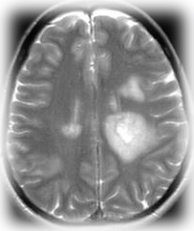
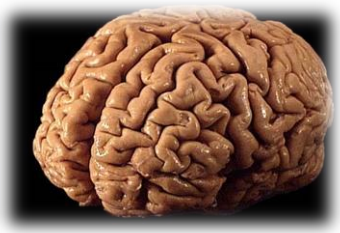
vitamin D AND HUMAN HEALTH

from the gamete to the grave

Vitamin D and MS

Gavin Giovannoni





Barts and The London School of Medicine and Dentistry

UCLPartners Academic Health Science Partnership

Latitude

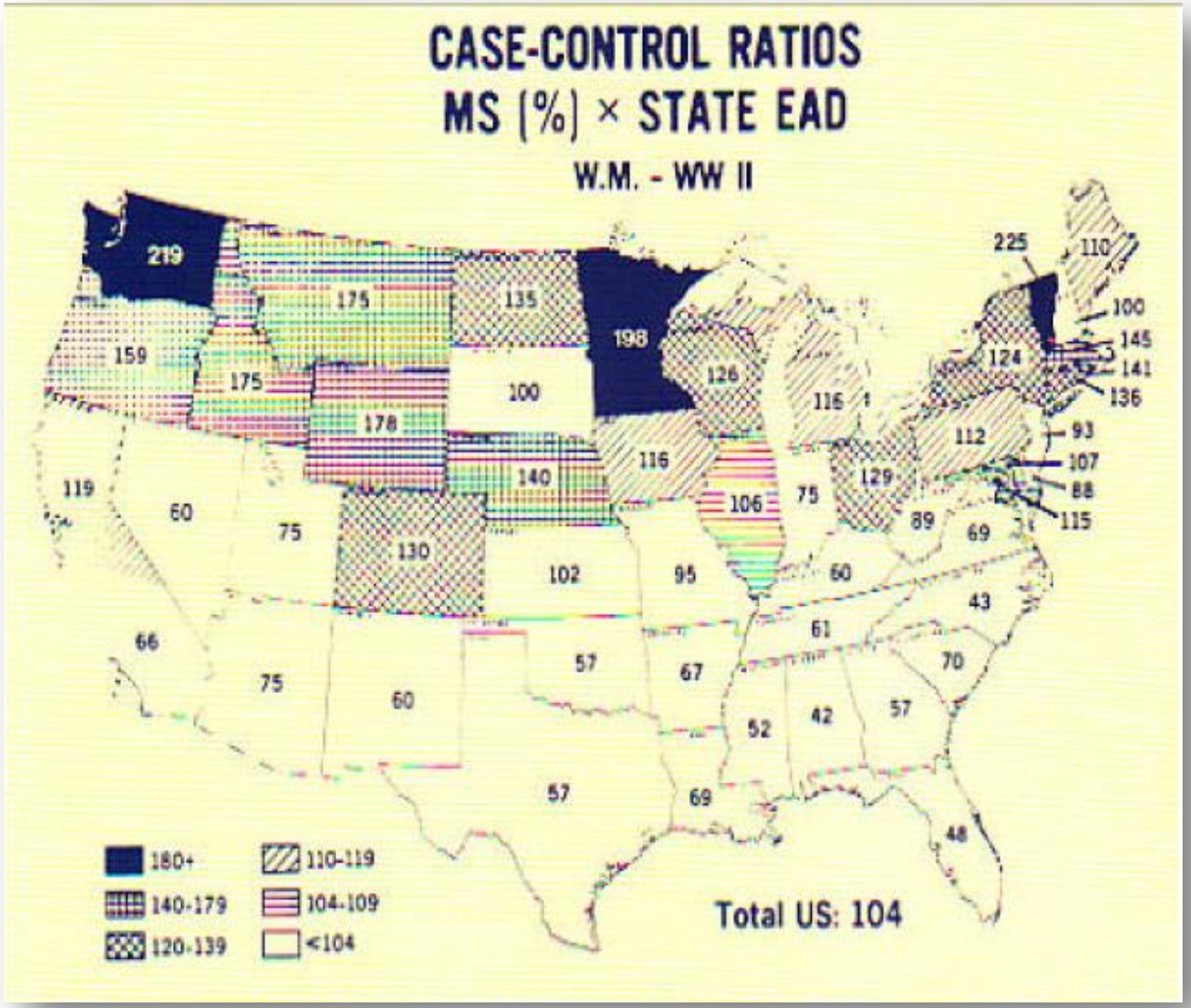
Geographical Distribution of MS

- First study of geographical distribution of MS prevalence by Davenport
- Key finding: Geographical variation in MS prevalence, implying population (genetic) and environmental contributions to MS risk

This article was published in *McAlpine's Multiple Sclerosis* 4th edition. Compston A. ed. London Churchill Livingstone Elsevier 2006;55 Fig 1.33 Copyright Elsevier (2007)

Davenport CB. In: *Association for Research in Nervous and Medical Conditions (ARNMD)*, vol 2. New York: Hoeber, 1921;pp8–19.

Prevalence of MS in the USA



Kurtzke et al, 1980

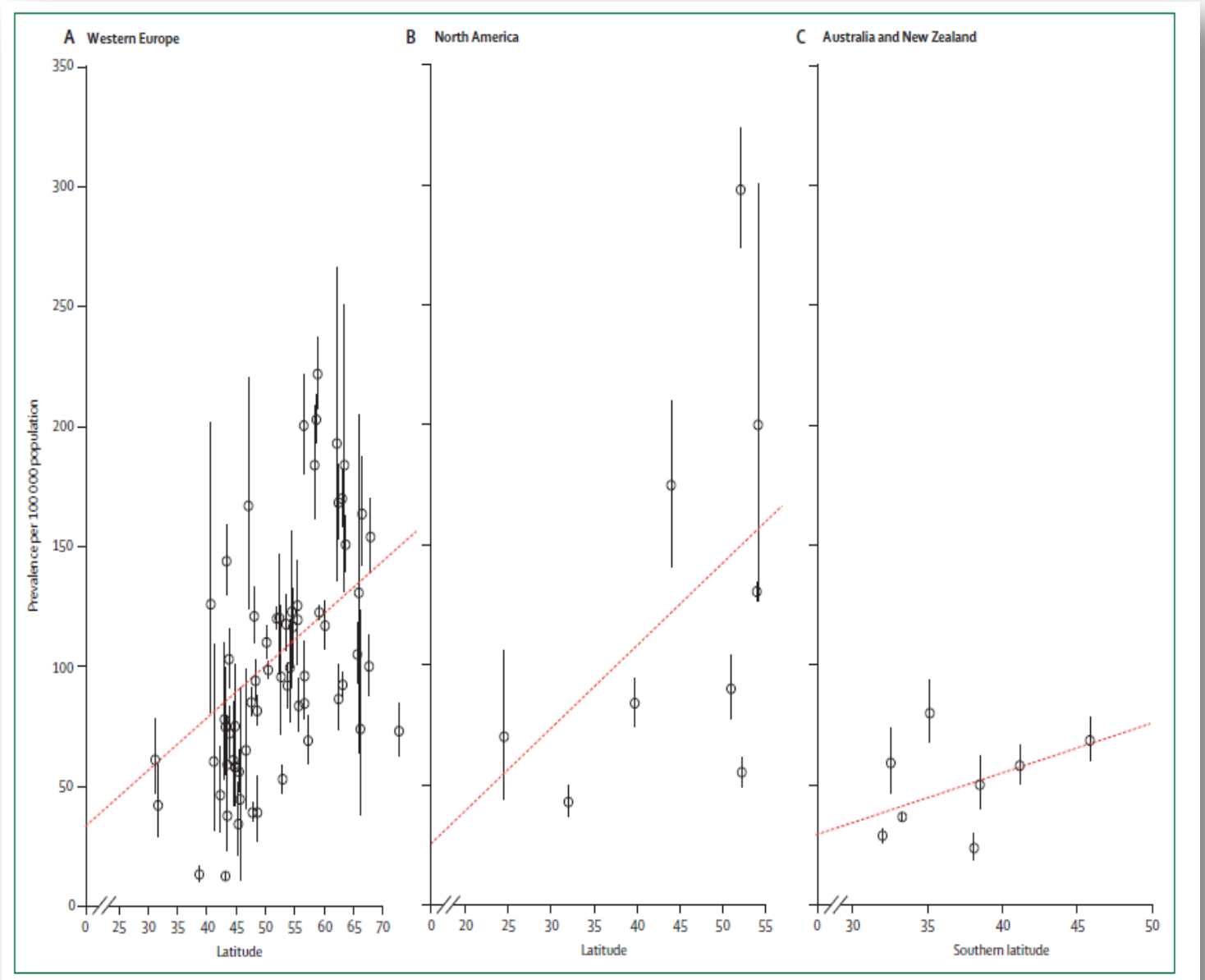
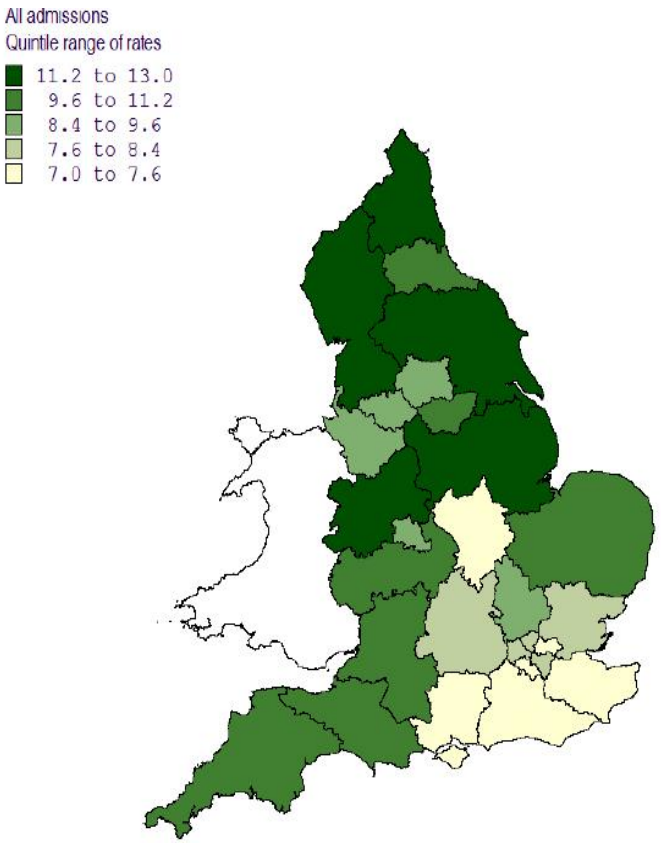


Figure 2: Prevalence by geographical latitude

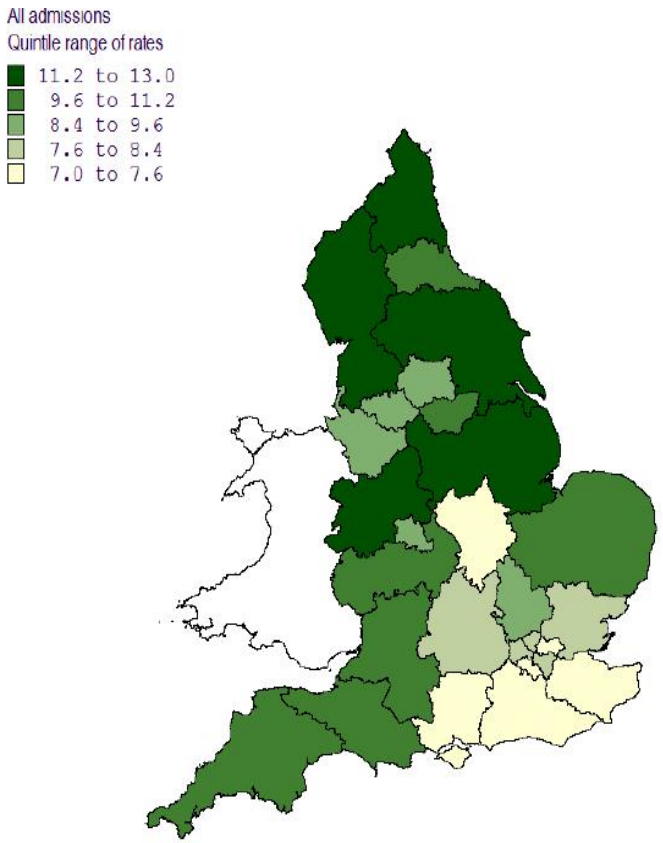
Koch-Henriksen and Sorenson, 2010

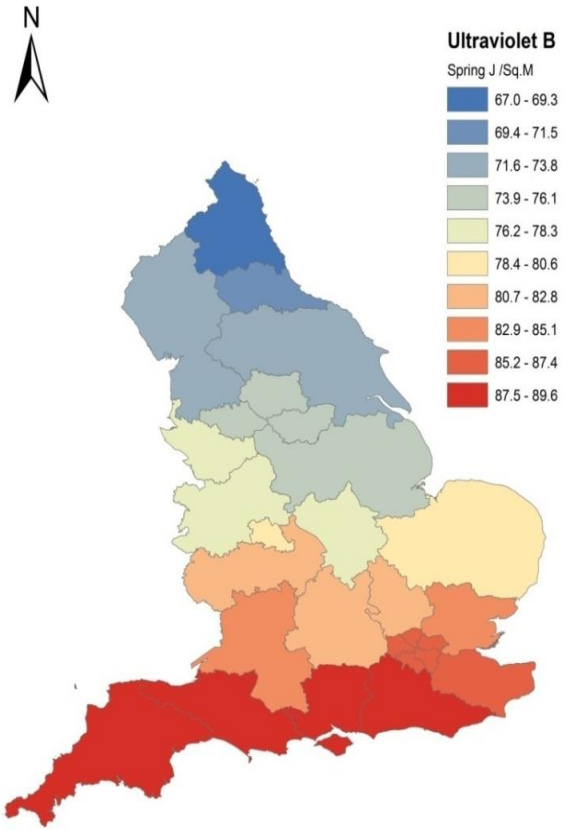
MS-related hospital admissions England



Ramagopalan et al, 2011

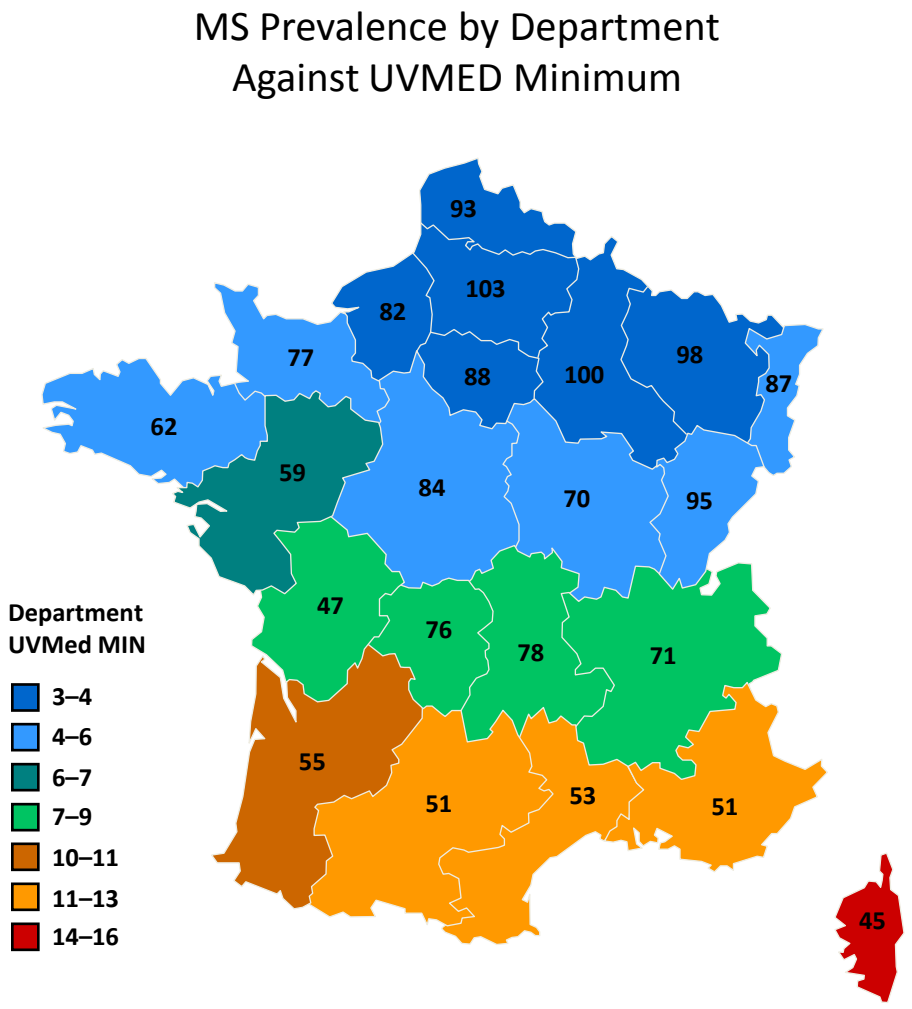
Relationship of MS prevalence to ultraviolet exposure





Ramagopalan et al, 2011

UVB and MS prevalence in France



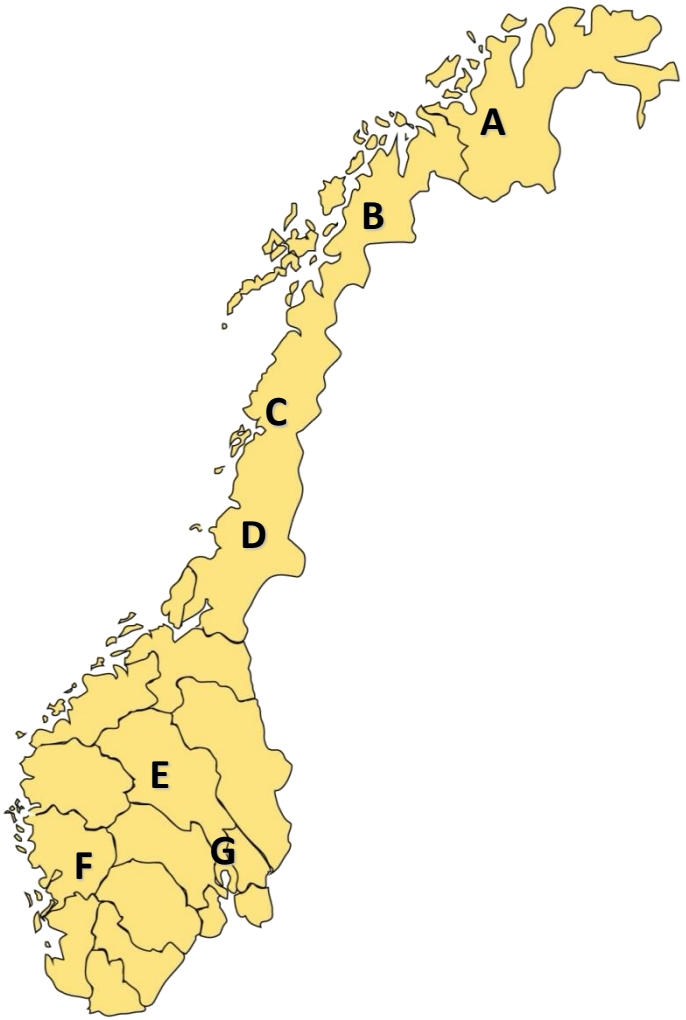
Orton et al. Neurology. 2011 Feb 1;76(5):425-31.

