPMS	1.6	2.6	4.7

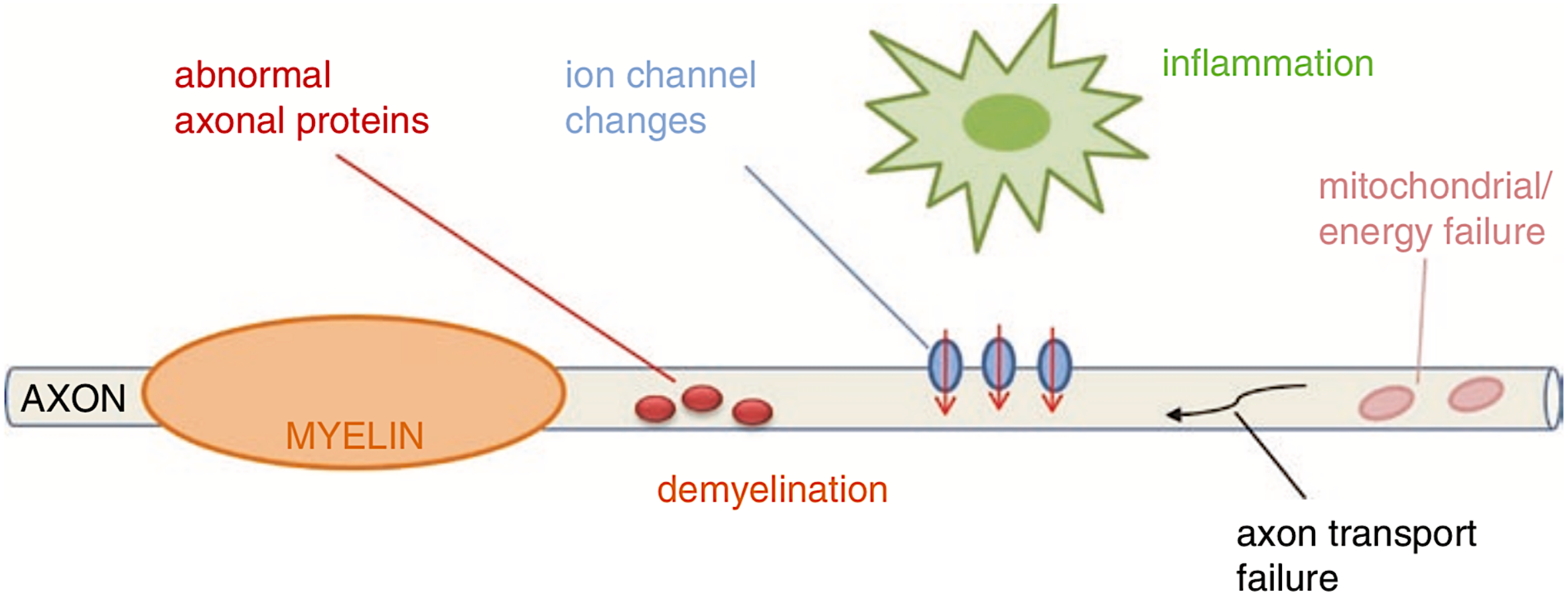

Early disease
SAS
CNS parenchyma
Soluble mediators recruit immune cells
CD8+ T cell
Perivascular DC or macrophage
T cell reactivation
Perivascular immune cell accumulation
Soluble mediators promote inflammation at distal sites
1
CD4+ T cell
Vessel activation
Antibody
Myelin sheath
ODC
Neuron
Axon
Degraded myelin protein
Demyelination
CD8+ MAIT cell
TH1 cell
IFNγ
IL-17
TH17 cell
GM-CSF
Monocyte
2
Phagocytosis
Complement proteins
B cell
Pericyte
Plasma cell
Microglial cell
Astrocyte
Ependyma
Choroid plexus
Capillary
Choroid plexus macrophage
Meningeal vessel
3
T cell reactivation by choroid plexus and meningeal APCs
CSF
Pial basement membrane
Glia limitans

Late disease



- Rate of disease progression appears to correlate with the severity of cortical inflammation
- Cortical lesions have reduced levels of inflammatory cellular infiltrate and pure intracortical lesions typically have low levels of inflammation
- In both SPMS and PPMS there appears to be a correlation between the degree of subpial demyelination and leptomeningeal inflammation, suggesting a potent driver for the process
- However, the association between meningeal inflammation and cortical demyelination remains unclear
- How do cortical lesions induce neuronal cell body injury?

Potential Mechanisms Of Axonal Injury



Non-disease-related Factors For Remyelination Failure

The efficiency of remyelination is affected by the non disease related factors age, sex and genetic background

The efficiency of remyelination decreases with age this is compounded by an age associated increase in the vulnerability of demyelinated axons to atrophy

The age associated effects on remyelination are due to a decrease in the efficiency of both OPC recruitment and OPC differentiation

The impairment of OPC differentiation with age mirrors the failure of oligodendrocyte lineage differentiation that is associated with many chronically demyelinated MS plaques

The decline in remyelination efficiency occurs more rapidly in males than in females

There is a critical age associated change in the epigenetic regulation of OPC differentiation during remyelination

Disease-specific Factors For Remyelination Failure

MS lesions fail to remyelinate not because of a shortage of available precursor cells but rather because of a failure of OPC recruitment, involving proliferation, migration and repopulation of areas of demyelination

Why?

