ON-LINE APPENDIX: METHODS

Subjects

The diagnosis of CIS or MS was determined following the McDonald criteria.[1,2] HI included non-genetically related relatives of patients with MS and subjects recruited through local advertisements who participated in a large study of cardiovascular, genetic, and environmental factors in MS and were scanned serially on 1.5T and 3T scanners for 5 years.[3] HI participants were enrolled in the study if they presented with normal neurologic and age-compatible MR imaging findings. Collected clinical information for the patients included disease duration, disease subtype, and EDSS.[4] DP was defined as an absolute change in EDSS from the first to most recent follow-up MR imaging with an increase in EDSS of ≥1.5 points if the baseline EDSS was 0, or ≥1.0 point if the baseline was between 1.0 and 5.0, or ≥0.5 points if the baseline EDSS was ≥5.5 and was confirmed after at least 24 weeks. The Multiple Sclerosis Severity Score, an algorithm that combines disability level and disease duration, was also used to rate disease severity.[5]

MR Imaging Acquisition

The 3T and 1.5T sequences were acquired with matrix of 256 × 192 and an FOV of 25.6 cm with 75% phase FOV. The in-plane resolution was 1 × 1 × 3 mm^3 without a gap for T2-FLAIR and 1 × 1 × 1 mm^3 without a gap for 3D T1WI. Additional sequence parameters for 3T T2-FLAIR included TE/TI/TR = 120/2100/8500 ms. The additional parameters for 1.5T T2-FLAIR were TE/TI/TR = 120/2000/8000 ms. The 3D high-resolution T1WI used a fast spoiled gradient-echo with magnetization-prepared inversion recovery pulse, and parameters were TE/TI/TR = 2.8/900/5.9 ms, flip angle = 10° for 3T, and TE/TI/TR = 3.7/900/7.7 ms, flip angle = 10° for 1.5T.

Results

Study Sample. The mean interval between the first MR imaging and most recent follow-up was 4.7 ± 2.6 years for MS, 3.7 ± 2.4 years for CIS, and 3.1 ± 2.1 years for HI ($P < .0001$). In the MS group, 1219 (80.5%) had relapsing-remitting, 255 (16.8%) had secondary-progressive, and 40 (2.6%) had primary-progressive MS disease subtypes. During the study, 37 (27%) patients with CIS converted to clinically definite MS and 361 (23.8%) patients with MS and 12 (8.8%) patients with CIS developed DP.

MR Imaging Characteristics at Baseline and during the Follow-Up. Reasons for MR imaging analysis failures with each technique, according to the disease type, are listed in On-line Table 3. The most frequent reason for failure was change in orientation/thickness/protocol, examinations acquired on different scanners, poor scan quality, excessive motion artifacts, and anatomic variations.

Brain Volume Changes with Time. Annualized cumulative brain volume changes were also significantly different among MS, CIS, and HI for percentage LVV change ($P = .01$) and PBVC ($P = .001$), but not for percentage NBV change ($P = .077$). Table 1 also shows differences in MS and HI, while On-line Table 6 shows percentage LVV and NBV changes in a subsample of patients who had PBVC available between the first MR imaging and the most recent follow-up in the MS, CIS, and HI groups.

Brain volume changes from the first MR imaging to most recent follow-up, as well as annualized and annualized cumulative brain volume changes, were not significantly different among MS subtypes (On-line Table 4). On-line Table 5 shows percentage LVV and NBV change in the subsample of patients who had an available PBVC between the first MR imaging and most recent follow-up, according to the MS subtype.

Longitudinal Relationship between Brain Volume Changes and Clinical Measures. In a subsample of patients with MS who had PBVC available between the first MR imaging and most recent follow-up, patients with MS with DP had an increased rate (+33.1%) of annualized LVV enlargement ($P = .004$) and a decreased rate (−21.9%) of annualized NBV change ($P = .002$) compared with patients without DP (On-line Tables 7 and 8 and On-line Fig 2, lower row).