Prevalence of MS in Norway

- Prevalence data for counties in Norway (/10^5):

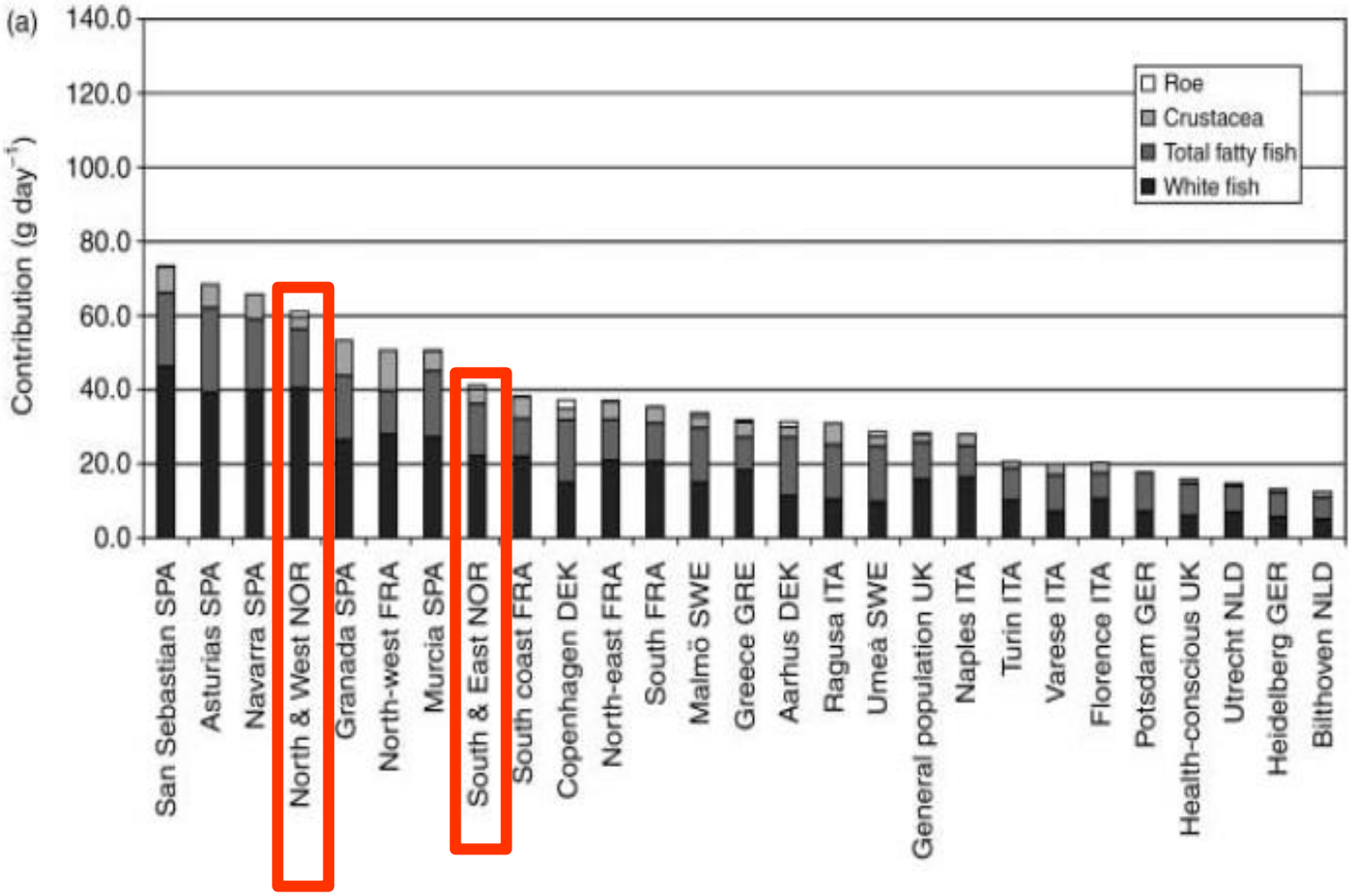
A Finnmark[1] (2003)	>83
B Troms[1] (2003)	>104
C Nordland (1999)	106
D Nord Trøndelag (1999)	164
E Oppland[2] (2002)	190
F Hordaland (2003)	151
G Oslo[2] (2005)	154

- In Norway, MS prevalence does not rise with increasing latitude, unlike other northern European countries and the USA
- As expected, measured UV radiation levels decrease with increasing latitude



Kampman et al, 2007

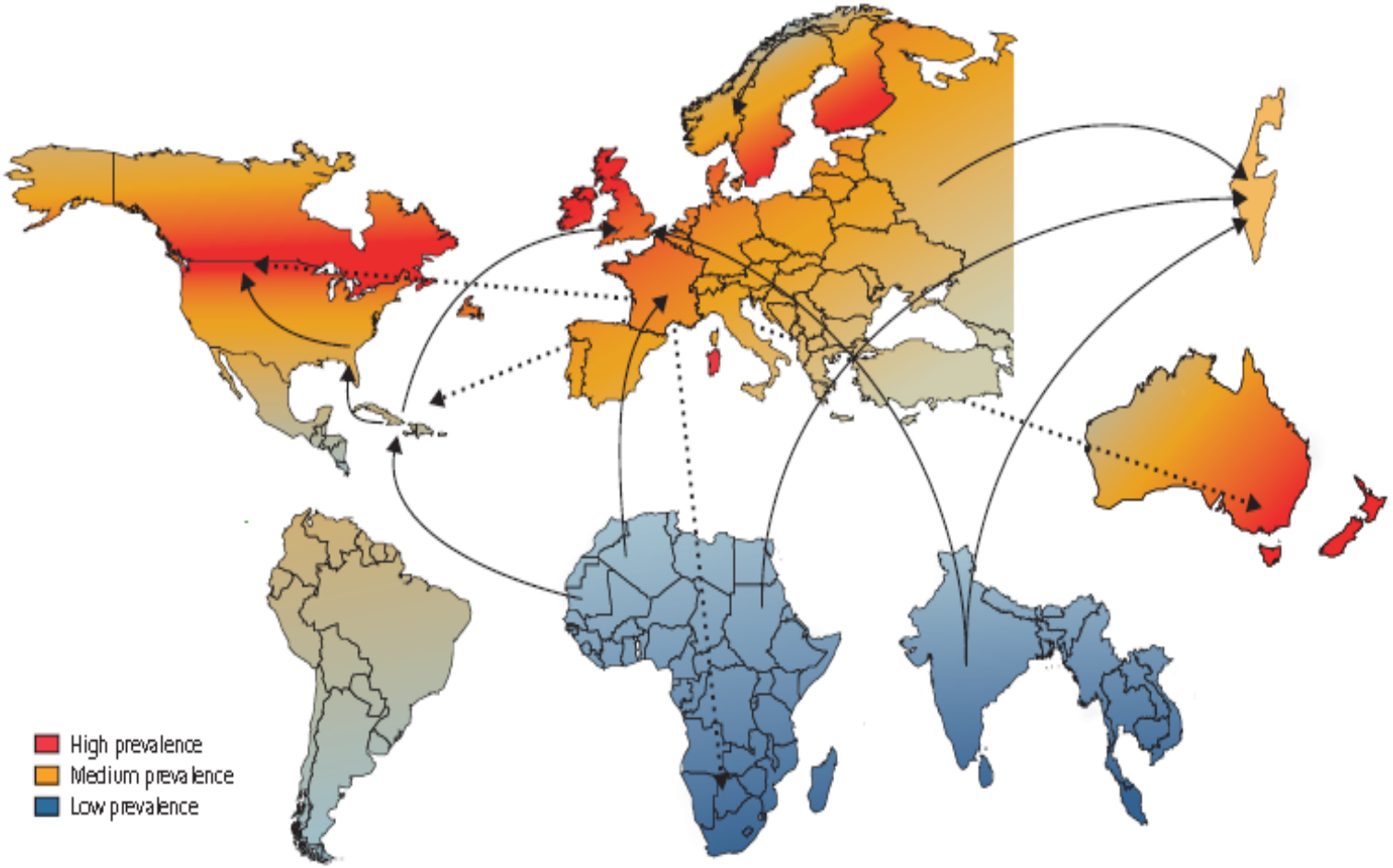
Fish consumption



Kampman et al, 2007

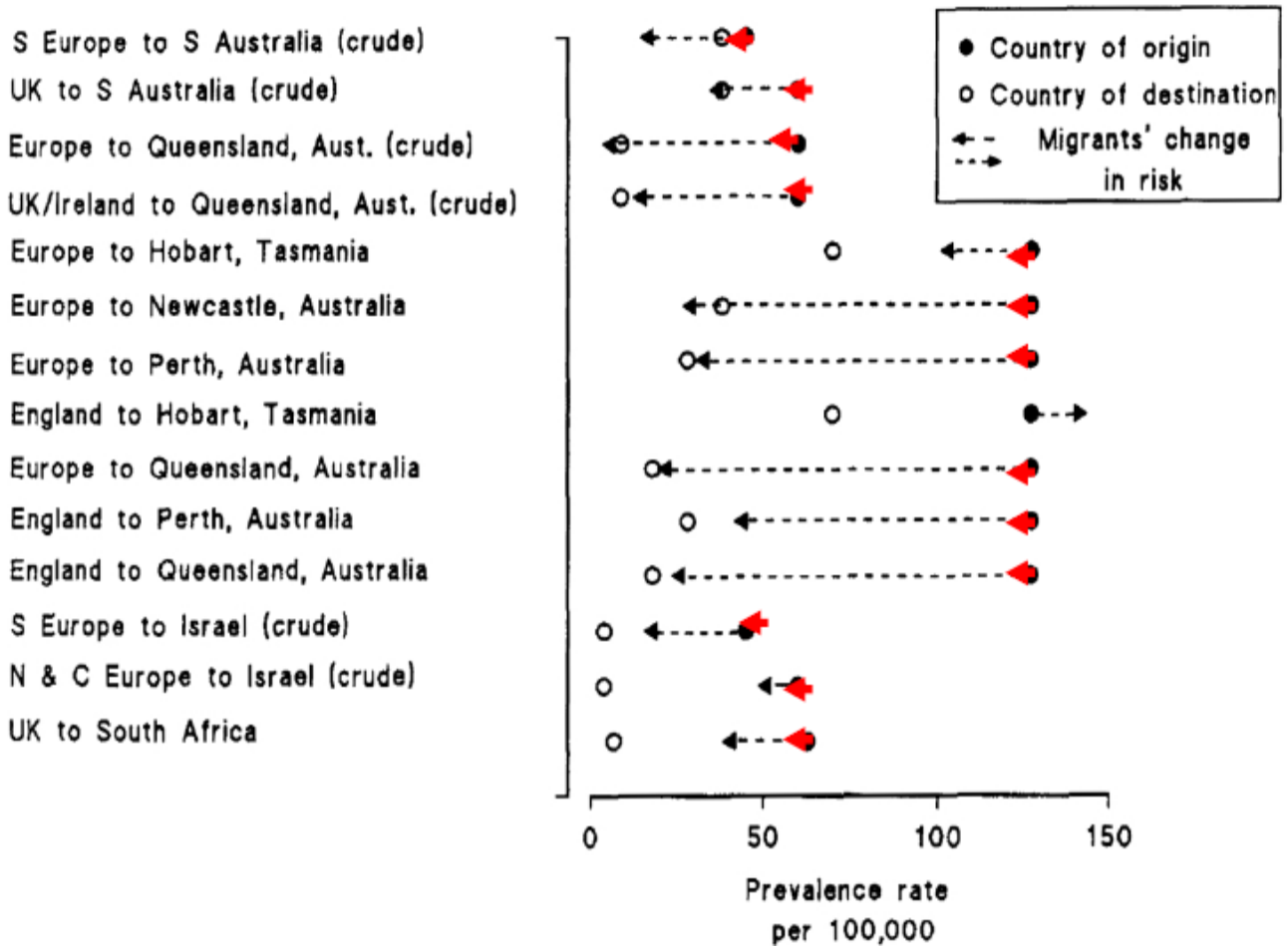
Migration

Migration studies



Compston & Coles, Lancet 2008.

The effect of migration on MS prevalence

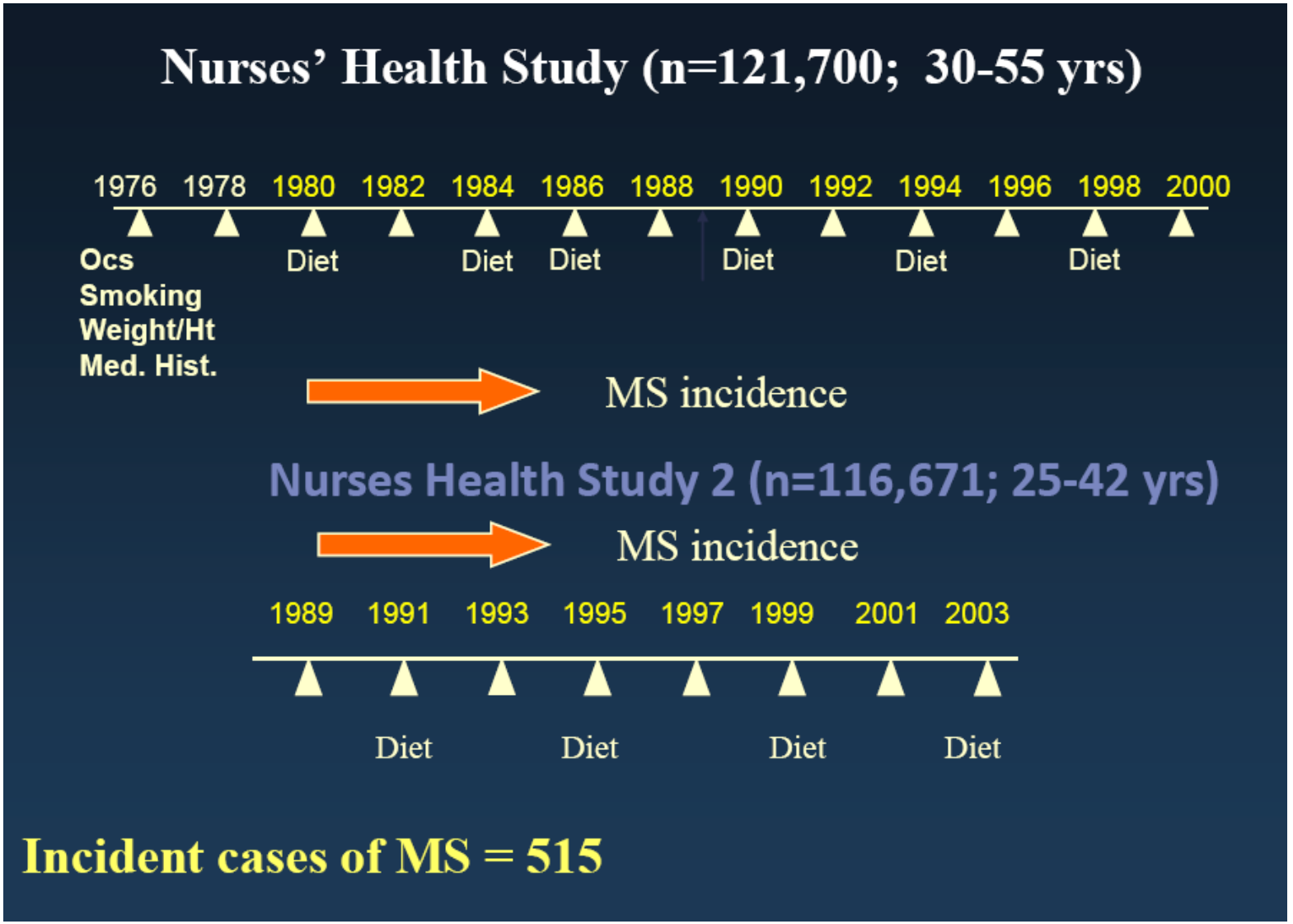


Gale , 1995

Prevention

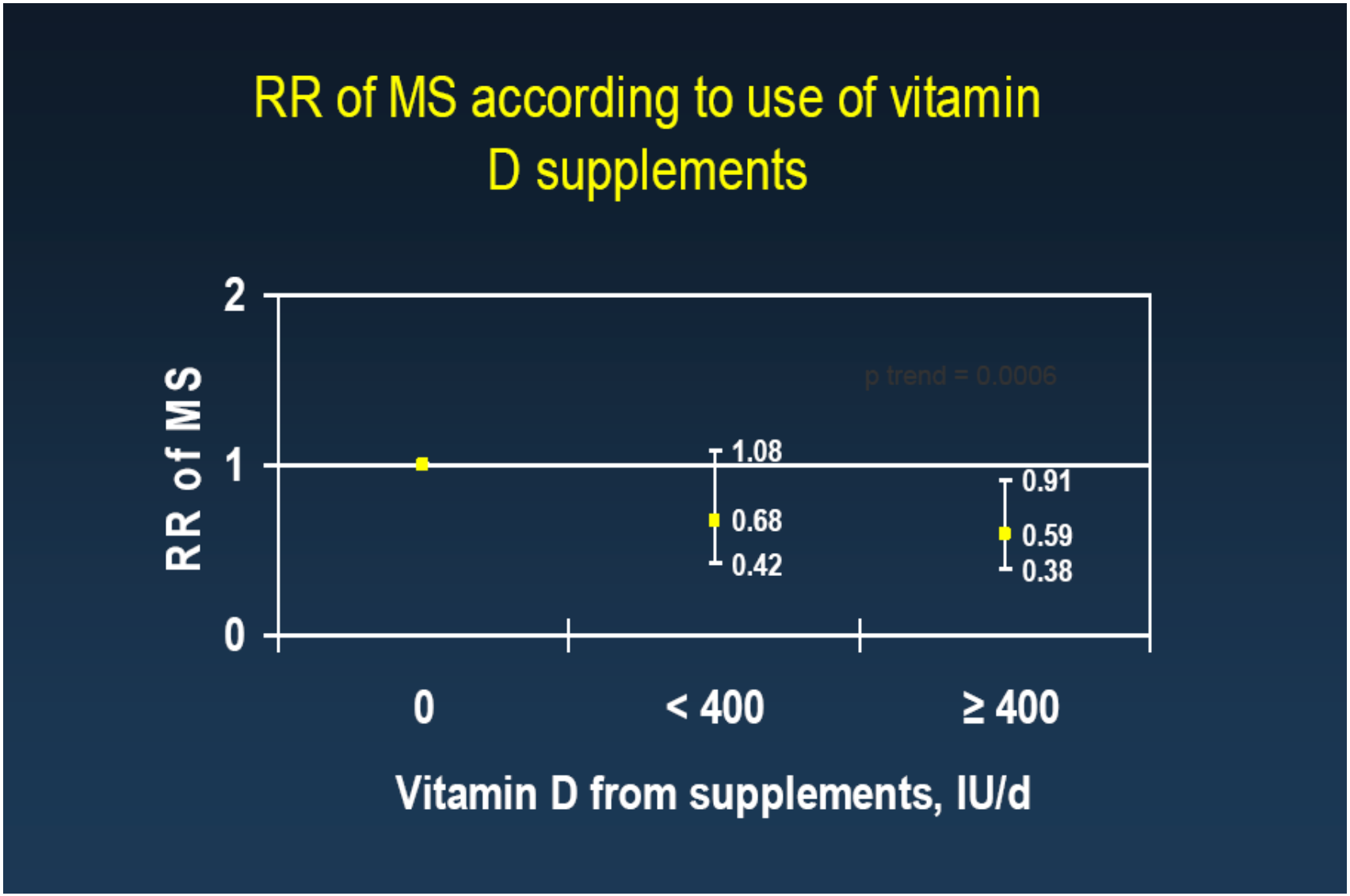
vD supplementation

Vitamin D and MS



Munger et al, 2004

Vitamin D and MS

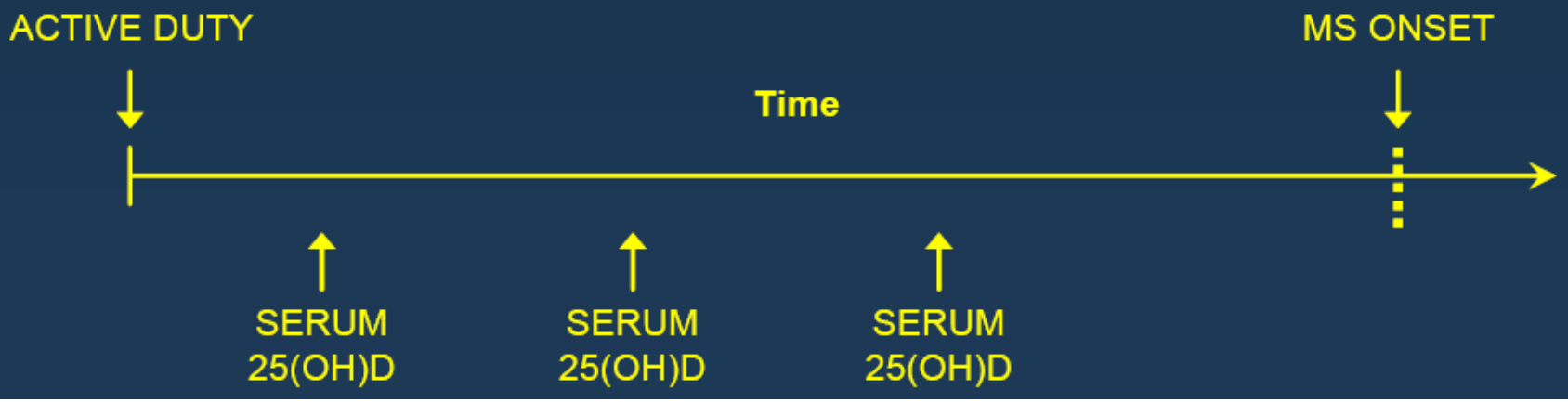


Munger et al, 2004

vD levels

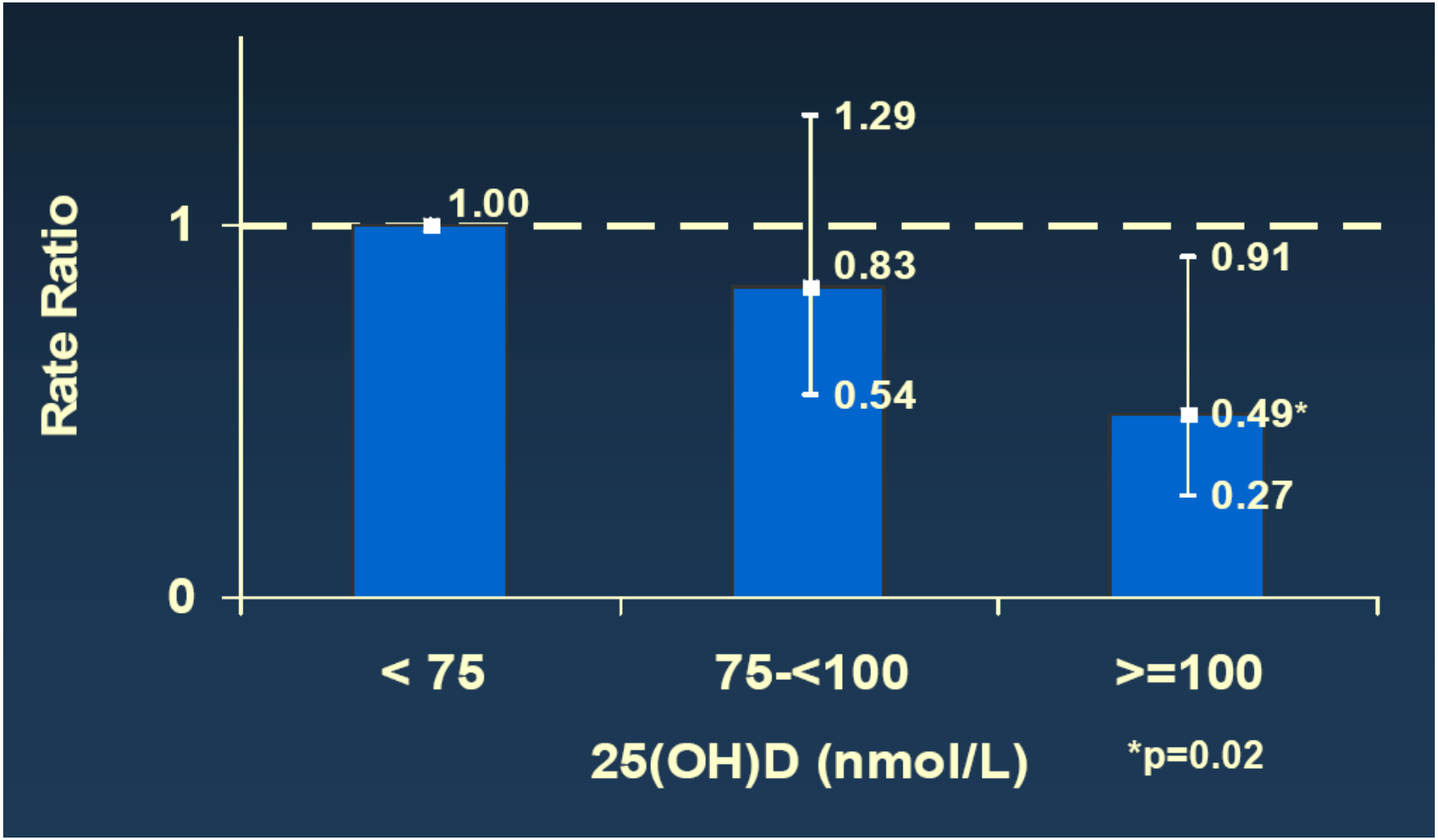
Vitamin D and MS

- >40 million serial blood samples since 1990 from over 8 million US military personnel
- Cases (n=257) identified via Physical Disability Agencies
- Controls (n=514) matched by age, sex, race/ethnicity, dates of blood collection