1- OPCs are direct targets of the disease process in the lesion
2- OPC recruitment into areas of demyelination may fail owing to disturbances in the local expression of the OPC migration guidance cues semaphorin 3a and 3F
3- failure of differentiation and maturation. Several studies have shown that OPC availability is not a limiting factor for remyelination in MS lesions

- chronically demyelinated lesions contain factors that inhibit precursor differentiation
- the absence of positive factors

Differentiation block of oligodendroglial progenitors is a major determinant of remyelination failure in chronic multiple sclerosis lesions

Imaging corelates of progression

Cortical Lesions In MS

Cortical lesions were detected by MRI in the majority (64%) of patients with relapsing remitting (RRMS) and secondary progressive (70%) MS (SPMS), as well as in more than one-third (36.8%) of patients with clinically isolated syndromes (CIS) suggestive of MS

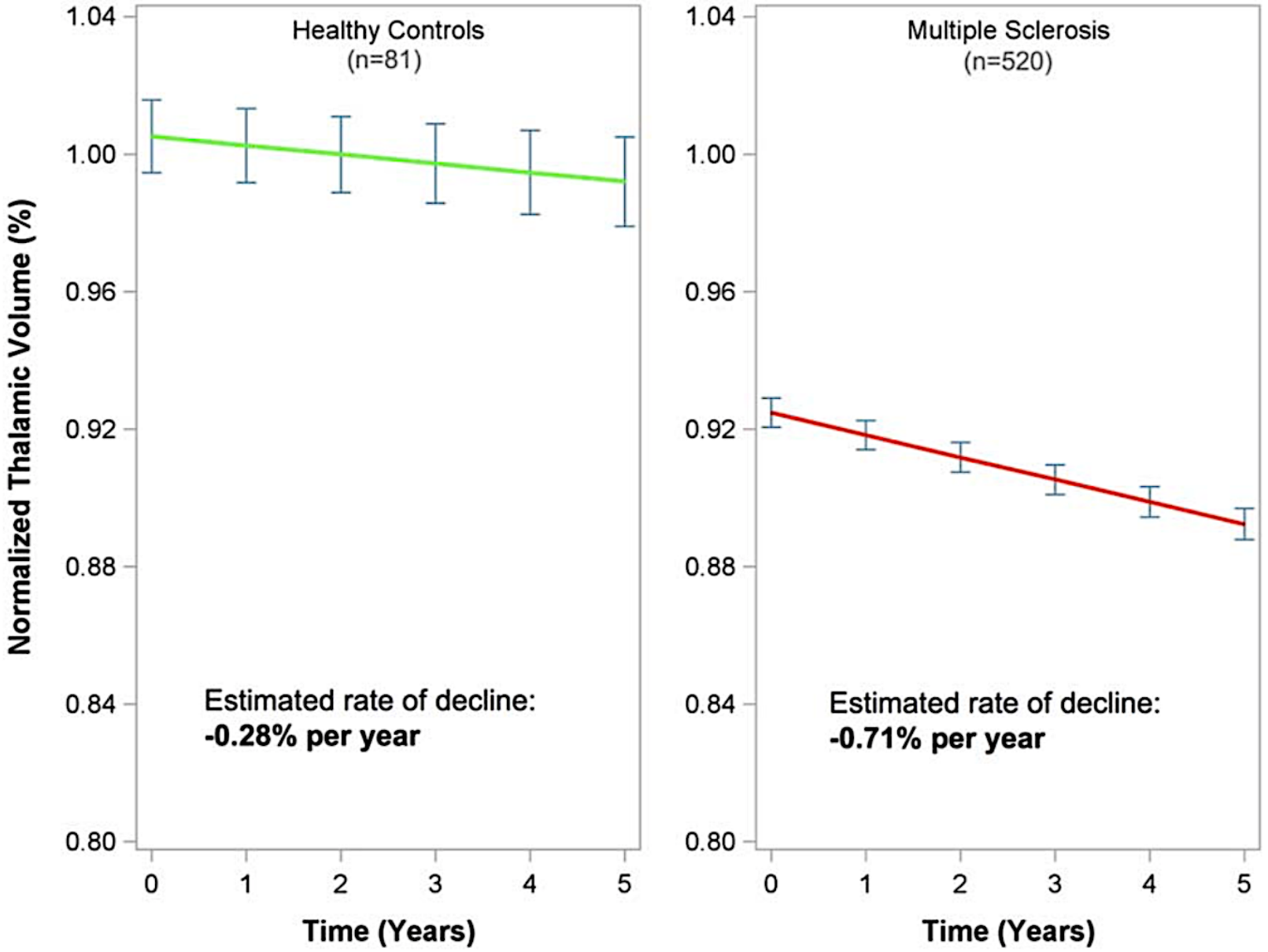
A recent study based on 5-year longitudinal observations of more than 300 MS patients with different clinical phenotypes showed that patients with a high cortical lesion load at baseline had the worst clinical evolution and the fastest progression of cortical atrophy after 5 years.

Cortical lesion volume was an independent predictor of disability progression

Interestingly, RRMS and SPMS patients were found to accumulate new cortical lesions at a similar rate

Patients suffering from RRMS with cognitive deficits had more cortical lesions and atrophy than cognitively normal MS patients.

