Supplementary Online Content

Ascherio A, Munger KL, White R, et al. Vitamin D as an early predictor of multiple sclerosis activity and progression. *JAMA Neurol*. Published online January 20, 2014. doi:10.1001/jamaneurol.2013.5993.

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eTable 1. BENEFIT Participants According to Changes in EDSS Scores Between Baseline and 6 Months

EDSS at Baseline	EDSS at 6 months						
	≤1.5	2.0	2.5	3.0	3.5	4.0+	Subtotal
	N (%)						
≤1.5	227 (85.0)	31 (11.6)	5 (1.9)	1 (0.4)	2 (0.7)	1 (0.4)	267 (100)
2.0	59 (52.7)	40 (35.7)	9 (8.0)	2 (1.8)	1 (0.9)	1 (0.9)	112 (100)
2.5	13 (37.1)	7 (20.0)	8 (22.9)	4 (11.4)	2 (5.7)	1 (2.9)	35 (100)
3.0	4 (21.1)	5 (26.3)	4 (21.1)	3 (15.8)	2 (10.5)	1 (5.3)	19 (100)
3.5	1 (10.0)	2 (20.0)	1 (10.0)	1 (10.0)	3 (30.0)	2 (20.0)	10 (100)
4.0+	0 (0.0)	0 (0.0)	1 (100)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100)

Abbreviation: EDSS, Expanded Disability Status Scale.

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eTable 2. Selected Characteristics of Patients in BENEFIT With 25(OH)D Measurements at Months 6 and 12 by Level of the Average of Season-Adjusted 25(OH)D at Baseline, 6 Months, and 12 Months

	Quintiles of 25(OH)D					Low vs. high 25(OH)D	
	1	2	3	4	5	Low (<50 nmol/L)	High (≥50 nmol/L)
N patients[a]	60	74	71	60	69	183	151
25(OH)D, nmol/L							
range	22-36	36-45	45-52	53-61	62-98	22-50	50-98
median	31	40	49	56	70	40	60
Age at recruitment, mean (SD)	31.5 (7.9)	33.5 (6.9)	29.0 (7.1)	30.4 (7.0)	30.8 (7.5)	31.9 (7.4)	30.0 (7.3)
Female, %	65.0	74.3	66.2	71.7	73.9	69.9	70.9
Randomized to IFNB-1b, %	66.7	60.8	59.2	65.0	72.5	60.1	70.2
Monofocal onset, %	48.3	51.4	45.1	45.0	56.5	47.5	51.7
Number of T2 lesions at baseline, median (Q1–Q3)	29.5 (11.8–38.0)	18.0 (8.3–47.0)	14.0 (7.5–31.0)	15.5 (7.0–44.3)	16.0 (6.0–40.0)	20 (9.0–38.5)	15 (7.0–37.0)
T2 volume at baseline, median (Q1–Q3)	2596 (1101.8–5471.8)	1947 (743.3–5310.8)	1883 (705.5–3411.5)	1947 (593.0–4454.0)	1714 (521.0–5215.0)	2141 (741.0–4891.0)	1851 (621.0–4694.5)
Central brain volume at baseline, median (Q1–Q3)	1053.3 (1020.2–1089.6)	1040.5 (1015.9–1070.9)	1056.9 (1022.2–1083.8)	1060.2 (1029.4–1082.7)	1073.3 (1029.9–1094.6)	1053.0 (1018.3–1074.2)	1066.5 (1030.6–1088.8)
BMI, mean (SD)	25.7 (5.6)	23.9 (4.1)	24.2 (3.7)	23.6 (3.6)	23.1 (3.8)	24.6 (4.7)	23.4 (3.7)
Steroids for 1st clinical event, %	75.0	60.8	70.4	73.3	56.5	67.8	65.6
Time to last EDSS, mean (days)	1780.2	1757.7	1762.6	1796.4	1791.1	1768.3	1786.7
Time to last MRI, mean (days)	1744.2	1704.7	1714.7	1745.5	1753.5	1722.2	1742.4

[a] N=334 patients with 25(OH)D measurements at both 6 and 12 months. To convert 25(OH)D to ng/mL divide by 2.5.