Munger et al, 2006

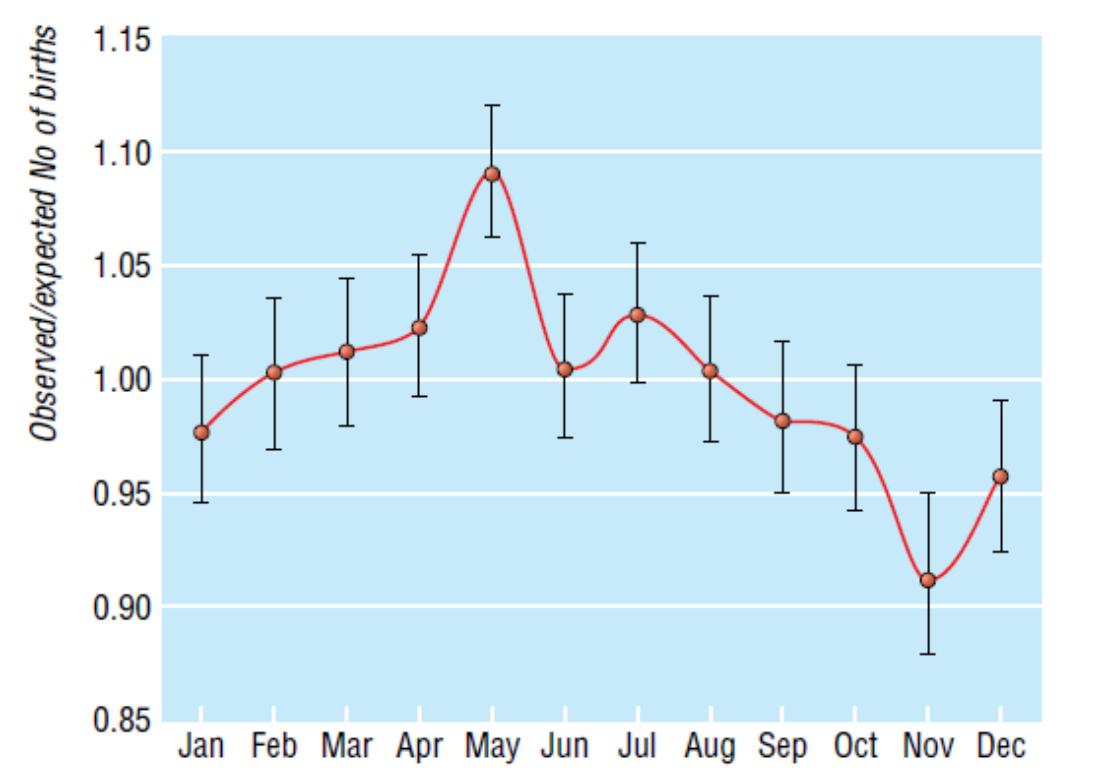
Vitamin D and MS



Munger et al, 2006

When to supplement?

Vitamin D and MS- Month of Birth



- Role of light exposure in MS supported by month of birth effect
- In northern hemisphere, significantly more people with MS are born in May (less light during pregnancy) than November (more light during pregnancy)
- Birth month effect is inverse in the southern hemisphere

Willer et al, 2005

Disanto et al. BMC Medicine 2012, 10:69
http://www.biomedcentral.com/1741-7015/10/69

BMC Medicine

RESEARCH ARTICLE Open Access

Month of birth, vitamin D and risk of immune-mediated disease: a case control study

Giulio Disanto[1,2†], George Chaplin[3†], Julia M Morahan[1,2], Gavin Giovannoni[4], Elina Hyppönen[5], George C Ebers[1,2*] and Sreeram V Ramagopalan[1,2,4,6*]

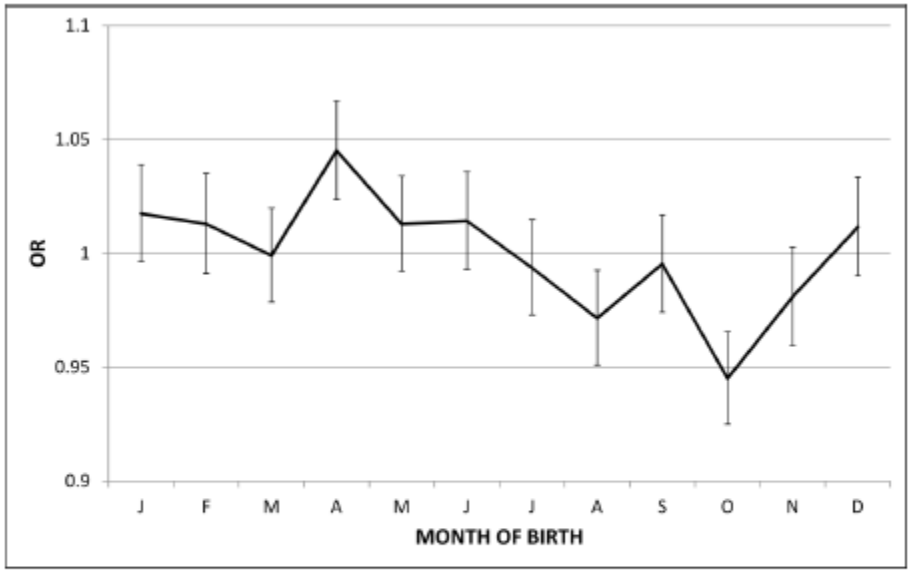


Figure 1 Odds ratio distribution with 95% CI based on month of birth in all immune-mediated diseases (n = 115,172) versus general population. April peak and October trough of risk can be observed.

Table 2 Birth percentages and monthly odds ratios with 95%CI for each and all immune-mediated diseases

Month	All immune-mediated diseases			Multiple sclerosis			Rheumatoid arthritis		
	Birth %	OR	95% CI	Birth %	OR	95% CI	Birth %	OR	95% CI
Jan	**8.63**	**1.02 +**	**0.99 to 1.04**	8.51	1.01	0.97 to 1.05	8.44	0.99	0.95 to 1.03
Feb	7.90	1.01	0.99 to 1.04	7.76	0.99	0.95 to 1.03	7.94	1.02	0.98 to 1.06
Mar	8.88	1.00	0.98 to 1.02	8.67	0.97	0.93 to 1.01	8.99	1.01	0.98 to 1.05
Apr	**8.77**	**1.05 +**	**1.02 to 1.07**	**8.79**	**1.05 +**	**1.002 to 1.09**	**8.78**	**1.05 +**	**1.01 to 1.08**
May	8.83	1.01	0.99 to 1.03	**9.41**	**1.08 +**	**1.04 to 1.13**	8.64	0.99	0.95 to 1.03
Jun	8.44	1.01	0.99 to 1.04	8.70	1.04	1.01 to 1.09	8.47	1.02	0.98 to 1.06
Jul	8.49	0.99	0.97 to 1.01	8.51	0.99	0.95 to 1.04	8.37	0.98	0.94 to 1.01
Aug	**8.16**	**0.97 -**	**0.95 to 0.99**	8.20	0.98	0.94 to 1.02	**8.14**	**0.97 -**	**0.93 to 1.00**
Sep	8.12	1.00	0.97 to 1.02	7.94	0.96	0.92 to 1.01	8.10	1.00	0.96 to 1.03
Oct	**8.05**	**0.95 -**	**0.92 to 0.97**	**8.08**	**0.96 -**	**0.92 to 1.00**	**8.20**	**0.96 -**	**0.93 to 0.99**
Nov	7.61	0.98	0.96 to 1.00	**7.43**	**0.96 -**	**0.91 to 1.00**	7.65	0.99	0.95 to 1.02
Dec	8.11	1.01	0.99 to 1.03	8.01	1.00	0.96 to 1.04	**8.30**	**1.04 +**	**1.00 to 1.07**
Month	Ulcerative colitis			Systemic lupus erythematosus			Crohn's disease		
	Birth %	OR	95% CI	Birth %	OR	95% CI	Birth %	OR	95% CI
Jan	8.63	1.02	0.97 to 1.06	**9.57**	**1.14 +**	**1.03 to 1.27**	**8.99**	**1.06 +**	**1.01 to 1.11**
Feb	**8.07**	**1.04 +**	**0.99 to 1.09**	7.86	1.00	0.90 to 1.13	7.84	1.01	0.96 to 1.06
Mar	8.90	1.00	0.96 to 1.05	8.75	0.98	0.88 to 1.09	8.94	1.01	0.96 to 1.06
Apr	**8.92**	**1.06 +**	**1.02 to 1.11**	8.85	1.05	0.95 to 1.18	8.54	1.02	0.97 to 1.07
May	8.73	1.00	0.96 to 1.05	**9.71**	**1.12 +**	**1.01 to 1.24**	**8.40**	**0.96 -**	**0.91 to 1.01**
Jun	8.25	0.99	0.94 to 1.04	7.61	0.90	0.81 to 1.02	8.44	1.02	0.97 to 1.07
Jul	8.44	0.99	0.94 to 1.03	8.58	1.00	0.90 to 1.12	8.75	1.03	0.98 to 1.08
Aug	**8.15**	**0.97 -**	**0.93 to 1.02**	8.40	1.00	0.90 to 1.12	8.13	0.97	0.92 to 1.02
Sep	8.18	1.00	0.96 to 1.05	**7.51**	**0.91 -**	**0.81 to 1.02**	**8.45**	**1.04 +**	**0.99 to 1.10**
Oct	**7.91**	**0.93 -**	**0.88 to 0.97**	7.93	0.94	0.84 to 1.05	**7.89**	**0.92 -**	**0.87 to 0.97**
Nov	7.69	0.99	0.95 to 1.04	**7.09**	**0.91 -**	**0.81 to 1.03**	7.78	1.00	0.95 to 1.06
Dec	8.13	1.01	0.97 to 1.06	8.13	1.02	0.91 to 1.14	7.84	0.97	0.93 to 1.03

+ and - indicate highest and lowest odds ratios, respectively. CI: confidence intervals; OR: odds ratio.

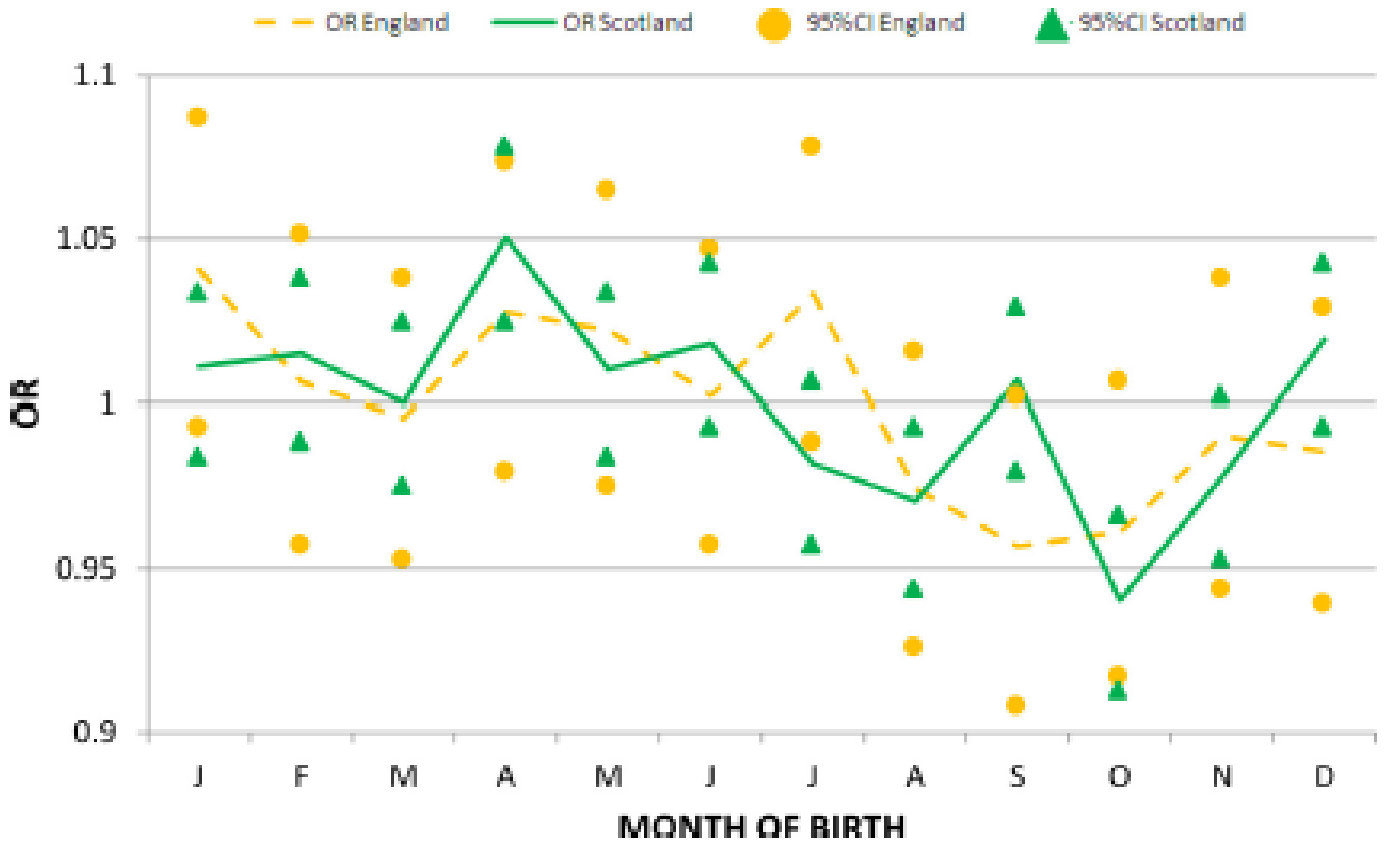
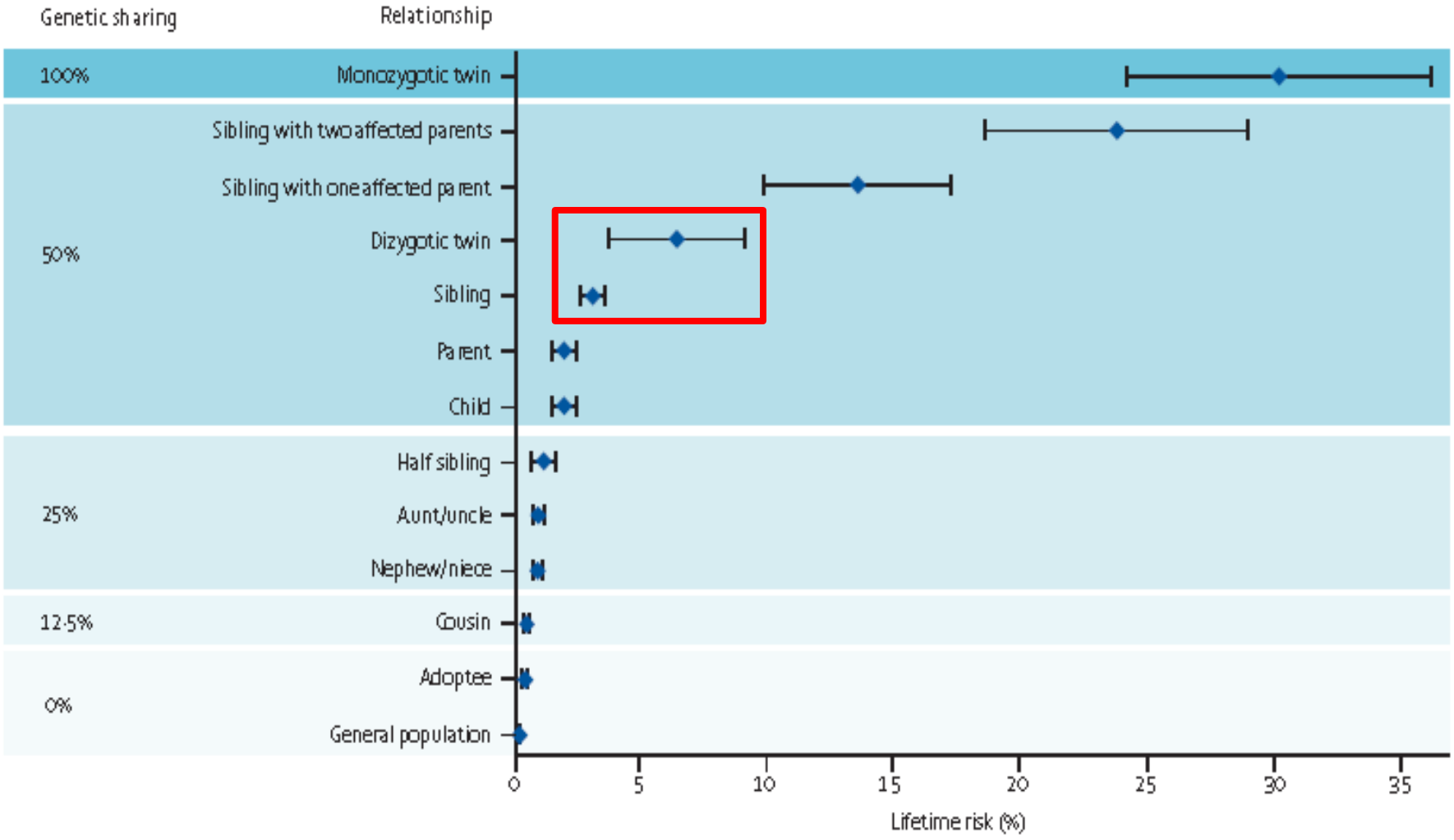
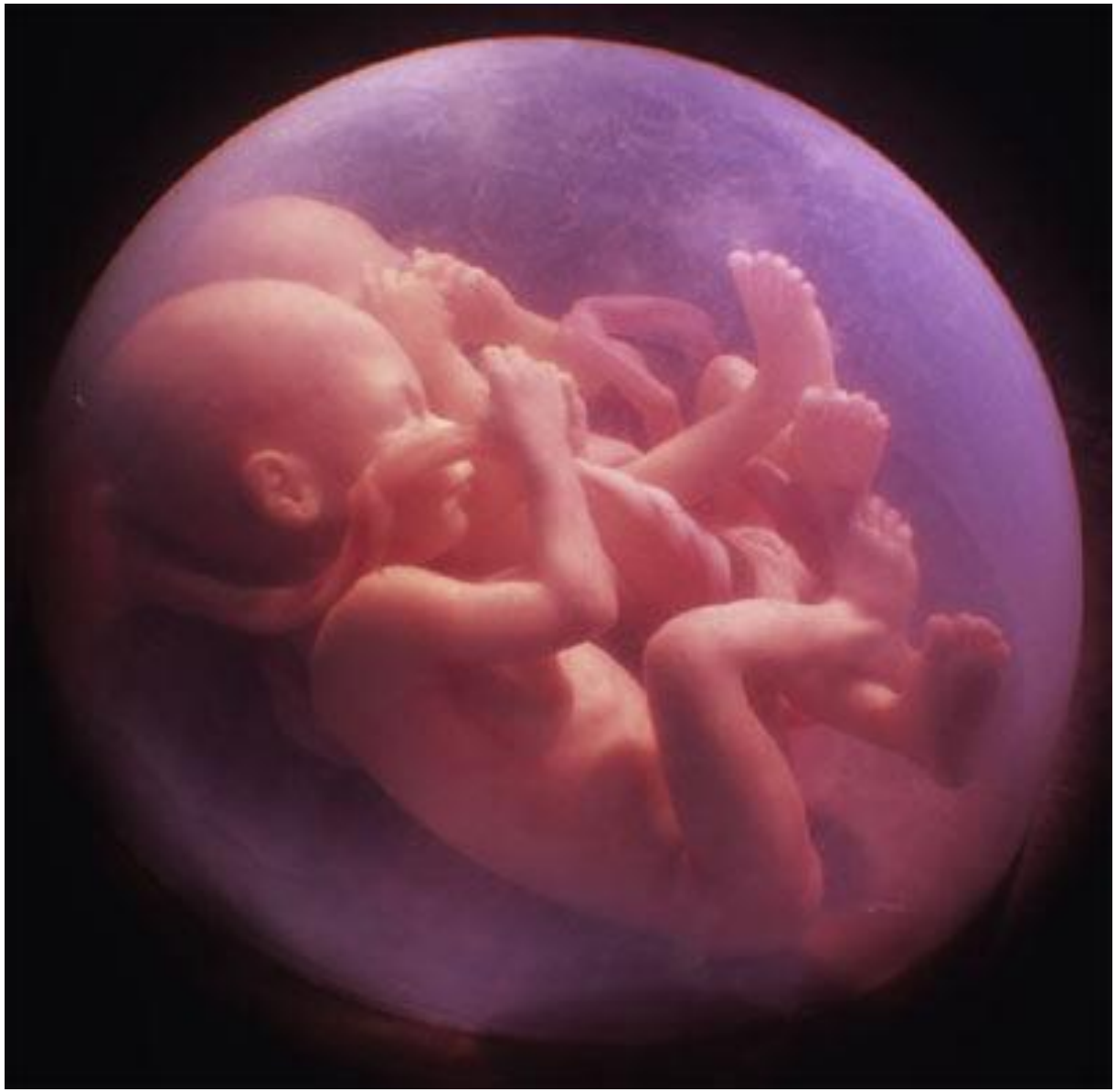


Figure 2 Odds ratio distribution based on month of birth in England and Scotland. The highest and lowest odds ratios are observed in Scotland but 95%CI substantially overlap.

