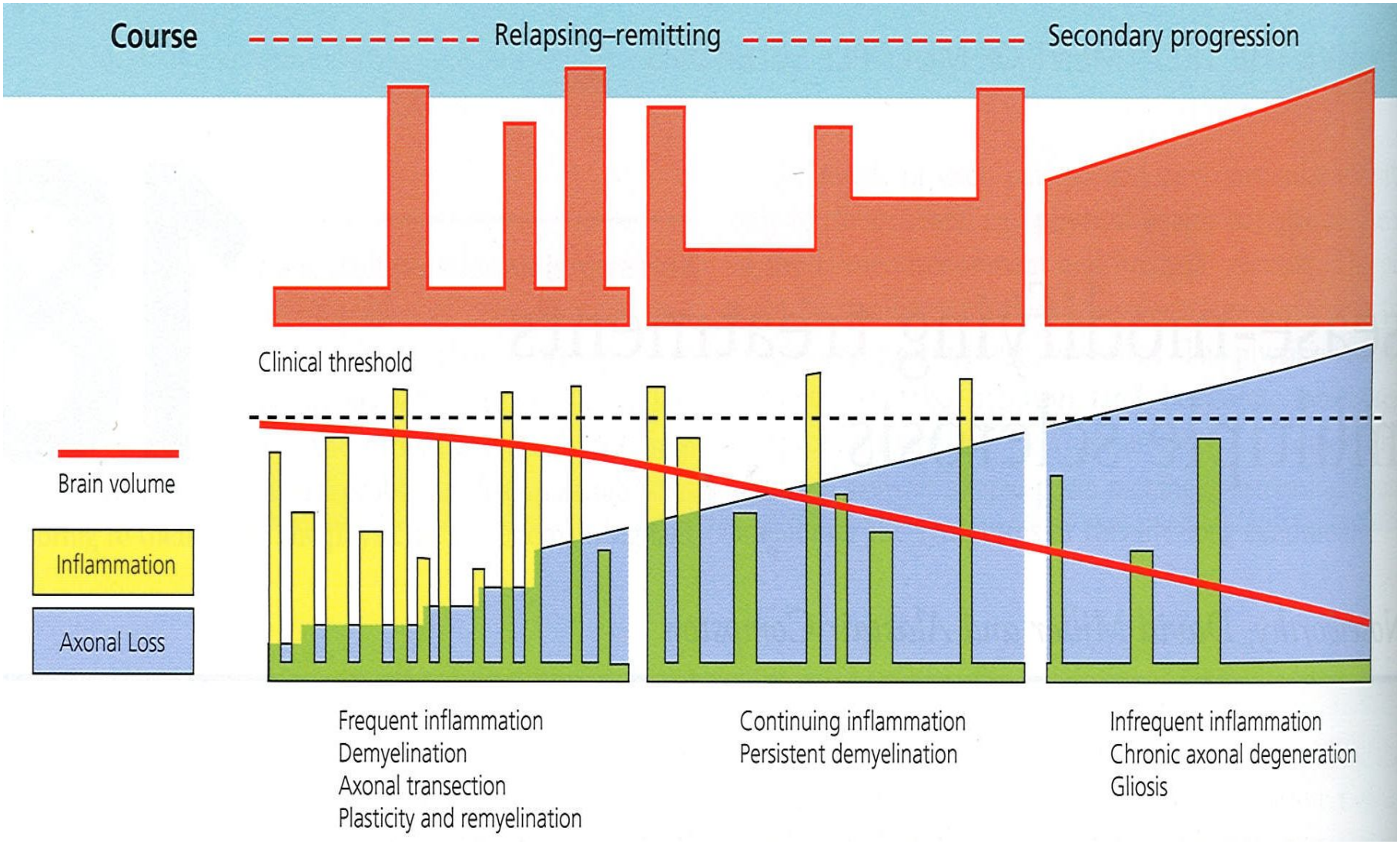
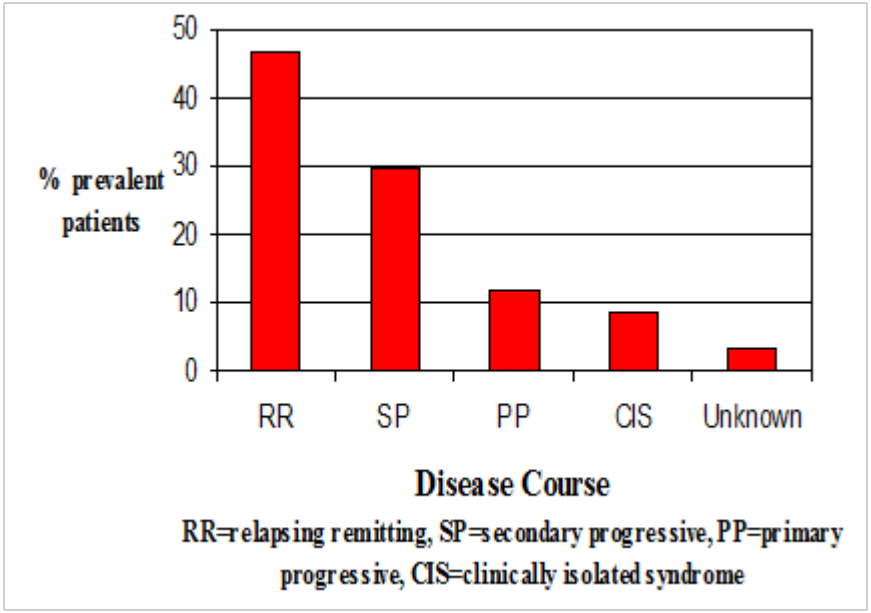
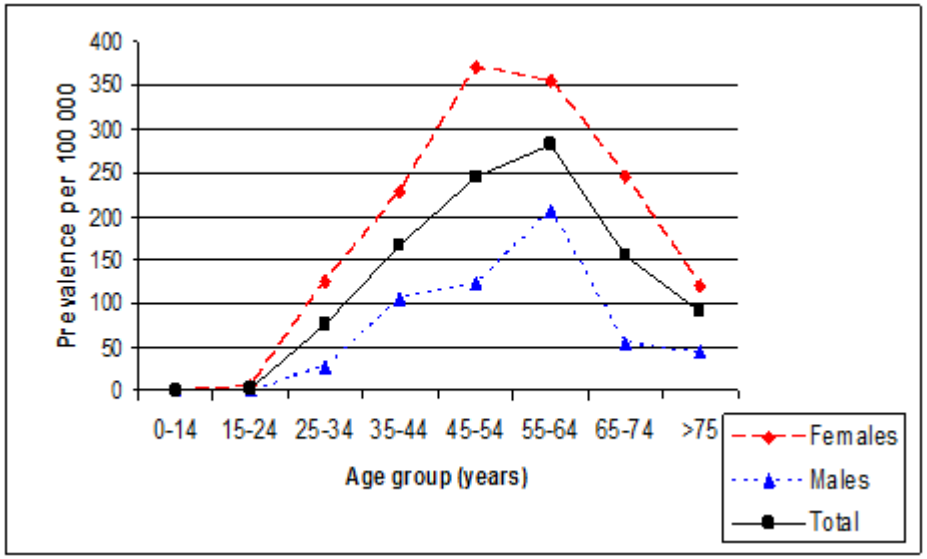

Course
Relapsing–remitting
Secondary progression
Clinical threshold
Brain volume
Inflammation
Axonal Loss
Frequent inflammation
Demyelination
Axonal transection
Plasticity and remyelination
Continuing inflammation
Persistent demyelination
Infrequent inflammation
Chronic axonal degeneration
Gliosis





	Population (thousands)	Incidence (/10^5/year)	Incident cases	Prevalence (/10^5)	Prevalent cases
UK	62 262.3	9.64	6003	203.4	126 669
England	52 233.9	9.08	4745	199.9	104 451
Wales	3006.3	7.92	238	168.0	5052
Scotland	5222.3	15.29	798	255.2	13 328
Northern Ireland	1799.8	12.25	221	213.2	383