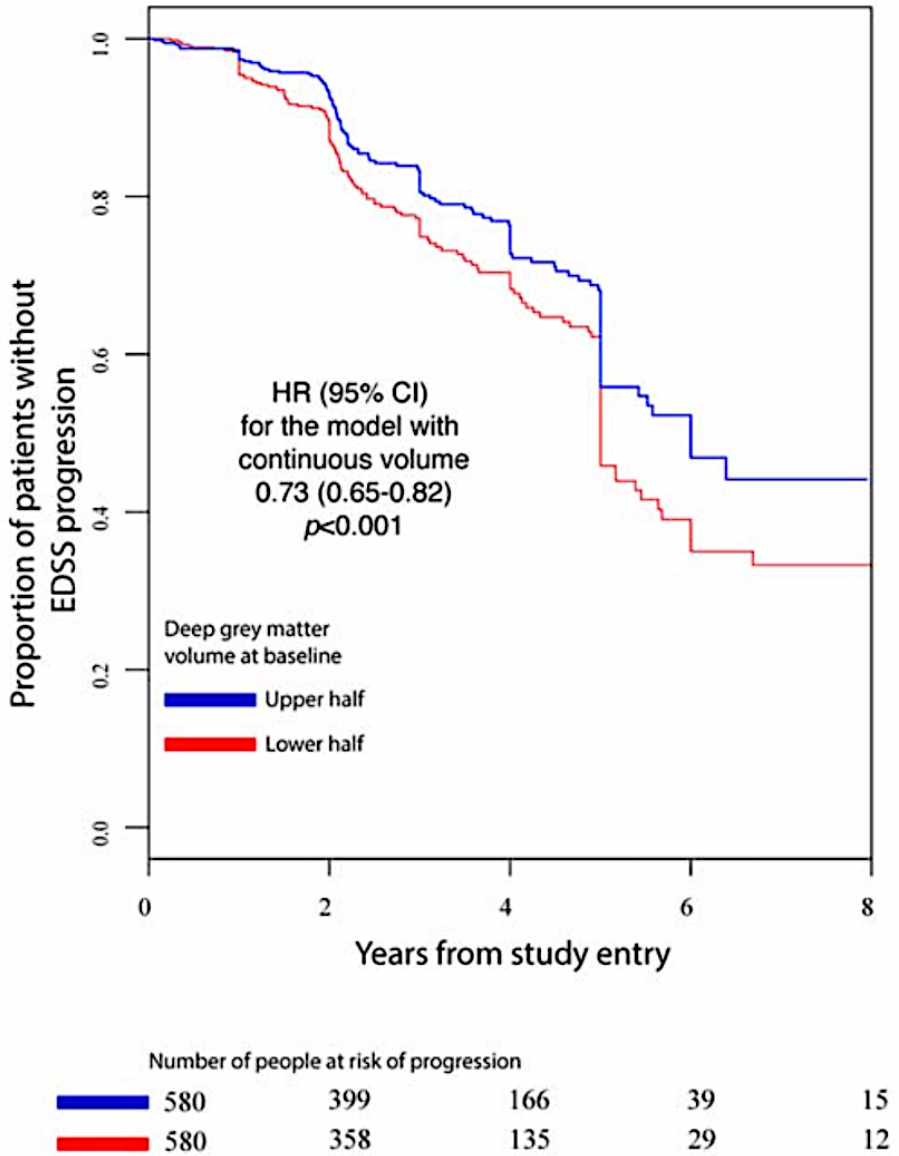
Normalized Thalamic Volume Decline

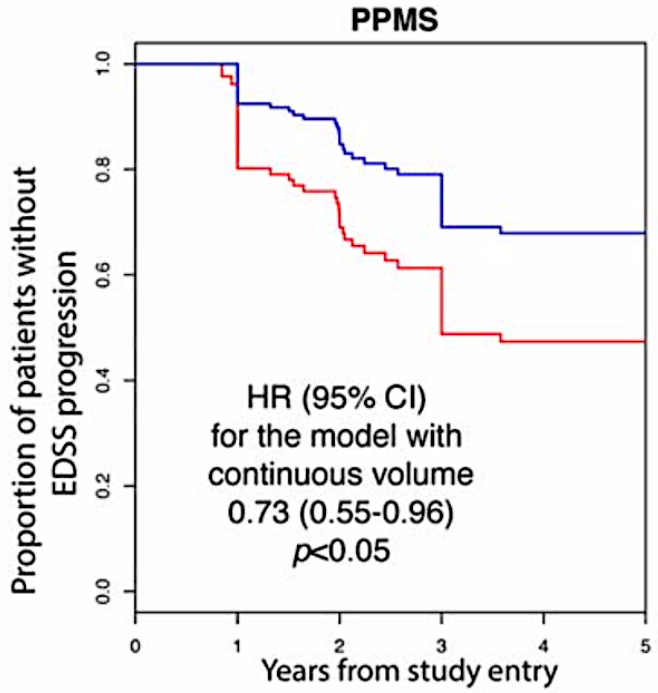


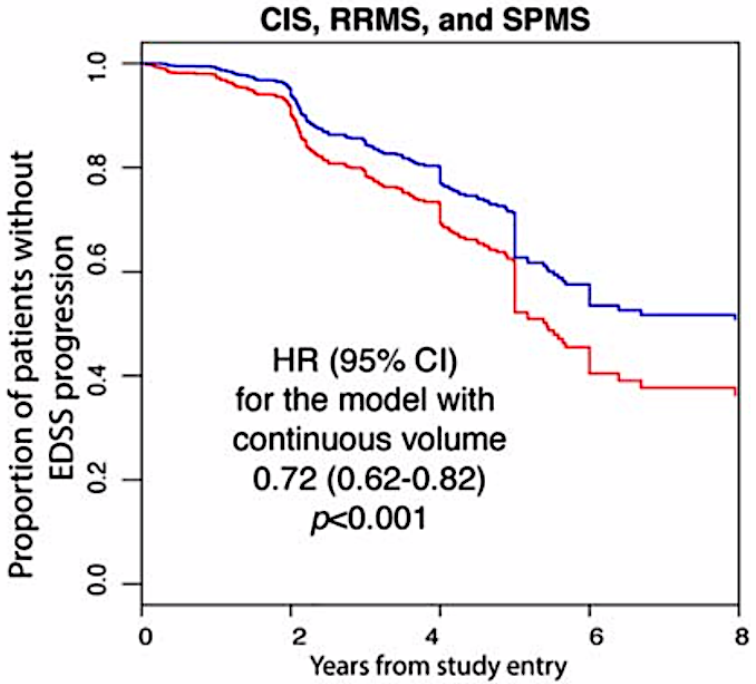
ANN NEUROL 2018;83:223–234

DGM volume predicts future progression of EDSS

(A) ***Baseline*** DGM volume, but not baseline lobar cortical grey matter or whol brain volumes, can predict ***future*** EDSS progression.
Predictive value of DGM volume is indepenedent of clinical phenotypes.