Familial risk



Compston & Coles, Lancet 2008.



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PLoS GENETICS

Expression of the Multiple Sclerosis-Associated MHC Class II Allele *HLA-DRB1*1501* Is Regulated by Vitamin D

Sreeram V. Ramagopalan[1,2☯], Narelle J. Maugeri[1☯], Lahiru Handunnetthi[1,2], Matthew R. Lincoln[1,2], Sarah-Michelle Orton[1,2], David A. Dyment[1,2], Gabriele C. DeLuca[1,2], Blanca M. Herrera[1,2], Michael J. Chao[1,2], A. Dessa Sadovnick[3,4], George C. Ebers[1,2]*, Julian C. Knight[1]*

1 Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, United Kingdom, 2 Department of Clinical Neurology, University of Oxford, John Radcliffe Hospital, Oxford, United Kingdom, 3 Department of Medical Genetics, Division of Neurology, University of British Columbia, UBC Hospital, Vancouver, British Columbia, Canada, 4 Faculty of Medicine, Division of Neurology, University of British Columbia, UBC Hospital, Vancouver, British Columbia, Canada

TTACAAGGCTCAAACTTGTGAACACATCACTGACCAGCACAGAGCTGGCT

ACAATAGCTCCCCAATTAAGGTGTTTTACATGCAACTGGTTCAAACCTTC

CAAGTGCTAAATTAAAACAATCCTTTAAAGAAGGAAATTCTGTTTCAGAA

S-Box X-box

GAGGACCTTCATACAGCATCTCTGACCAGCAACTGATGATGCTATTGAAC

Y-box

TCAGATGCTGATTGGTTCTCCAACACGAGATTACCCAACCCAGGAGCAAG

VDRE

GAAATCAGTAACTTCCTCCCTATAACTTGGAATGTGGGTGGAGGGGTTCA

Transcriptional start site

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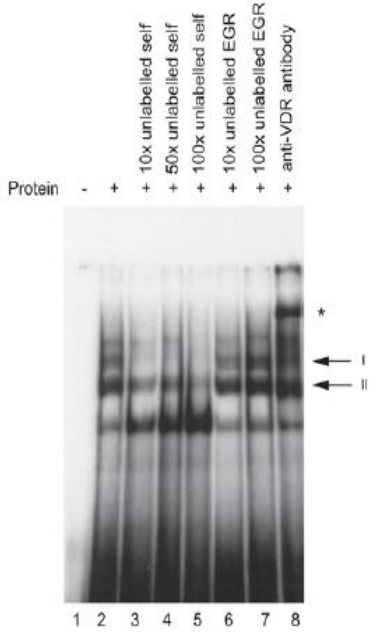
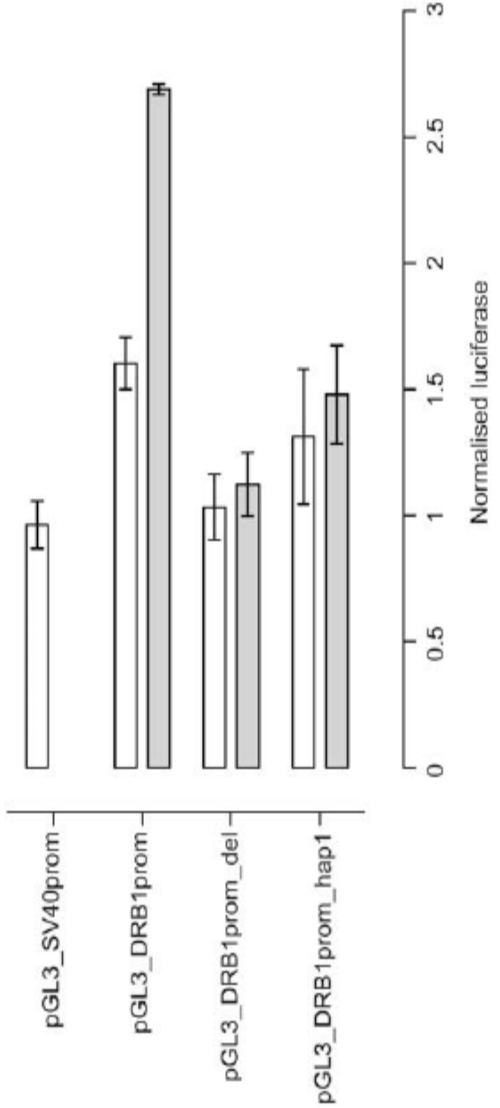
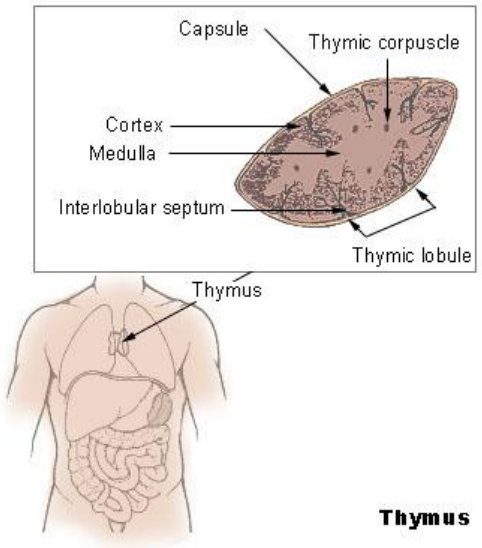
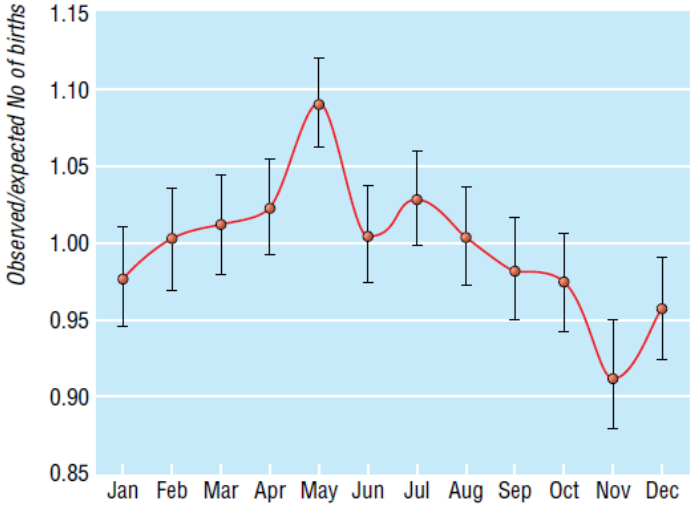




Ramagopalan et al. PLoS Genet. 2009 Feb;5(2):e1000369.

Thymic Education Hypothesis





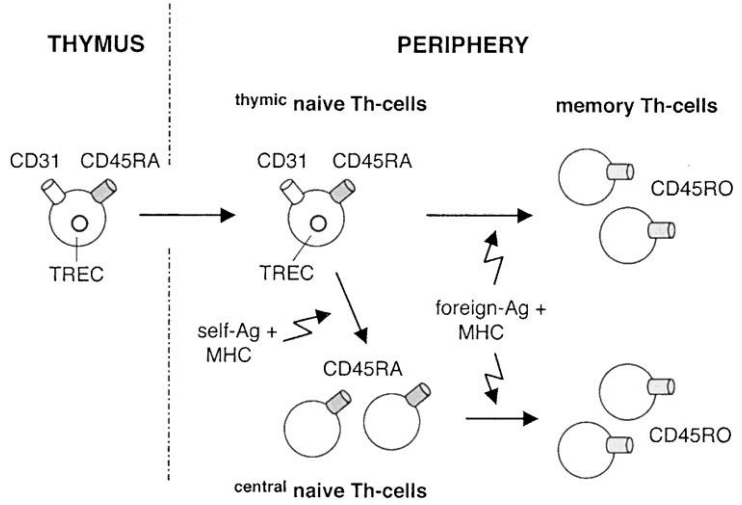


Table. CD4+ and CD8+ sjTRECs and 25-hydroxyvitamin D Among Individuals Born in May and November

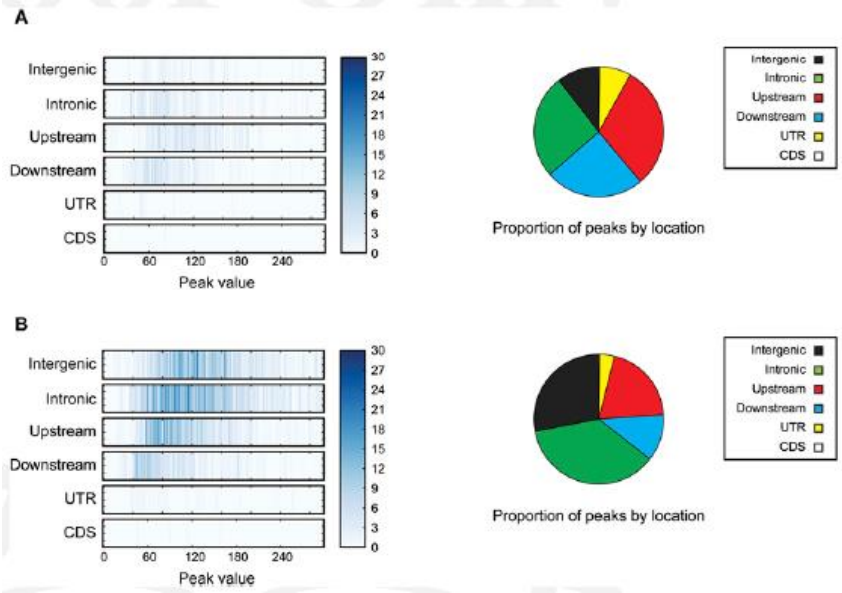
	sjTRECs/100 000 Cells, Mean (95% CI)	Monthly 25-hydroxyvitamin D, Mean, nmol/L
November		
CD4+	11 089 (10 205-11 973)	50.9
CD8+	10 414 (9509-11 319)	
May		
CD4+	19 547 (17 609-21 485)	38.4
CD8+	25 520 (22 488-28 552)	

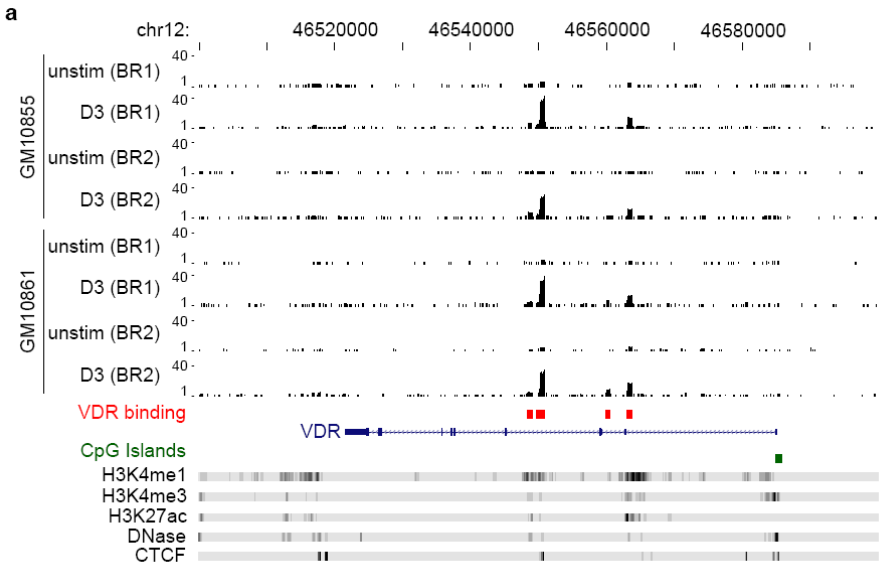
Abbreviation: sjTRECs, signal joint T-cell receptor excision circles.

Disanto et al. JAMA Neurol. 2013 Apr;70(4):527-8.

Genome-wide vitamin D receptor mapping using ChIP-seq in Lymphoblastoid Cell Lines

	No. of intervals
FDR 1%	
Calcitriol stimulated	2776
Unstimulated	623





Ramagopalan et al, 2010

Enrichment for genes associated to autoimmune disease and cancer

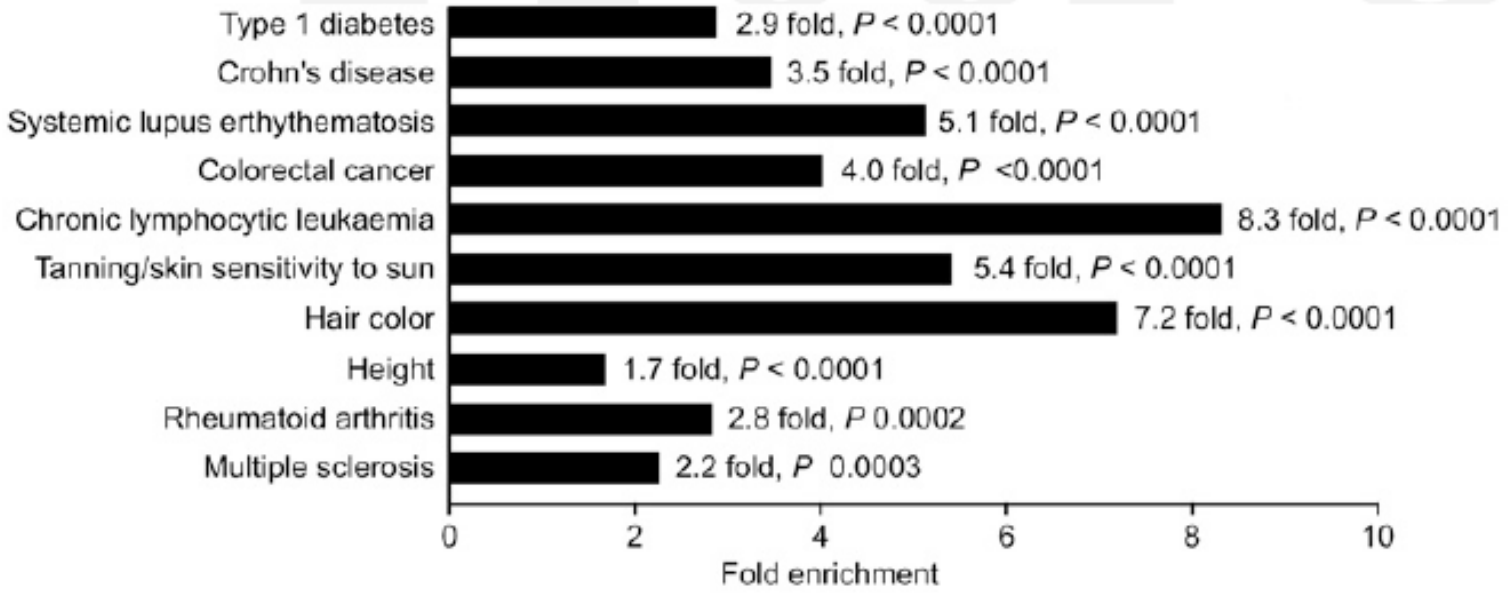
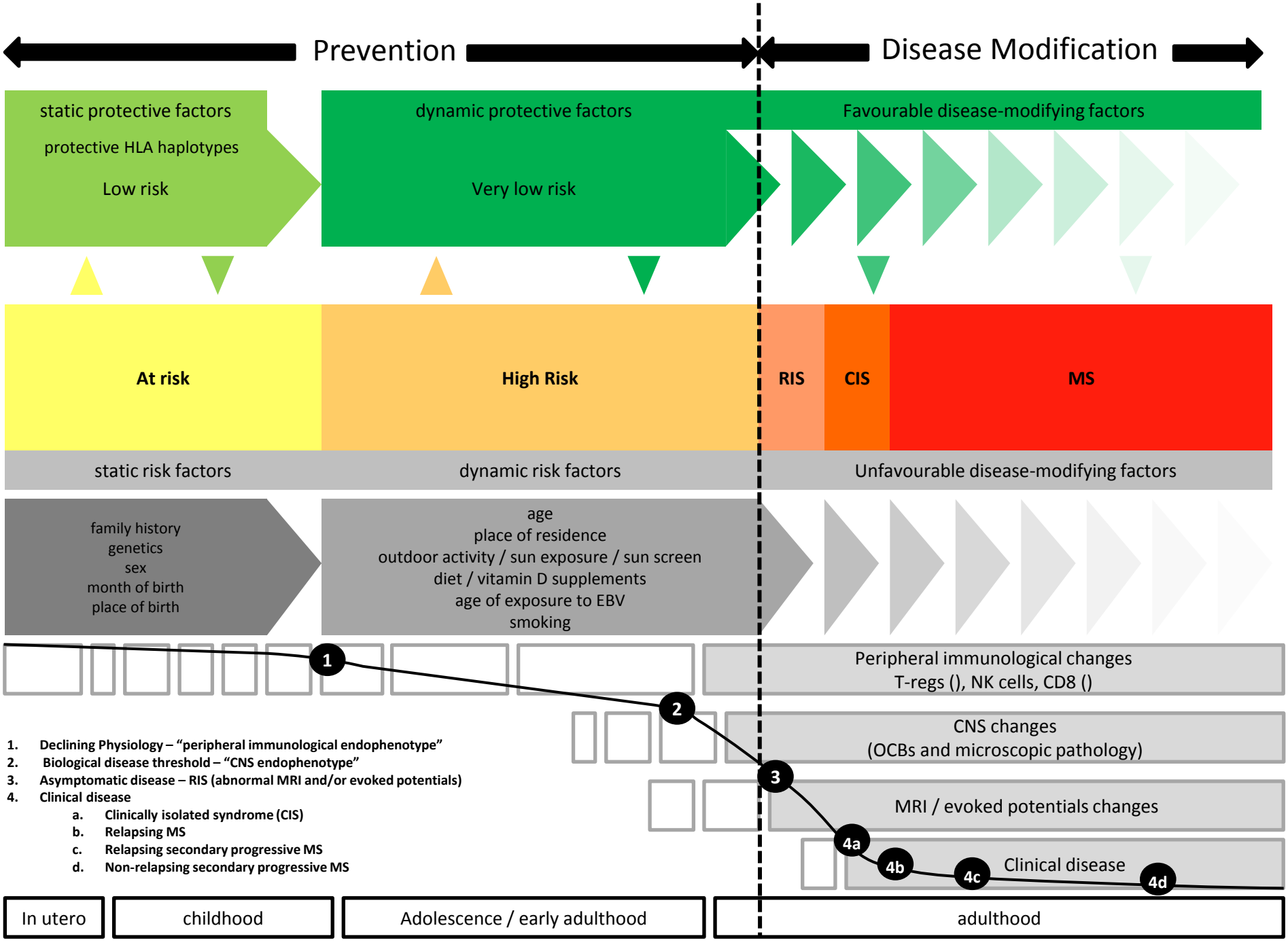


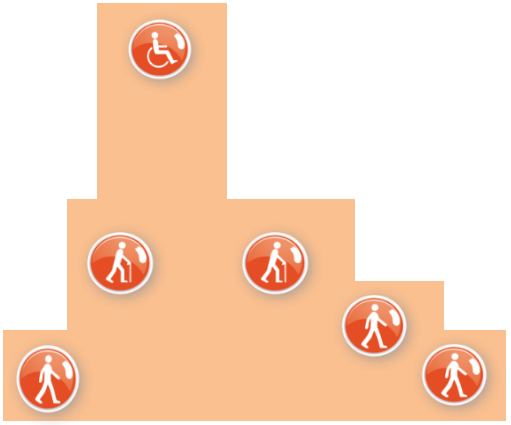
Figure 3. Common traits showing enrichment of VDR binding within intervals identified by GWAS. A total of 47 common diseases and traits were analyzed (see Methods and Supplemental Table 5) and those showing significant enrichment of VDR binding defined by ChIP-seq in two LCLs after calcitriol stimulation with a 1% FDR are shown.

