SELÇUK ÜNİVERSİTESİ

MULTİPL SKLEROZ

TUZ, OBEZİTE, SİGARA

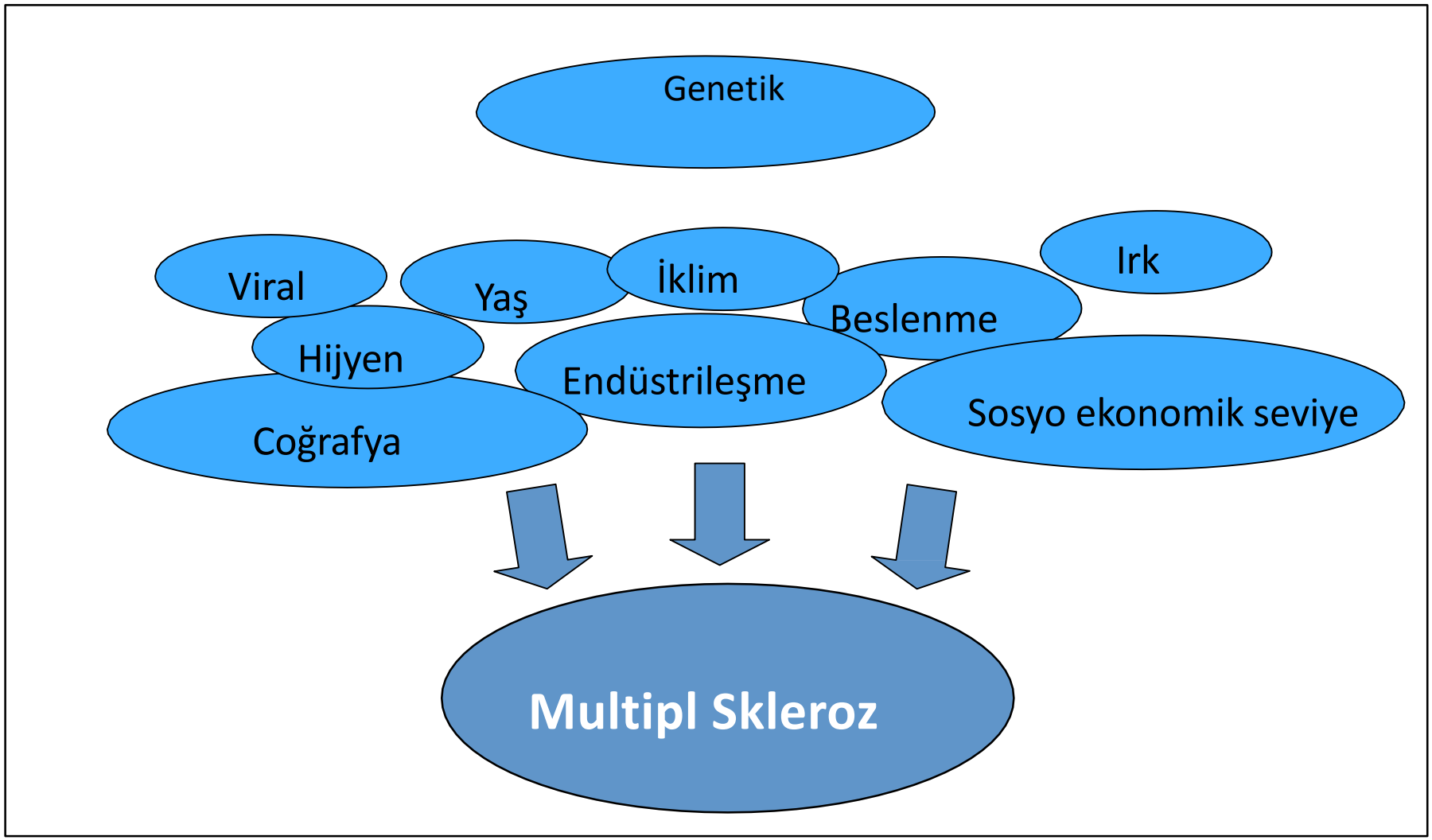
Dr. Haluk GÜMÜŞ

Selçuk Üniversitesi Tıp Fakültesi
Nöroloji Kliniği

Uluslararası Türk Dünyası Multipl Skleroz Kongresi

14-17 Şubat 2019 Ankara

MULTİPL SKLEROZ



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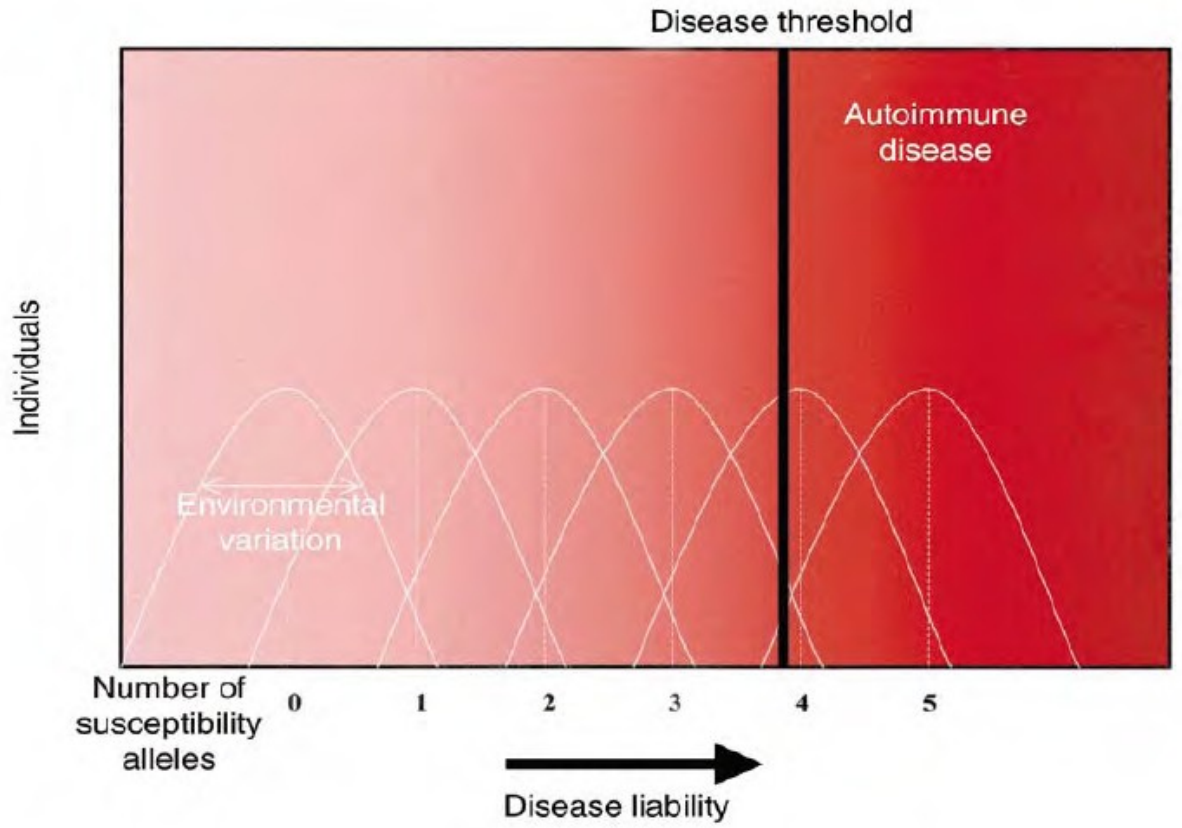

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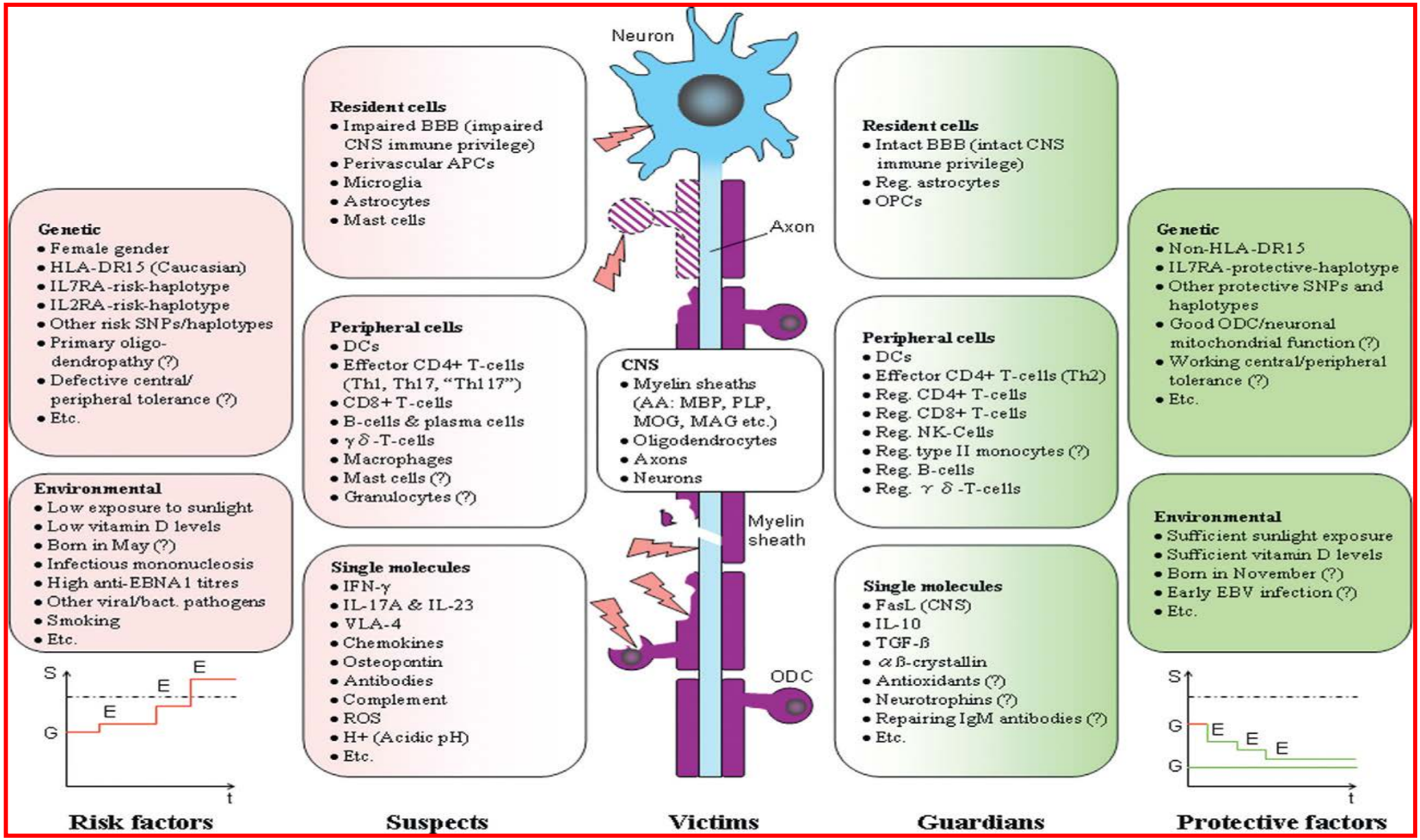


MULTİPL SKLEROZ

- Çevresel Risk Faktörleri:

-> Gerçek suçlu kim?

-> Onu değiştirebilirmiyiz ? Etkileyebilirmiyiz?

-> Hasta ve ailesi için danışmalık ?

-> Gelecekte daha fazla araştırmaya değer mi?

MULTİPL SKLEROZ

-> Hastalarda çevresel risk faktörlerinin yönetimi?