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eTable 3. HRs for Conversion to MDMS and CDMS for 50-nmol/L (20-ng/mL) increase in 25(OH)D

Period of follow-up	Group	MDMS			CDMS		
		N	HR (95% CI)	p-value	N	HR (95% CI)	p-value
Baseline –60M	All	465	0.74 (0.53-1.02)	0.065	465	0.76 (0.49-1.19)	0.23
	Initial IFNb	290	0.70 (0.46-1.05)	0.087	290	0.90 (0.51-1.56)	0.70
	Initial Placebo	175	0.80 (0.47-1.36)	0.41	175	0.57 (0.27-1.20)	0.14
6M-60M	All	259	0.51 (0.31-0.84)	0.008	386	0.67 (0.39-1.17)	0.16
	Initial IFNb	182	0.55 (0.31-0.99)	0.04	247	0.72 (0.37-1.42)	0.34
	Initial Placebo	77	0.40 (0.14-1.15)	0.088	139	0.59 (0.22-1.57)	0.29
6M-60M Both 6M & 12M 25(OH)D	All	202	0.44 (0.25-0.77)	0.003	302	0.48 (0.25-0.91)	0.025
	Initial IFNb	146	0.43 (0.22-0.84)	0.01	200	0.48 (0.22-1.04)	0.06
	Initial Placebo	56	0.48 (0.15-1.57)	0.23	102	0.49 (0.15-1.63)	0.24

Abbreviations: CDMS, clinically definite MS; HR, hazard ratios; MDMS, McDonald et al multiple sclerosis criteria.
Adjusted for age, treatment group (except in stratified analyses) sex, T2scr, and type of onset.

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eTable 4. MS Activity and Vitamin D by Treatment Group: RRs for New Active MRI Lesions and MS Relapses According to a 50-nmol/L (20-ng/mL) Increment in Serum 25(OH)D Levels

Patients		**All patients**		**Excluding missing 6 or 12 M 25(OH)D**					
Period		**Baseline to 60 M**		**Baseline to 60 M**		**12M to 60 M**		**24M to 60 M**	
25(OH)D		**Cumulative average -Updated to 24 M**		**Cumulative average -Updated to 24 M**		**Cumulative average – updated to 12M**		**Cumulative average – updated to 12M**	
		RR (95% CI)	p	RR (95% CI)	p	RR (95% CI)	p	RR (95% CI)	p
New active lesions	Initial IFNb	.45 (.29-.69)	.0003	.35 (.21-.58)	.00004	.31 (.15-.61)	.0008	.27 (.13-.57)	.0007
	Initial Placebo	.69 (.44-1.09)	.12	.77 (.45-1.32)	.35	.61 (.30-1.27)	.19	.49 (.22-1.11)	.09
Relapses	Initial IFNb	.99 (.53-1.95)	.97	.89 (.42-1.87)	.75	.38 (.14-.99)	.048	.41 (.14-1.19)	.099
	Initial Placebo	.48 (.24-.97)	.04	.45 (.18-1.10)	.08	.59 (.18-1.96)	.39	.46 (.07-1.84)	.40

Abbreviations: MRI, magnetic resonance imaging; MS, multiple sclerosis; RR, rate ratio.
RR adjusted for age, sex, treatment, time of follow-up, and T2 lesion score at baseline.

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eTable 5. Disease Progression and Vitamin D Levels by Treatment Group: Relative Annual Change Percentage in T2 Lesion Volume and Brain Volume as well as Change of EDSS With 95% Confidence Intervals for a 50-nmol/L (20-ng/mL) Increment in Serum 25(OH)D