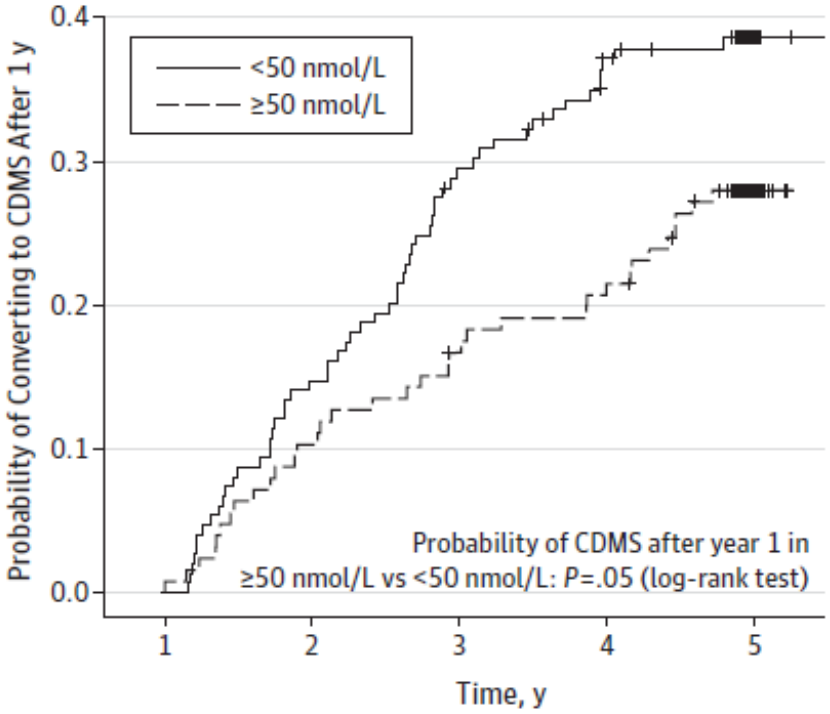
Ramagopalan et al, 2010

Can vD be used as a MS disease modifying therapy?


Prevention
Disease Modification
static protective factors
protective HLA haplotypes
Low risk
dynamic protective factors
Very low risk
Favourable disease-modifying factors
At risk
High Risk
RIS
CIS
MS
static risk factors
dynamic risk factors
Unfavourable disease-modifying factors
family history
genetics
sex
month of birth
place of birth
age
place of residence
outdoor activity / sun exposure / sun screen
diet / vitamin D supplements
age of exposure to EBV
smoking
1
2
3
4a
4b
4c
4d
Peripheral immunological changes
T-regs (), NK cells, CD8 ()
CNS changes
(OCBs and microscopic pathology)
MRI / evoked potentials changes
Clinical disease
1. Declining Physiology – "peripheral immunological endophenotype"
2. Biological disease threshold – "CNS endophenotype"
3. Asymptomatic disease – RIS (abnormal MRI and/or evoked potentials)
4. Clinical disease
a. Clinically isolated syndrome (CIS)
b. Relapsing MS
c. Relapsing secondary progressive MS
d. Non-relapsing secondary progressive MS
In utero
childhood
Adolescence / early adulthood
adulthood

Vitamin D as an early predictor of MS activity and progression

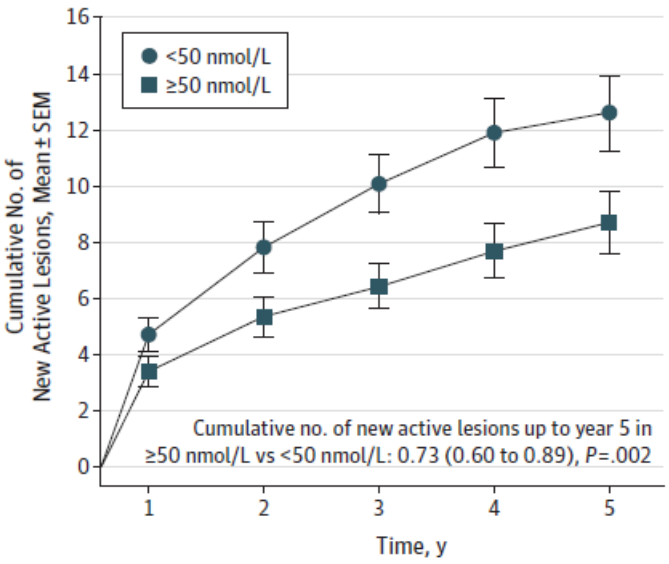




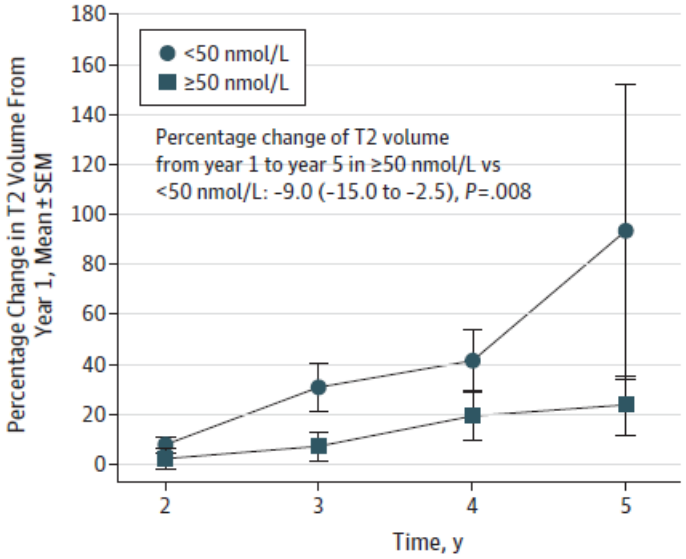
No.					
(<50 nmol/L)	150	128	106	95	85
(≥50 nmol/L)	127	114	106	100	88

Ascherio JAMA Neurol. 2014 Mar;71(3):306-14.

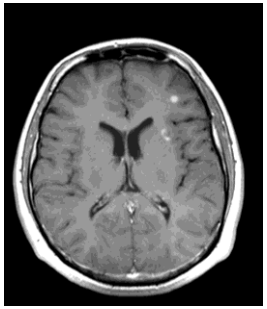
Vitamin D as an early predictor of MS activity and progression

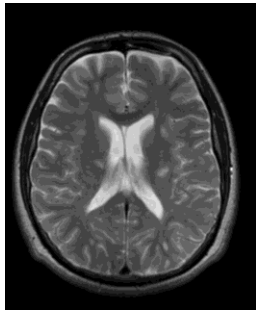


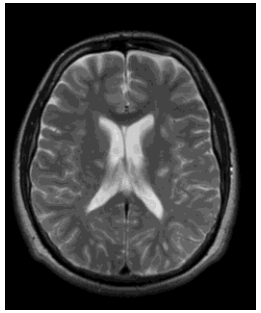
No.					
(<50 nmol/L)	182	183	174	162	157
(≥50 nmol/L)	149	146	143	143	132



No.				
(<50 nmol/L)	178	172	160	154
(≥50 nmol/L)	143	142	139	131

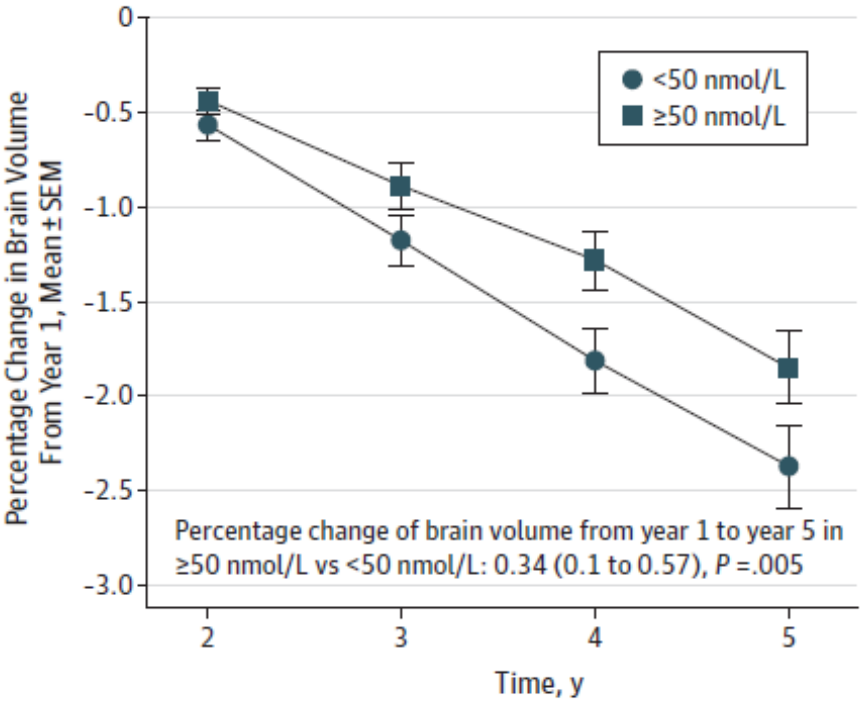




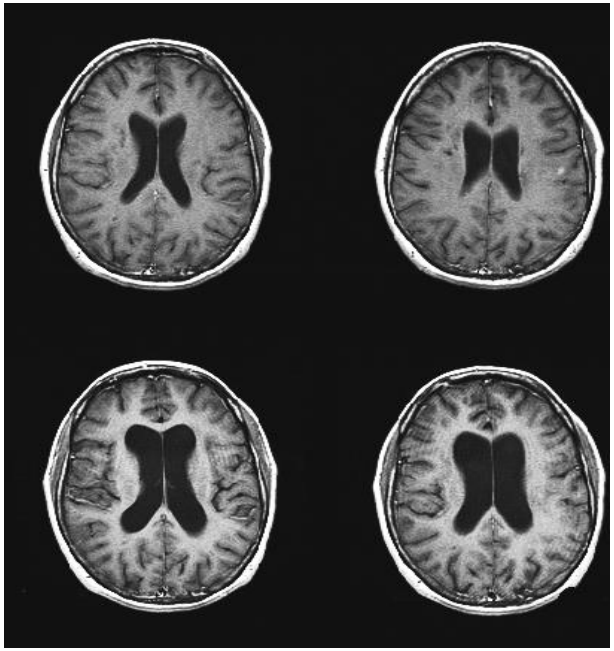


Ascherio JAMA Neurol. 2014 Mar;71(3):306-14.

Vitamin D as an early predictor of MS activity and progression

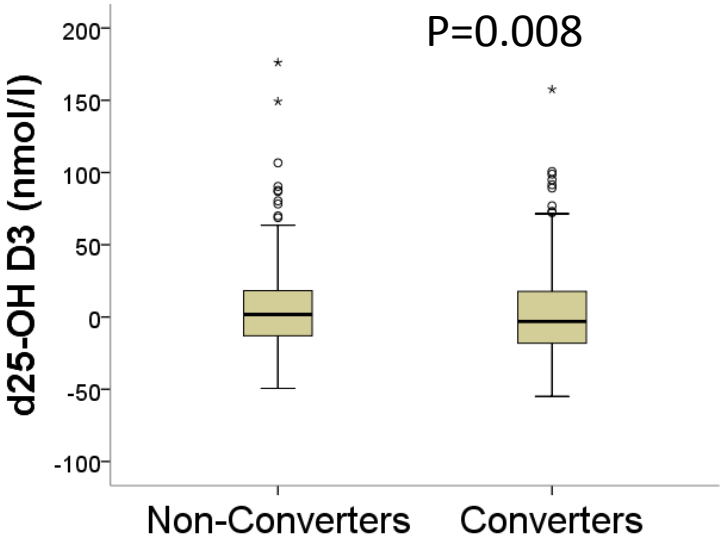


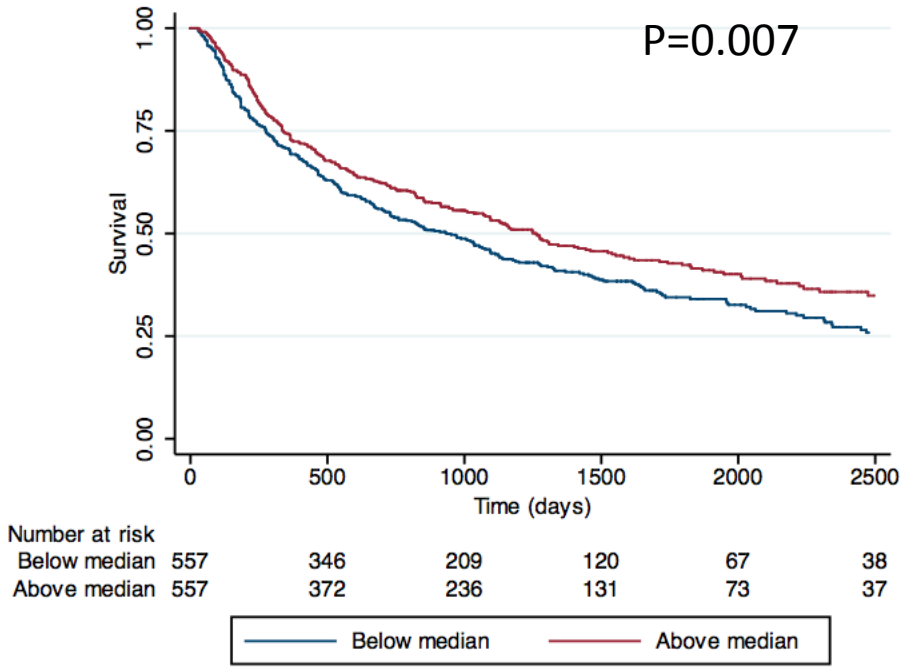
No.				
(<50 nmol/L)	129	114	103	97
(≥50 nmol/L)	102	98	96	85



Ascherio JAMA Neurol. 2014 Mar;71(3):306-14.

Multivariate International CIS risk factor study - 25-OH D3



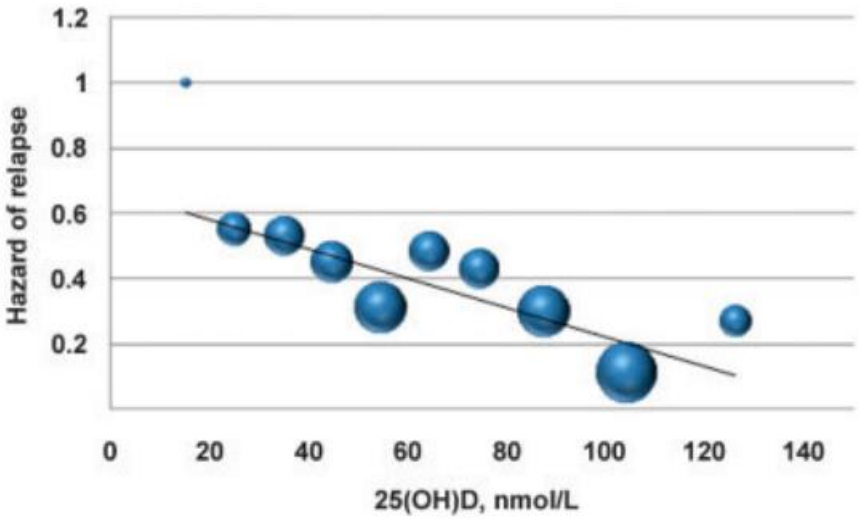


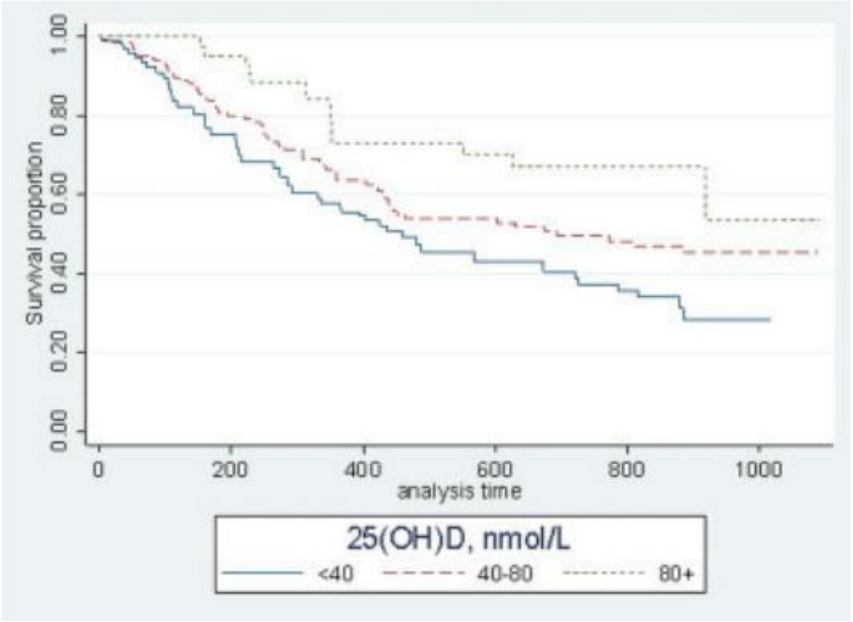
Median Survival: 935 days vs. 1262 days

Conversion to CDMS]	HR	95% CI	**P value**
25-OH D_3	0.996	0.993-0.999	**0.01**

Kuhle et al. submitted 2014.

Higher 25-OH vD is associated with lower relapse risk





Simpson et al. Ann Neurol. 2010;68:193–203.

vD status predicts new brain MRI activity in MS

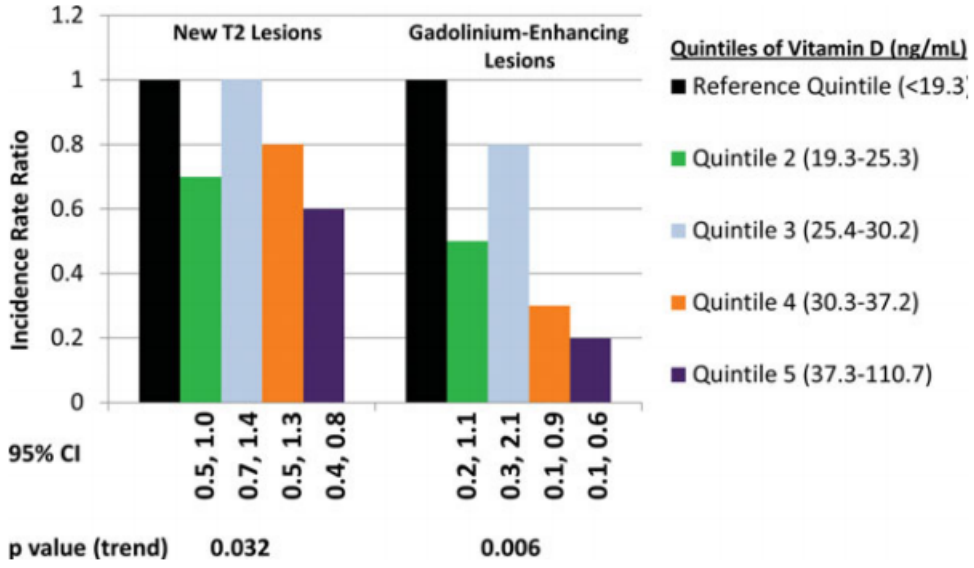
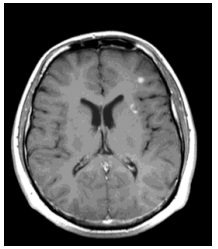
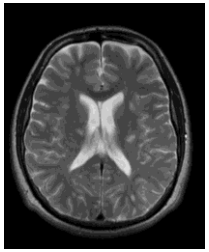


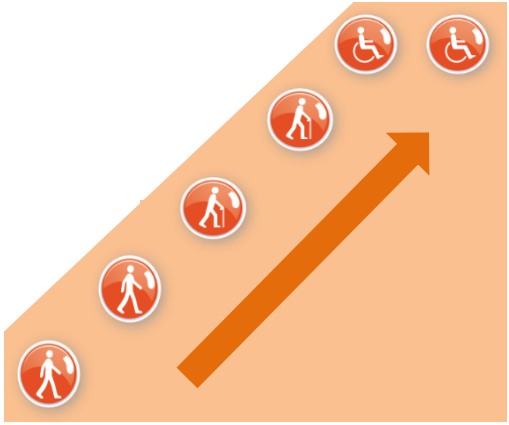
FIGURE: Magnetic resonance imaging outcomes associated with quintiles of vitamin D. CI = confidence interval.