Table 3 Crude and age-adjusted risks for first degree, half-siblings and adopted relatives

Proband	Female			Male			Total		
Relative	*n* (affected)	Crude risk (%)	Age-adjusted risk (%) (95% CI)	*n* (affected)	Crude risk (%)	Age-adjusted risk (%) (95% CI)	*n* (affected)	Crude risk (%)	Age-adjusted risk (%) (95% CI)
Monozygotic							78 (12)	15.38	17.26 (8.38–26.14)
Dizygotic							237 (4)	1.69	1.92 (0.00–0.38)
Child							43 078 (526)	1.22	2.03 (1.86–2.20)
Daughter	14 206 (251)	1.77	2.96 (2.60–3.32)	6737 (107)	1.59	2.57 (2.09–3.05)	20 943 (358)	1.71	2.83 (2.54–3.12)
Son	15 003 (99)	0.66	1.12 (0.90–1.34)	7132 (69)	0.97	1.55 (1.12–1.91)	22 135 (168)	0.76	1.26 (1.07–1.45)
Sibling							28 531 (652)	2.29	2.55 (2.09–3.01)
Sister	9537 (288)	3.02	3.36 (2.98–3.74)	4379 (136)	3.11	3.43 (2.86–4.00)	13 916 (424)	3.05	3.38 (3.16–3.60)
Brother	10 038 (136)	1.35	1.52 (1.13–1.78)	4577 (92)	2.01	2.23 (1.77–2.69)	14 615 (228)	1.56	1.74 (1.51–1.97)
Maternal half-sibling							4359 (62)	1.42	1.68 (1.26–2.10)
Sister	1382 (29)	2.10	2.40 (1.26–2.94)	681 (13)	1.91	2.14 (0.96–3.32)	2063 (42)	2.04	2.46 (1.72–3.20)
Brother	1569 (12)	0.76	0.95 (0.52–1.49)	727 (8)	1.10	1.31 (0.41–2.21)	2296 (20)	0.87	1.51 (0.96–2.06)
Paternal half-sibling							4117 (44)	1.07	1.40 (0.99–1.81)
Sister	1400 (16)	1.14	1.54 (0.79–2.29)	647 (10)	1.55	2.01 (0.78–3.24)	2047 (26)	1.27	1.69 (0.99–1.81)
Brother	1468 (10)	0.68	0.92 (0.35–1.49)	662 (8)	1.21	1.55 (0.05–2.62)	2130 (18)	0.85	1.12 (0.60–1.64)
Adopted child							497 (2)	0.4	0.67 (0.00–1.58)
Adopted sibling							65 (1)	1.54	1.76 (0.00–5.18)
Adoption							562 (3)	0.53	0.84 (0.00–1.79)

The age adjusted risks were calculated using Strömgren's unmodified method. The confidence intervals were estimated using the binomial distribution with the sum of the weights as the total sample size.