ANN NEUROL 2018;83:210–222

Conclusions

Baseline thalamic volume had the highest predictive value of EDSS progression

No significant differences in rates of loss in patients who were receiving disease-modifying drugs and those who were not

The pathological events that underpin DGM atrophy are not known, but this is generally interpreted as the result of neurodegeneration

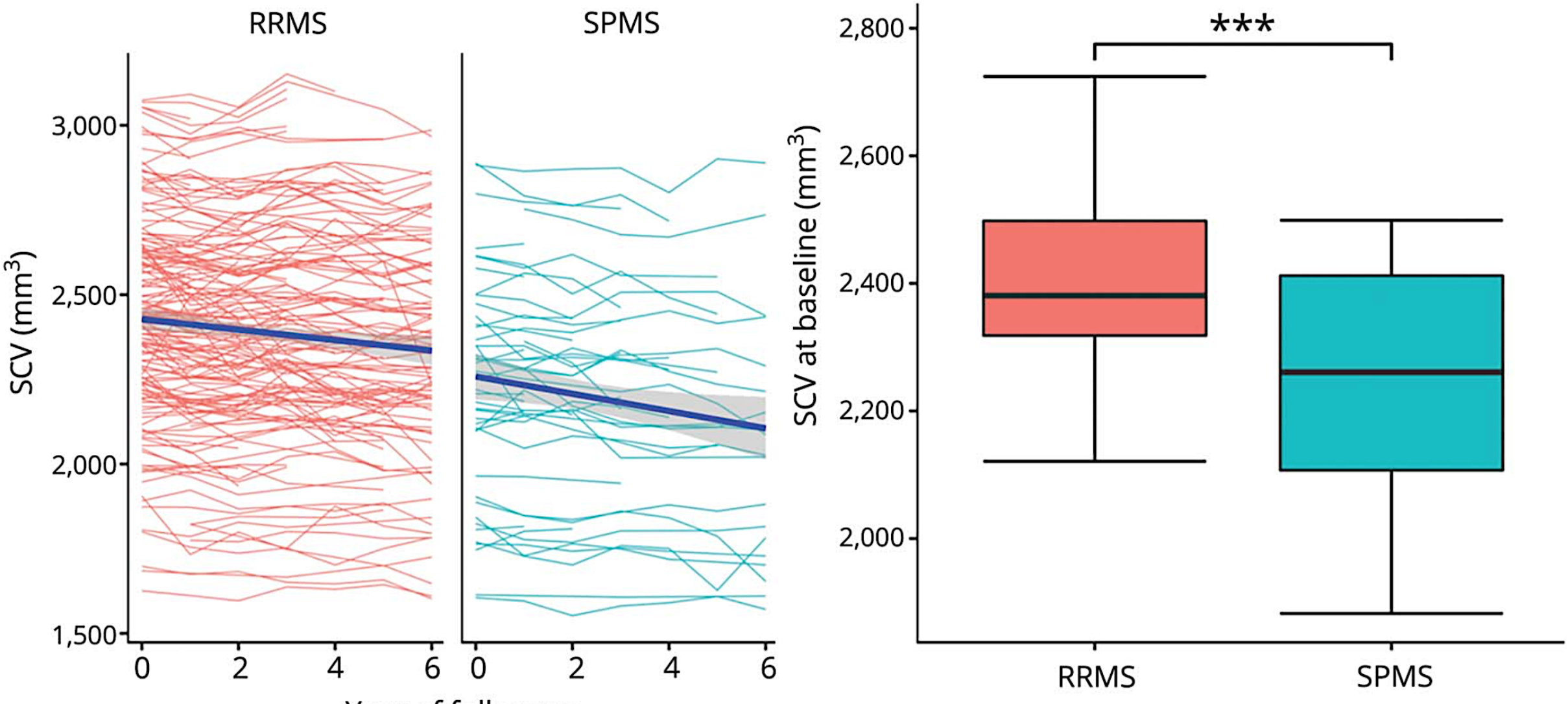
In healthy controls, rate of DGM atrophy was faster than that in other regions, suggesting that it may be a hotspot for both age- and disease-related atrophy in the human brain

Whereas lower thalamic volume and higher rates of atrophy were associated with worse disability in these studies, the effect size was small