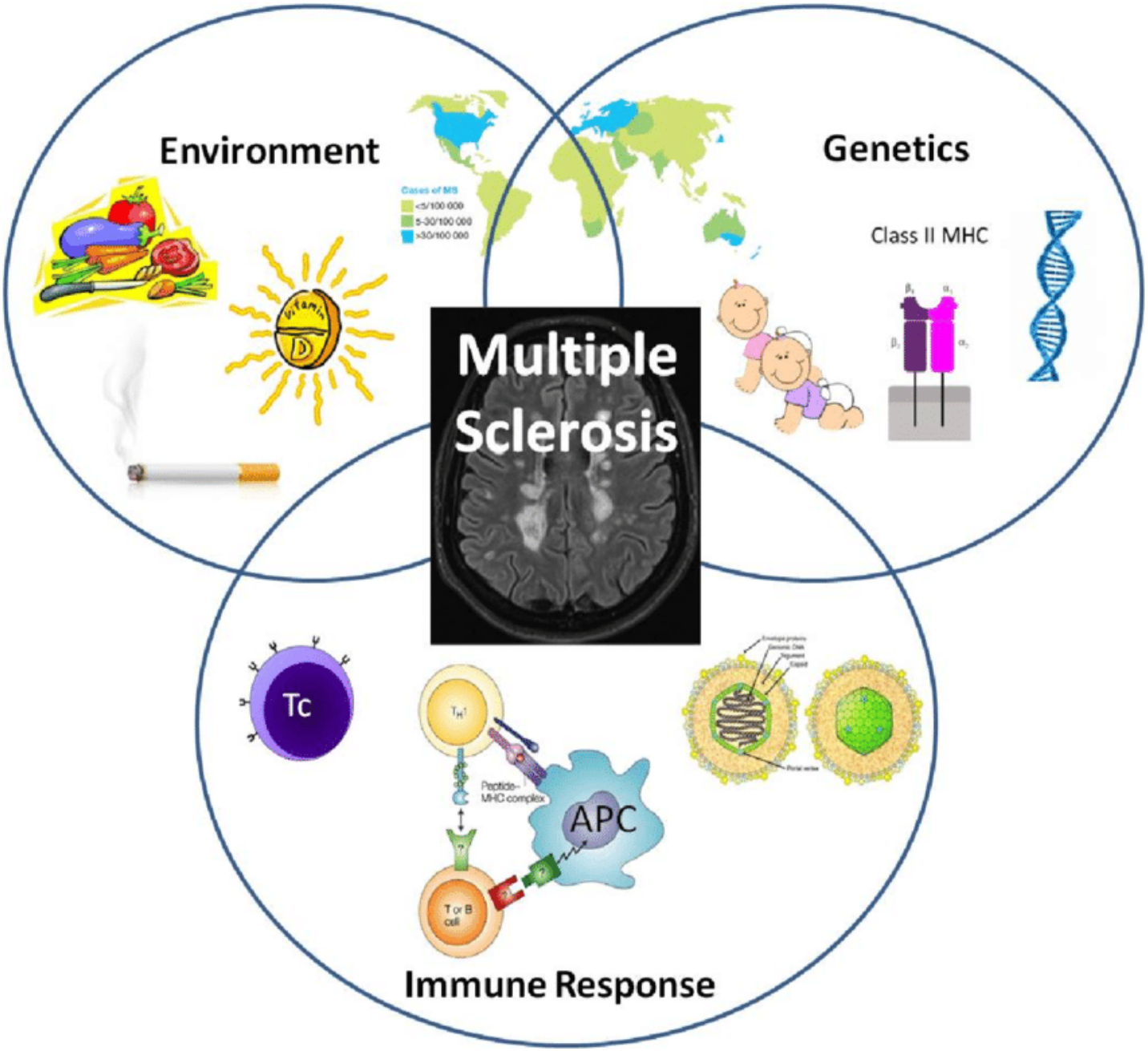
- Sadece istendiğinde tavsiye vermek?
- Kan testi?
- Vit. D ?
- Diyet ?
- Sigara ?

-> Bu durumun hastalık seyrini etkilediğini yada değiştirdiğini düşünüyormusunuz??

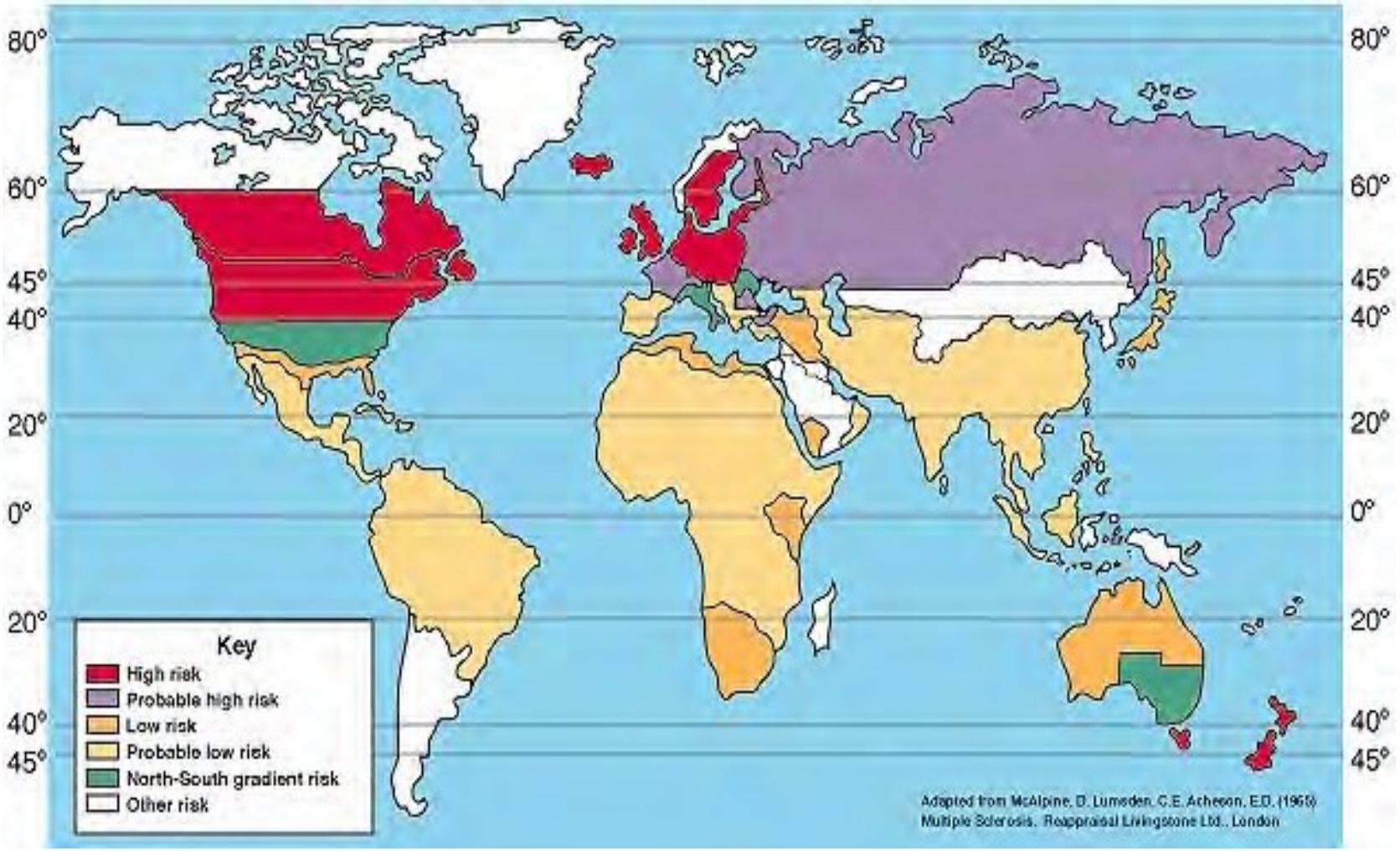
MULTİPL SKLEROZ : RİSK FAKTÖRLERİ

1. İklim ve Vitamin D
2. Sigara
3. Diyet
   - Obezite
   - Tuz
4. Gut immunoloji
   - Parazit Enf.
   - Bagırsak Flora