Patients	**Group**	**All**		**Excluding missing 6M or 12 M 25(OH)D**			
Period		**12M to 60 M**		**12M to 60 M**		**24M to 60 M**	
25(OH)D		**Cumulative average -Updated to 24 M**		**Cumulative average – updated to 12M**		**Cumulative average – updated to 12M**	
		% change (95% CI)	p	% change (95% CI)	p	% change (95% CI)	p
T2 volume	Initial IFNb	-21 (-32 to -10)	.0007	-26 (-39 to -12)	.0007	-30 (-43 to -15)	.0004
	Initial Placebo	-19 (-31 to -7)	.004	-25 (-38 to -8)	.005	-26 (-40 to -8)	.006
Brain volume	Initial IFNb	.40 (-.05 to .86)	.08	.64 (.08 to 1.2)	.02	.68 (.02 to 1.35)	.04
	Initial Placebo	.11 (-.42 to . 64)	.69	.04 (-.69 to .79)	.9	.16 (-.66 to .99)	.7
Patients		All		Excluding missing 6M or 12 M 25(OH)D			
Period		6M to 60 M		6M to 60 M		24M to 60 M	
25(OH)D		Cumulative average -Updated to 24 M		Cumulative average – updated to 12M		Cumulative average – updated to 12M	
		change (95% CI)	p	change (95% CI)	p	change (95% CI)	p
EDSS	Initial IFNb	-.07 (-.32 to .18)	.59	-.03 (-.37 to .30)	.86	-.04 (-.41 to .33)	.84
	Initial Placebo	-.25 (-.59 to .08)	.14	-.39 (-.85 to .07)	.09	-.42 (-.91 to .07)	.09

Abbreviation: EDSS, Expanded Disability Status Scale.

Results adjusted for age, sex, treatment, time of follow-up, and T2 lesion score at baseline.

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- **eFigure 1**. Unadjusted Serum 25(OH)D Levels by Visit

- **eFigure 2.** Unadjusted and Adjusted 25(OH)D Levels by Season. To convert to ng/mL divide by 2.5

- **eFigure 3.** Hazard Ratios for Conversion to MDMS (A) or CDMS (B) by Quintiles of Serum 25(OH)D. Period of follow-up is from 6 to 60 months. Analyses are based on patients with Month 6 and Month 12 measurements of 25(OH)D. Group comparisons are adjusted for age, sex, treatment, time of follow-up, and T2 lesion score at baseline. To convert nmol/L of 25(OH)D to ng/mL divide by 2.5. Error bars are 95% confidence intervals; the lowest quintile is used as reference. A) *p=0.042 for q4, p=0.045 for q5.

- **eFigure 4.** Rate Ratio of Relapses up to Year 5 by Quintiles of Serum 25(OH)D. Analyses are based on patients with Month 6 and Month 12 measurements of 25(OH)D. Group comparisons are adjusted for age, sex, treatment, time of follow-up, and T2 lesion score at baseline. To convert nmol/L of 25(OH)D to ng/mL divide by 2.5. Error bars are 95% confidence intervals; the lowest quintile is used as reference.

- **eFigure 5.** Percentage Change of Brain Volume From Year 1 to Year 5 by Quintiles of Serum 25(OH)D. Analyses are based on patients with Month 6 and Month 12 measurements of 25(OH)D. Group comparisons are adjusted for age, sex, treatment, time of follow-up, and T2 lesion score at baseline. To convert nmol/L of 25(OH)D to ng/mL divide by 2.5.Error bars are 95% confidence intervals; the lowest quintile is used as reference. A) *Compared with q1: p=0.004 for 2; p=0.03 for q3. Compared with q2: p=0.01 for q4; p=0.0002 for q5; compared with q3: p=0.03 for q4; p=0.001 for q5.