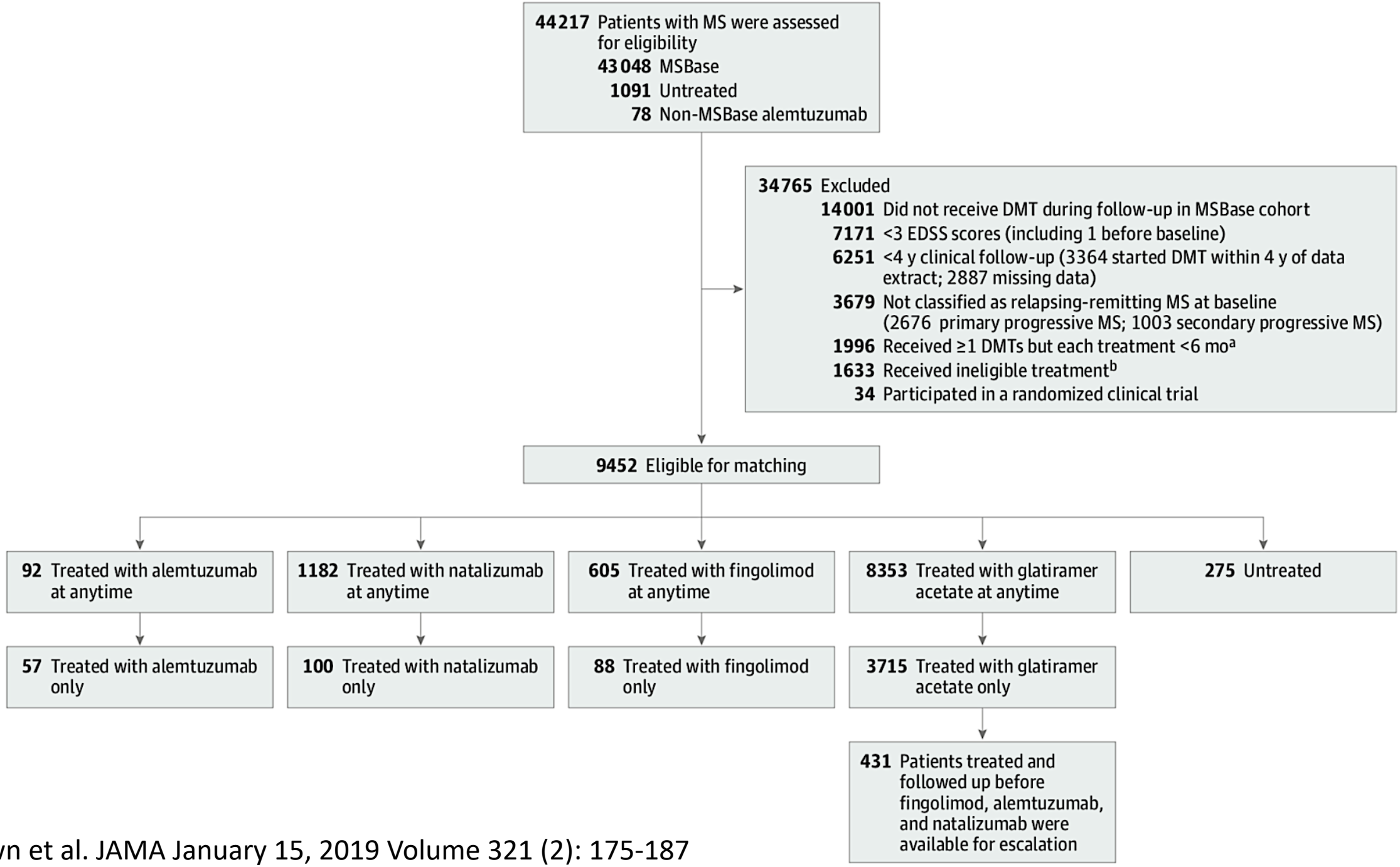
Given the constancy of atrophy rates over disease epochs and in different MS clinical phenotypes, it seems likely that any therapy targeting atrophy should be started at the time of clinical presentation to achieve maximal benefit.

Spinal Cord Volume Loss
A marker of disease progression in multiple sclerosis

Neurology® 2018;91:e349-e358

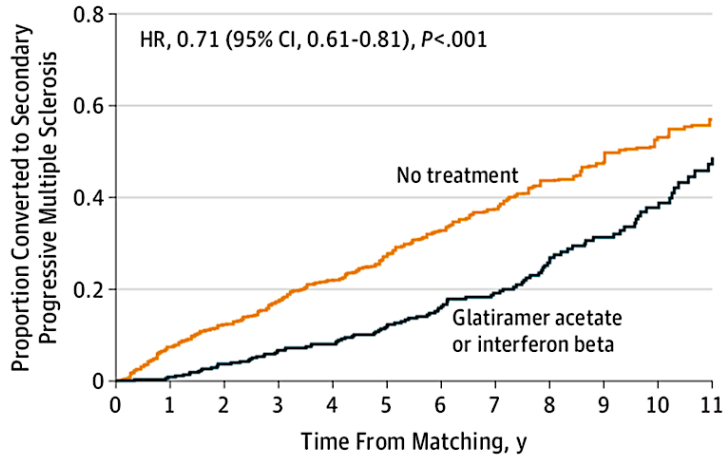


What’s the effect of treatment on disease progression



Brown et al. JAMA January 15, 2019 Volume 321 (2): 175-187

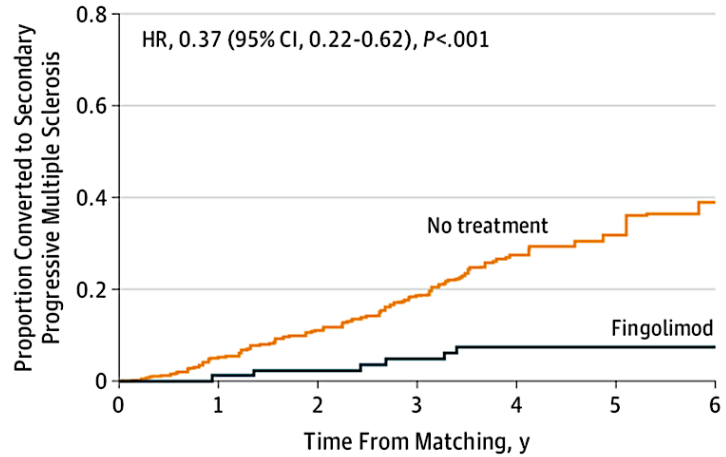
A Glatiramer acetate or interferon beta vs no treatment



No. with follow-up data

No treatment	213	213	213	213	213	180	153	126	96	74	51	33
Glatiramer acetate or interferon beta	407	407	407	407	407	355	300	251	191	142	98	62