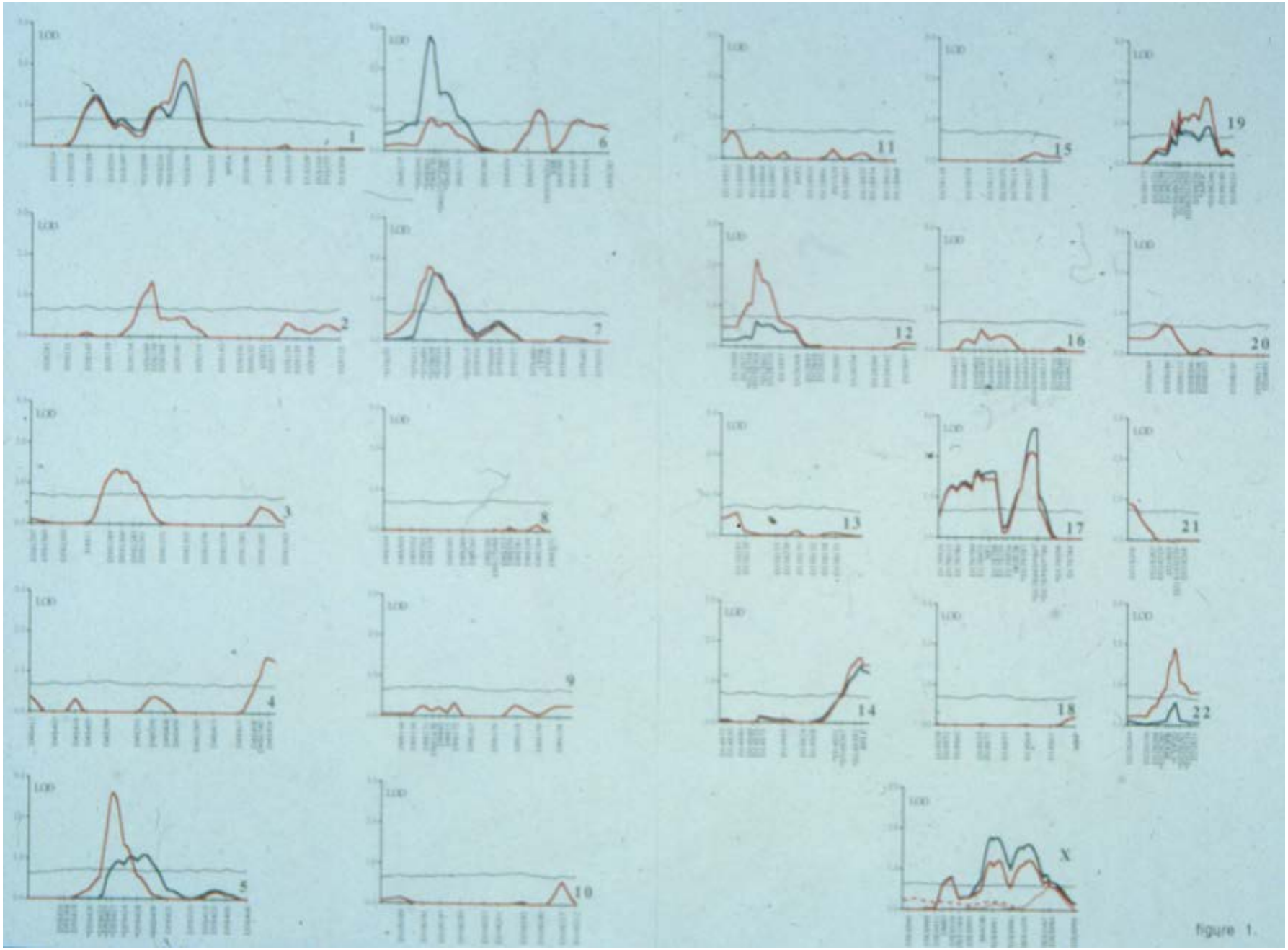


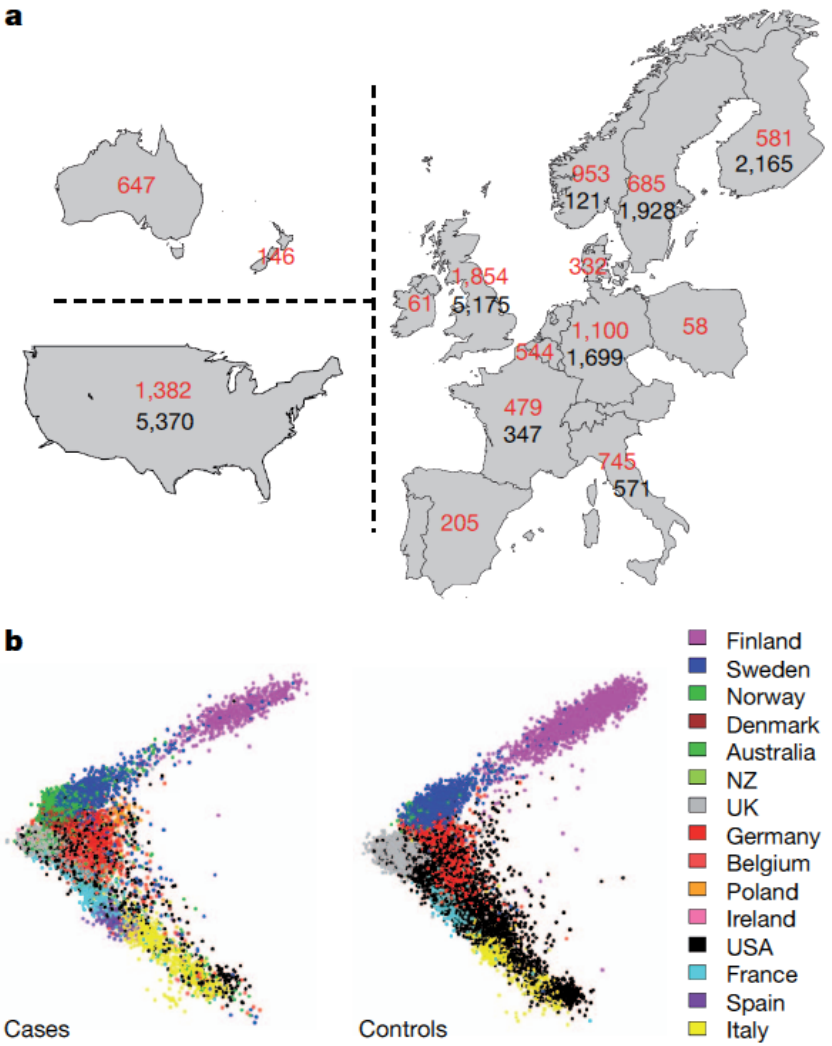
figure 1.