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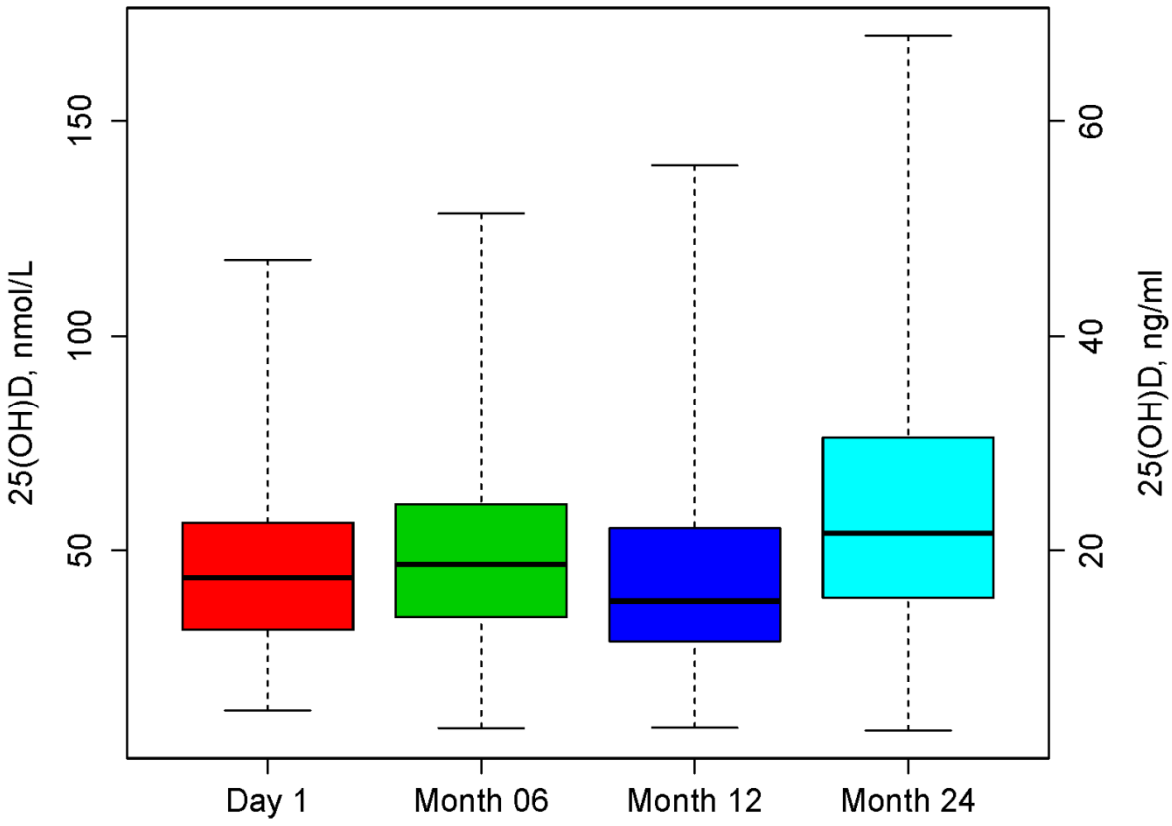
eFigure 1. Unadjusted Serum 25(OH)D Levels by Visit



Serum 25(OH)D levels by visit in nmol/L (to convert to ng/mL divide by 2.5).

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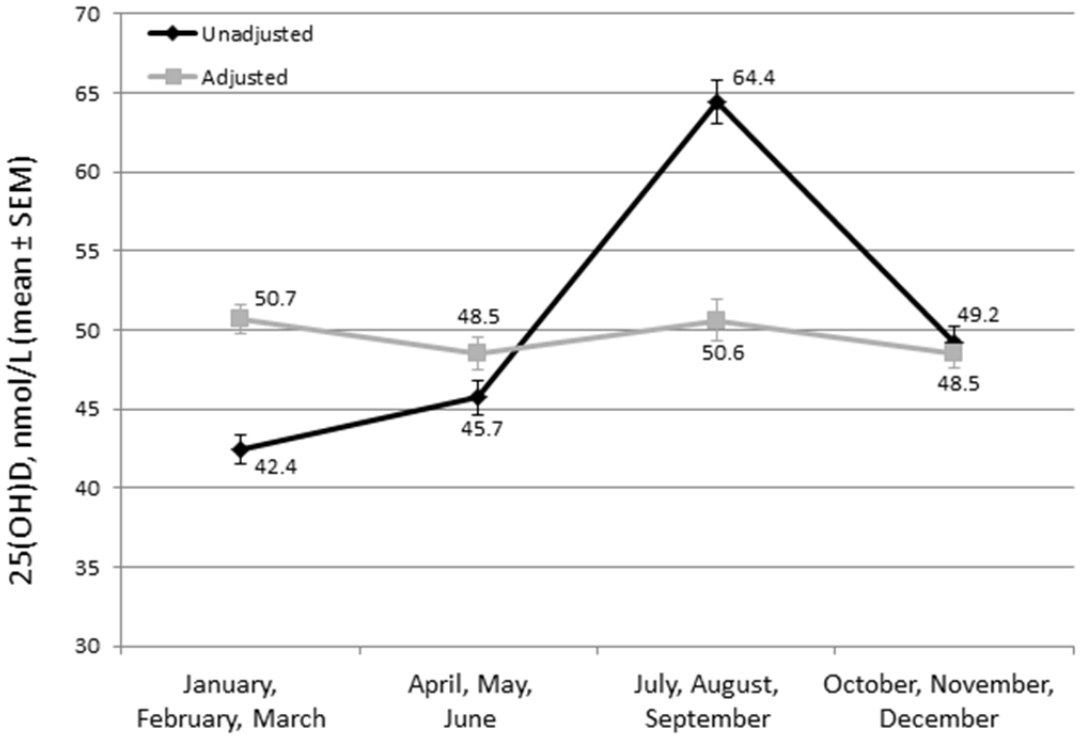
eFigure 2. Unadjusted and Adjusted 25(OH)D Levels by Season