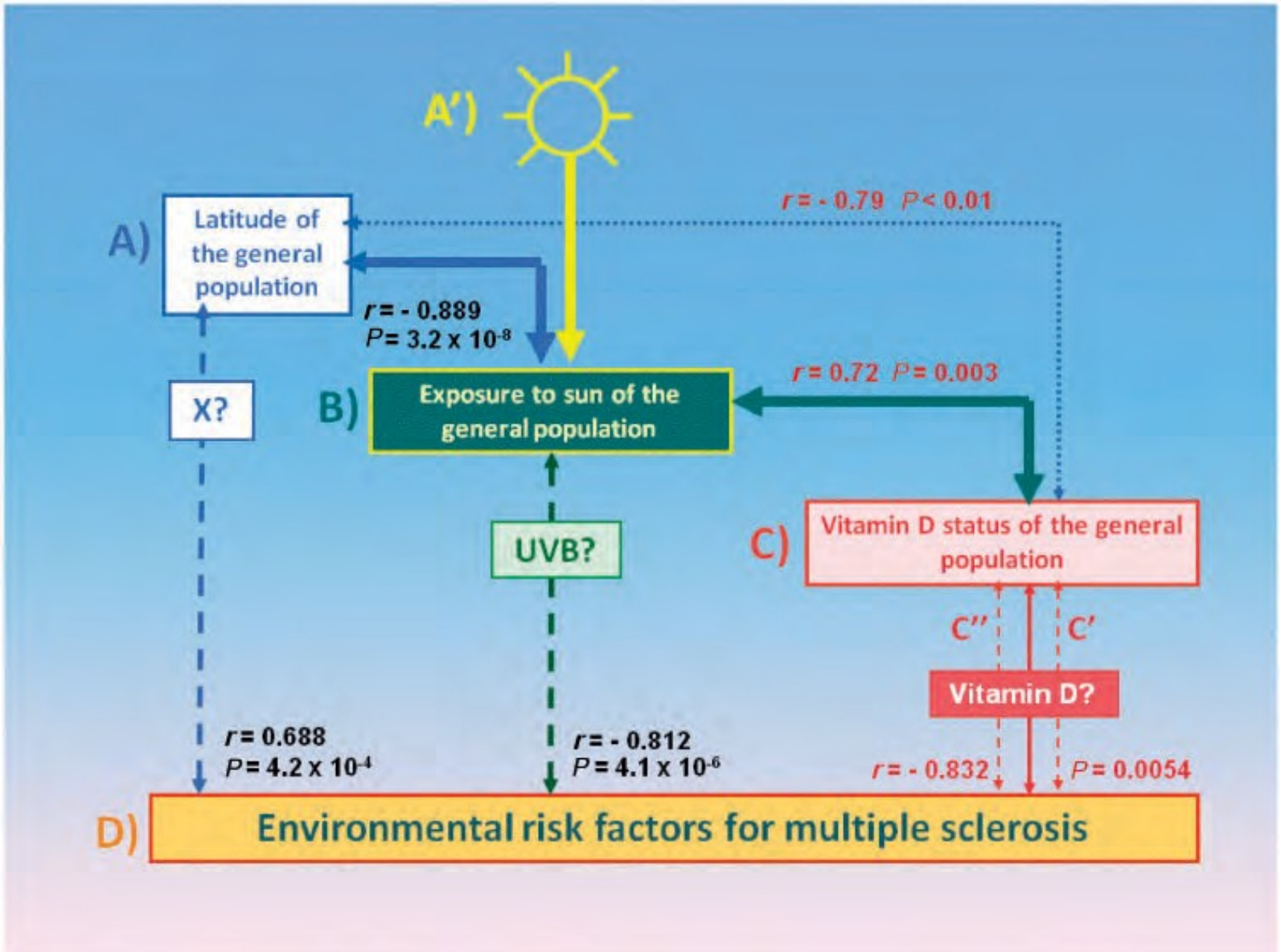
MULTİPL SKLEROZ: RİSK FAKTÖRLERİ



MULTİPL SKLEROZ: DÜNYADA YAYILIMI

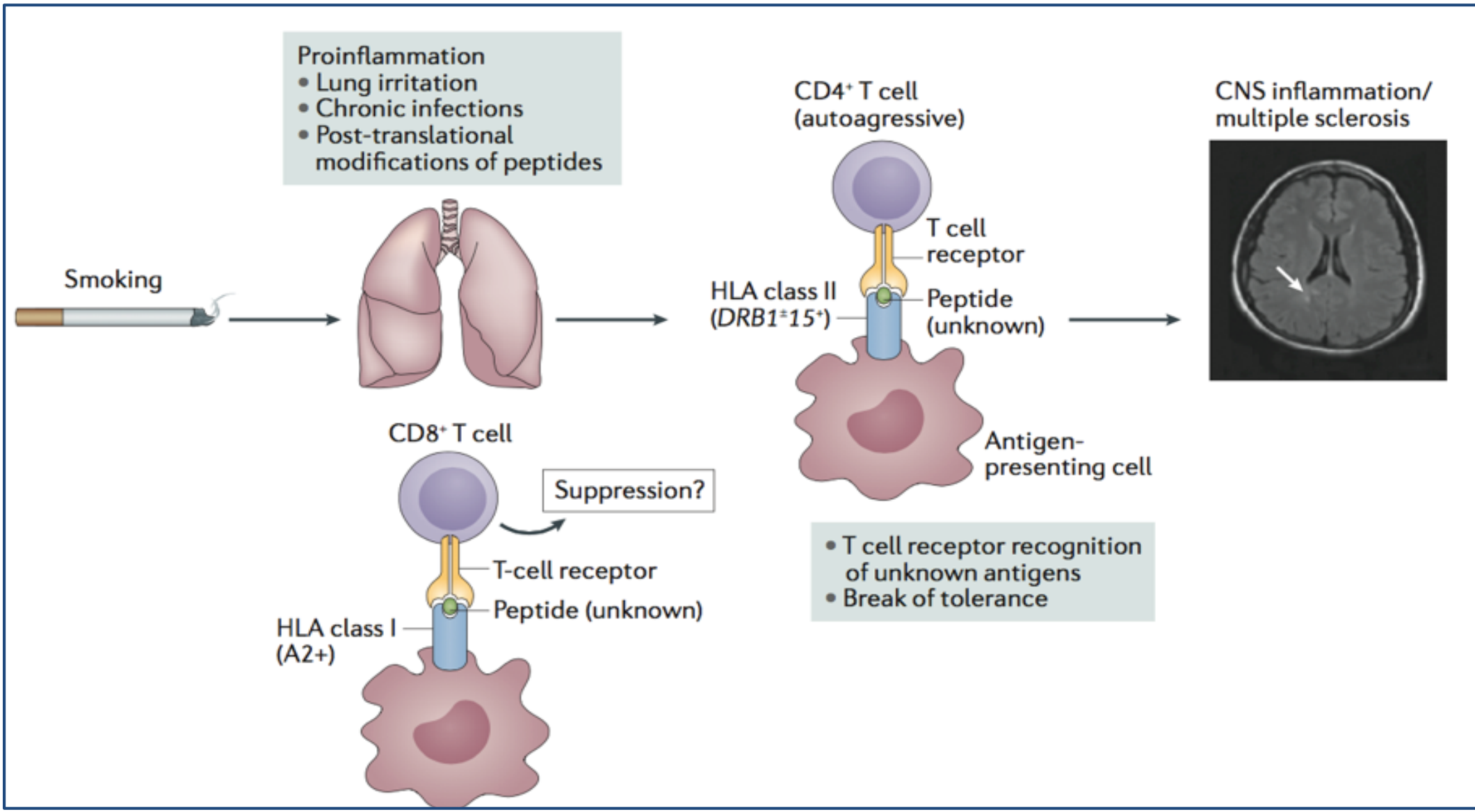


MULTİPL SKLEROZ: ÇEVRESEL RİSK FAKTÖRLERİ



MULTİPL SKLEROZ : ÇEVRESEL RİSK FAKTÖRLERİ

SİGARA VE MULTİPL SKLEROZ



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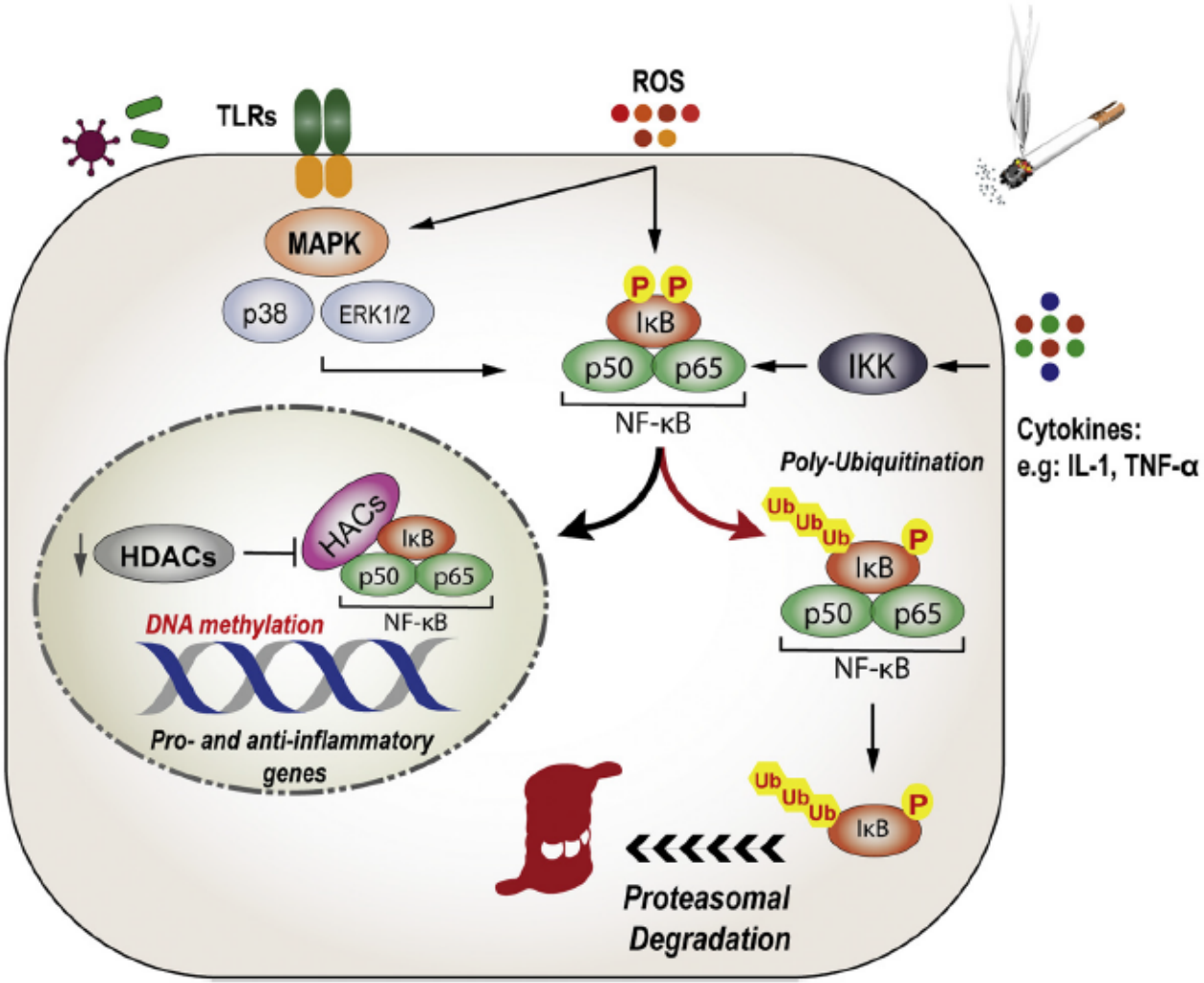


Fig. 1. Molecular mechanisms underlying the effect of cigarette smoke (CS): A schematic model of the impact of cigarette smoke (CS) on immune cells' transcriptional

SİGARA VE MULTİPL SKLEROZ

Sigara içimi (Hipoksi)

↓

Genetik / epigenetik modifikasyonlar; oksidatif stres, reaktif oksijen türleri (ROS) ve serbest radikal üretimi ve nikotin ve ağır metal toksisitesinde artış

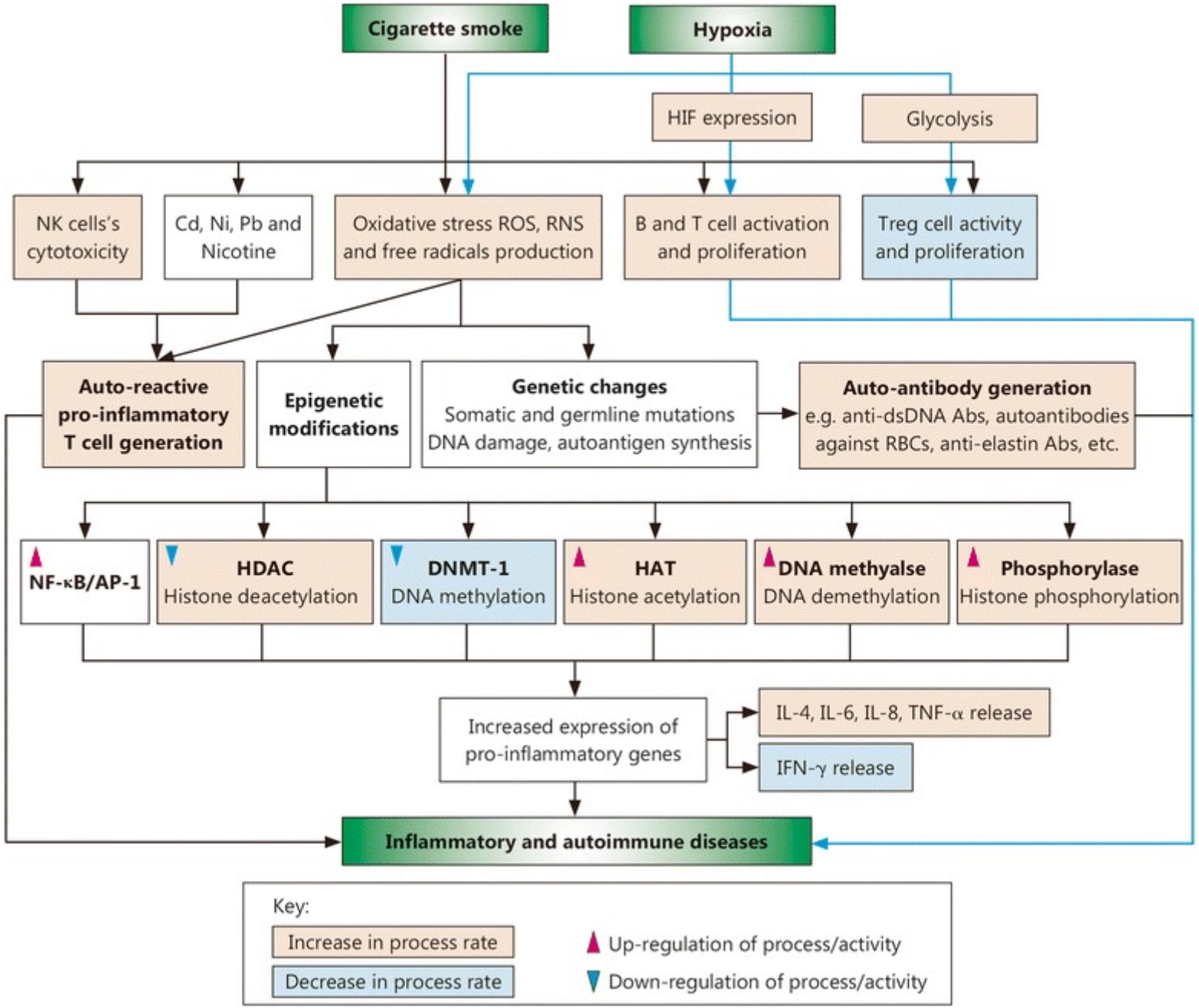
↓

Proinflamatuvar yolakların aktivasyonu
Treg seviyesinde azalma
Hipoksi-indüklenebilir faktörün (HIF) artmış ekspresyonunu

↓

Akciğerde SSS'e yönelik otoreaktif hücrelerin aktivasyonu ve SSS'e saldırı

SİGARA VE MULTİPL SKLEROZ



SİGARA VE MULTİPL SKLEROZ

Norveçte 22312 denekte yapılan çalışma

Table *The number of smokers and risk estimate (rate ratio) for six common diseases among 22,312 subjects in the general population of Hordaland County, Norway*

Disease	No. of patients*	Never smoker, n (%)	Current or past smoker, n (%)	Ratio ratio† (95% CI)
Multiple sclerosis	86	21 (24.4)	65 (75.6)	1.81 (1.13–2.92)
Myocardial infarction	76	9 (11.8)	67 (88.2)	4.53 (2.26–9.01)
Angina pectoris	108	17 (15.7)	91 (84.3)	3.30 (1.96–5.55)
Stroke	93	27 (29.0)	66 (71.0)	1.48 (0.94–2.35)
Asthma	1,350	446 (33.0)	904 (67.0)	1.21 (1.05–1.39)
Diabetes	216	85 (39.4)	131 (60.6)	0.86 (0.65–1.13)
Total population	22,240	8,239 (37.0)	7,892 (35.5)	1.00

* Information on smoking was missing for 72 individuals including one patient with multiple sclerosis.
† Rate ratio estimated in a Cox proportional hazard regression model with smoking as a time-dependent covariate. Smoking individuals are being compared with nonsmoking individuals at the same age for the risk of developing the disease. All analyses were performed stratified by sex.