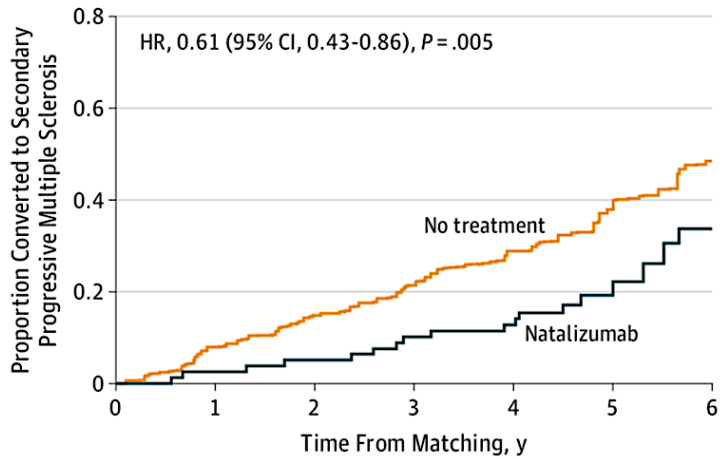
B Fingolimod vs no treatment



No. with follow-up data

No treatment	174	174	174	174	174	39	20
Fingolimod	85	85	85	85	85	21	11

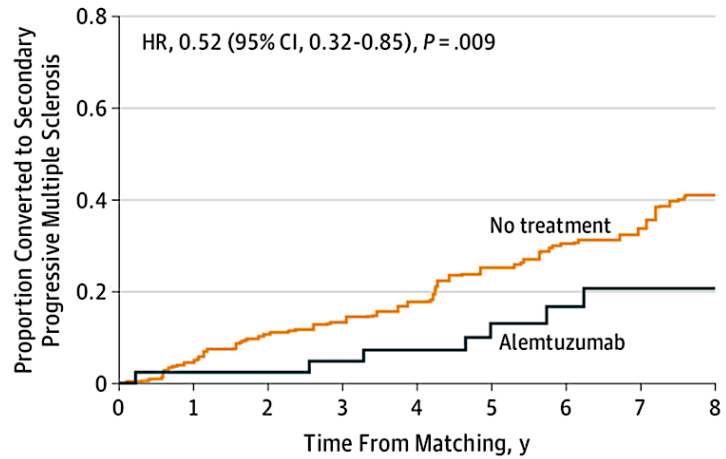
C Natalizumab vs no treatment



No. with follow-up data

No treatment	164	164	164	164	164	77	35
Natalizumab	82	82	82	82	82	36	17

D Alemtuzumab vs no treatment

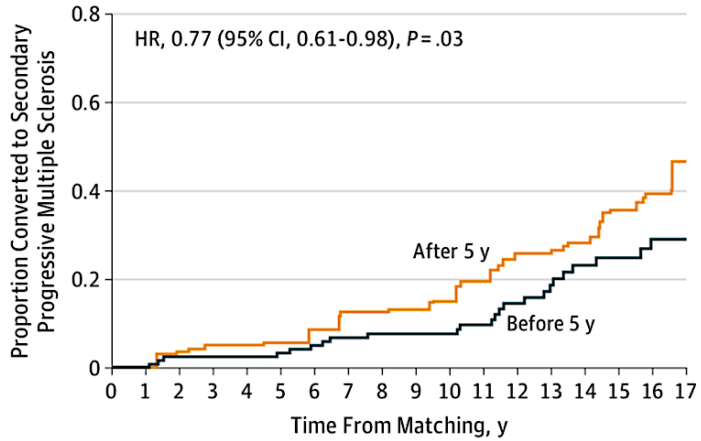


No. with follow-up data

No treatment	92	92	92	92	92	77	68	50	36
Alemtuzumab	44	44	44	44	44	37	34	24	17

A, The median follow-up was 7.6 years (interquartile range [IQR], 5.8-9.6); B, 4.5 years (IQR, 4.3-5.1); C, 4.9 years (IQR, 4.4-5.8); and D, 7.4 years (IQR, 6-8.6) years. HR indicates hazard ratio.

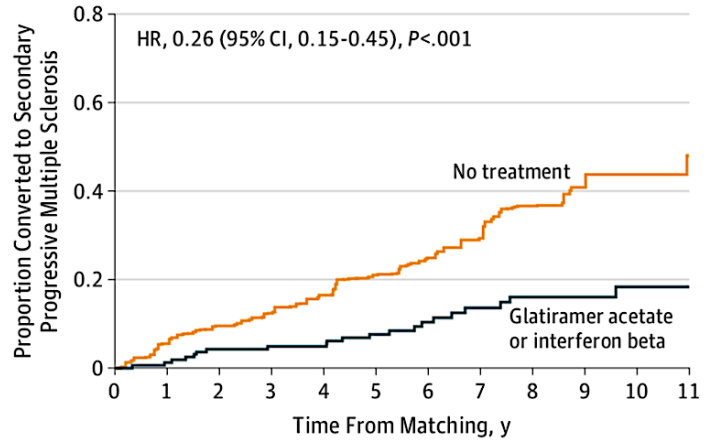
A Treatment with glatiramer acetate or interferon beta ≤5 y vs >5 y of onset



No. with follow-up data

Glatiramer acetate or interferon beta									
>5 y	38	38	38	38	36	31	23	15	11
≤5 y	120	120	120	119	115	102	77	60	44

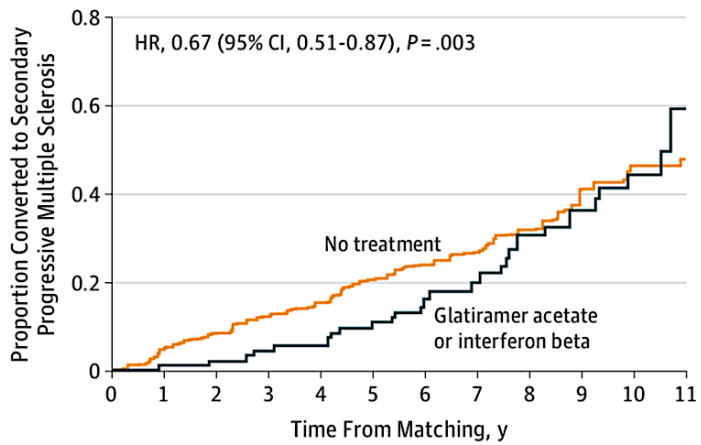
B Treatment with glatiramer acetate or interferon beta within 5 y vs no treatment