To convert to ng/mL divide by 2.5

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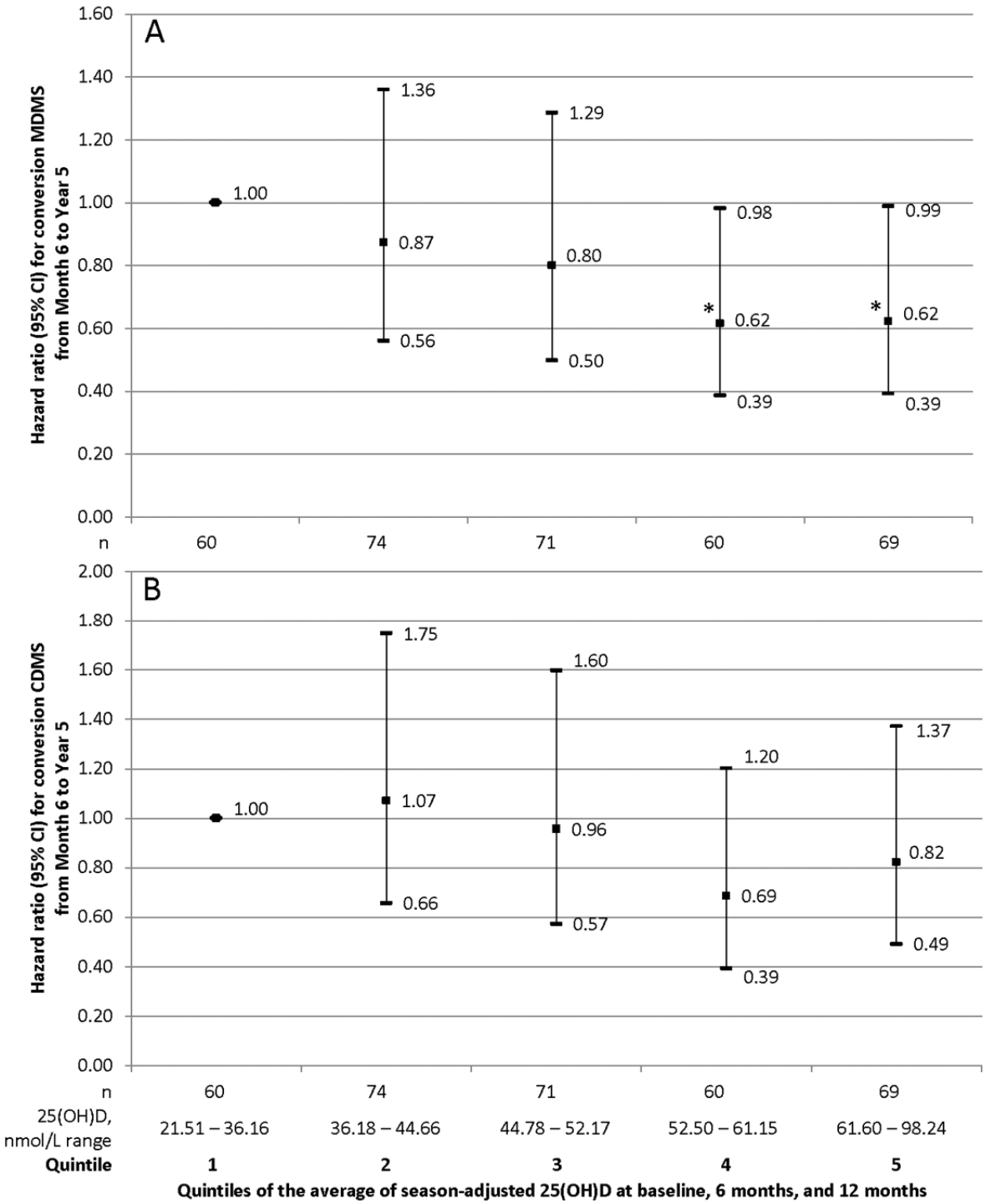
eFigure e3. Hazard Ratios for Conversion to MDMS (A) or CDMS (B) by Quintiles of Serum 25(OH)D