Neurology 2003; 61: 1122-1124

SİGARA VE MULTİPL SKLEROZ

Table *Smoking and the risk of MS: Findings from population-based studies*

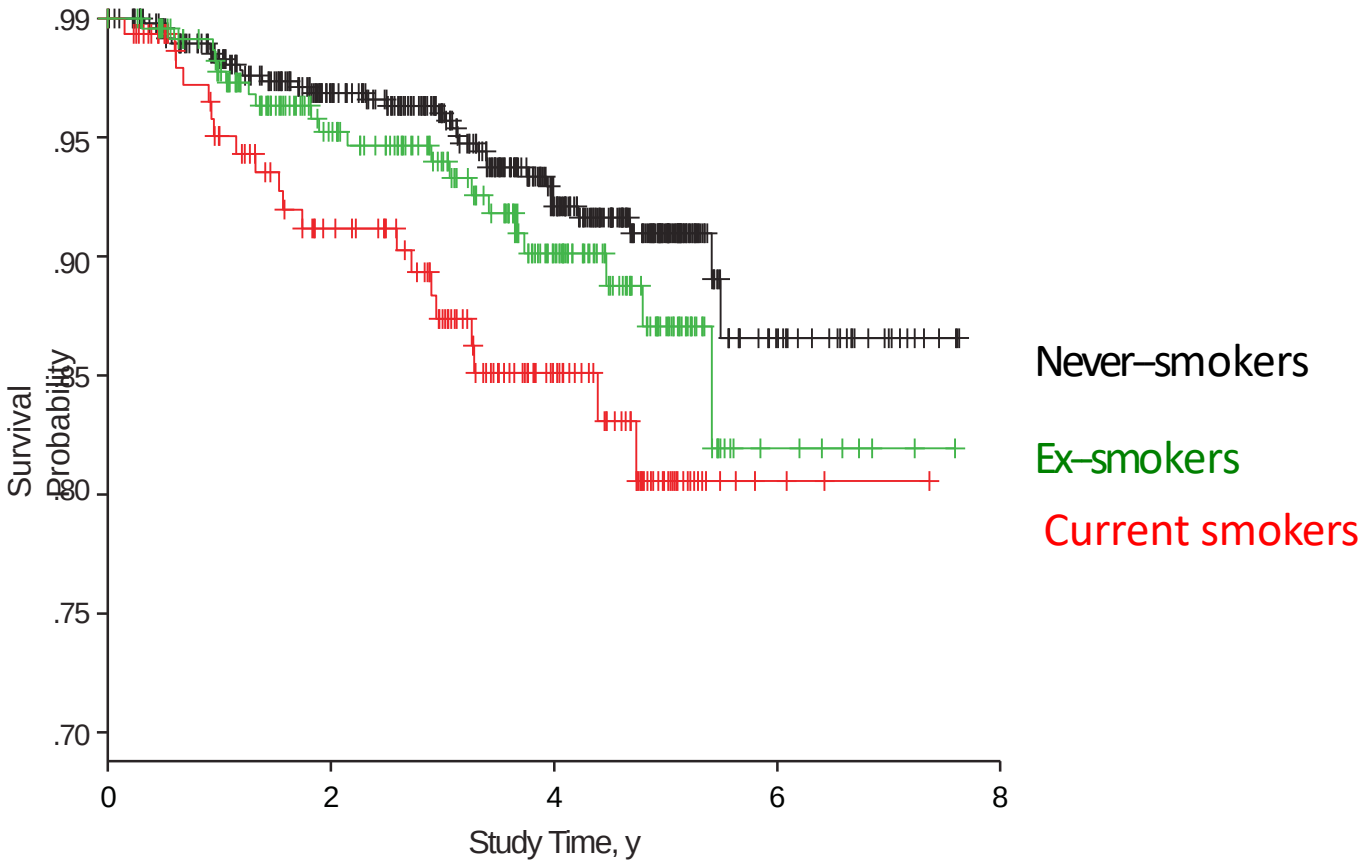
Study	Design, location	Smoking measure	Odds ratio (95% CI)
Reference 4	Prospective cohort study of incident cases among British women	> 15 cigarettes/day*	1.4 (0.9–2.2)
Reference 5	Prospective cohort study of incident cases among British women	>15 cigarettes/day*	1.4 (0.9–2.2)
Reference 6	Case-control study of incident cases in Montreal	ever vs never smoked	1.6 (1.0–2.4)
		20–40 cigarettes/day*	1.9 (1.2–3.2)
Reference 7	Prospective cohort study among U.S. women	ever vs never smoked	1.6 (1.2–2.1)
		2:25 pack-years*	1.7 (1.2–2.4)
Reference 3	Case-control study of prevalent cases in Hordaland, Norway	ever vs never smoked (dose response not reported)	1.8 (1.1–2.9)

* Comparison group for cigarette dosage categories is never smokers.

Neurology 2003; 61: 1032-1034

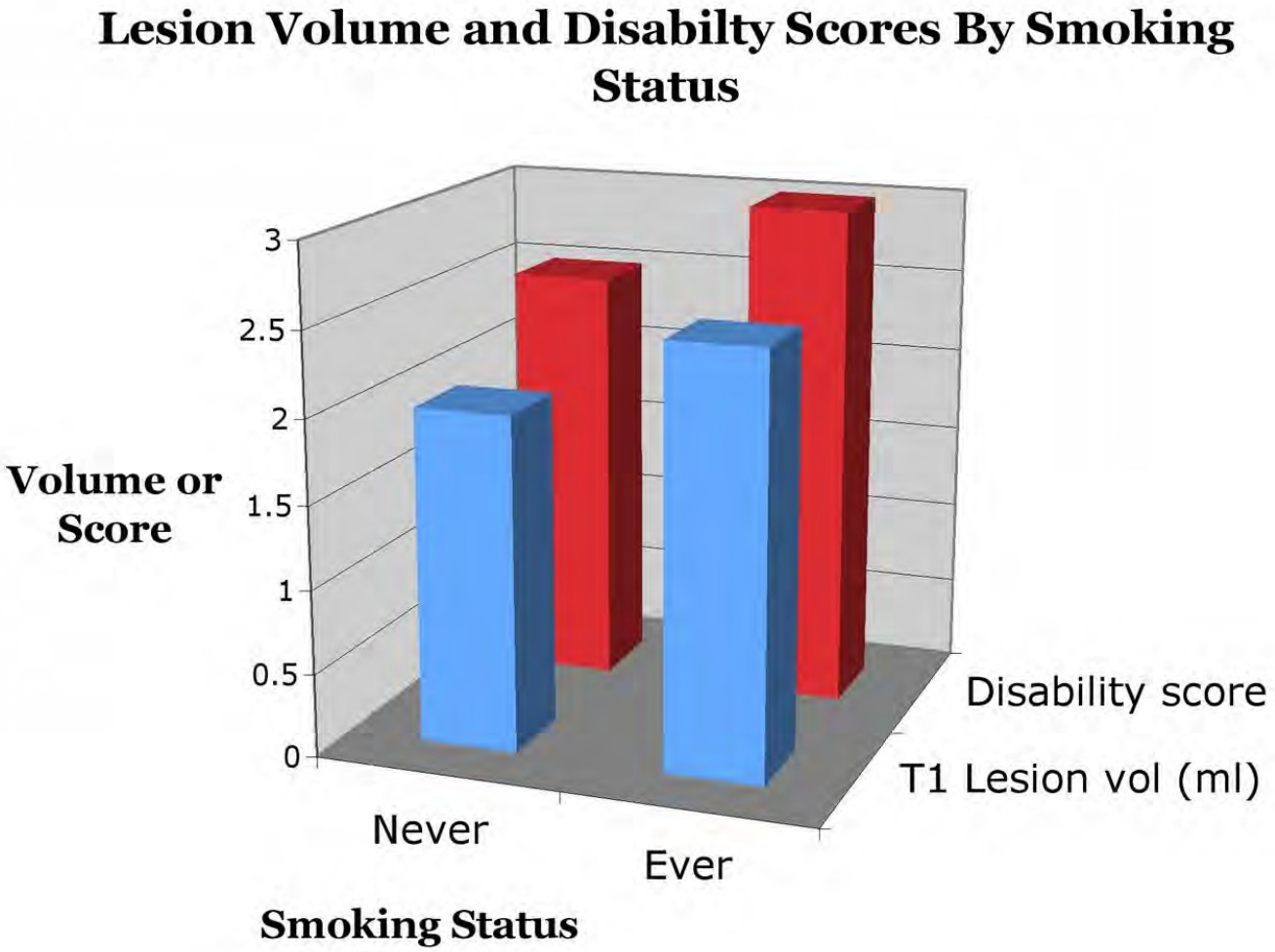
SİGARA VE MULTİPL SKLEROZ

Time to conversion from RR–MS to SP–MS



Arch Neurol. 2009; 66 (7): 858-864

SİGARA VE MULTİPL SKLEROZ



Neurology 2009; 73;504-510

SİGARA VE MULTİPL SKLEROZ

Original Research Paper

Smoking is a major preventable risk factor for multiple sclerosis

AK Hedström, T Olsson and L Alfredsson

Multiple Sclerosis Journal

2016, Vol. 22(8) 1021–1026

DOI: 10.1177/1352458515609794

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Abstract

Background: Both smoking and exposure to passive smoking have repeatedly been associated with increased multiple sclerosis (MS) risk, but have never before been studied together. We assessed the public health impact of these factors.

Methods: In a Swedish population-based case-control study (2455 cases, 5336 controls), we calculated odds ratios of developing MS associated with different categories of tobacco smoke exposure, together with 95% confidence intervals, by using logistic regression. The excess proportion of cases attributable to smoking and passive smoking was calculated as a percentage.

Results: Both smoking and exposure to passive smoking contribute to MS risk in a dose-dependent manner. At the population level, 20.4% of all cases were attributable to smoke exposure. Among subjects carrying the genetic risk factor HLA-DRB1*15 but lacking HLA-A*02, 41% of the MS cases were attributable to smoking.

Conclusions: From a public health perspective, the impact of smoking and passive smoking on MS risk is considerable. Preventive measures in order to reduce tobacco smoke exposure are, therefore, essential. In particular, individuals with a history of MS in the family should be informed regarding the impact of smoking on the risk of MS, and the importance of preventing their children from being exposed to passive smoke.

Correspondence to:
Anna Karin Hedström, MD
Institute of Environmental Medicine, Karolinska Institute, Stockholm, 14153, Sweden.
anna.hedstrom@ki.se

AK Hedström
L Alfredsson
Institute of Environmental Medicine, Karolinska Institute, Sweden

T Olsson
Neuroimmunology Unit, Department of clinical neuroscience and Center for Molecular Medicine, Karolinska Institute at Karolinska University Hospital, Sweden

SİGARA VE MULTİPL SKLEROZ

Original Research Paper

Smoking is a major preventable risk factor for multiple sclerosis

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DOI: 10.1177/1352458515609794
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Smoking (no. of pack years (p/y))	Passive smoking (years)	ca/co[a]	OR (95% CI)[b]	OR (95% CI)[c]	*P* value
0	0	698/1897	1.0 (reference)	1.0 (reference)	1.0 (reference)
0	Ever (1–20 years)	346/878	1.1 (1.0–1.3)	1.1 (1.0–1.3)	0.2
0	Ever (>20 years)	111/237	1.4 (1.1–1.8)	1.4 (1.1–1.8)	0.009
Ever (0–10 p/y)	0	431/839	1.4 (1.2–1.6)	1.6 (1.2–2.0)	0.0005
Ever (0–10 p/y)	Ever (1–20 years)	366/681	1.5 (1.3–1.8)	1.7 (1.3–2.3)	0.0003
Ever (0–10 p/y)	Ever (>20 years)	91/165	1.6 (1.1–2.0)	1.8 (1.3–2.6)	0.0006
Ever (>10 p/y)	0	94/164	1.8 (1.4–2.4)	2.0 (1.4–2.7)	<0.0001
Ever (>10 p/y)	Ever (1–20 years)	207/330	1.9 (1.6–2.3)	2.1 (1.6–2.8)	<0.0001
Ever (>10 p/y)	Ever (>20 years)	111/145	2.4 (1.8–3.2)	2.7 (2.0–3.8)	<0.0001

One pack year is the equivalent to smoking 20 cigarettes daily for one year.
[a]number of exposed cases and controls.
[b]adjusted for age, gender, residential area, and ancestry.
[c]adjusted for age, gender, residential area, ancestry, snuff use, alcohol consumption habits and past/current smoking.

of smoking on the risk of MS, and the importance of preventing their children from being exposed to passive smoke.