No. with follow-up data

No treatment	104	104	104	104	104	88	74	60	51	39	27	20
Glatiramer acetate or interferon beta	164	164	164	164	164	144	116	93	78	61	43	28

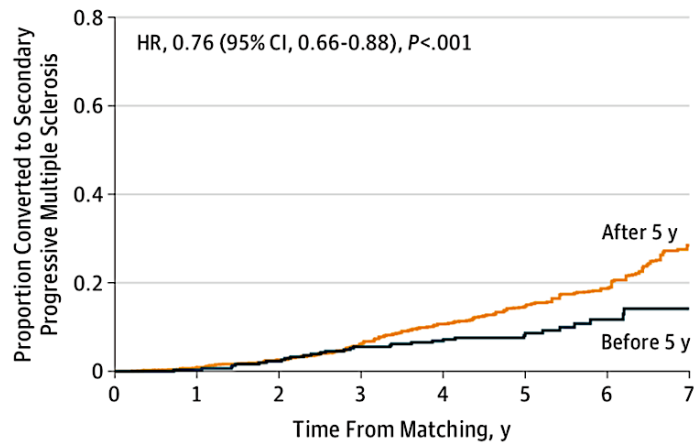
C Treatment with glatiramer acetate or interferon beta between 5 y and 10 y vs no treatment



No. with follow-up data

No treatment	158	158	158	158	158	128	108	86	66	50	34	25
Glatiramer acetate or interferon beta	95	95	95	95	95	83	69	53	44	32	20	15

D Escalation from glatiramer acetate or interferon beta treatment to fingolimod, alemtuzumab, or natalizumab treatment ≤5 y vs >5 y of onset

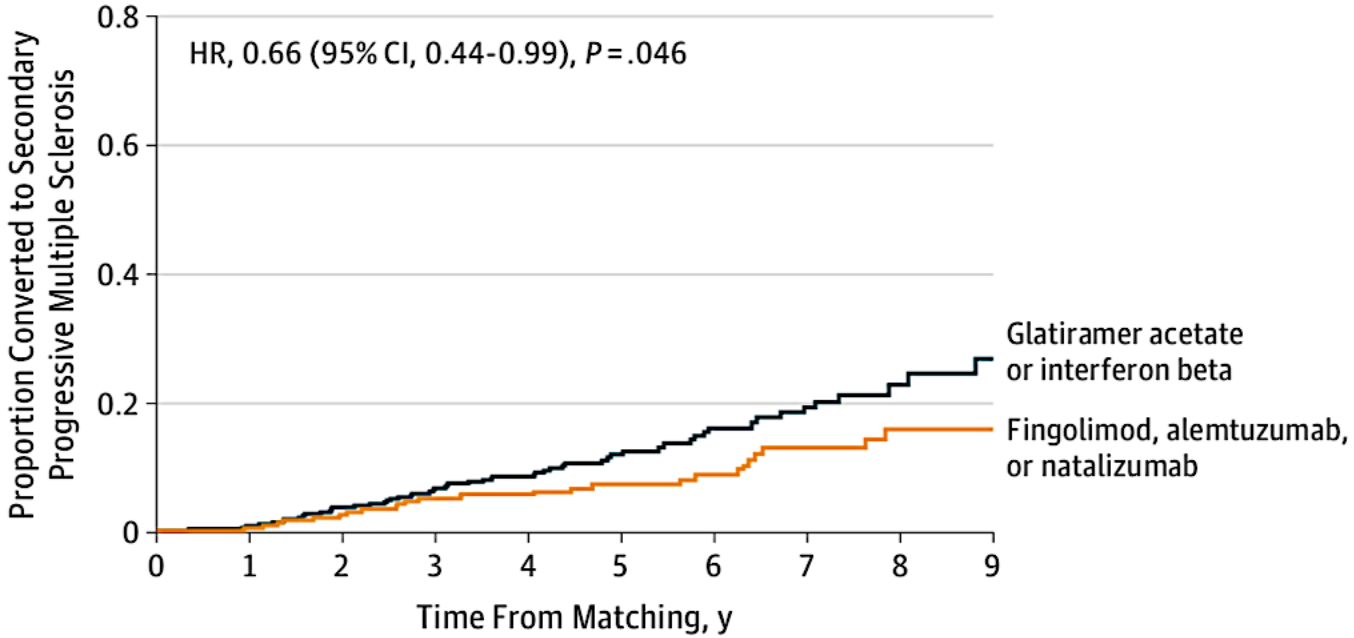


No. with follow-up data

Escalation to fingolimod, alemtuzumab, or natalizumab								
>5 y after onset	331	331	331	331	331	204	106	49
≤ 5 y after onset	307	307	307	307	307	191	97	47

A, The median follow-up was 13.4 years (interquartile range [IQR], 11-18.1); B, 7.5 years (IQR, 5.7-9.8); C, 7.7 years (IQR, 5.8-9.7); and D, 5.3 years (IQR, 4.6-6.4).

HR indicates hazard ratio.