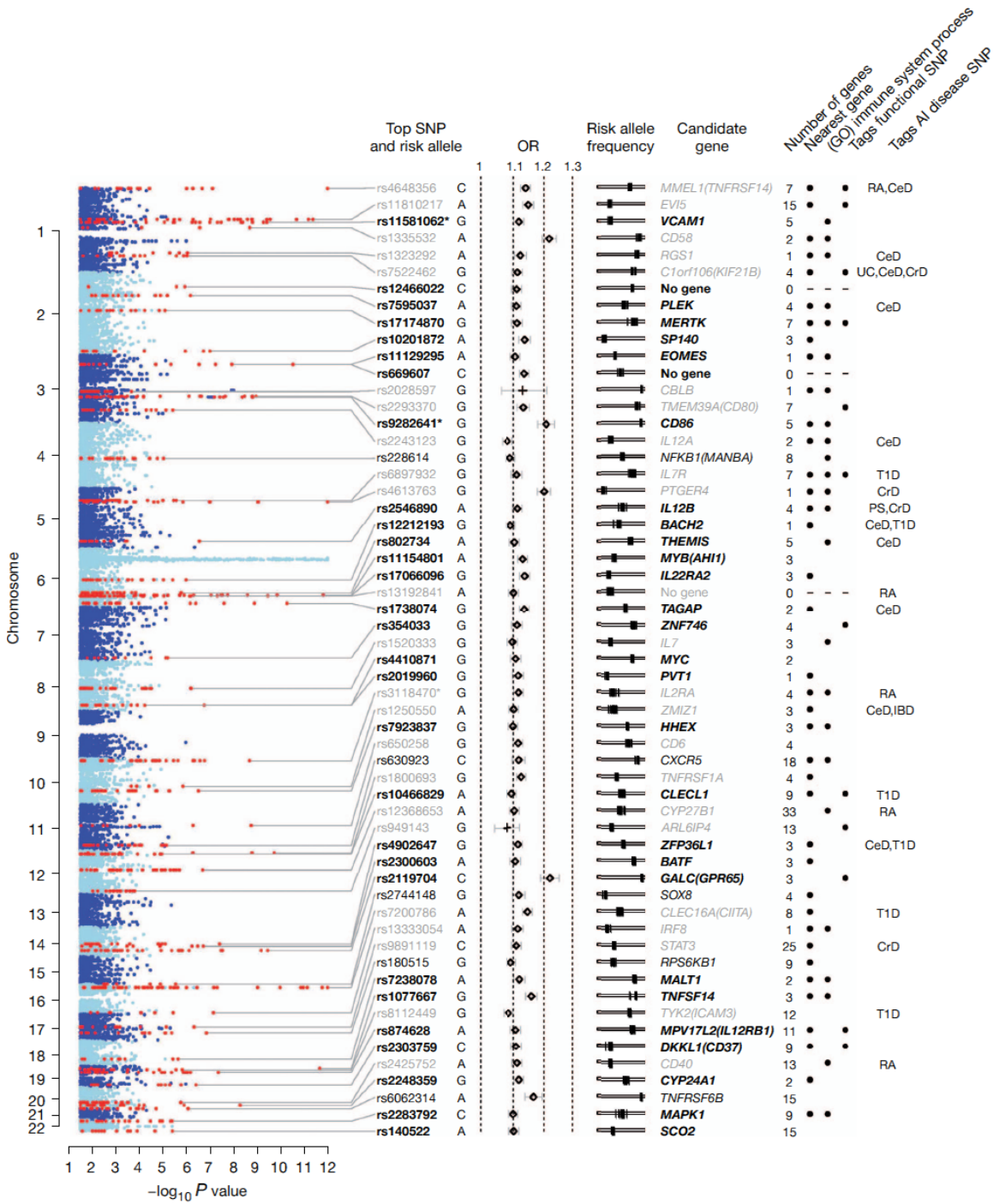
LETTER

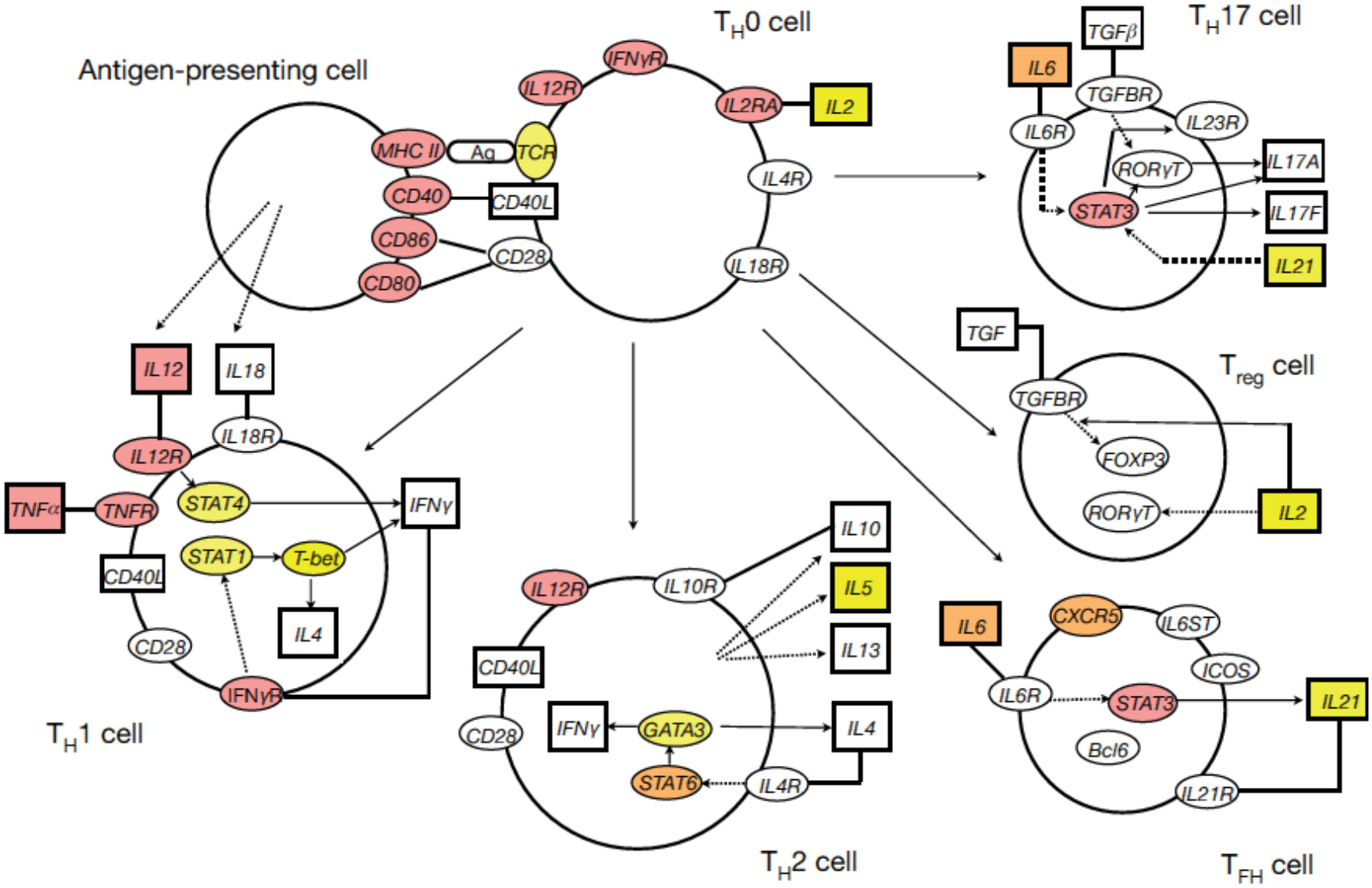
doi:10.1038/nature10251

Genetic risk and a primary role for cell-mediated immune mechanisms in multiple sclerosis

The International Multiple Sclerosis Genetics Consortium* & the Wellcome Trust Case Control Consortium 2*




Top SNP and risk allele
OR
Risk allele frequency
Candidate gene
Number of genes
Nearest gene
(GO) immune system process
Tags functional SNP
Tags AI disease SNP
1
1.1
1.2
1.3
Chromosome
1 2 3 4 5 6 7 8 9 10 11 12
−log10 P value
rs4648356 C
rs11810217 A
rs11581062* G
rs1335532 A
rs1323292 A
rs7522462 G
rs12466022 C
rs7595037 A
rs17174870 G
rs10201872 A
rs11129295 A
rs669607 C
rs2028597 G
rs2293370 G
rs9282641* G
rs2243123 G
rs228614 G
rs6897932 G
rs4613763 G
rs2546890 A
rs12212193 G
rs802734 A
rs11154801 A
rs17066096 G
rs13192841 A
rs1738074 G
rs354033 G
rs1520333 G
rs4410871 G
rs2019960 G
rs3118470* G
rs1250550 A
rs7923837 G
rs650258 G
rs630923 C
rs1800693 G
rs10466829 A
rs12368653 A
rs949143 G
rs4902647 G
rs2300603 A
rs2119704 C
rs2744148 G
rs7200786 A
rs13333054 A
rs9891119 C
rs180515 G
rs7238078 A
rs1077667 G
rs8112449 G
rs874628 A
rs2303759 C
rs2425752 A
rs2248359 G
rs6062314 A
rs2283792 C
rs140522 A
MMEL1(TNFRSF14) 7 RA,CeD
EVI5 15
VCAM1 5
CD58 2
RGS1 1 CeD
C1orf106(KIF21B) 4 UC,CeD,CrD
No gene 0
PLEK 4 CeD
MERTK 7
SP140 3
EOMES 1
No gene 0
CBLB 1
TMEM39A(CD80) 7
CD86 5
IL12A 2 CeD
NFKB1(MANBA) 8
IL7R 7 T1D
PTGER4 1 CrD
IL12B 4 PS,CrD
BACH2 1 CeD,T1D
THEMIS 5 CeD
MYB(AHI1) 3
IL22RA2 3
No gene 0 RA
TAGAP 2 CeD
ZNF746 4
IL7 3
MYC 2
PVT1 1
IL2RA 4 RA
ZMIZ1 3 CeD,IBD
HHEX 3
CD6 4
CXCR5 18
TNFRSF1A 4
CLECL1 9 T1D
CYP27B1 33 RA
ARL6IP4 13
ZFP36L1 3 CeD,T1D
BATF 3
GALC(GPR65) 3
SOX8 4
CLEC16A(CIITA) 8 T1D
IRF8 1
STAT3 25 CrD
RPS6KB1 9
MALT1 2
TNFSF14 3
TYK2(ICAM3) 12 T1D
MPV17L2(IL12RB1) 11
DKKL1(CD37) 9
CD40 13 RA
CYP24A1 2
TNFRSF6B 15
MAPK1 9
SCO2 15


Antigen-presenting cell
T_H0 cell
IFNγR
IL12R
IL2RA
IL2
MHC II
Ag
TCR
IL4R
CD40
CD40L
CD86
CD28
CD80
IL18R
T_H17 cell
TGFβ
IL6
TGFBR
IL23R
IL6R
RORγT
IL17A
STAT3
IL17F
IL21
TGF
T_reg cell
TGFBR
FOXP3
RORγT
IL2
IL12
IL18
IL18R
IL12R
TNFα
TNFR
STAT4
IFNγ
STAT1
T-bet
CD40L
IL4
CD28
IFNγR
T_H1 cell
IL10
IL12R
IL10R
IL5
CD40L
IL13
CD28
IFNγ
GATA3
IL4
STAT6
IL4R
T_H2 cell
IL6
CXCR5
IL6ST
ICOS
IL6R
STAT3
IL21
Bcl6
IL21R
T_FH cell

World Sunlight levels

Vitamin D and MS

- **Vitamin D deficiency and susceptibility to MS** Prospective studies have shown that vitamin D deficiency prior to MS onset predisposes individuals to increased risk of MS (Munger et al., 2004; 2006); geography and sunlight

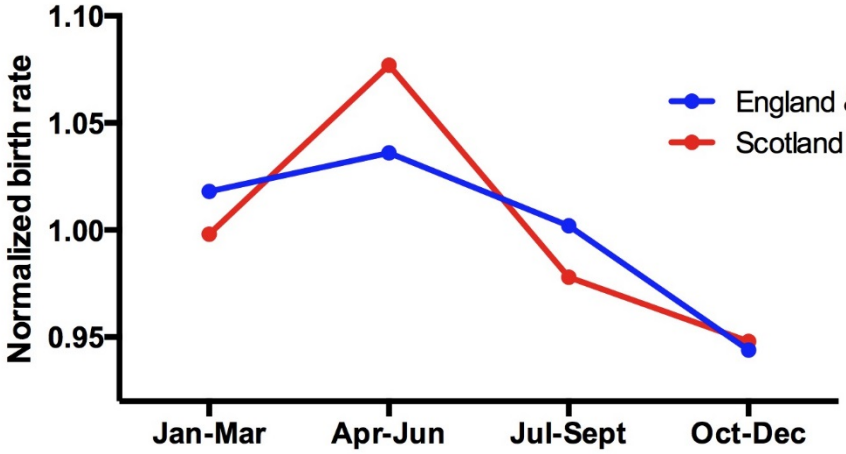
- **Vitamin D levels and disease activity in RRMS** For every 10ng/mL increase in baseline vitamin D level there was a 34% decrease in rate of subsequent relapse (Mowry et al., 2010).