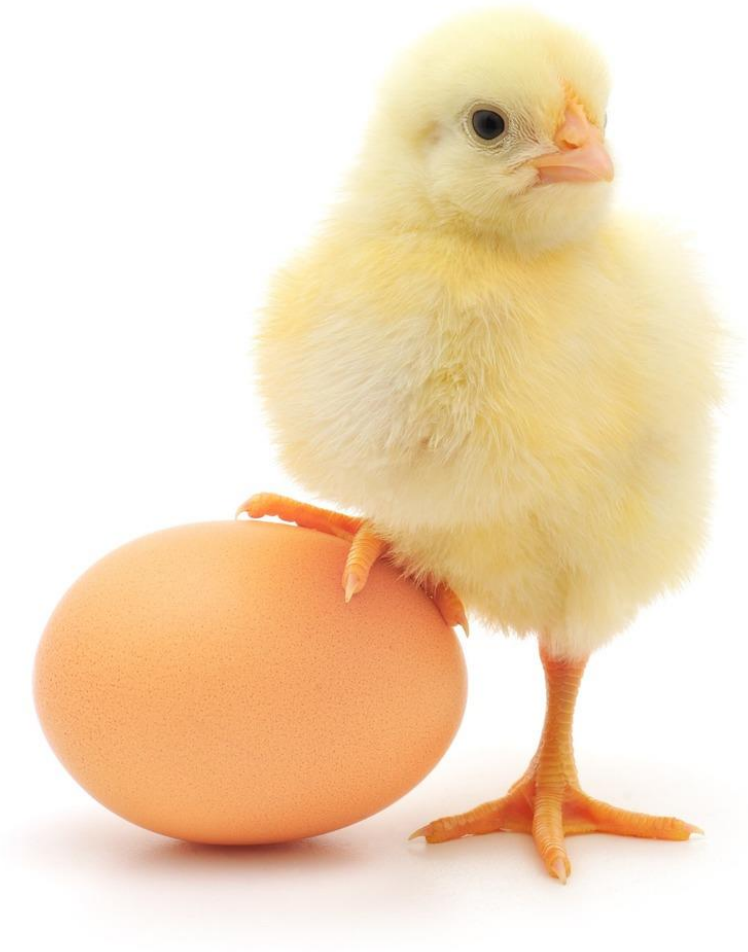
- EPIC is a 5-year longitudinal MS cohort study at the UCSF.
- 469 subjects annual clinical evaluations, brain MRI, and biomarkers.

- Each 10ng/ml higher vitamin D level was associated with lower subsequent disability (-0.047; 95% CI = -0.091 to -0.003; *p* = 0.037).



Mowry et al. ANN NEUROL 2012;72:234–240.

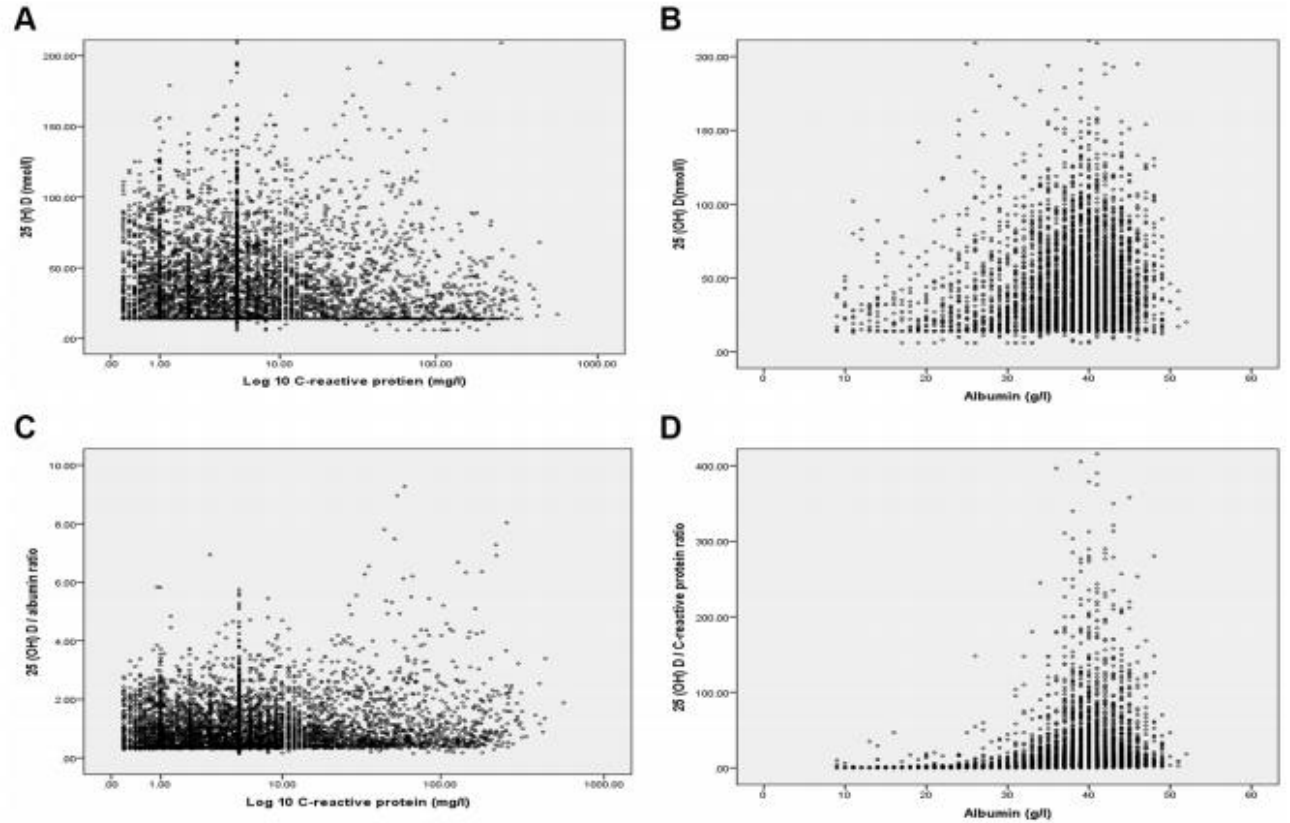
Chicken or Egg

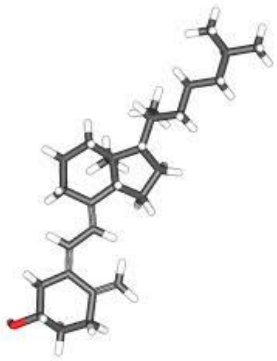


Association?

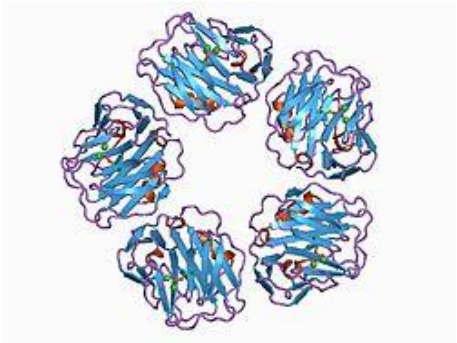
Causation?

The effect of the systemic inflammatory response on plasma vitamin 25 (OH) D concentrations adjusted for albumin

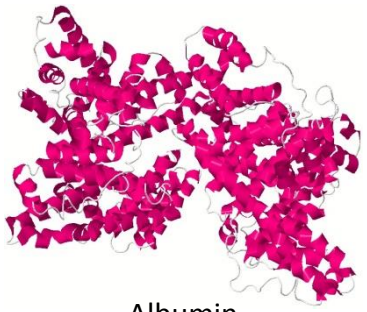




Vitamin D3



CRP



Albumin

Ghashut et al. PLoS One. 2014 Mar 25;9(3):e92614.

Hypothesis

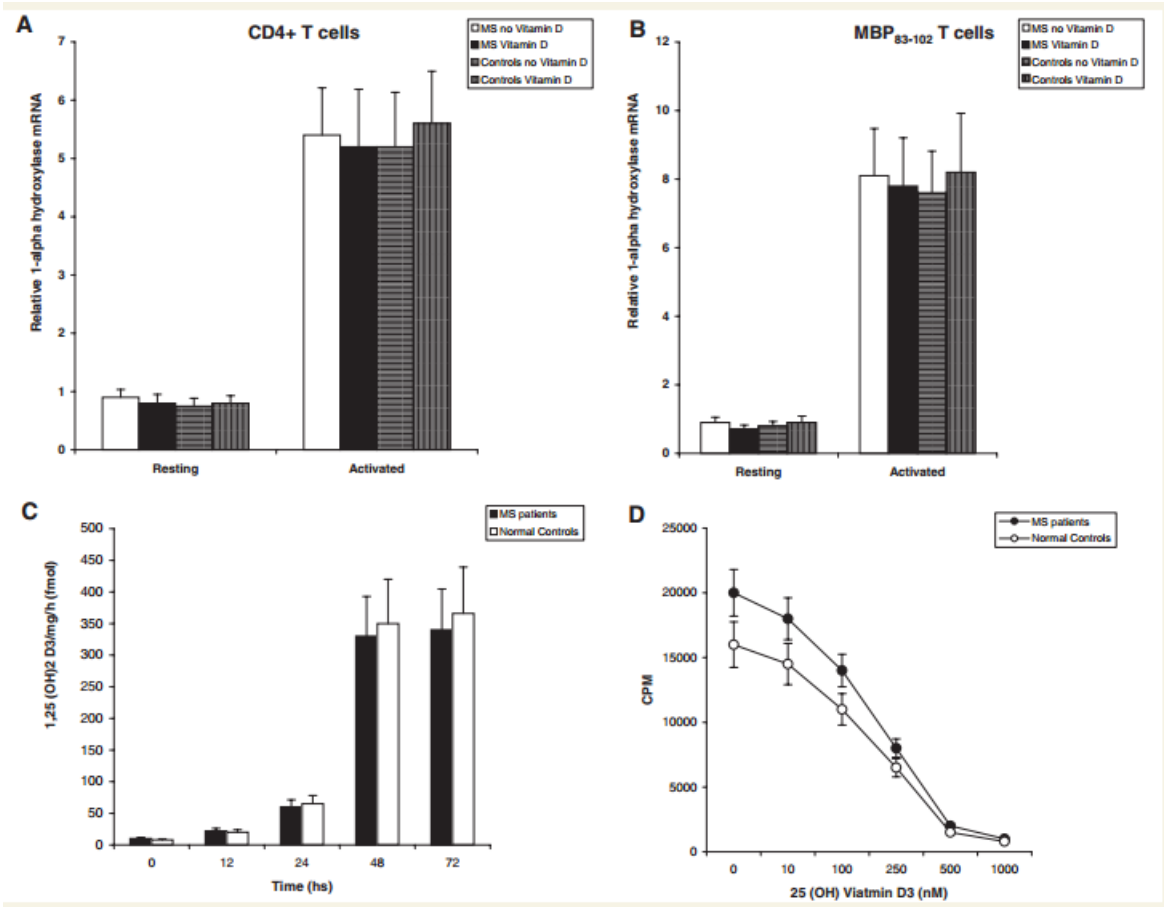
"Hypovitaminosis D3 is a consumptive vitaminopathy."

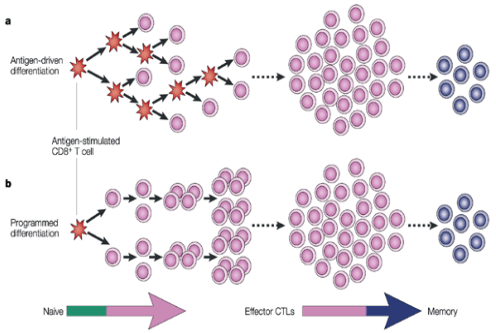
Therefore, the association between low vD levels and disease is due to reverse causation.

Association?

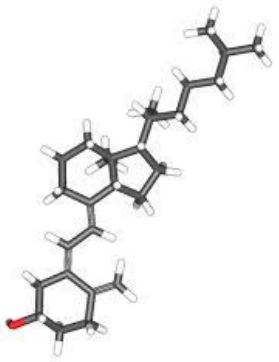
Causation?

Immunomodulatory effects of vD in MS





Immune response



Vitamin D3

Correale et al. Brain 2009: 132; 1146–1160.

Seasonal Effects

Seasonal patterns in optic neuritis and MS: a meta-analysis

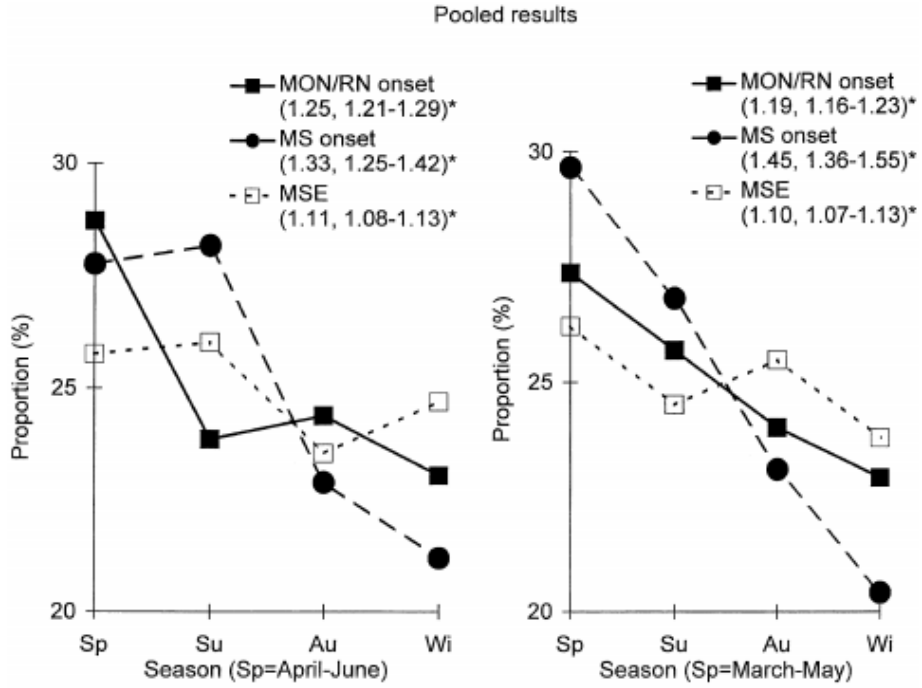
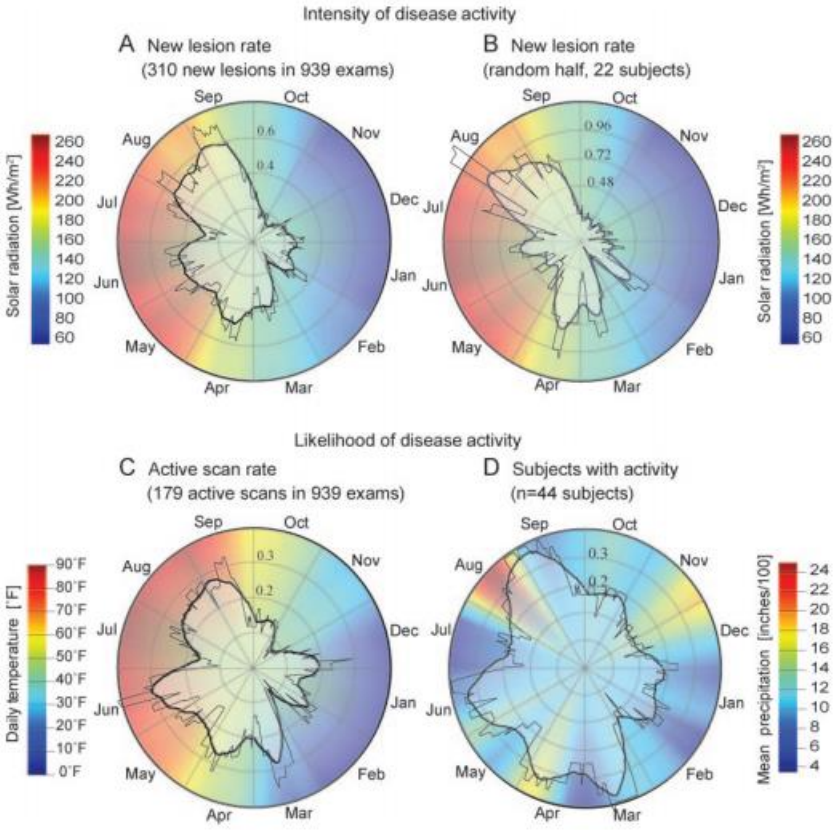
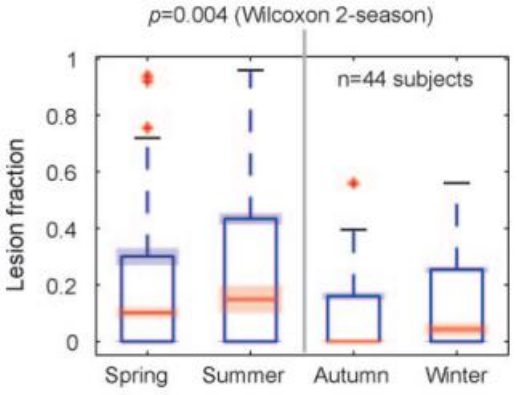


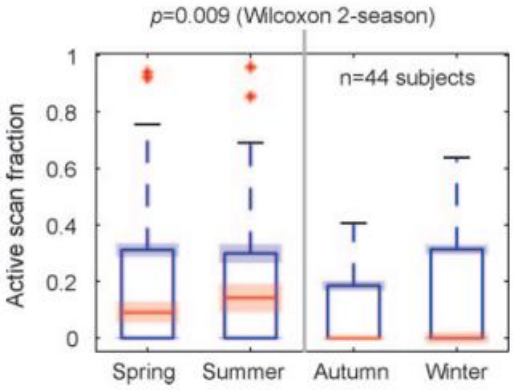
Fig. 3. Seasonal proportion in pooled MON/RN, MS onsets and MSE. Sp=Spring; Su=Summer; Au=Autumn; Wi=Winter. *HL ratio and 95% CI.

Jin et al. J Neurol Sci 2000:181;56–64.

Seasonal prevalence of MS disease activity

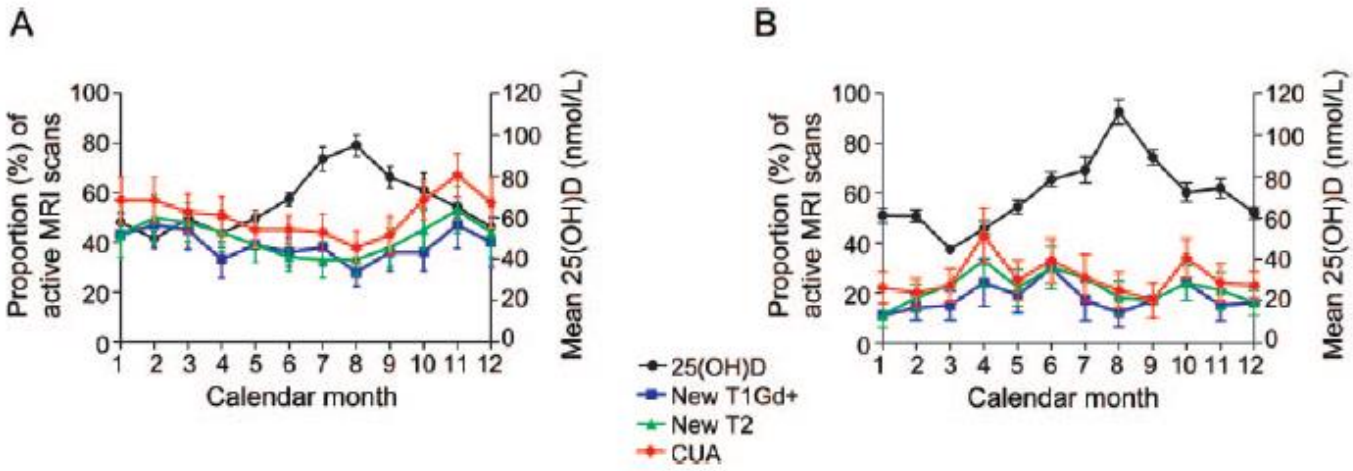


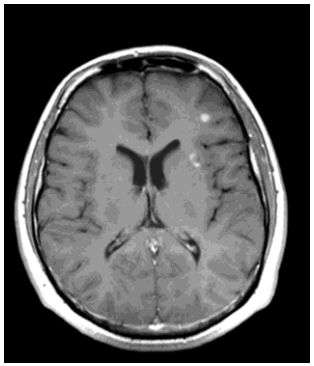




Meier et al. Neurology 2010;75:799–806.

vD and disease activity in MS before and during IFN-beta treatment





Løken-Amsrud et al. Neurology. 2012 Jul 17;79(3):267-73.