SİGARA ve MULTİPL SKLEROZ

Multiple Sclerosis and Related Disorders 17 (2017) 207–216

Study	n Cases	n Controls	Weight (Cons)	Weight (Non-Cons)	Odds Ratio (95% CI)
Conservative					
Al-Afasy 2013	101	202	0.7%	1.5%	1.70 (0.87, 3.30)
Alonso 2011	394	394	0.7%	1.5%	1.72 (0.90, 3.29)
Antonovsky 1965	241	964	3.8%	3.2%	1.40 (1.05, 1.86)
Asadollahi 2013	662	394	2.2%	2.7%	1.78 (1.22, 2.59)
Bjornevik 2015	953	1717	7.9%	3.7%	1.70 (1.39, 2.07)
Carlens 2010 (CO)	187	240,318	3.2%	3.1%	1.90 (1.39, 2.59)
Ghadirian 2001	200	202	1.6%	2.4%	1.60 (1.03, 2.48)
Hedstrom 2009	902	1855	11.7%	3.9%	1.50 (1.27, 1.77)
Hedstrom 2013	6085	5357	32.9%	4.2%	1.50 (1.36, 1.65)
Hernan 2001 (CO)	314	237,264	3.9%	3.2%	1.39 (1.05, 1.84)
Hernan 2005	201	1913	4.4%	3.3%	1.30 (1.00, 1.69)
Jafari 2009	136	204	1.4%	2.2%	1.09 (0.68, 1.74)
Kotzamani 2012	504	591	5.3%	3.5%	
Maghzi 2011	516	1090	1.5%		
Mansouri 2014	1217	787			
Riise 2003 (CS)	86	22			
Salzer 2012	141				
Simon 2010	1				
Simon 2015					
Sundstrom 2008					
Thorogood 1998 (CO)					
Villard-Mackintosh 1993 (CO)					
Zorzon 2003					
Total (95% CI)					
Additional Studies – Non-Conservative					
Al-Shammri 2015	195	142			
Briggs 2014	1012	576	-		
Dahl 2007 (CS)	250	371,878	-	3.1%	
Gustavsen 2014	518	903	-	3.5%	2.41 (1.90, 3.06)
Kappus 2015 (CS)	480	167	-	2.8%	1.91 (1.33, 2.74)
Moccia 2015	265	530	-	3.1%	1.05 (0.77, 1.43)
Mouhieddine 2015	248	216	-	2.7%	0.97 (0.67, 1.40)
O'Gorman 2014	560	480	-	3.4%	1.90 (1.47, 2.45)
Ploughman 2014 (CS)	743	8.8M*	-	3.4%	0.54 (0.42, 0.69)
Ramagopalan 2013	3157	756	-	3.8%	1.32 (1.09, 1.59)
Russo 2008	94	53	-	1.2%	1.11 (0.51, 2.42)
Silva 2009	81	81	-	1.2%	2.00 (0.92, 4.37)
Simpson 1966	584	10,692	-	3.9%	1.10 (0.93, 1.30)
Total (95% CI)				**100%**	**1.46 (1.32, 1.61)**

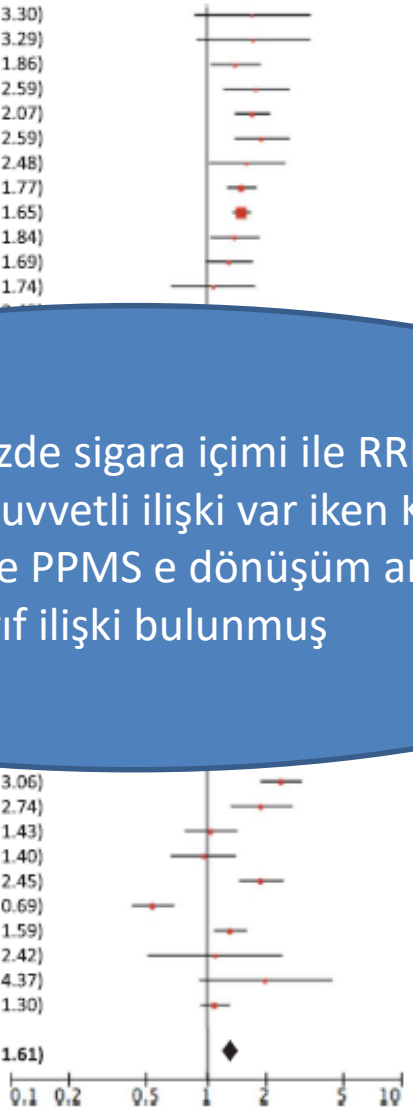

Fig. 2. Meta-analysis and forest plot: Relationship between smoking and MS risk – Conservative (23 studies) and non-conservative (36 studies) analyses. IV = inverse variance; CI = confidence interval. Studies identified by first author and year. All studies case-control design unless noted: CO = Cohort; CS = Cross-Sectional. *n is weighted.

Bu meta analizde sigara içimi ile RRMS ve SPMS arasında kuvvetli ilişki var iken KIS RRMS e dönüşümü ve PPMS e dönüşüm arasında zayıf ilişki bulunmuş

SİGARA VE MULTİPL SKLEROZ

- Daha ağır atak semptomları, daha sık atak ve daha ağır dizabilite
- Sigara içiminden 10 dakika sonra semptomlarda artış ve motor performansta azalma
- Sık akciğer enfeksiyonu atak riskini artırır
- IMD lardan yararlanım az

  (IFN ve Natalizumaba karşı antikor gelişimi !!)

- SPMS'e dönüşüm hızlı ve dizabilite yüksek
- Sigara içme süre ve miktarı dizabilite düzeyi ile korele
- Kognitiv bozulma sigara içenlerde daha fazla

Anna K Hedström *Multiple Sclerosis Journal 2017*

SİGARA VE MULTİPL SKLEROZ

Original Research Paper

Waterpipe smoking associated with multiple sclerosis: A population-based incident case–control study

Multiple Sclerosis Journal
2017, Vol. 23(10) 1328–1335
DOI: 10.1177/1352458516677867

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Ibrahim Abdollahpour, Saharnaz Nedjat, Mohammad Ali Sahraian, Mohammad Ali Mansournia, Petr Otahal and Ingrid van der Mei

Abstract

Background: While cigarette and ... as modifiable risk factors for multiple sclerosis (MS), the... association.

Objective: We examin... king with MS.

Methods: Populati... ases and 1057 general population contro... was used. Multiplicative along with a... dex (SI), respectively, and the populati...

Results: Having ... ive smoking were all significantly associate... 69 (1.24–2.31), and OR= 1.85 (1.48–2.32), respectiv... observed with the duration exposed ($p<0.001$ for all three) and the ... for Waterpipe and tobacco). Those who had all three types of smoking had an odds that was 4.1 times higher than those without any type. The three types of smoking jointly contributed to 30.9% of the MS incidence.

Conclusion: We identified Waterpipe smoking as a novel risk factor for MS. Given the global increase in Waterpipe smoking, especially among young adults, this finding reinforces the need for public health interventional and educational programs to combat this global increase.

Sigara, Nargile ve Pasif sigara içiciliği MS oluşumunu tetiklemektedir

Correspondence to:
MA Mansournia
Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran.
mansournia_ma@yahoo.com

Ibrahim Abdollahpour
Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran/ School of Public Health, Arak University of Medical Sciences, Arak, Iran

Saharnaz Nedjat
Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran/ Knowledge Utilization

SİGARA VE MULTİPL SKLEROZ

- SİGARA MS ÜZERİNDE NEGATİF YÜKE SAHİP
- SİGARA KESİLDİKTEN SONRA BU NEGATİF ETKİYİ AZALMAKTA
- SİGARAYI BIRAKANLARDA SPMS'E DÖNÜŞÜM YILI
- BIRAKMAYANLARDAN 8 YIL DAHA FAZLA
- YAŞAM KALİTESİNİ ARTIRAN ÖNEMLİ BİR FAKTÖR

SİGARA DEĞİŞTİRİLEBİLİR RİSK FAKTÖRÜ

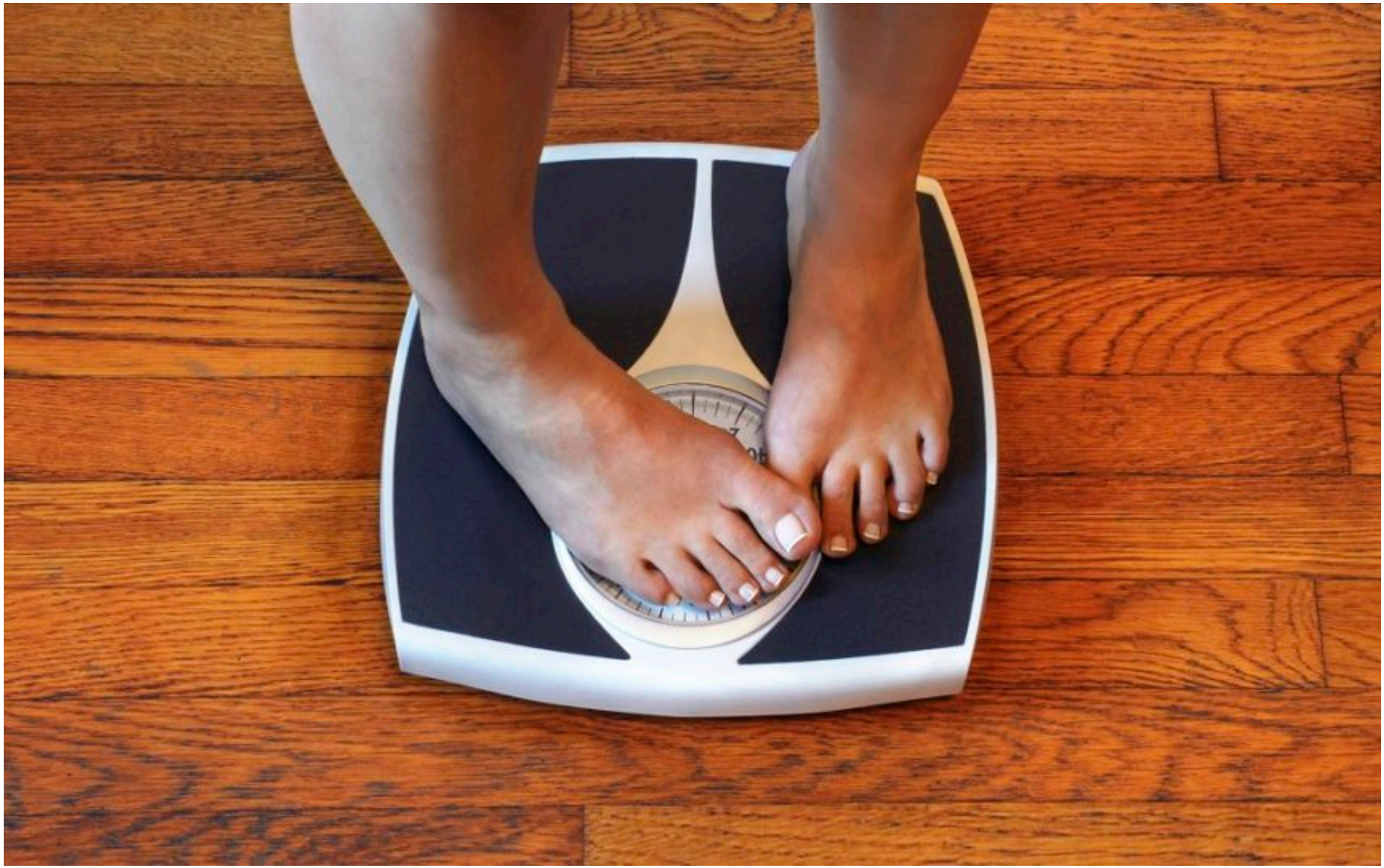
SMOKİNG AND İTS İNTERACTİON WİTH GENETİCS İN MS ETİOLOGY. MULTİPLE SCLEROSİS JOURNAL 2018

SİGARA VE MULTİPL SKLEROZ

Sigarayı bırakmak için geç değildir!!!!!

Aile içinde çocuklarınızı sigara maruziyetinden kurtarın !!!!