No. with follow-up data										
Initial treatment										
Glatiramer acetate or interferon beta	380	380	380	380	380	252	182	142	93	44
Fingolimod, alemtuzumab, or natalizumab	235	235	235	235	235	148	103	80	54	30

Comparison of Cumulative Hazard of Conversion to Secondary Progressive Multiple Sclerosis for Initial Treatment With Glatiramer Acetate or Interferon Beta vs Fingolimod, Alemtuzumab, or Natalizumab

Conclusions

The current understanding of the disease pathogenesis assumes that inflammation is closely associated with demyelination and with irreversible axonal and cortical damage, thus reduction of neurodegeneration should be a logical consequence of stopping inflammation

Early treatment is better than late, but late treatment is better than never

?Early aggressive treatment is better than escalation

Modifiable Risk Factors For Progression

Risk factor and outcome measure	Study design, number of studies	Findings: direction, magnitude of effect	QoE
Vitamin D: correlation 25(OH)D level and EDSS	11 concurrent, 2 retrospective, 2 prospective studies	Weak correlation ($r=-0.22$; CI=−0.28, −0.10; 11 studies) indicating that lower levels of vitamin D are associated with higher EDSS scores	Moderate (indirect)[a]
Sun exposure: no outcome assessed in >1 study	5 retrospective studies	Association but predictor and outcome measures varied (see text)	Insufficient
Sunscreen use: no outcome assessed in >1 study	2 retrospective studies	No association but predictor and outcome measures varied (see text)	Insufficient
Month of birth: no outcome assessed in >1 study	3 retrospective studies	No association but outcome measures varied (see text)	Insufficient
Smoking: risk of progression comparing smokers and nonsmokers	1 concurrent, 9 retrospective, 4 prospective studies	Smoking is associated with an increased risk of progression (HR=1.55; CI=1.10, 2.19; 7 studies)	Moderate (heterogeneity)[a]
>1 study	retrospective, 1 prospective studies		
Fish consumption: no outcome assessed in >1 study	2 concurrent, 3 retrospective studies	Conflicting results (see text)	Insufficient
Alcohol-related predictors: no outcome assessed in >1 study reporting on the same operationalization	3 concurrent, 2 retrospective studies	Association but predictor and outcome measures varied (see text)	Insufficient
Exercise: no outcome assessed in >1 study	2 retrospective, 3 prospective studies	Conflicting results (see text)	Insufficient
Brain trauma: no outcome assessed in >1 study	2 retrospective studies	No association but predictor and outcome measures varied (see text)	Insufficient
Epidural analgesia: EDSS scores	2 prospective studies, 1 retrospective study	1 study showed no association with EDSS (sign. N/A), 1 study no association with 3 EDSS score categories ($p>0.1$); 1 study no association with EDSS or DSS ($p=0.66$)	Low (exploratory design, no effect estimate)[b]
Oral contraception: no outcome assessed in >1 study	3 retrospective studies	Conflicting results (see text)	Insufficient
Geographic region: no outcome assessed in >1 study	1 retrospective, 1 prospective study	Conflicting results (see text)	Insufficient
Education: no outcome assessed in >1 study	2 retrospective studies	Conflicting results (see text)	Insufficient

Multiple Sclerosis Journal
2017, Vol. 23(4) 525–533

Phase 3 Trials In PMS Since 2016

	Drug	Main mechanism	Multiple sclerosis type	Number of participants	Primary outcome for progression	Mean age, years (SD, active; placebo)	Mean duration of progression, years (SD, active; placebo)	Patients with baseline T1-GdE lesions, n/N (%)	Placebo versus active CDP, n/N (%)	Primary outcome HR or OR (95% CI) and result
INFORMS[5]	Fingolimod	S1P receptor modulation	PPMS	823	Composite*: time to 3-month CDP	49 (8·6; 8·3)	6 (2·5; 2·4)	107/820 (13%)	338/487 (69%) *vs* 232/336 (69%)	HR 0·95 (0·80–1·12); negative
ORATORIO[6]	Ocrelizumab	Anti-CD20-expressing B cells	PPMS	732	EDSS: time to 3-month CDP	45 (7·9; 8·3)	7 (4·0; 3·6)	193/727 (27%)	96/244 (39%) *vs* 160/487 (33%)	HR 0·76 (0·59–0·98); positive
EXPAND[4]	Siponimod	S1P receptor 1 and 5 modulation	SPMS	1651	EDSS: time to 3-month CDP	48 (7·8; 7·9)	4 (3·6; 3·3)	351/1599 (22%)	173/545 (32%) *vs* 288/1096 (26%)	HR 0·79 (0·65–0·95); positive
ASCEND[7]	Natalizumab	Anti-integrin-α4	SPMS	887	Composite*: proportion with 6-month CDP	47 (7·4; 7·8)	5 (3·0; 3·7)	210/884 (24%)	214/448 (48%) *vs* 195/439 (44%)	OR 0·86 (0·66–1·13); negative

HR=hazard ratio. OR=odds ratio. S1P= sphingosine 1-phosphate. PPMS=primary progressive multiple sclerosis. SPMS=secondary progressive multiple sclerosis. CDP=confirmed disability progression. EDSS=Expanded Disability Status Scale. T1-GdE=T1-gadolinium enhancing. *Composite: one or more of progression in EDSS, 25 foot timed-walk test, nine-hole peg test.

Table: **Summary of four phase 3 trials published since 2016 in progressive multiple sclerosis**

Phase II Trial Of Ibudilast In Progressive MS

- Ibudilast inhibits several cyclic nucleotide phosphodiesterases, macrophage migration inhibitory factor, and toll-like receptor 4
- It can cross the blood–brain barrier
- In a phase 2 trial involving patients with relapsing multiple sclerosis, ibudilast at a dose of 30 to 60mg per day did not prevent the development of new lesions on MRI but slowed the progression of brain atrophy in a dose-dependent fashion and decreased the proportion of GD+ lesions that converted to black holes on T1-weighted images
- 255 patients with primary or secondary progressive multiple sclerosis in a phase 2 randomized trial of oral ibudilast (≤100 mg daily) or placebo for 96 weeks. The primary efficacy end point was the rate of brain atrophy

N Engl J Med 2018;379:846-55

Treatment targets in Progressive MS

Neuroprotective therapy

Remyelination

Inhibition of microglia activation

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