Patients with CIS who developed CDMS had an increased rate (+29.5%) of annualized LVV enlargement compared with patients who did not; however, this was not significant ($P = .968$). Similarly, no significant differences were found for annualized NBV change and PBVC (On-line Tables 7 and 8). Restricting the mixed-effects models to the subsample of patients with CIS who had PBVC available between the first MR imaging and most recent follow-up yielded similar results (On-line Tables 7 and 8).

REFERENCES

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3. Zivadinov R, Ramasamy DP, Benedict RR, et al. **Cerebral microbleeds in multiple sclerosis evaluated on susceptibility-weighted images and quantitative susceptibility maps: a case-control study.** *Radiology* 2016;281:884–95 CrossRef Medline
4. Kurtzke JF. **Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS).** *Neurology* 1983;33:1444–52 CrossRef Medline
5. Roxburgh RH, Seaman SR, Masterman T, et al. **Multiple sclerosis severity score: using disability and disease duration to rate disease severity.** *Neurology* 2005;64:1144–51 CrossRef Medline

On-line Table 1: Cumulative no. of subjects, total no. of MRIs, and mean follow-up time of patients with MS and CIS and HI[a]

	1.5T			3T			Total (1.5T and 3T)		
No. of MRI Time Points (Any)	Cumulative No. of Subjects	Total No. of MRIs	Mean Follow-Up Time (mo) (SD)	Cumulative No. of Subjects	Total No. of MRIs	Mean Follow-Up Time (mo) (SD)	Cumulative No. of Subjects	Total No. of MRIs	Mean Follow-Up Time (mo) (SD)
1	472	472	0.0 (0.0)	349	349	0.0 (0.0)	58	58	0.0 (0.0)
2	856	768	27.6 (21.3)	791	884	29.7 (22.6)	492	868	28.3 (21.7)
3	1076	660	44.1 (23.9)	1132	1023	43.9 (24.3)	826	1002	35.5 (21.5)
4	1208	528	59.9 (20.9)	1324	768	55.4 (24.5)	1079	1012	51.7 (23.0)
5	1285	385	68.5 (20.1)	1455	655	66.9 (19.2)	1256	885	65.3 (22.6)
6	1318	198	74.3 (15.3)	1538	498	71.2 (19.5)	1407	906	78.6 (19.0)
7	1339	147	71.9 (22.2)	1584	322	77.2 (18.8)	1540	931	78.6 (19.1)
8	1349	80	77.8 (20.2)	1615	248	82.8 (16.3)	1624	672	83.9 (18.1)
9	1355	54	72.1 (35.6)	1627	108	80.6 (14.0)	1692	612	87.8 (16.9)
10	1358	30	86.0 (12.1)	1631	40	92.0 (13.8)	1732	400	90.0 (11.6)
11	1359	11	87.0 (0.0)	1637	66	81.7 (22.4)	1764	352	86.5 (18.3)
12	1360	12	99.0 (0.0)	1640	36	75.0 (8.0)	1782	216	94.3 (9.4)
13	1362	26	80.0 (26.9)	1642	26	95.0 (7.1)	1790	104	95.4 (11.2)
14				1643	14	92.0 (0.0)	1797	98	88.9 (10.6)
15				1644	15	101.0 (0.0)	1805	120	92.9 (10.7)
16							1809	64	87.5 (21.4)
18							1810	18	99.0 (0.0)
19							1811	19	101.0 (0.0)
20							1813	40	108.5 (6.4)
22							1814	22	96.0 (0.0)
24							1815	24	99.0 (0.0)

Note:—No. of MRI time points indicates No. of MRI time points per subject; Cumulative No. of subjects, increasing No. of subjects with MS, CIS, and HI by successive additions; Total No. of scans, total numbers of MRIs performed.

[a] Cumulative No. of subjects represents all subjects in the reference database who obtained ≥1 MRI time point. Total No. of MRIs refers to the No. of multiple MRIs present. Mean follow-up time is expressed in months from the first MRI to the most recent follow-up.