MULTİPL SKLEROZ VE OBEZİTE

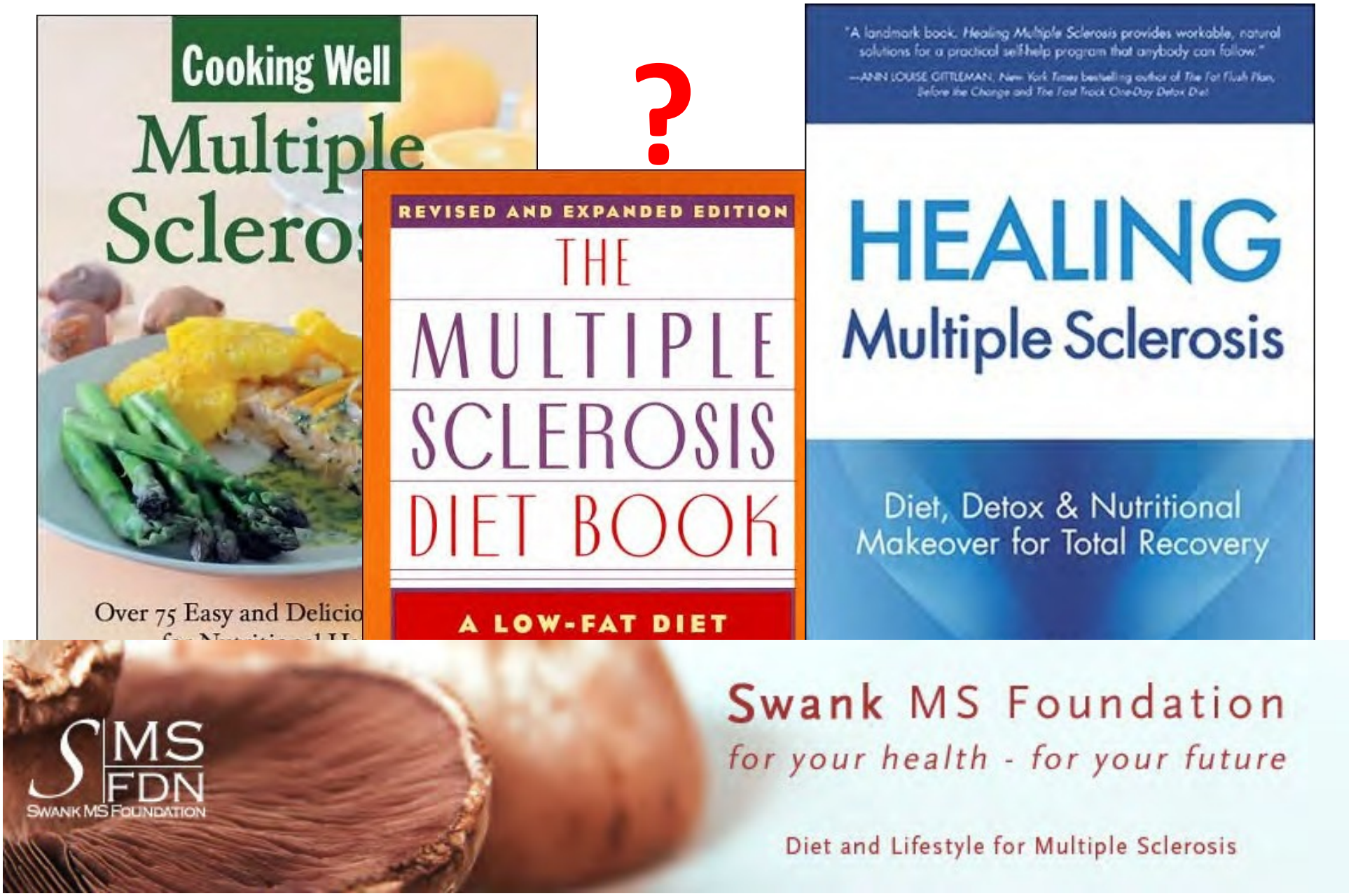


MULTİPL SKLEROZ VE OBEZİTE

Obezite, dünya çapında güncel bir halk sağlığı sorunudur; ABD'deki yetişkinlerin yaklaşık % 35'i obez .
Obezite çocuklarda iki kattan fazla artmış ve ergenlerde son 30 yılda 4 katına çıkmıştır

Obesity and Multiple Sclerosis Susceptibility: A Review J Neurol Neuromedicine. 2016

DİYET VE MULTİPL SKLEROZ



MULTİPL SKLEROZ VE OBEZİTE

Body size and risk of MS in two cohorts of US women.

	NHS, cases/ person-years	NHSII, cases/ person-years	Pooled relative risks (95% CI)		Multivariate* adjusted
			Age-adjusted	Age-, smoking-adjusted	
BMI age 18 (kg/m²)					
<18.5	21/292,421	45/231,006	0.94 (0.71–1.24)	0.94 (0.71–1.24)	0.96 (0.73–1.27)
18.5–<21	77/963,413	134/656,714	1 (ref)	1 (ref)	1 (ref)
21–<23	55/648,273	84/347,962	1.15 (0.92–1.42)	1.13 (0.91–1.40)	1.13 (0.91–1.40)
23–<25	24/281,999	31/161,737	1.00 (0.74–1.35)	0.97 (0.72–1.31)	0.97 (0.72–1.31)
25–<27	20/130,338	17/72,559	1.51 (0.90–2.52)	1.45 (0.86–2.43)	1.44 (0.87–2.39)
27–<30	8/72,619	16/50,889	1.47 (0.96–2.24)	1.40 (0.92–2.14)	1.40 (0.92–2.14)
>30	6/45,583	21/39,839	2.41 (1.61–3.60)	2.26 (1.50–3.38)	2.25 (1.50–3.37)
Total	211/2,434,647	348/1,560,707			
***p*, trend**			<0.001	<0.001	<0.001
***p*, het**			0.98	0.96	0.997

Neurology 2009:73:1543.

"20 yaşından önce BMI yüksekliği hem kadınlar hem erkekler için MS gelişimi açısından risk teşkil etmektedir"

Mult. Scler. 2012 Sep 18(9)

MULTİPL SKLEROZ VE OBEZİTE

Erken yaşamda Obesite MS riskini artırır

A. Langer-Gould, et al.“Childhood obesity and risk of pediatric multiple sclerosis and clinically isolated syndrome,” *Neurology*, vol. 80, no. 6, pp. 548–552, 2013.

K. L. Munger, et al. “Childhood body mass index and multiple sclerosis risk: A Long-Term Cohort Study,” *Multiple Sclerosis Journal*, vol. 19, no. 10, pp. 1323–1329, 2013.

K. L. Munger, et al. “Body size and risk of MS in two cohorts of US women,” *Neurology*, vol. 73, no. 19, pp. 1543–1550, 2009.

Wesnes, et al. “Body size and the risk of multiple sclerosis in Norway and Italy: the Env. MS study,” *Multiple Sclerosis Journal*, vol. 21, no. 4, pp. 388–395, 2015.

Obesitede MS riski azalır !!

M. Markianos, et al. “Body mass index in multiple sclerosis: associations with CSF neurotransmitter metabolite levels,” *ISRN Neurology*, vol. 2013

MS ve genel populasyonda obesite oranları aynı

S. R. Khurana, et al., “The prevalence of overweight and obesity in veterans with multiple sclerosis,” *American Journal of Physical Medicine and Rehabilitation*, vol. 88, no. 2, pp. 83–91, 2009.

ÇELİŞKİLİ SONUÇLAR!!!

MULTİPL SKLEROZ VE OBEZİTE

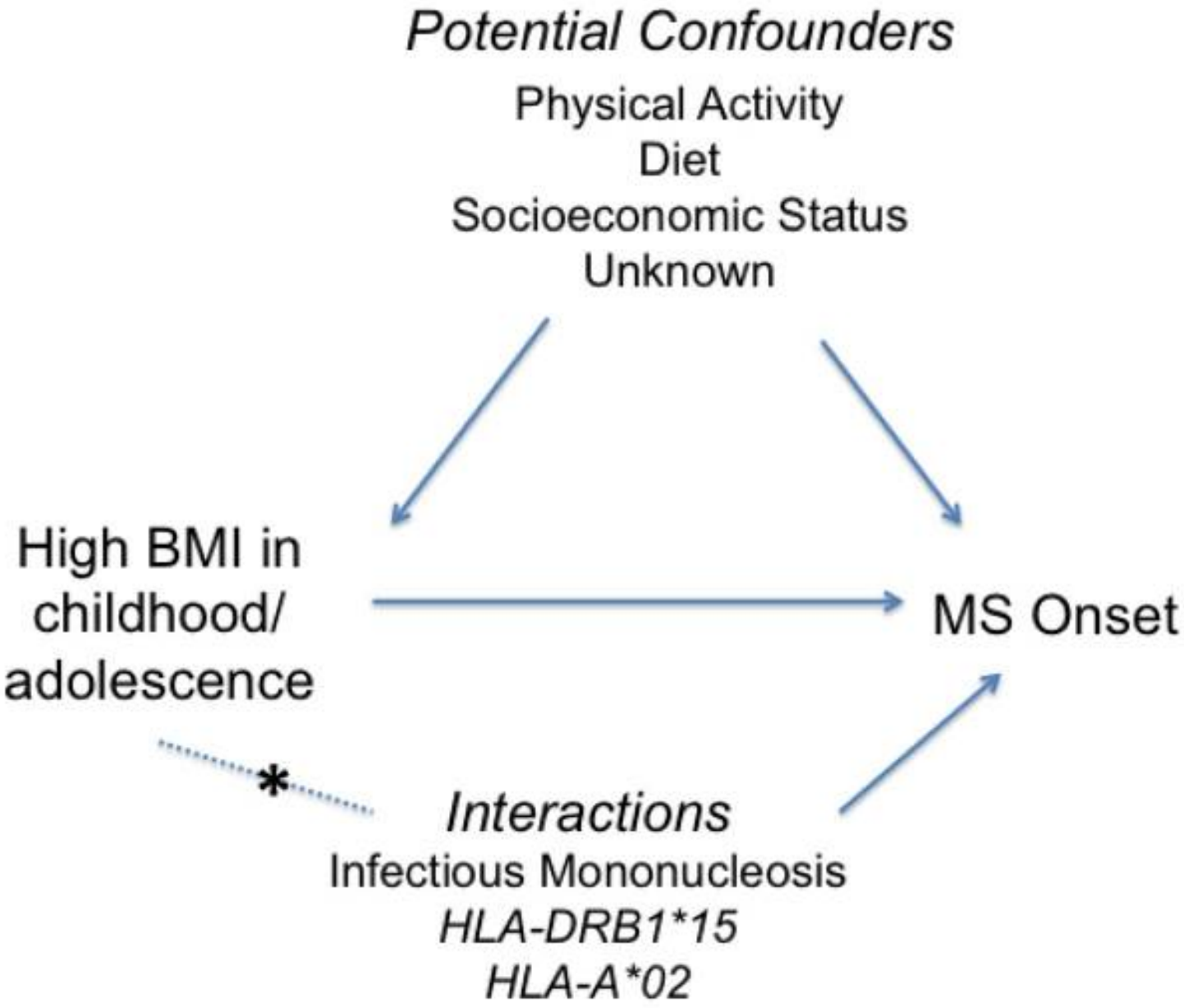
- Özellikle çocukluk çağı yüksek BMİ MS hastalığı gelişimi üzerine etkili
- 18-25 yaş arası yüksek kilo en fazla risk teşkil ettiği saptanmış*
- 8-10 yaş arası obezitede MS için risk tespit edilmemiş**
- Kadınlarda ki obezitenin MS gelişimi üzerine etkisi daha fazla
- Yetişkin dönemde ortaya çıkan obezite ise tedaviye yanıtı ve hastalık progresyonu üzerine etkili***

*The Role of Diet in Multiple Sclerosis: Mechanistic Connections and Current Evidence: Current Nutrition Reports (2018)

****Obesity and Multiple Sclerosis Susceptibility: A Review** J Neurol Neuromedicine. 2016

***Environmental factors in the development of multiple sclerosis r e v u e n e u r o l o g i q u e 2 0 1 8

MULTİPL SKLEROZ VE OBEZİTE



Obesity and Multiple Sclerosis: A Mendelian Randomization Study. PLOS Medicine 2016