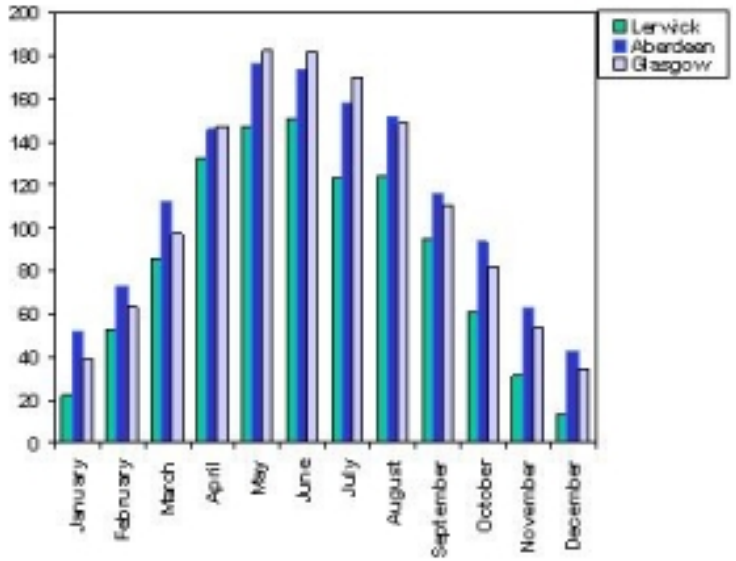
- **Vitamin D supplementation and disease activity in RRMS**

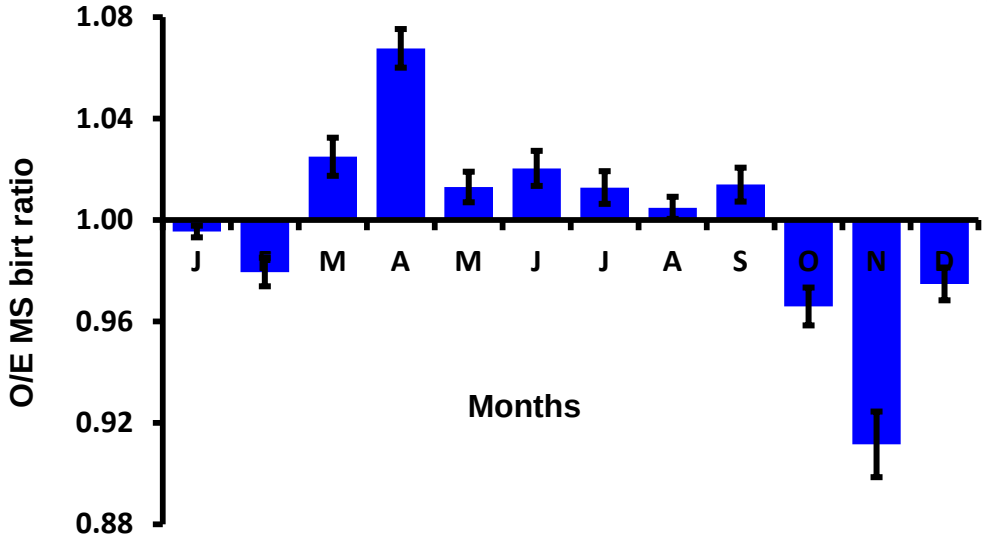
- **Vitamin D as an immunomodulator**

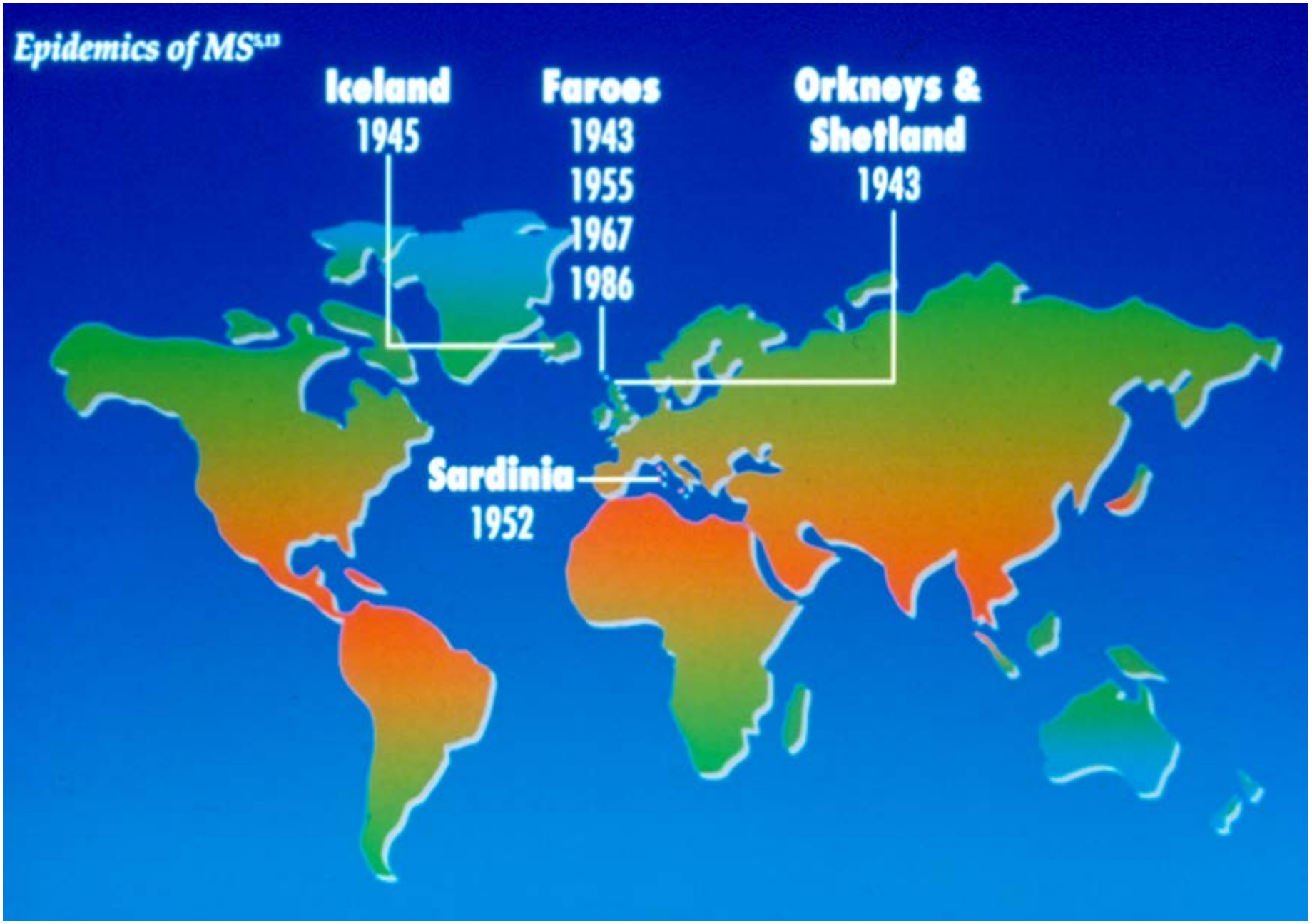
PreVANZ study

- 240 patients with CIS and MRI lesions
- 12 months FU to new lesions or new episode
- 4 groups – 0, 1000, 5000, 10000 iu Vit D3/day
- Current recruitment 61


Normalized birth rate
1.10
1.05
1.00
0.95
England & Wales
Scotland
Jan-Mar
Apr-Jun
Jul-Sept
Oct-Dec


200
180
160
140
120
100
80
60
40
20
0
Lerwick
Aberdeen
Glasgow
January
February
March
April
May
June
July
August
September
October
November
December