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Period of follow-up is from 6 to 60 months. Analyses are based on patients with Month 6 and Month 12 measurements of 25(OH)D. Group comparisons are adjusted for age, sex, treatment, time of follow-up, and T2 lesion score at baseline. To convert nmol/L of 25(OH)D to ng/mL divide by 2.5. Error bars are 95% confidence intervals; the lowest quintile is used as reference. A) *p=0.042 for q4, p=0.045 for q5.

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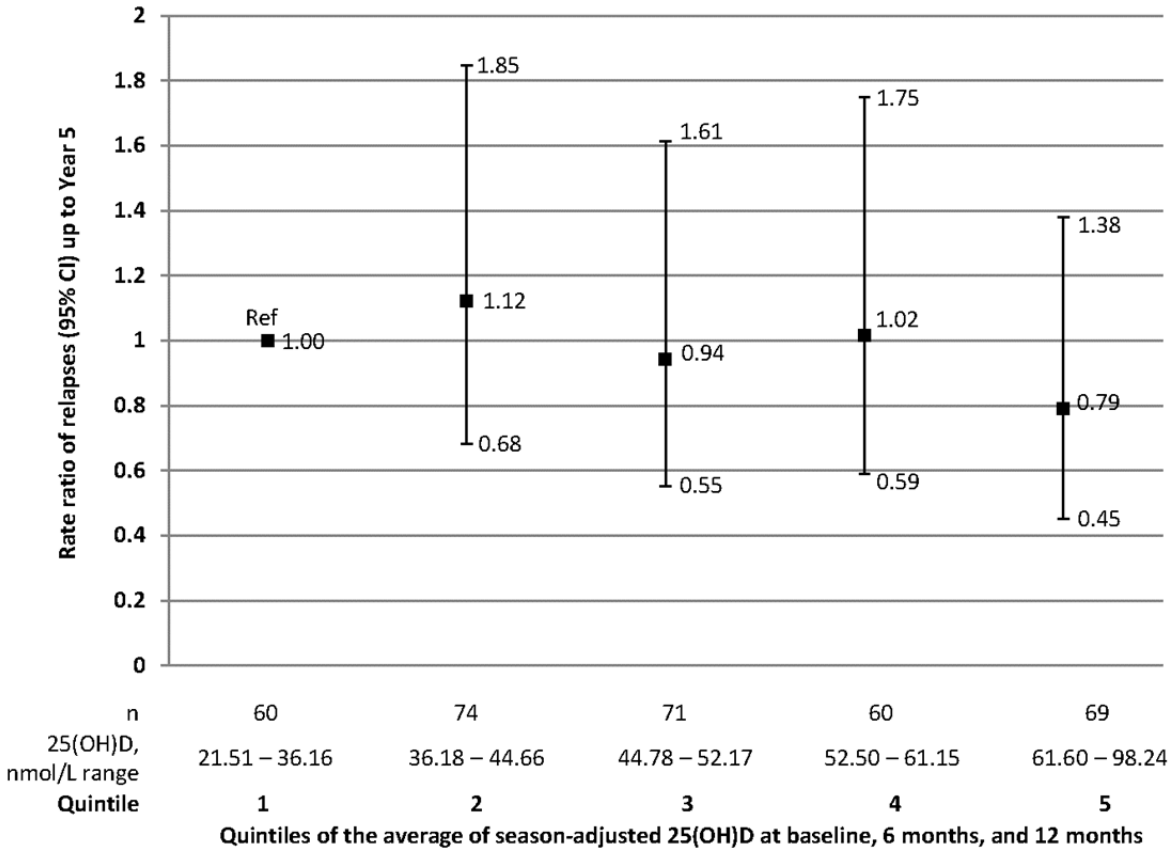
eFigure 4. Rate Ratio of Relapses up to Year 5 by Quintiles of Serum 25(OH)D



Analyses are based on patients with Month 6 and Month 12 measurements of 25(OH)D. Group comparisons are adjusted for age, sex, treatment, time of follow-up, and T2 lesion score at baseline. To convert nmol/L of 25(OH)D to ng/mL divide by 2.5. Error bars are 95% confidence intervals; the lowest quintile is used as reference.