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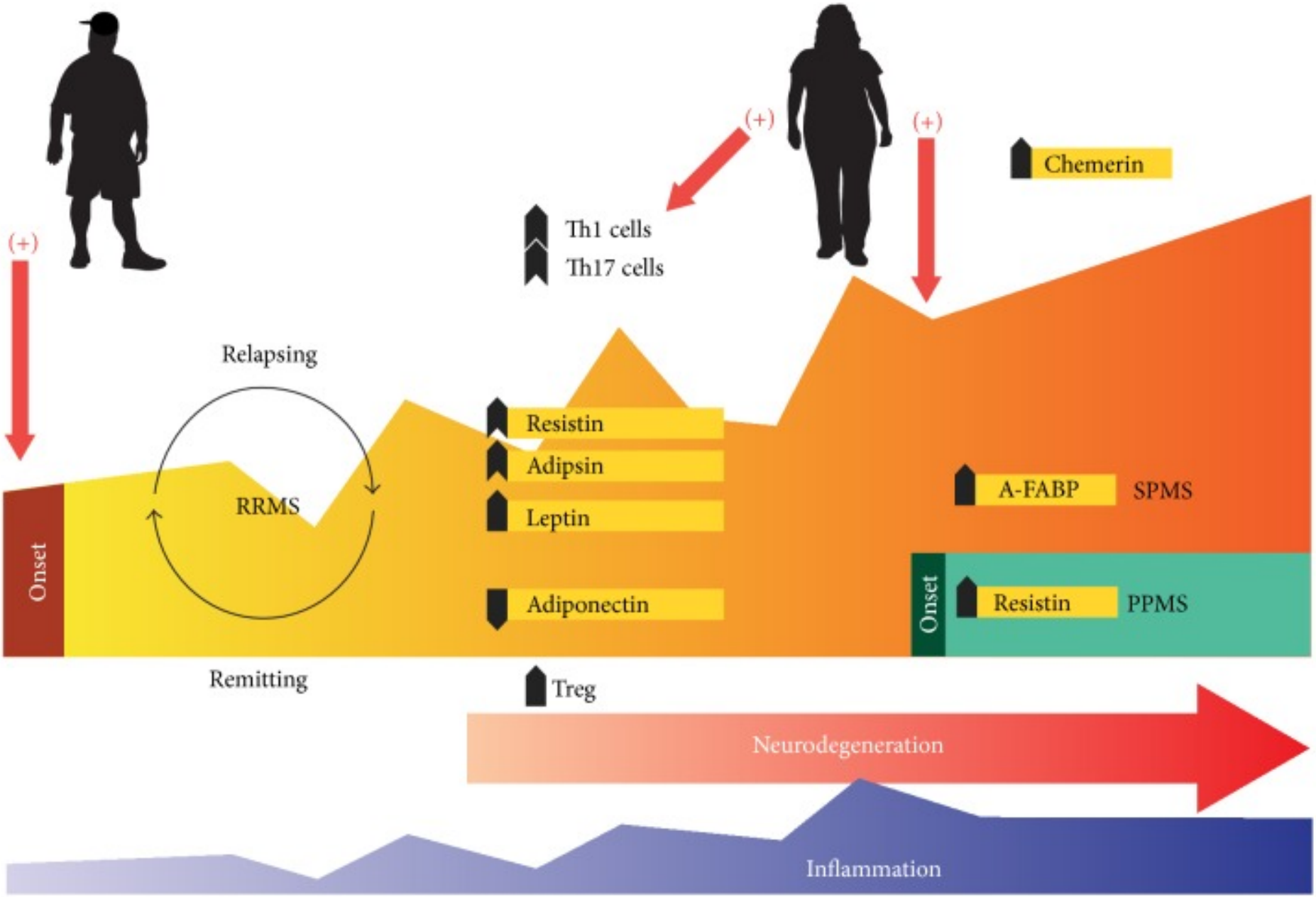

Multiple Sclerosis and Obesity: Possible Roles of Adipokines Mediators İnflamation 2016

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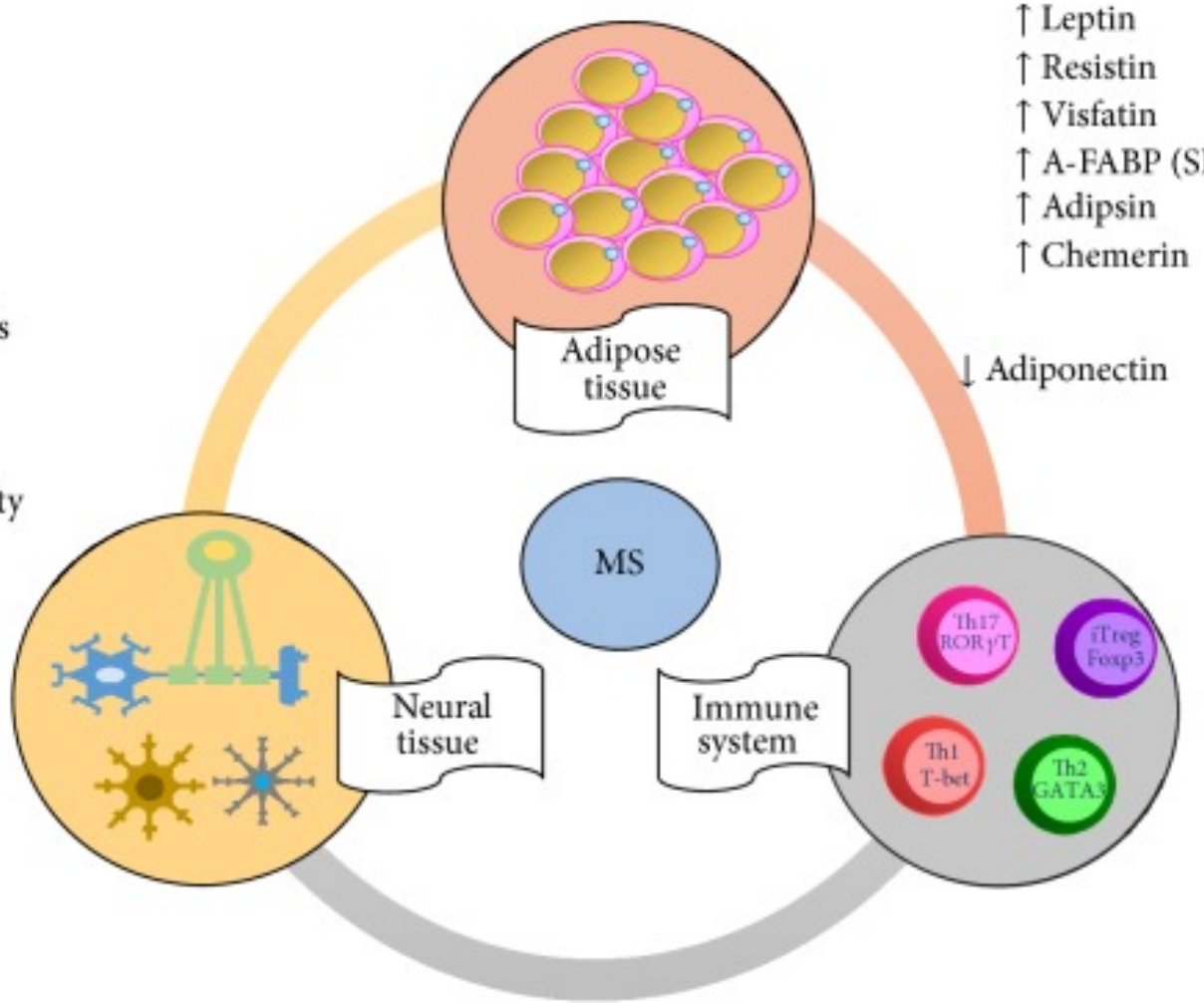

Multiple Sclerosis and Obesity: Possible Roles of Adipokines Mediators İnflamation 2016

MULTİPL SKLEROZ VE OBEZİTE

Obesity Research & Clinical Practice (2015) 9, 533–535

ELSEVIER

RESEARCH LETTER

The association between obesity and oligoclonal band formation in multiple sclerosis patients

KEYWORDS
Body-mass index;
Obesity;
Oligoclonal band;
Multiple sclerosis

Summary Since some neurological disorders present with increased body-mass index (BMI) and cerebr… (OCB), obesity-induced inflammation h… B. We investigated the asso… res of MS in 120 patie… ase with high OCB po… 0 patients displayed … able BMI and weight val- u… were not correlated with BMI and … gh BMI did not significantly differ by means of … nual attack number, disease duration and EDSS scores. Our results argue against a possible role of obesity in OCB formation. Moreover, obesity does not appear to influence disability and clinical progression of MS patients.

OKB oluşumu obezite ile korele değil

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MULTİPL SKLEROZ VE DİYET

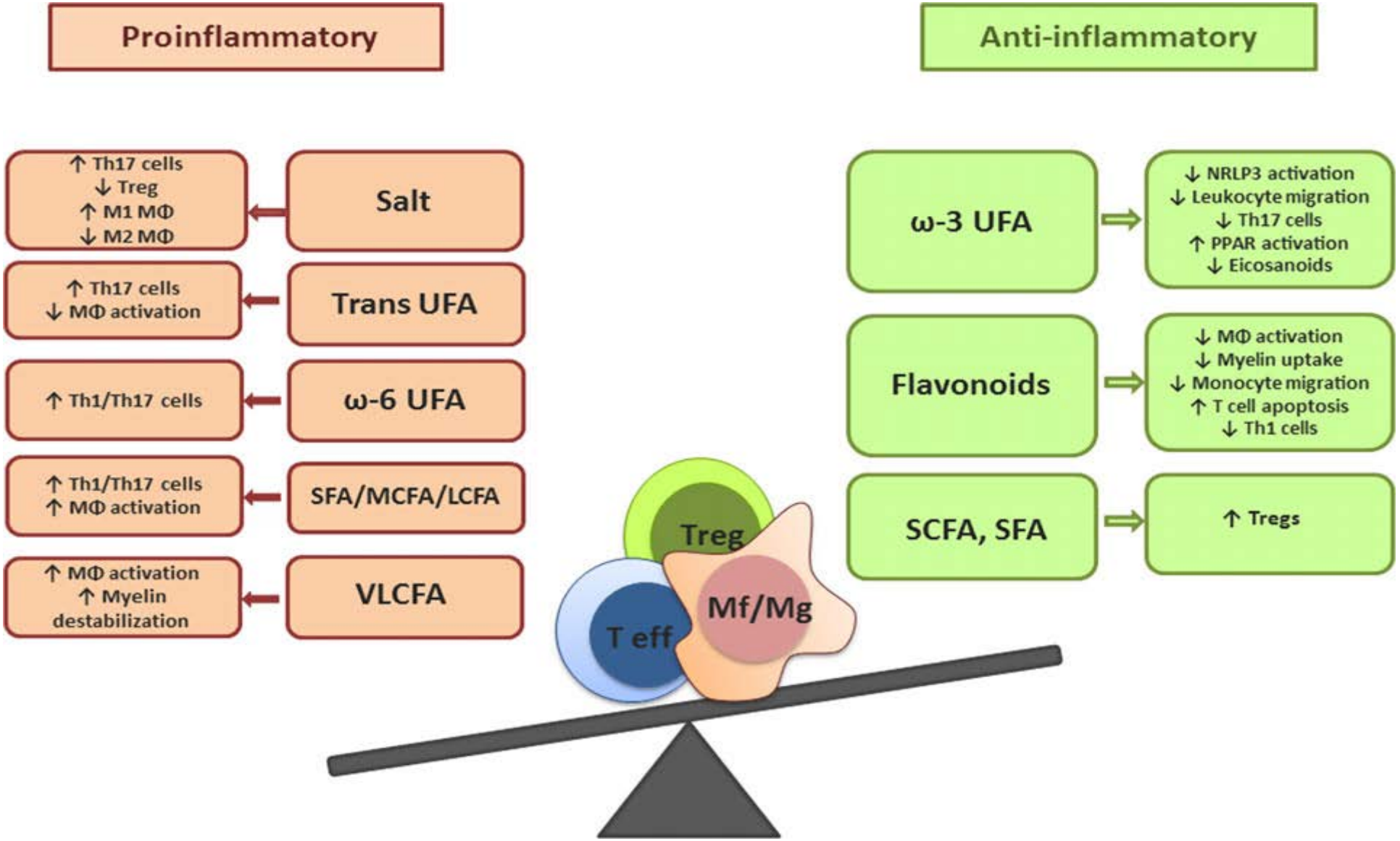
Spesifik bir diyet yok maalesef

Kanıtlanmış iki nutrisyonel takviye tavsiyesi var bunlar;

1. D vitamini : MS'in potansiyel bir biyobelirteç olduğunu belirtmek için yeterli kanıt vardır
2. B12 vitamini : B-12 konsantrasyonu ile EDSS skoru arasında negatif bir ilişki olduğunu gösterilmiştir

Influence of Diet in Multiple Sclerosis: A Systematic Review. Adv Nutr. 2017 May 15;8(3):463-472

MULTİPL SKLEROZ VE DİYET



Western lifestyle and immunopathology of multiple sclerosis. ANNALS OF THE NEW YORK ACADEMY OF SCIENCES 2018