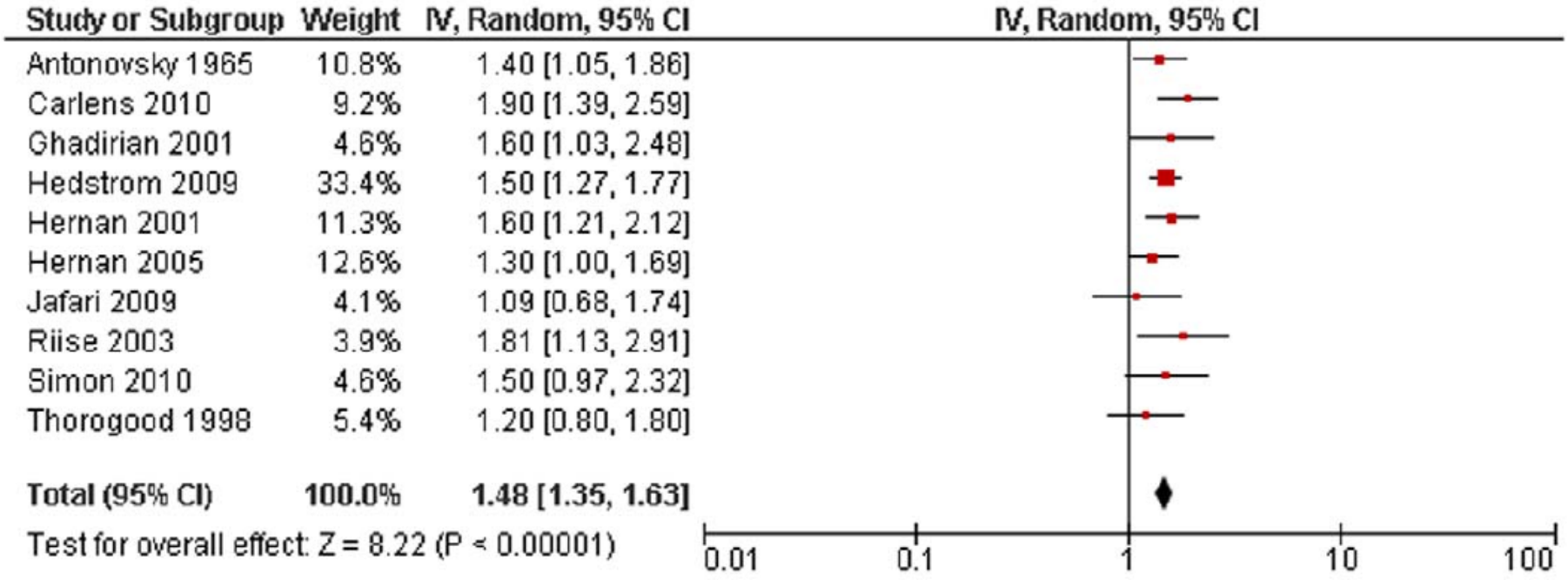

O/E MS birt ratio
1.08
1.04
1.00
0.96
0.92
0.88
J
F
M
A
M
J
J
A
S
O
N
D
Months


Epidemics of MS[5,13]
Iceland
1945
Faroes
1943
1955
1967
1986
Orkneys &
Shetland
1943
Sardinia
1952

Summary of the evidence

1. Virtually all subjects with MS (>99%) are infected with EBV compared to only ~90% of control subjects.
2. MS is very rare in subjects who are not infected with EBV.
3. People with MS have an increased tendency to spontaneous in-vitro lymphocyte transformation in clinically active multiple sclerosis.
4. People who have had symptomatic EBV infection or glandular fever have a higher risk of developing MS compared to people who have not had glandular fever.
5. People with higher levels of antibodies to EBV have a higher risk of developing MS compared to subjects with low antibody levels.
6. A unusual cluster of MS in children attending a school in rural Denmark occurred shortly after an outbreak of glandular fever.
7. Oligoclonal antibodies in the spinal fluid of subjects with MS recognise EBV antigens.
8. Autoimmune T cells in the circulation of subjects with MS, which are capable of orchestrating an attack on myelin producing cells also recognise EBV.
9. Subjects with MS have a higher number of CD8+-T-cells cells that recognise EBV than controls subjects (proliferation and tetramer).
10. During an MS relapse there is preliminary evidence that EBV is actively replicating compared to subjects with stable MS.
11. Anti-CD20 therapy may work by suppressing peripheral EBV replication.

Smoking and MS



Objectives

1) Understand impact of MS from patient perspective

to provide indicators that can be used to improve services and treatments for people with MS.

2) Improve outcome measurement

with application to improving clinical trial methodology.

3) Develop method to forecast future impact of MS

with application to treatment-targeting.

4) Facilitate other research

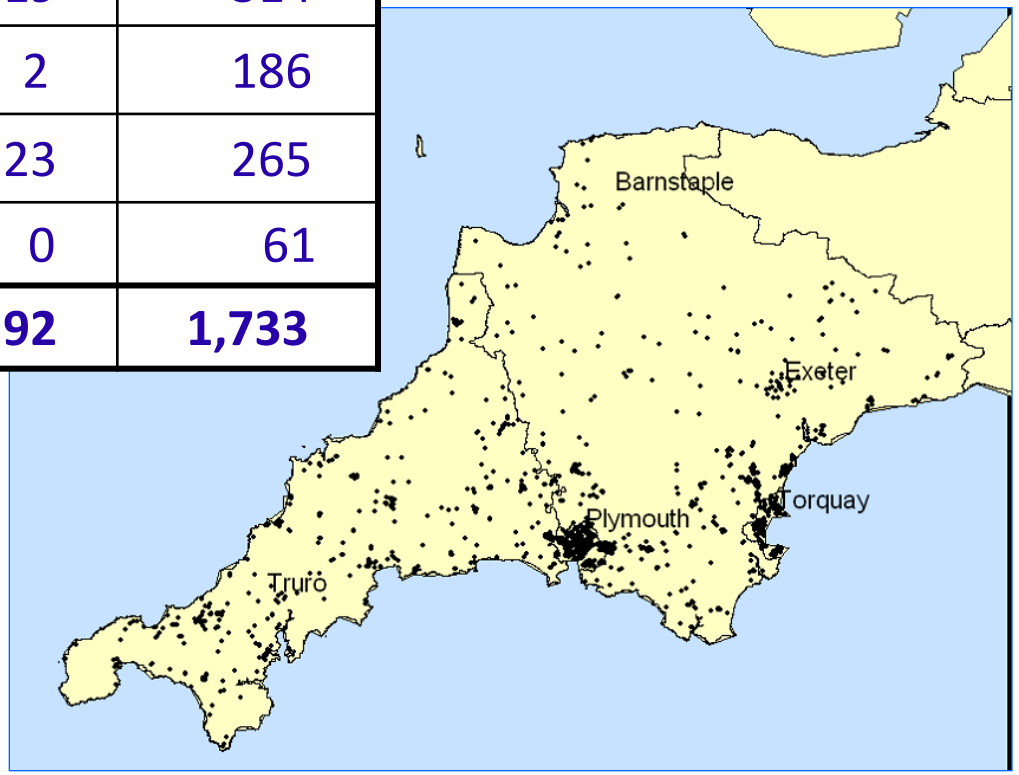
e.g. health economics, physiotherapist-led research; genetic markers.

MS Questionnaire Booklet

Current Contents		Baseline	6-monthly	12-monthly
Date of first symptom(s)		✓		
Date of first visit to GP		✓		
Date of diagnosis		✓		
Type of MS		✓		✓
Investigations		✓	✓	
MS relapses		✓	✓	
Symptoms		✓	✓	
Service use		✓	✓	
Medications		✓		✓
Perceived deterioration of MS			✓	
Patient-Determined Disease Steps		✓	✓	
Patient-reported outcome measures (PROMs)		After baseline participants are randomly allocated either version A or B , and receive alternate booklets every six months.		
A	MS Impact Scale (MSIS-29) version 2	✓		✓
	MS Walking Scale (MSWS-12) version 2	✓		✓
	Fatigue Severity Scale (FSS)	✓		✓
	General Health Questionnaire (GHQ-30)	✓		✓
	EuroQol (EQ-5D)	✓		✓
B	Functional Assessment of MS (FAMS)	✓		✓
	MS Neuropsychological Screening Questionnaire (MSNQ)	✓		✓
	Postal Barthel Index (PBI)	✓		✓
	Short-Form Medical Outcomes Survey (SF-36) version 2	✓		✓

Recruitment
Aug 2004 to Aug 2015 inclusive

Centre	Number recruited		Total
	MS#	CIS	
01 Plymouth	859	48	907
02 Torbay	295	19	314
03 Exeter + N Devon	184	2	186
04 Cornwall	242	23	265
05 N Devon	61	0	61
TOTAL	**1,641**	**92**	**1,733**