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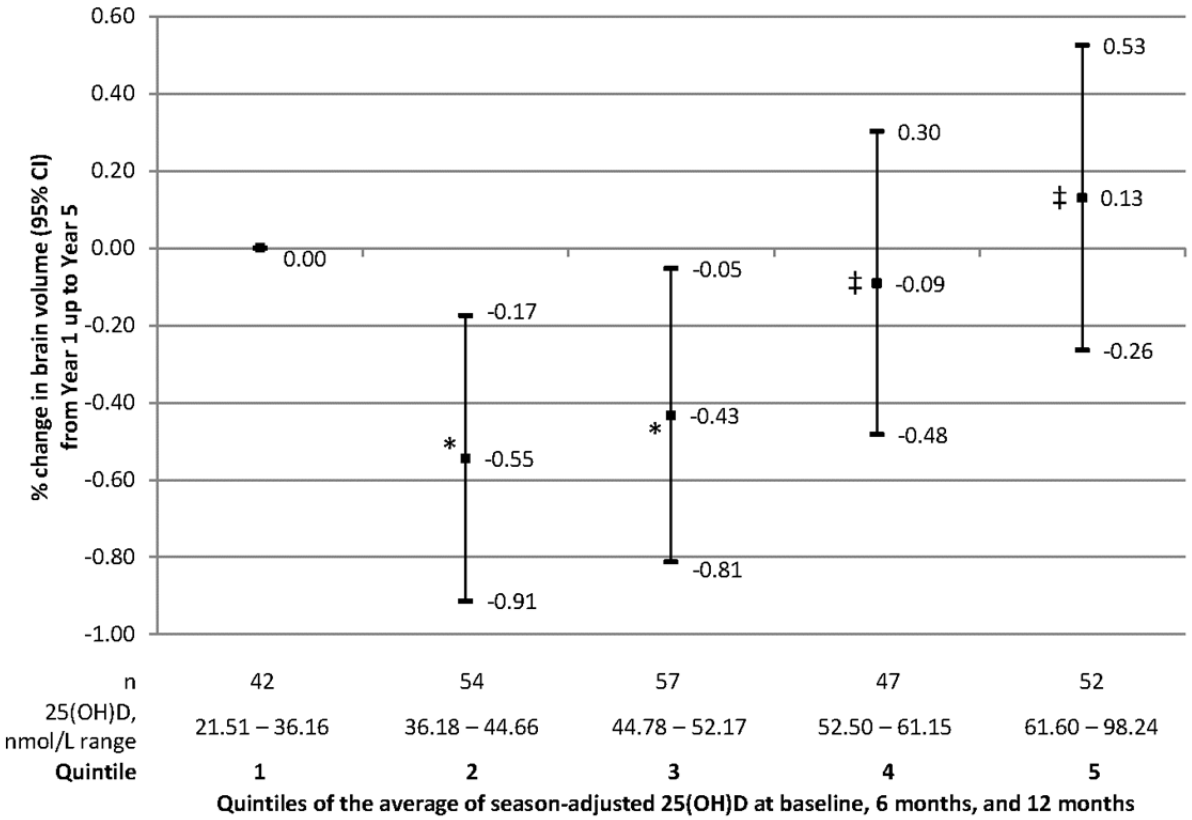
eFigure 5. Percenage Change of Brain Volume From Year 1 to Year 5 by Quintiles of Serum 25(OH)D



Analyses are based on patients with Month 6 and Month 12 measurements of 25(OH)D. Group comparisons are adjusted for age, sex, treatment, time of follow-up, and T2 lesion score at baseline. To convert nmol/L of 25(OH)D to ng/mL divide by 2.5.Error bars are 95% confidence intervals; the lowest quintile is used as reference. A) *Compared with q1: p=0.004 for 2; p=0.03 for q3. Compared with q2: p=0.01 for q4; p=0.0002 for q5; compared with q3: p=0.03 for q4; p=0.001 for q5.

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