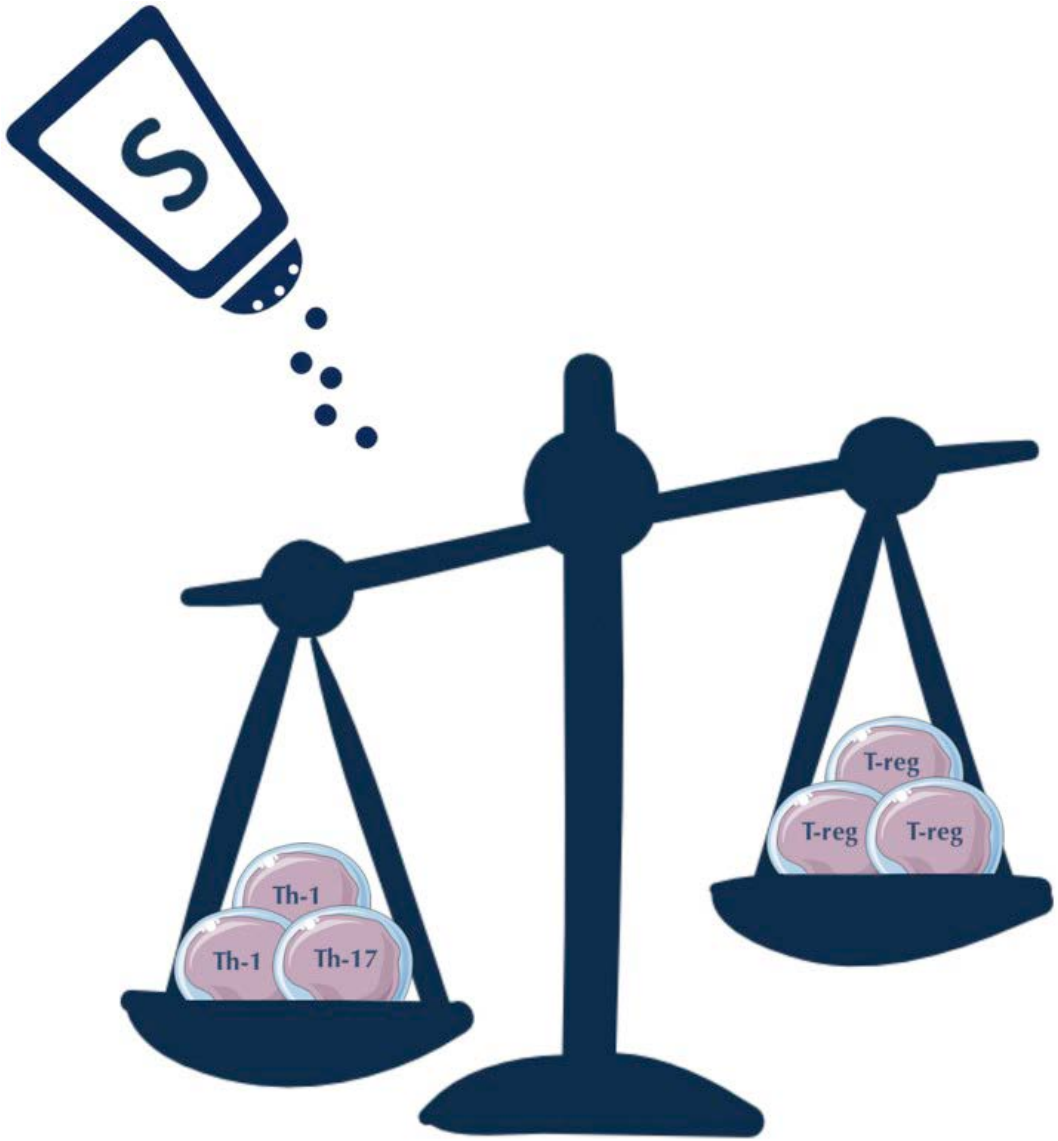
MULTİPL SKLEROZ VE TUZ

MULTİPL SKLEROZ VE TUZ

İnsan vücudunun günlük tuz ihtiyacı 6 gramdır. 1 tatlı kaşığı kadar

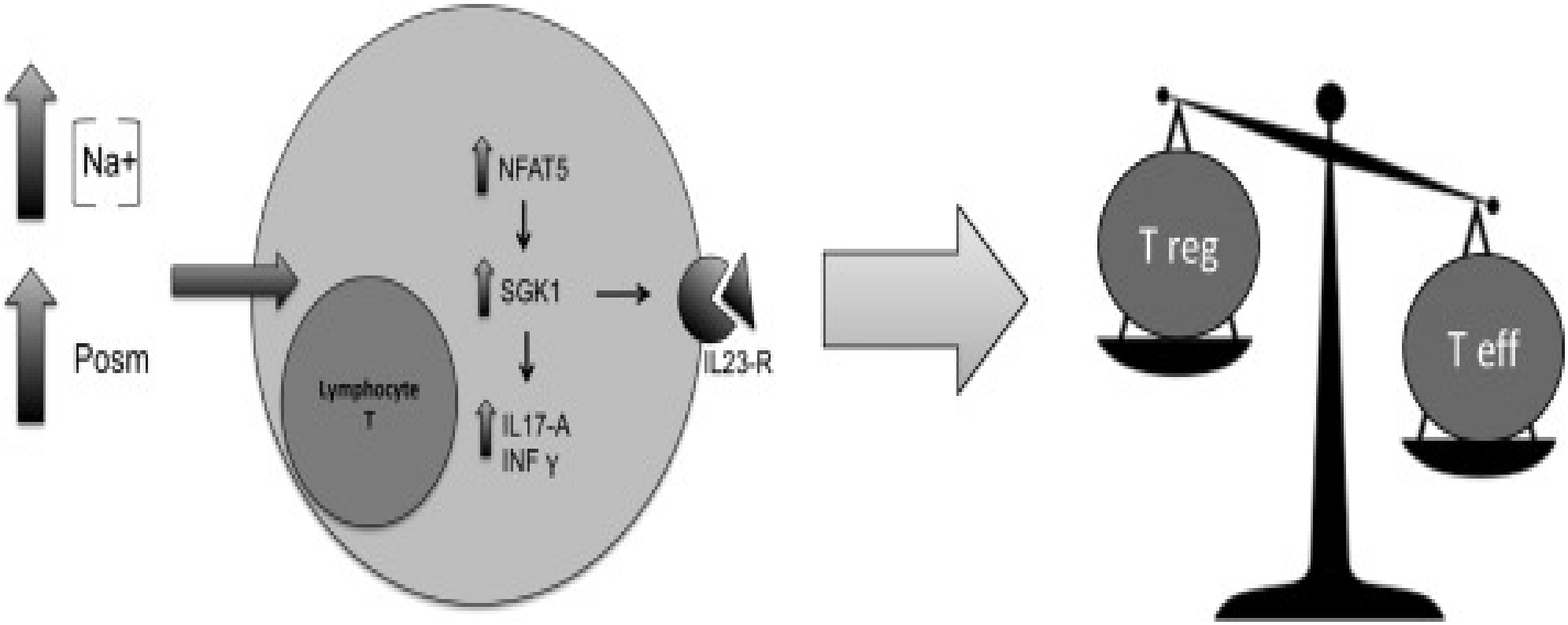
BESİN (100 gr)	TUZ (mg.)	SODYUM (mg.)
Beyaz ekmek	858	33
Tam buğday ekmeği	100	40
Çavdar ekmeği	664	265
Kepekli ekmek	1112	445
Dana eti	123	49
Kuzu eti	180	72
Tavuk eti	199	82
Hindi eti	179	72
Balık eti	299	59
Pastırma	6201	2480
Sucuk	2548	1019
İnek peyniri	1118	447
Keçi peyniri	3575	1430
Koyun peyniri	2452	481
Yumurta	120	48
Kuru baklagiller	20	8
Süt	50	20
Yoğurt	51	20
Zeytin	3475	1390
Taze fasulye	1118	447
Enginar	1088	455
Bamya	1124	450

MULTİPL SKLEROZ VE TUZ



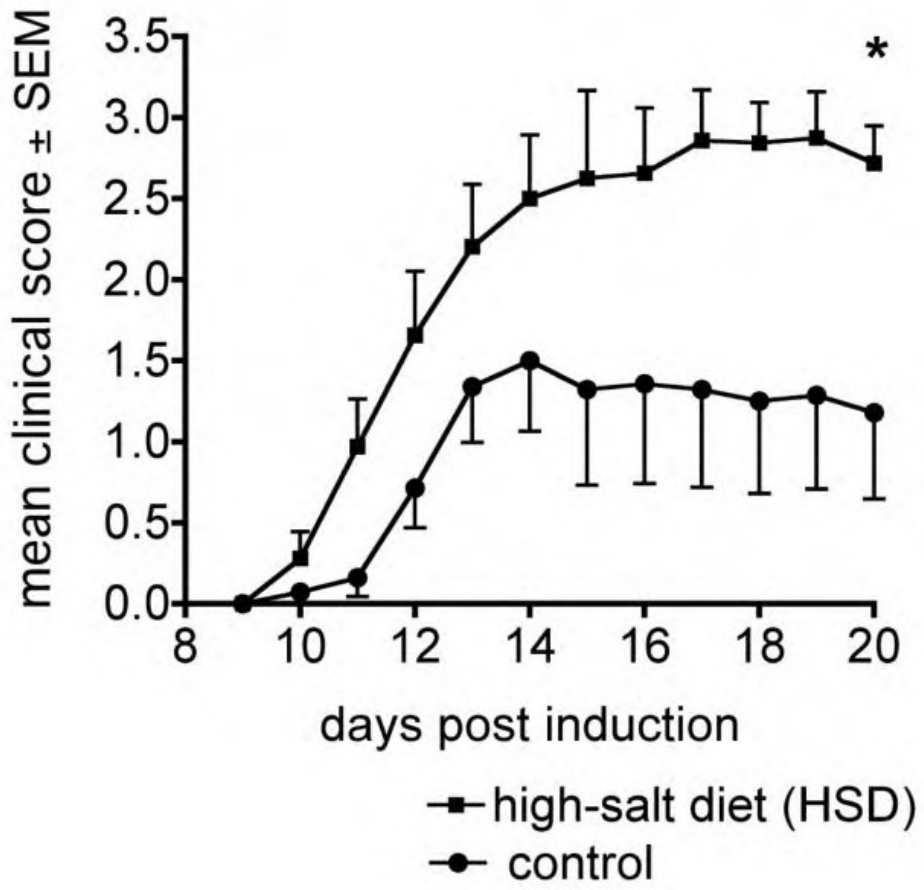
Autoimmunity Reviews 17 (2018)

MULTİPL SKLEROZ VE TUZ



Salt, inflammatory joint disease, and autoimmunity. Joint Bone Spine 2018

MULTİPL SKLEROZ VE TUZ



Nature. 2013

MULTİPL SKLEROZ VE TUZ

122 RR-MS hastası

Tahmini günlük sodyum alımı: Günlük sodyum atılımını tahmin etmek için spot idrar toplama

Tuz alımı şu şekilde sınıflandırılmıştır: yüksek:> 4.8 g / gün orta: 2 ila 4.8 g / gün Düşük: <2 g / gün

Nüks oranı, 2 g / gün'den daha az alım yapılanlara göre yüksek tuz alımında 3.95 kat daha fazla (% 95 CI 1.39--11.21)

Günde 2.0 ila 4.8 g / gün alım yapan katılımcılar düşük alım grubunun 2.75 katı olan nüks oranlarına sahip(% 95 CI 1.30-5.81).

Kohort ortalamasının 1 g üstündeki her artış, T2 sayımında 3.65- lezyon artışı ile ilişkili (SD 0.77, P <0.001).

Sodium intake is associated with increased disease activity in multiple sclerosis. j Neurol Neurosurg Psychiatry. 2015

Kesin ve Olası Yaşam Stili ve Çevresel Risk Faktörleri

Factor	OR	HLA gene interaction	Combined OR (nongenetic factor + HLA allele)	Effect during adolescence	Immune system implied	Level of evidence
Smoking	~1.6	Yes	14	No	Yes	+++
EBV infection (seropositivity)	~3.6	Yes	~15	Yes	Yes	+++
Vitamin D level <50 nM	~1.4	No	NA	Probably	Yes	+++
Adolescent obesity (BMI >27 at age 20 years)	~2	Yes	~15	Yes	Yes	+++
CMV infection (seropositivity)	0.7	No	NA	Unknown	Yes	++
Night work	~1.7	No	NA	Yes	Yes	++
Low sun exposure	~2	No	NA	Probably	Yes	++
Infectious mononucleosis	~2	Yes	7	Yes	Yes	++
Passive smoking	~1.3	Yes	6	No	Yes	+
Organic solvent exposure	~1.5	Unknown	Unknown	Unknown	Unknown	+
Oral tobacco/nicotine	0.5	No	NA	Unknown	Yes	+
Alcohol	~0.6	No	NA	Unknown	Yes	+
Coffee	~0.7	No	NA	Unknown	Yes	+

Sizler farkında değilsiniz ama, onlar şu gerçeğin farkındadırlar: Tarihten Türk çıkarılırsa tarih kalmaz.

Alman İktisatçı Fritz Neumark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