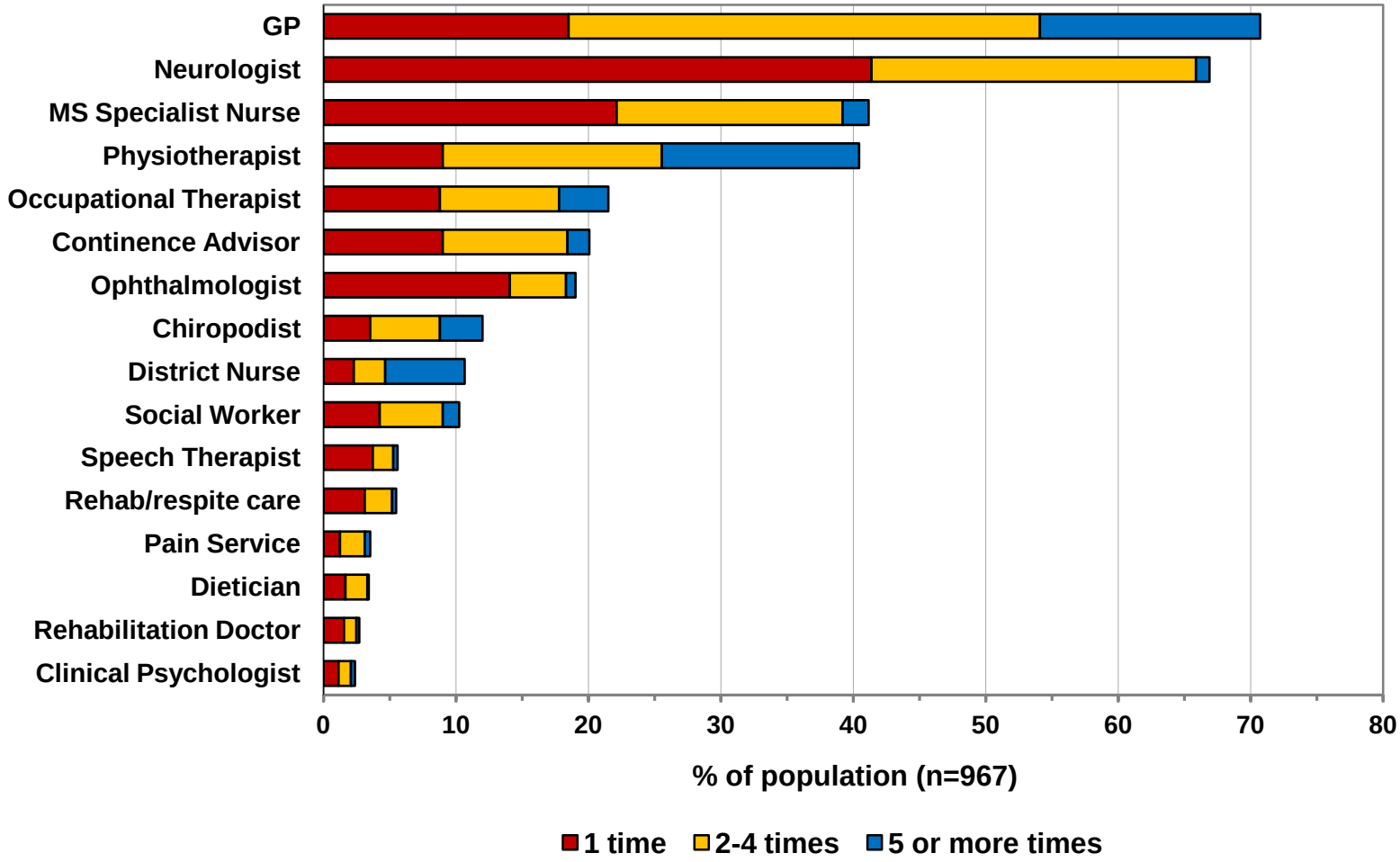
Response rate for Plymouth:
MS = 75%
CIS = 88%

includes 20 participants with CIS at entry to SWIMS

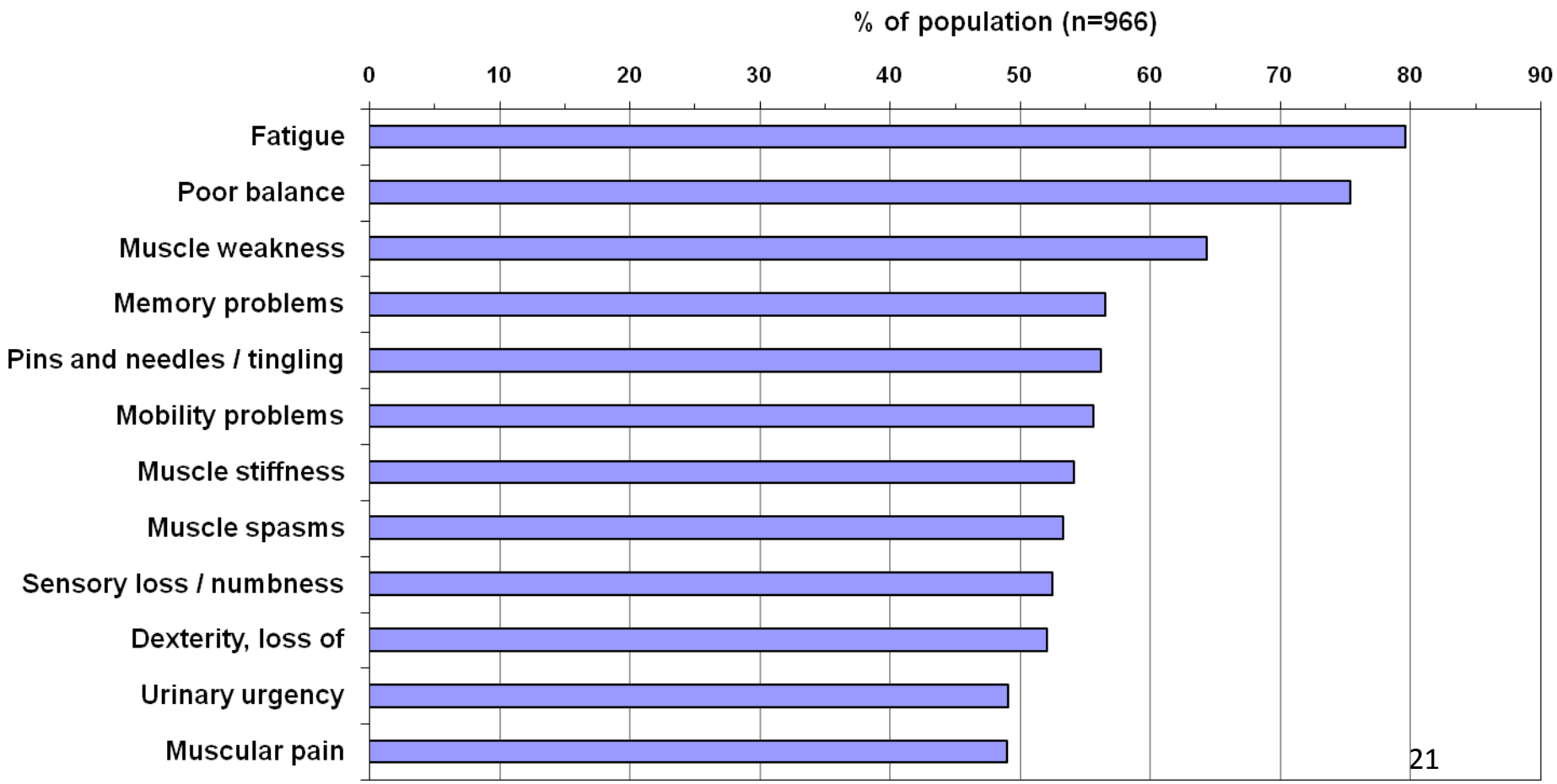
Relapses in last 12 months.