On-line Table 2: Demographic, clinical, and MRI characteristics of patients with MS and CIS and HI[a]

Demographic and Clinical Variables	MS (*n* = 1514)	CIS (*n* = 137)	HI (*n* = 164)	*P* Value (MS/CIS/HI)	*P* Value (MS/HI)
Women (No.) (%)	1141 (75.4)	109 (79.6)	115 (70.1)	.158	.0001
Age at onset of the first clinical event (mean) (SD) (yr)	33.0 (10.4)	36.5 (10.4)	NA	.0001	NA
Age at first MRI (mean) (SD) (yr)	45.6 (11.2)	39.5 (11.6)	46.2 (14.6)	.0001	.0001
Time from first to MRF MRI (mean) (SD) (yr)	4.7 (2.6)	3.7 (2.4)	3.1 (2.1)	.0001	.0001
Average No. of MRIs per year (mean) (SD)	1.4 (1.4)	1.5 (1.1)	2.0 (2.6)	.0001	.0001
Total No. of MRIs from first to MRF MRI (mean) (SD)	4.9 (3.1)	3.8 (1.9)	2.9 (1.1)	.0001	.0001
Disease duration to first MRI (mean) (SD)	12.2 (9.8)	3.0 (4.7)	NA	.0001	NA
Disease subtype (No.) (%)					
RR	1219 (80.5)	NA	NA	NA	NA
SP	255 (16.8)	NA	NA	NA	NA
PP	40 (2.6)	NA	NA	NA	NA
EDSS score at first MRI (median) (IQR)	2.5 (2.5)	1.5 (1.0)	NA	.0001	NA
MSSS score at first MRI (mean) (IQR) (median)	4.1 (4.3) 3.7	3.4 (3.0) 3.1	NA	.011	NA
Disease-modifying therapy at first MRI (No.) (%)				.0001	NA
No therapy	204 (13.5)	57 (41.6)	NA		
Interferon-β-1a	638 (42.1)	32 (23.4)	NA		
Glatiramer acetate	286 (18.9)	13 (9.5)	NA		
Natalizumab	113 (7.5)	0 (0.0)	NA		
Immunosuppressive therapies	15 (1.0)	1 (0.7)	NA		
Other therapies	72 (4.8)	8 (5.9)	NA		
Missing data	186 (12.2)	26 (18.9)			
EDSS score change from first to MRF MRI (mean) (IQR)	0.4 (1.2)	0.1 (0.8)	NA	.019	NA
MSSS score change from first to MRF MRI (mean) (IQR)	−0.3 (1.7)	−0.8 (1.8)	NA	.004	NA
Relapse No. between first and MRF MRI (mean) (SD)	0.9 (1.9)	0.4 (0.9)	NA	.014	NA
DP between first and MRF MRI (No.) (%)	361 (23.8)	12 (8.8)	NA	.0001	NA
Conversion to CDMS between first and MRF MRI (No.) (%)	NA	37 (27.0)	NA		
Disease-modifying therapy at MRF (No.) (%)			NA	.0001	NA
Interferon-β-1a	424 (28.0)	48 (35.0)	NA		
Glatiramer acetate	301 (19.9)	14 (10.2)	NA		
Natalizumab	162 (10.7)	1 (0.7)	NA		
Immunosuppressive therapies	20 (1.3)	2 (1.5)	NA		
Other therapies	274 (18.1)	11 (8.0)	NA		
No therapy	232 (15.3)	47 (34.4)	NA		
Missing data	101 (6.7)	14 (10.2)			
T2-LV	17.9 (16.4)	8.5 (8.2)	1.5 (1.7)	.0001	.0001

Note:—SP indicates secondary-progressive; MRF, most recent follow-up; PP, primary-progressive; IQR, interquartile range; NA, not applicable; T2-LV, T2-lesion volume.

[a] The differences in demographics among the MS, CIS, and HI groups were calculated using χ^2, Student *t*, and Mann-Whitney rank sum tests and 1-way ANOVA, as appropriate.