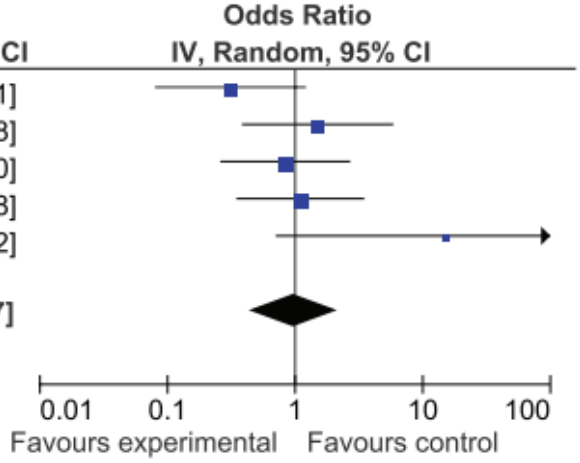
Treatment effects

The effect of vitamin D-related interventions on multiple sclerosis relapses: a meta-analysis

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio IV, Random, 95% CI
Burton 2010	4	24	9	23	21.3%	0.31 [0.08, 1.21]
Kampman 2012	6	35	4	33	21.2%	1.50 [0.38, 5.88]
Shayganeejad 2012	8	25	9	25	25.5%	0.84 [0.26, 2.70]
Soilu-Hanninen 2012	8	34	7	32	25.9%	1.10 [0.35, 3.48]
Stein 2012	4	11	0	12	6.0%	15.00 [0.70, 319.52]
Total (95% CI)		**129**		**125**	**100.0%**	**0.98 [0.44, 2.17]**
Total events	30		29			

Heterogeneity: Tau² = 0.29; Chi² = 6.24, df = 4 (P = 0.18); I² = 36%

Test for overall effect: Z = 0.05 (P = 0.96)



James et al. Mult Scler. 2013 Oct;19(12):1571-9.

The effect of vitamin D-related interventions on multiple sclerosis relapses: a meta-analysis

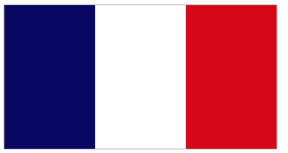


Table 4. Characteristics of currently on-going trials.

Clinicaltrials.gov identifier	Vitamin D group intervention	Placebo group intervention	Study duration [weeks]	Estimated enrolment
NCT01198132	100,000IU/month vitamin D3 Rebif 3×/week	Rebif 3×/week	96	250
NCT01490502	5000IU/day vitamin D3 Copaxone	600IU/day vitamin D3 Copaxone	104	172
NCT01024777	10,000IU/day vitamin D3	400IU/day vitamin D3	26	40
NCT01285401	6670IU/day (4 weeks), 14,007IU/day (92 weeks) vitamin D3 Rebif 3×/week	Rebif 3×/week	96	358
NCT01440062	20,400IU alternate day vitamin D3. Interferon ß1b.	400IU alternate day vitamin D3. Interferon ß1b	78	80

James et al. Mult Scler. 2013 Oct;19(12):1571-9.

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

Example: "Heart attack" AND "Los Angeles"
Search for studies: Search
Advanced Search | Help | Studies by Topic | Glossary

Find Studies | About Clinical Studies | Submit Studies | Resources | About This Site

Home > Find Studies > Search Results

Text Size

29 studies found for: Vitamin D multiple sclerosis
Modify this search | How to Use Search Results

List | By Topic | On a Map | Search Details

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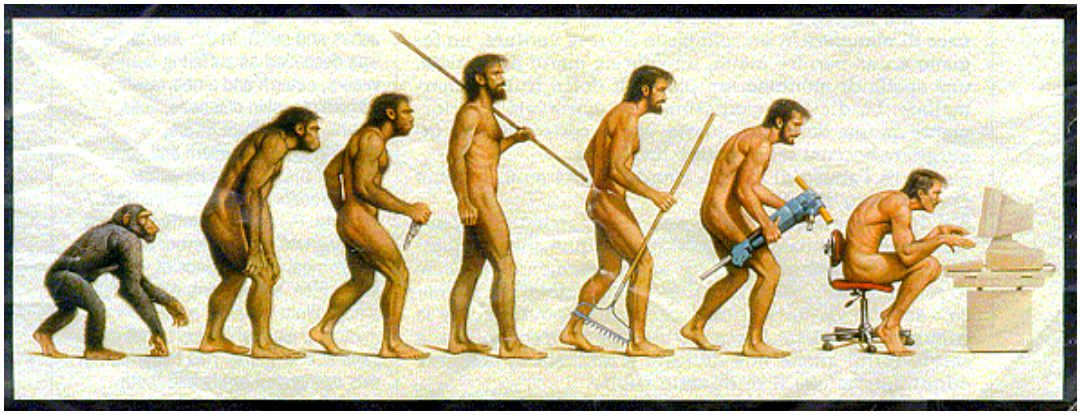
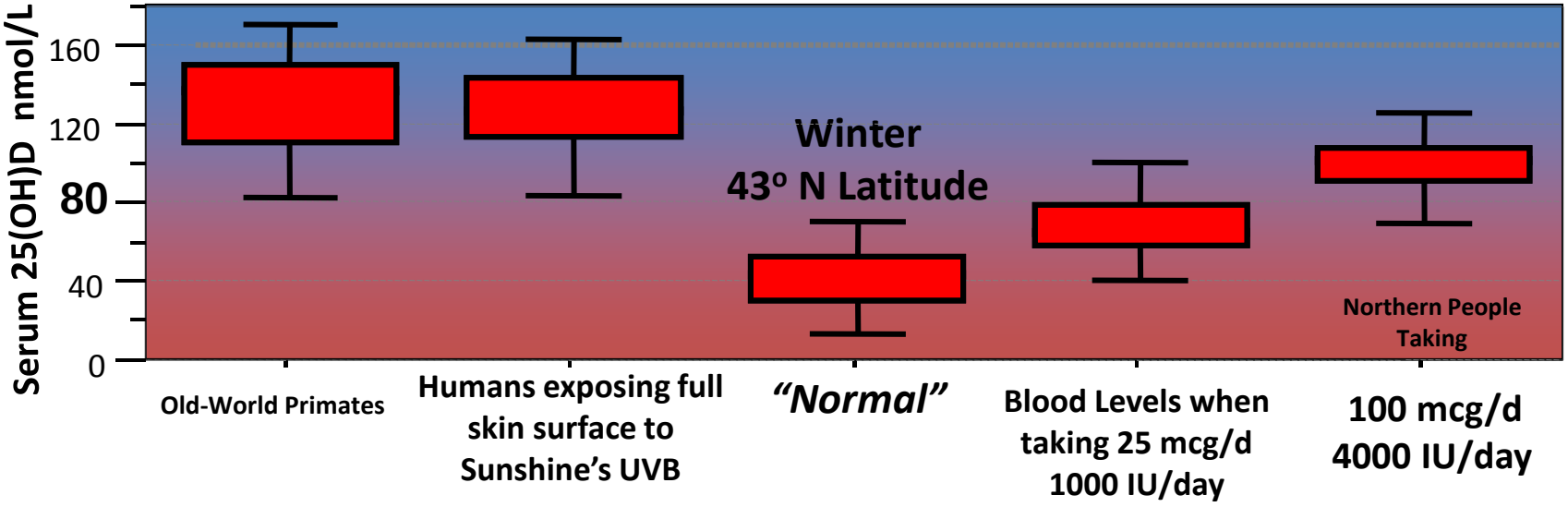
Include only open studies | Exclude studies with unknown status

Rank	Status	Study
1	Not yet recruiting	Role of Vitamin D in Reducing the Relapse Rate in Patients With Multiple Sclerosis **Condition:** Multiple Sclerosis **Interventions:** Dietary Supplement: Vitamin D3; Dietary Supplement: Placebo
2	Completed	Safety and Immunologic Effect of Low Dose Versus High Dose Vitamin D3 in Multiple Sclerosis **Conditions:** Multiple Sclerosis; Vitamin D Deficiency **Intervention:** Drug: Cholecalciferol
3	Completed	Safety Trial of High Dose Oral Vitamin D3 With Calcium in Multiple Sclerosis **Condition:** Multiple Sclerosis **Intervention:** Dietary Supplement: Vitamin D3
4	Completed	Vitamin D3 Supplementation and the T Cell Compartment in Multiple Sclerosis (MS) **Condition:** Multiple Sclerosis **Intervention:** Dietary Supplement: vitamin D3
5	Recruiting	Pharmacokinetics of Vitamin D in Multiple Sclerosis and in Health **Condition:** Multiple Sclerosis, Relapsing-remitting **Intervention:** Dietary Supplement: Vitamin D3
6	Terminated	The Effects of Interferon Beta Combined With Vitamin D on Relapsing Remitting Multiple Sclerosis Patients **Condition:** MULTIPLE SCLEROSIS **Intervention:** Dietary Supplement: Vitamin D3
7	Recruiting	Correlation Between Relapses in Multiple Sclerosis (MS) and Vitamin D Intake **Condition:** Multiple Sclerosis **Intervention:**
8	Completed	Vitamin D Pilot Study in Patients With Multiple Sclerosis **Condition:** Relapsing Remitting Multiple Sclerosis **Intervention:** Drug: 19 nor vitamin d
9	Recruiting	Vitamin D Supplementation in Multiple Sclerosis **Condition:** Relapsing Remitting Multiple Sclerosis **Intervention:** Drug: Vitamin D3

What dose of vitamin D?

Vitamin D Status in Primates and Early Humans

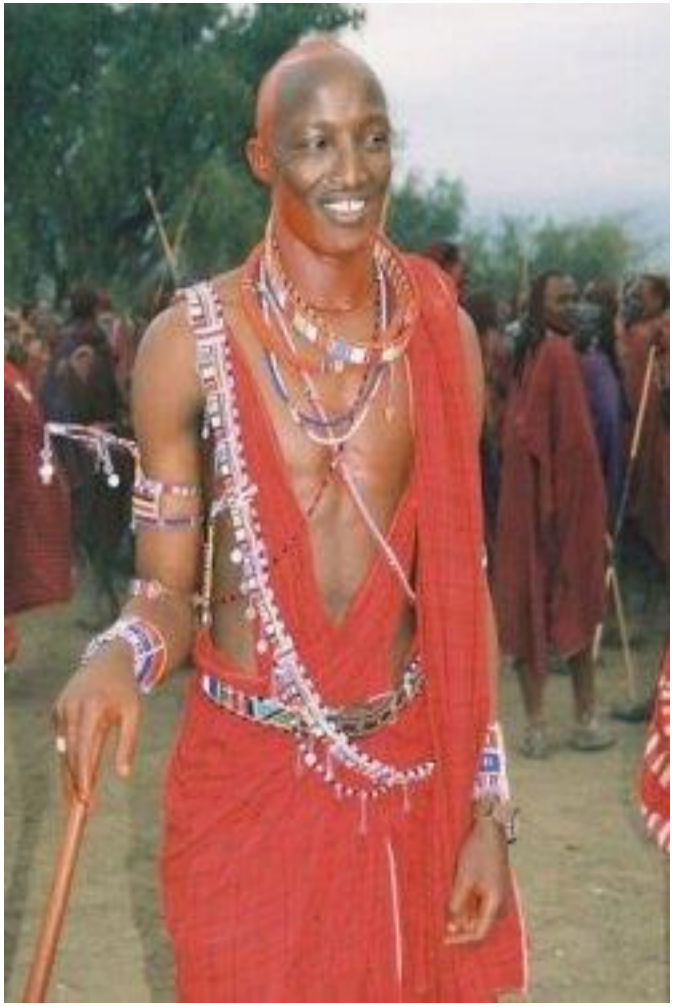


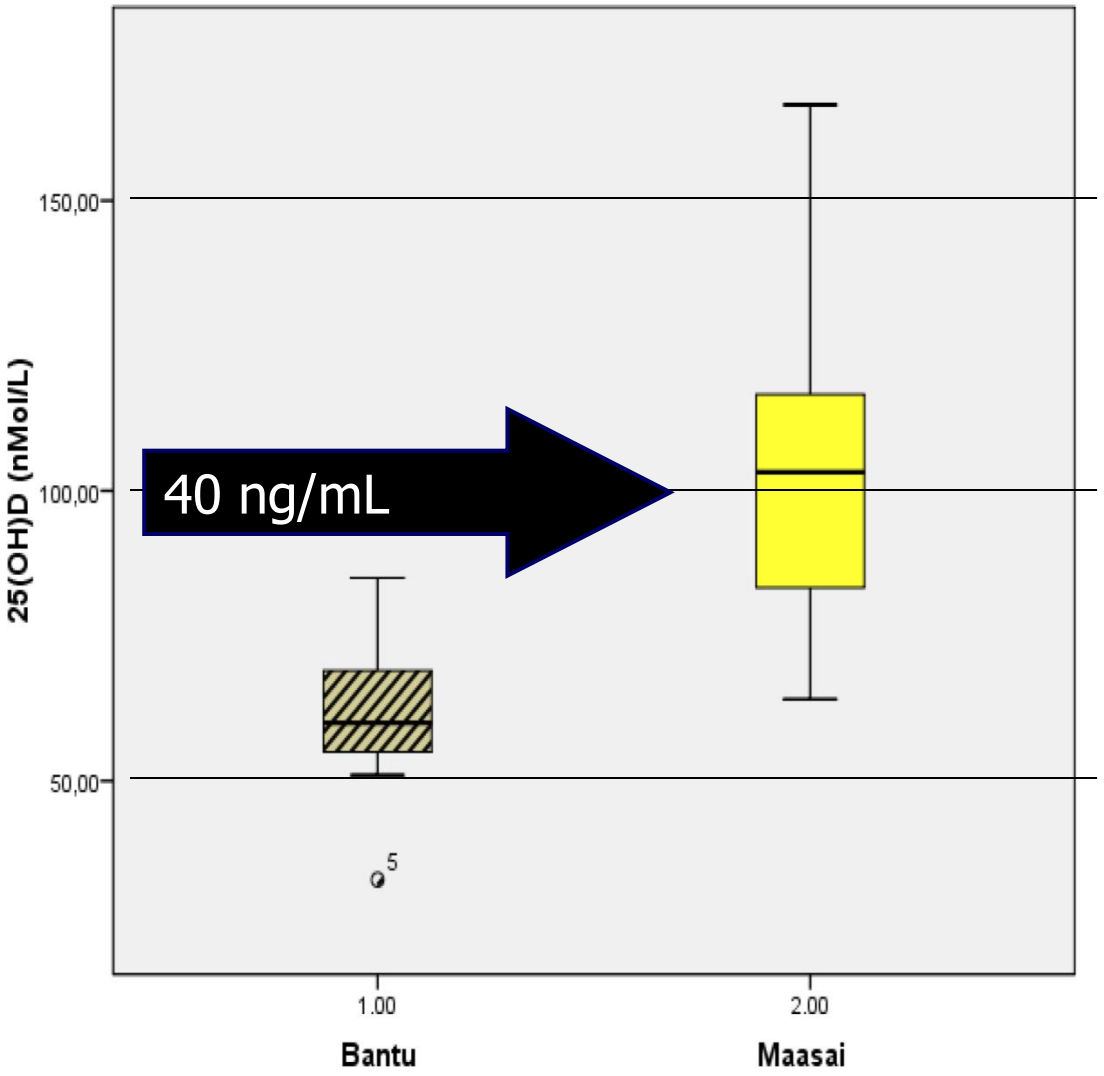


Slide adapted from Reinhold Vieth

Sources, include Cosman, Osteoporosis Int 2000; Fuleihan NEJM 1999; Scharla Osteoporosis Int 1998; Vieth AJCN 1999, 2000

Maasai median 25(OH)D = 104 nmol/L = 41 ng/mL



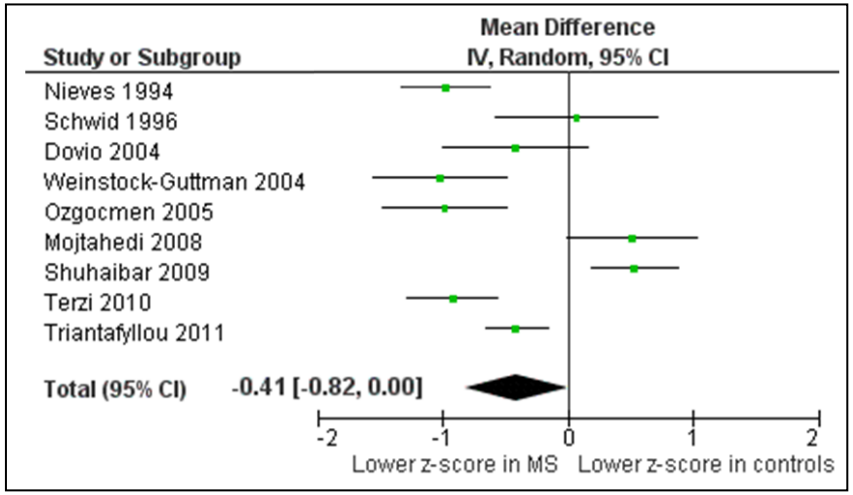


Slide adapted from Reinhold Vieth

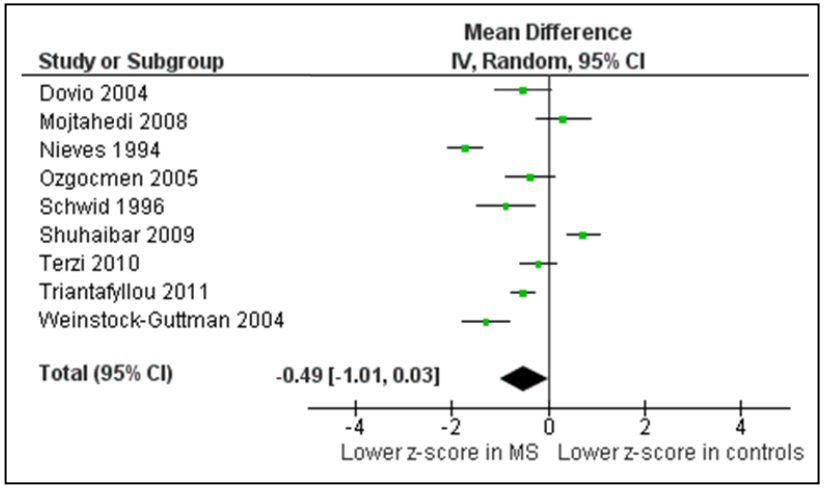
Luxwolda et al. British Journal of Nutrition (2012), 108, 1557–1561

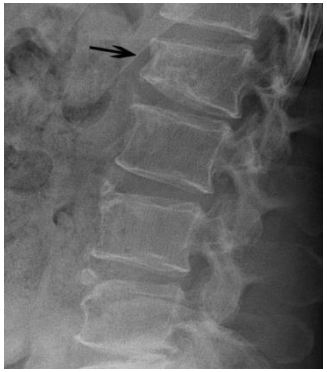
Osteopaenia: z-scores are lower in MSers

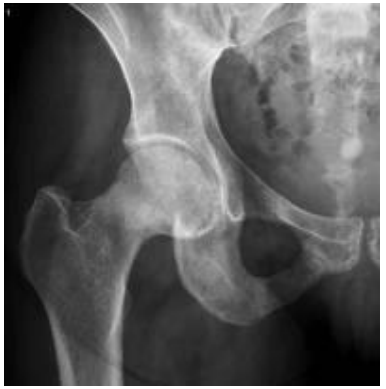
Lumbar spine



Femoral neck (NS)







Dobson et al. Mult Scler. 2012 Nov;18(11):1522-8.

HES data: risk ratio of fractures in MS

Fracture (ICD code*)	Observed	Expected	Rate Ratio (95% confidence interval)	P value
All fractures†	4414	2238.3	1.99 (1.93-2.05)	<0.001
Ribs (S22.2-S22.4)	161	130	1.24 (1.06-1.45)	0.007
Clavicle (S42.0)	83	52.6	1.59 (1.26-1.97)	<0.001
Humerus (S42.2-S42.4, S42.7)	415	204.2	2.05 (1.86-2.26)	<0.001
Forearm (S52)	448	493.5	0.91 (0.82-1.00)	0.042
Wrist/Hand (S62)	157	188.1	0.83 (0.71-0.98)	0.025
Pelvis/Lumbar spine (S32.0-S32.8)	293	187.7	1.57 (1.39-1.76)	<0.001
Tibia/Ankle (S82)	1393	506.1	2.81 (2.66-2.96)	<0.001
Foot (S92)	194	95.5	2.05 (1.77-2.37)	<0.001
Femur - neck of (S72.0-S72.2)	1579	574.2	2.79 (2.65-2.93)	<0.001
Femur - other (S72.3-S72.8)	543	85.8	6.69 (6.12-7.29)	<0.001
Femur - unspecified (S72.9)	88	18.5	4.91 (3.92-6.08)	<0.001

Ramagopalan et al. BMC Neurol. 2012 Nov 5;12:135.