Impact of relapse (n=835)	yes	%
Admitted to hospital	93	11.1
Treated with oral steroids	130	15.6
Treated with iv steroids	112	13.4
Limited everyday activities other than employment	633	75.8
Time off work	201	24.1

How many times in last 12 months have you visited the following people for your MS?



Symptoms experienced at baseline? (12 most commonly reported)



Medications taken for MS at baseline or during previous 12 months

Disease-modifying therapies (DMT)

- Of 967 participants, 18.1% were currently, or had previously taken, a DMT.
  - Within the relapsing-remitting group, 31% were currently receiving, or previously received, a DMT.
  - The commonest DMTs in use were one of the forms of beta-interferon, and glatiramer acetate.

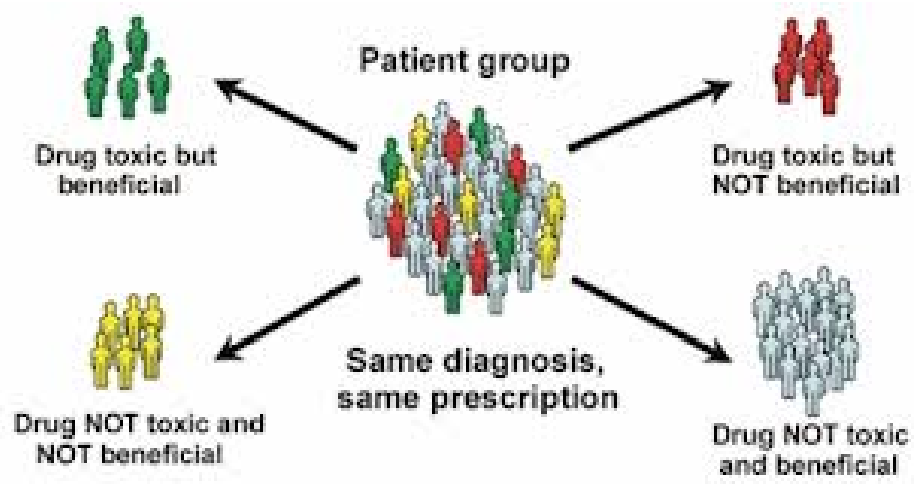
Fatigue

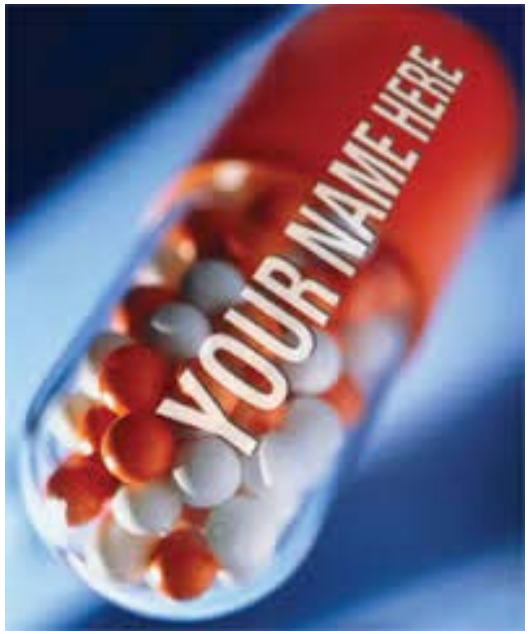
- Although 80% of the 967 participants experienced fatigue, only 3 people were taking amantadine or modafinil and were without fatigue.
- Fifty people taking amantadine or modafinil continued to have fatigue.

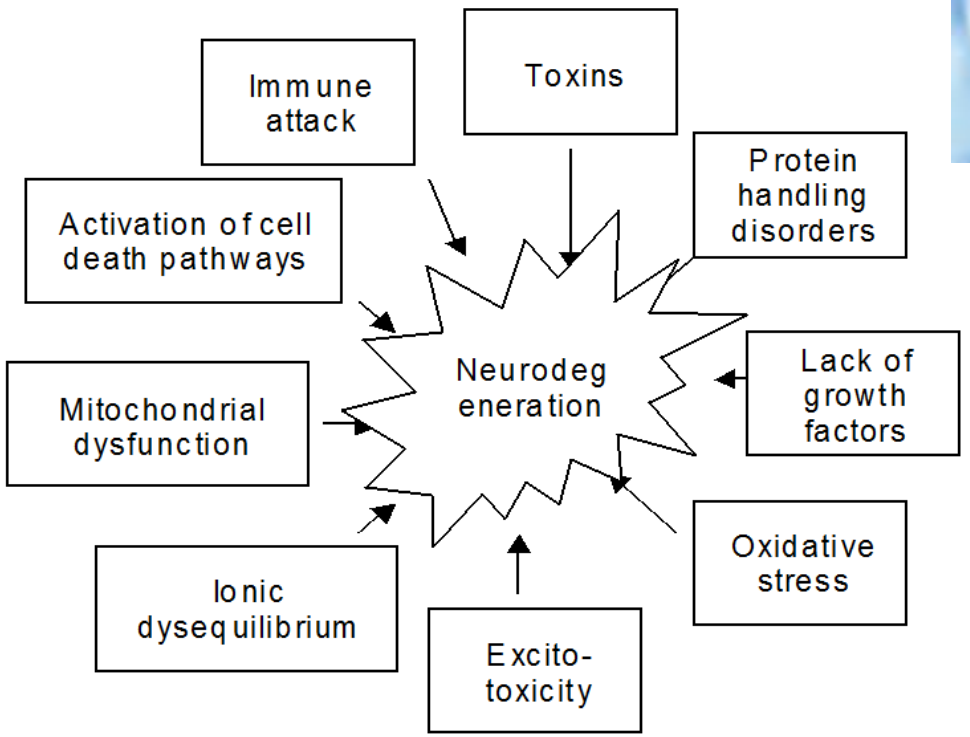
Facilitate other research

- Health economics
  Prof Colin Green, University of Exeter Medical School
- Physiotherapist-led
  Dr Jonathan Marsden, School of Health Professionals, UoP
  Jenny Freeman, School of Health Professions, UoP
- Genetics
  Prof DAS Compston, University of Cambridge
- Date of birth study
  Prof Jackie Palace, University of Oxford


ENTERING
HILLSVILLE
FOUNDED 1802
ALTITUDE 620
POPULATION 3,700
TOTAL 6,122
Dana Fradon


Patient group
Drug toxic but beneficial
Drug toxic but NOT beneficial
Same diagnosis, same prescription
Drug NOT toxic and NOT beneficial
Drug NOT toxic and beneficial


YOUR NAME HERE


Immune attack
Toxins
Protein handling disorders
Activation of cell death pathways
Neurodeg eneration
Lack of growth factors
Mitochondrial dysfunction
Oxidative stress
Ionic dysequilibrium
Excito-toxicity

Opportunities in Scotland

- Population Registers (e.g. SMSR, SWIMS), CHI.
- Clinical Trials – MS (incl. vit D, EBV)
- Data Linkage – Farr Institute
- Collaborations – (e.g. Future MS)
- Research as part of everyday clinical practice

Issues with Registers

- Length of FU compared to length of disease
- Bias from incomplete ascertainment
- Effort collecting information may not be used
- Loss of inertia, drop-out
- Why?

James Lind Alliance

1. Which treatments are effective to slow, stop or reverse the accumulation of disability associated with MS?
2. How can MS be prevented?
3. Which treatments are effective for fatigue in people with MS?
4. How can people with MS be best supported to self-manage their condition?
5. Does early treatment with aggressive disease modifying drugs improve the prognosis for people with MS?
6. Is Vitamin D supplementation an effective disease modifying treatment for MS?
7. Which treatments are effective to improve mobility for people with MS?
8. Which treatments are effective to improve cognition in people with MS?
9. Which treatments are effective for pain in people with MS?
10. Is physiotherapy effective in reducing disability in people with MS?