On-line Table 3: Reasons for analysis failures for longitudinal measurement of brain volume changes in study subjects using NeuroSTREAM lateral ventricle volume, SIENAX normalized brain, and SIENA percentage brain volume change according to the disease type[a]

	LVV (*n* = 59) (No.) (%)			NBV (*n* = 348) (No.) (%)			PBVC (*n* = 666) (No.) (%)		
	MS	CIS	HI	MS	CIS	HI	MS	CIS	HI
Scanner different	0 (0)	0 (0)	0 (0)	73 (4.8)	7 (5.1)	1 (0.6)	175 (11.6)	15 (10.9)	1 (0.6)
Orientation/thickness/protocol different	0 (0)	0 (0)	0 (0)	110 (7.3)	7 (5.1)	2 (1.2)	265 (17.5)	12 (8.8)	3 (1.8)
Excessive motion artifacts	25 (1.7)	2 (1.5)	3 (1.8)	36 (2.4)	4 (2.9)	2 (1.2)	48 (3.2)	7 (5.1)	3 (1.8)
Poor scan quality	16 (1.1)	2 (1.5)	2 (1.3)	70 (4.6)	5 (3.6)	1 (0.6)	95 (6.3)	9 (6.6)	3 (1.8)
Incomplete head coverage	0 (0)	0 (0)	0 (0)	29 (1.9)	1 (0.7)	0 (0)	29 (1.9)	1 (0.7)	0 (0)
Anatomic variations	7 (0.5)	1 (0.7)	1 (0.6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

[a] Subject failure was defined when there was no available longitudinal pair of MRI exam analysis by a specific software. The percentage of subject failures was calculated on the basis of successful analysis of longitudinal pairs of MRI examinations including 1514 subjects who had MS, 137 who had CIS, and 164 who were HI as a denominator.

On-line Table 4: Brain volume measures according to the MS disease subtype[a]

No. RR-SP-PP	Measures	RR (Mean) (SD)	SP (Mean) (SD)	PP (Mean) (SD)	*P* Value (RR/SP/PP)
1219-255-40	LVV at first MRI	21.3 (12.5)	30.4 (16.7)	25.9 (11.7)	.0001
1097-214-34	NBV at first MRI	1551.0 (97.2)	1464.2 (98.89)	1506.2 (98.6)	.0001
1189-240-36	Percentage LVV change from first MRI to MRF	12.4 (18.3)	10.4 (18.5)	11.9 (19.6)	.345
1189-240-36	Annualized percentage LVV change from first to MRF MRI	3.1 (9.6)	2.5 (5.2)	3.0 (4.7)	.498
1189-240-36	Annualized cumulative percentage LVV change from first to MRF MRI	3.1 (7.1)	2.0 (5.2)	2.9 (6.6)	.037
997-172-27	Percentage NBV change from first MRI to MRF	−3.5 (3.7)	−.3.4 (4.1)	−.2.6 (4.0)	.265
997-172-27	Annualized percentage NBV change from first to MRF MRI	−.0.7 (1.5)	−.0.6 (1.6)	−.0.6 (1.3)	.453
997-172-27	Annualized cumulative percentage NBV change from first to MRF MRI	−.0.8 (2.2)	−.0.7 (2.6)	−.0.2 (1.9)	.364
752-130-20	PBVC from first MRI to MRF	−.3.5 (2.9)	−.3.5 (2.6)	−.3.7 (2.5)	.562
752-130-20	Annualized PBVC from first to MRF MRI	−.0.8 (1.0)	−.0.9 (0.9)	−.1.1 (0.8)	.899
752-130-20	Annualized cumulative PBVC from first to MRF MRI	−.0.8 (1.3)	−.0.8 (1.0)	−.0.9 (0.9)	.978

Note:—No. RR-SP-PP indicates No. of patients with MS and CIS and HC included in each analysis; SP, secondary-progressive; MRF, most recent follow-up; PP, primary-progressive.

[a] The data are presented as mean (SD). The absolute values are expressed in milliliters. The differences among the RR, SP, and PP groups were calculated using analysis of covariance adjusted for age at first MRI, sex, and field strength as covariates.