Conclusions

- MS prevention
  - Population health-based initiatives
  - Targeted high-risk population studies (children and siblings of people with MS)
- Low vD levels are associated with MS disease activity
  - relapses, disease progression and MRI activity (Gd, T2 and brain volume loss)
- Possible reverse causation
  - The consumptive hypovitaminosis hypothesis
  - Arguments against consumptive hypovitaminosis hypothesis
    - Worldwide MS epidemiology (latitude, migration, sex ratio, changing incidence, MoB effects)
    - Seasonal variation of MS onset and disease activity
  - Current evidence-base regarding treatment is unconvincing
  - We need large well-controlled randomised clinical trials (easier said than done)
- We need more basic science to support the causation theory
- What dose?
  - Evolutionary medicine suggests we need to target a blood plasma level above 100nmol/L
- What advice?
  - To supplement to achieve a year long blood levels of > 100-120 nmol/L
  - In the UK we can't rely on diet or sun exposure to achieve these levels
  - EFSA or Vitamin D council recommendations
- Don't forget bone health as a justification to act now

Back-up slide

The effect of vitamin D-related interventions on multiple sclerosis relapses: a meta-analysis

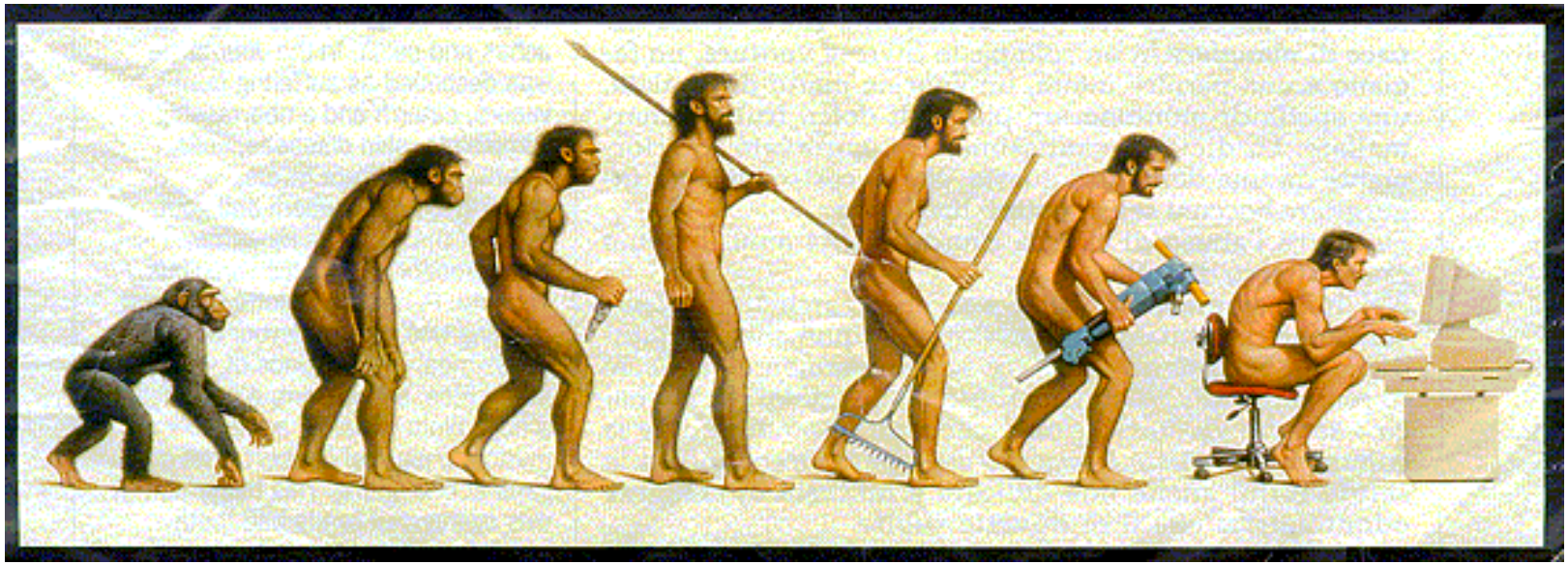
Table 3. Serum 25(OH)D levels at baseline and end of study for high dose vitamin D treated group and control group.

First author and year of publication	Mean high dose vitamin D 25(OH)D level [nmol/L]		Mean control 25(OH)D level [nmol/L]	
	Baseline	End of study	Baseline	End of study
Burton 2010	73	413*	83	N/A
Kampman 2012	55.56	123.17	57.33	61.8
Shayganeejad 2012	N/A	N/A	N/A	N/A
Soilu-Hänninen 2012	54	110	56	50
Stein 2012	59**	110**	54**	55**

25(OH)D – 25-hydroxyvitamin D.
*Following the 40,000IU/day dosing period.
**Median.

James et al. Mult Scler. 2013 Oct;19(12):1571-9.

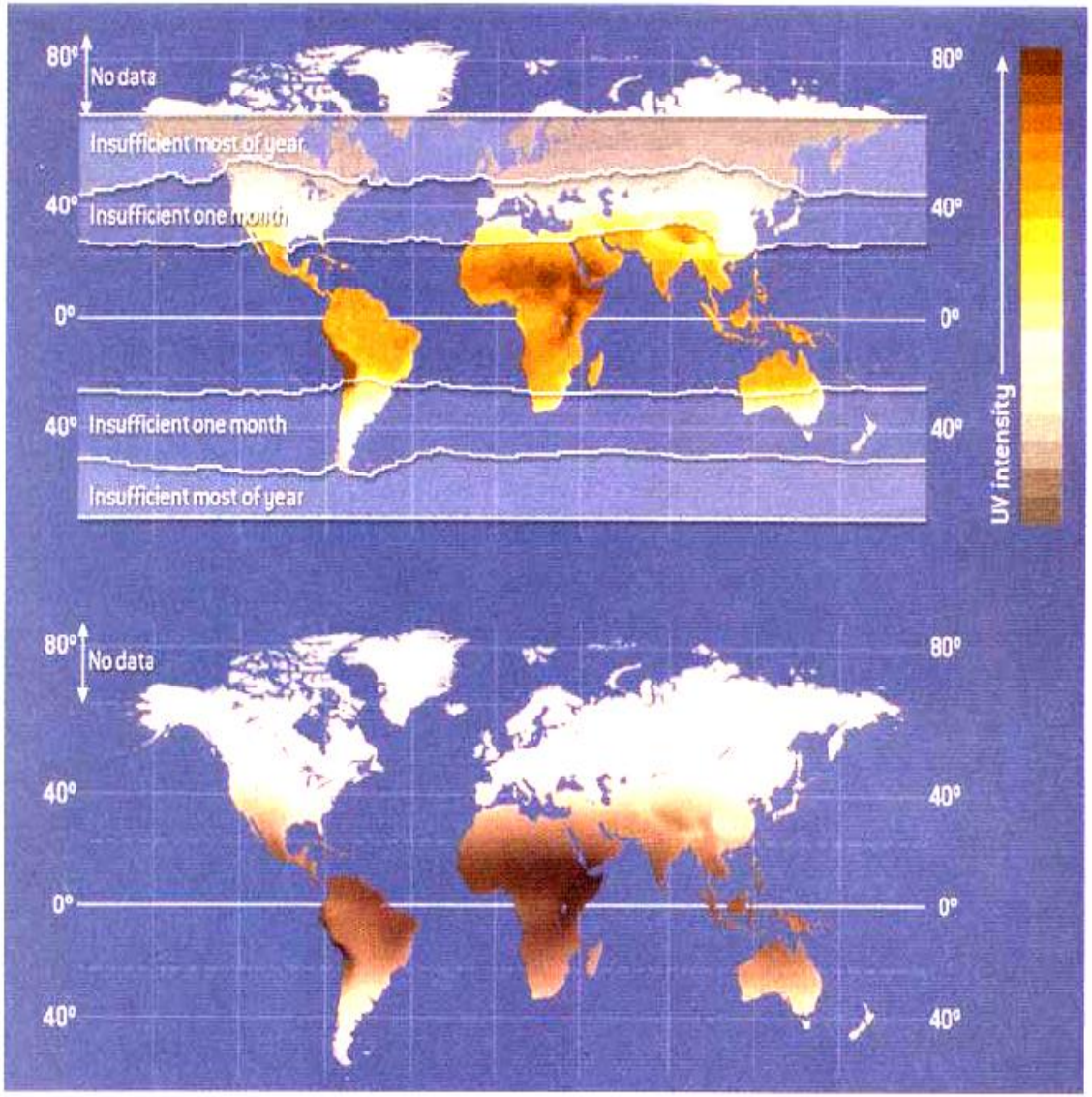
The conditions for which our human genome was selected offer a reasonable basis for optimal nutrition.



"Modern" humans have existed for 100,000 years

Slide adapted from Reinhold Vieth

What dose of vD depends where you live?



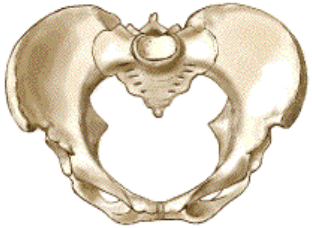
no vD for >6 mo/yr

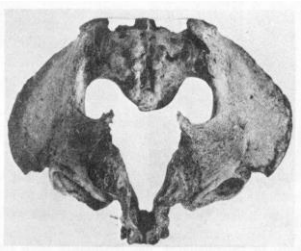
no vD for 1-6 mo/yr

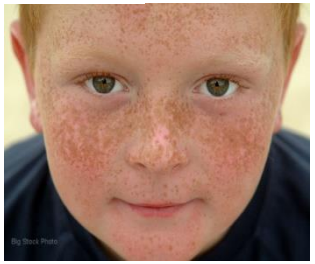
vD all year

no vD for 1-6 mo/yr

no vD for >6 mo/yr







Slide adapted from Reinhold Vieth

Level of vD supplementation

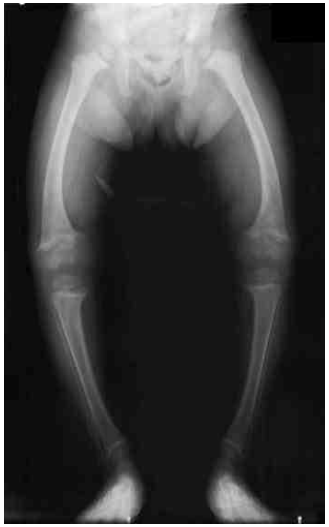
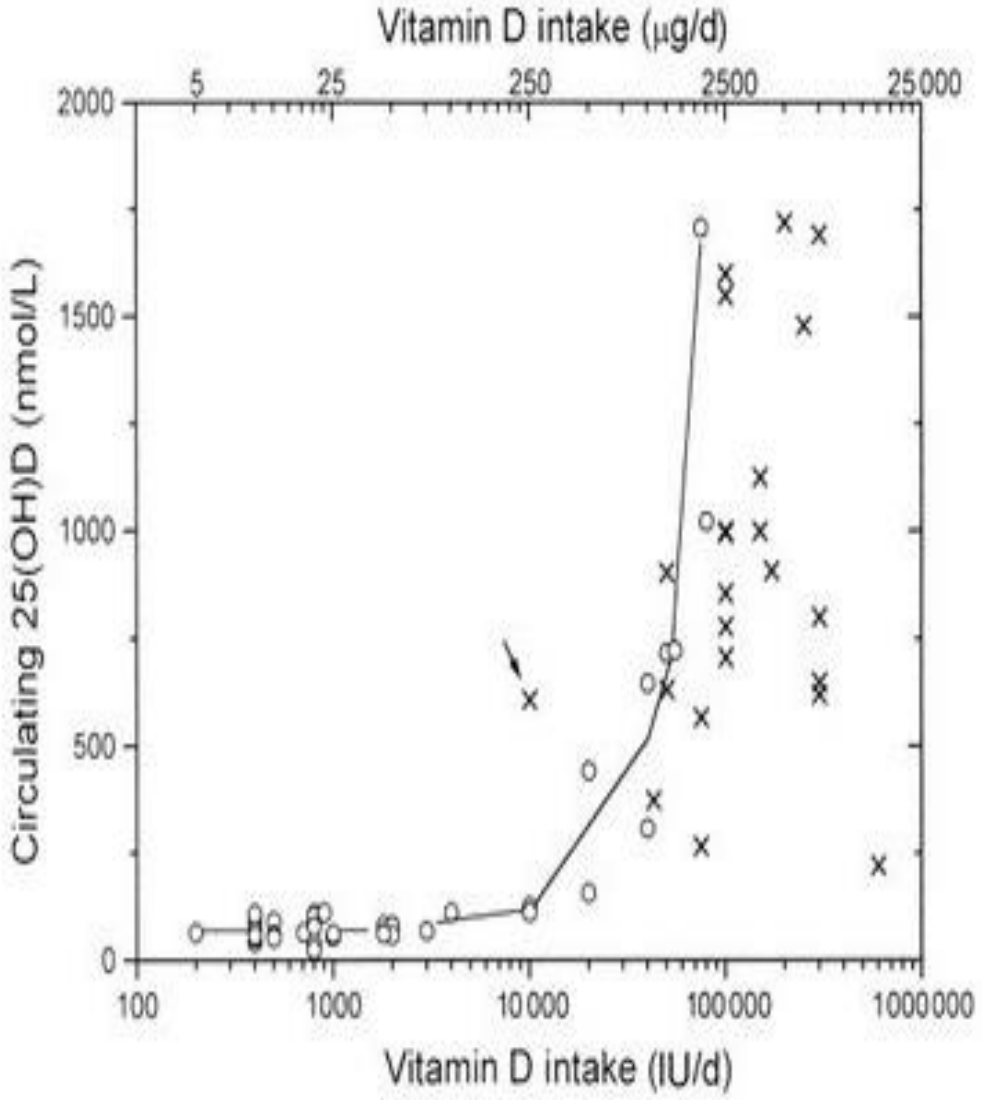


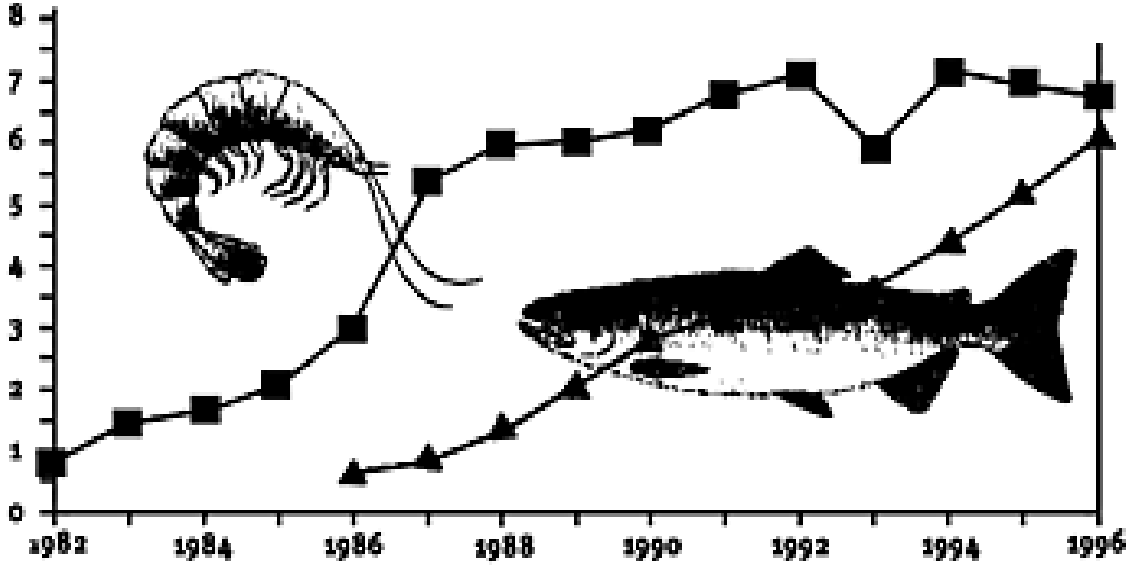
TABLE 1
25-Hydroxyvitamin [25(OH)D] concentrations under sun-rich living conditions

Reference, year, and subjects	Location	25(OH)D
		nmol/L
Haddock et al (23), 1982	Puerto Rico	
Hospital personnel ($n = 26$)		105
Farmers ($n = 18$)		135
Haddad and Kyung (24), 1971	St Louis	
Lifeguards ($n = 9$)		163
Better et al (25), 1980	Israel	
Lifeguards ($n = 34$)		148



Veith Am J Clin Nutr 1999;69:842–56.

Cultural changes



Cultural changes


SINCE KIEHL'S 1851
For a Refuel Land at Kiehl's
SPF 15
FACIAL FUEL
SPF 15 SUNSCREEN
ENERGIZING MOISTURE TREATMENT FOR MEN
2.5 fl.oz. - 75 ml

European Food Safety Authority

EFSA Journal 2012;10(7):2813

SCIENTIFIC OPINION

Scientific Opinion on the Tolerable Upper Intake Level of vitamin D[1]

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)[2, 3]

European Food Safety Authority (EFSA), Parma, Italy

ABSTRACT

Following a request from the European Commission, the Panel on Dietetic Products, Nutrition and Allergies was asked to re-evaluate the safety in use of vitamin D and to provide, if necessary, revised Tolerable Upper Intake Levels (ULs) of vitamin D for all relevant population groups. The ULs for adults including pregnant and lactating women, children and adolescents were revised. For adults, hypercalcaemia was selected as the indicator of toxicity. In two studies in men, intakes between 234 and 275 µg/day were not associated with hypercalcaemia, and a no observed adverse effect level (NOAEL) of 250 µg/day was established. Taking into account uncertainties associated with these studies, the UL for adults including pregnant and lactating women was set at 100 µg/day. Despite a continuing paucity of data for high vitamin D intakes in children and adolescents, the UL was adapted to 100 µg/day for ages 11-17 years, considering that owing to phases of rapid bone formation and growth this age group is unlikely to have a lower tolerance for vitamin D compared to adults. The same applies also to children aged 1-10 years, but taking into account their smaller body size, a UL of 50 µg/day is proposed. For infants, the UL of 25 µg/day based on previously available data relating high vitamin D intakes to impaired growth and hypercalcaemia was retained as limited additional evidence has emerged since the previous risk assessment. Data on vitamin D intakes from surveys in 14 European countries indicate that intakes in high consumers are below the revised ULs for vitamin D for all population groups.

www.vitamindcouncil.org

How much vitamin D do I need to take?

Different organizations recommend different daily intakes. Here are the recommendations from some organizations in the United States:

Recommended daily intakes from various organizations:

	Vitamin D Council	Endocrine Society	Food and Nutrition Board
Infants	1,000 IU/day	400-1,000 IU/day	400 IU/day
Children	1,000 IU/day per 25lbs of body weight	600-1,000 IU/day	600 IU/day
Adults	5,000 IU/day	1,500-2,000 IU/day	600 IU/day, 800 IU/day for seniors

The Food and Nutrition Board recommended daily intakes are the official recommendations by the United States government.

Why are the recommendations so different? Some researchers believe that there isn't enough evidence to support taking higher amounts of vitamin D yet. On the other hand, some researchers believe that research is proving, or will prove, that taking lower amounts isn't enough.

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Do I put my money where my mouth is?

Common genetic determinants of vitamin D insufficiency: a genome-wide association study

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Lancet 2010; 376: 180–88

Published Online June 10, 2010 DOI:10.1016/S0140-6736(10)60588-0

See Editorial page 142

See Comment page 148

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Summary

Background Vitamin D is crucial for maintenance of musculoskeletal health, and might also have a role in extraskeletal tissues. Determinants of circulating 25-hydroxyvitamin D concentrations include sun exposure and diet, but high heritability suggests that genetic factors could also play a part. We aimed to identify common genetic variants affecting vitamin D concentrations and risk of insufficiency.

Methods We undertook a genome-wide association study of 25-hydroxyvitamin D concentrations in 33 996 individuals of European descent from 15 cohorts. Five epidemiological cohorts were designated as discovery cohorts (n=16 125), five as in-silico replication cohorts (n=9367), and five as de-novo replication cohorts (n=8504). 25-hydroxyvitamin D concentrations were measured by radioimmunoassay, chemiluminescent assay, ELISA, or mass spectrometry. Vitamin D insufficiency was defined as concentrations lower than 75 nmol/L or 50 nmol/L. We combined results of genome-wide analyses across cohorts using *Z*-score-weighted meta-analysis. Genotype scores were constructed for confirmed variants.

Findings Variants at three loci reached genome-wide significance in discovery cohorts for association with 25-hydroxyvitamin D concentrations, and were confirmed in replication cohorts: 4p12 (overall $p=1\cdot9\times10^{-109}$ for rs2282679, in *GC*); 11q12 ($p=2\cdot1\times10^{-27}$ for rs12785878, near *DHCR7*); and 11p15 ($p=3\cdot3\times10^{-20}$ for rs10741657, near *CYP2R1*). Variants at an additional locus (20q13, *CYP24A1*) were genome-wide significant in the pooled sample ($p=6\cdot0\times10^{-10}$ for rs6013897). Participants with a genotype score (combining the three confirmed variants) in the highest quartile were at increased risk of having 25-hydroxyvitamin D concentrations lower than 75 nmol/L (OR 2·47, 95% CI 2·20–2·78, $p=2\cdot3\times10^{-48}$) or lower than 50 nmol/L (1·92, 1·70–2·16, $p=1\cdot0\times10^{-26}$) compared with those in the lowest quartile.

Interpretation Variants near genes involved in cholesterol synthesis, hydroxylation, and vitamin D transport affect vitamin D status. Genetic variation at these loci identifies individuals who have substantially raised risk of vitamin D insufficiency.

Funding Full funding sources listed at end of paper (see Acknowledgments).

Introduction

Vitamin D insufficiency affects as many as half of otherwise healthy adults in developed countries.[1] The musculoskeletal consequences of inadequate vitamin D concentrations are well established, and include childhood rickets, osteomalacia, and fractures.[2] A growing number of other disorders have also been linked to vitamin D insufficiency, although causal associations

Personal, social, and cultural factors are important determinants of vitamin D availability via their effects on sun exposure and diet. Sufficient exposure to ultraviolet light or adequate intake from diet or supplements is needed to maintain vitamin D status. Concentrations of the widely accepted biomarker for vitamin D, 25-hydroxyvitamin D, are highest in the summer and lowest in the winter in northern latitudes. However, only

Treat-2-Target

Interpretation Variants near genes involved in cholesterol synthesis, hydroxylation, and vitamin D transport affect vitamin D status. Genetic variation at these loci identifies individuals who have substantially raised risk of vitamin D insufficiency.


ONLY ALAN WAS PREPARED TO ACKNOWLEDGE THE ELEPHANT IN THE ROOM.
harrop