On-line Table 5: Brain volume changes in a subsample of subjects who had available percentage brain volume change between the first MRI and the most recent follow-up MRI in patients with MS and CIS and in HI[a]

No. MS-CIS-HI	Measures	MS (Mean) (SD)	CIS (Mean) (SD)	HI (Mean) (SD)	*P* Value (MS/CIS/HI)	*P* Value (MS/HI)
902-93-154	Percentage LVV change from first MRI to MRF	11.2 (17.0)	10.2 (15.7)	7.3 (10.9)	.01	.003
902-93-154	Annualized percentage LVV change from first to MRF MRI	3.2 (7.9)	4.0 (8.7)	1.7 (7.8)	.011	.005
902-93-154	Annualized cumulative percentage LVV change from first to MRF MRI	3.0 (6.9)	4.5 (10.5)	1.4 (9.6)	.008	.014
902-93-154	Percentage NBV change from first MRI to MRF	−2.9 (3.5)	−2.1 (2.6)	−1.1 (2.7)	.001	<.001
902-93-154	Annualized percentage NBV change from first to MRF MRI	−0.6 (1.6)	−0.6 (1.2)	−0.3 (1.7)	.064	.021
902-93-154	Annualized cumulative percentage NBV change from first to MRF MRI	−0.7 (2.3)	−0.5 (1.7)	−0.4 (2.0)	.211	.108

Note:—No. MS-CIS-HI indicates No. of patients with MS and CIS and HI included in each analysis.

[a] The data are presented as mean (SD). The absolute values are expressed in milliliters. The differences among the MS, CIS, and HI groups were calculated using analysis of covariance adjusted for age at first MRI, sex, and field strength as covariates.

On-line Table 6: Brain volume changes in a subsample of subjects who had percentage brain volume change available between the first MRI and the most recent follow-up MRI in patients with MS according to their disease course[a]

No. RR-SP-PP	Measures	RR (Mean) (SD)	SP (Mean) (SD)	PP (Mean) (SD)	*P* Value (RR/SP/PP)
752-130-20	Percentage LVV change from first MRI to MRF	11.6 (17.5)	9.3 (13.6)	11.4 (20.8)	.341
752-130-20	Annualized percentage LVV change from first to MRF MRI	3.2 (8.2)	2.7 (6.0)	3.2 (4.2)	.901
752-130-20	Annualized cumulative percentage LVV change from first to MRF MRI	3.1 (7.1)	2.1 (6.1)	2.8 (4.9)	.153
752-130-20	Percentage NBV change from first MRI to MRF	−2.9 (3.4)	−2.4 (4.1)	−2.4 (4.5)	.346
752-130-20	Annualized percentage NBV change from first to MRF MRI	−0.7 (1.6)	−0.5 (1.9)	−0.5 (1.4)	.450
752-130-20	Annualized cumulative percentage NBV change from first to MRF MRI	−0.7 (2.3)	−0.5 (2.6)	−0.2 (1.8)	.498

Note:—No. RR-SP-PP indicates No. of patients with MS and CIS and HI included in each analysis; SP, secondary-progressive; MRF, most recent follow-up; PP, primary-progressive.

[a] The data are presented as mean (SD). The absolute values are expressed in milliliters. The differences among the RR, SP, and PP groups were calculated using analysis of covariance adjusted for age at first MRI, sex, and field strength, as covariates.

On-line Table 7: Univariate linear mixed-effects models describing the longitudinal relationship between yearly change in clinical measures and lateral ventricle volume change in patients with MS[a]

	LVV (mL) PBVC Subsample (*n* = 902)		NBV (mL) PBVC Subsample (*n* = 902)	
Patients with MS	**Est**	***P* Value**	**Est**	***P* Value**
Intercept	22.668		1520.940	
DDY	0.023	.0001	−0.415	.0001
Intercept	22.612		1527.070	
EDSS	0.103	.0001	−2.094	.0001
Intercept	22.372		1519.496	
MSSS	0.084	.0001	−1.940	.0001
DP-intercept				
No	23.187		1529.309	
Yes	0.484	.0001	−9.461	.0001
Difference	0.644	.0001	−11.539	.0001
	+0.160 (33.1%)	.004	−2.08 (−21.9%)	.002

Note:—Est indicates estimate; DDY, disease duration.

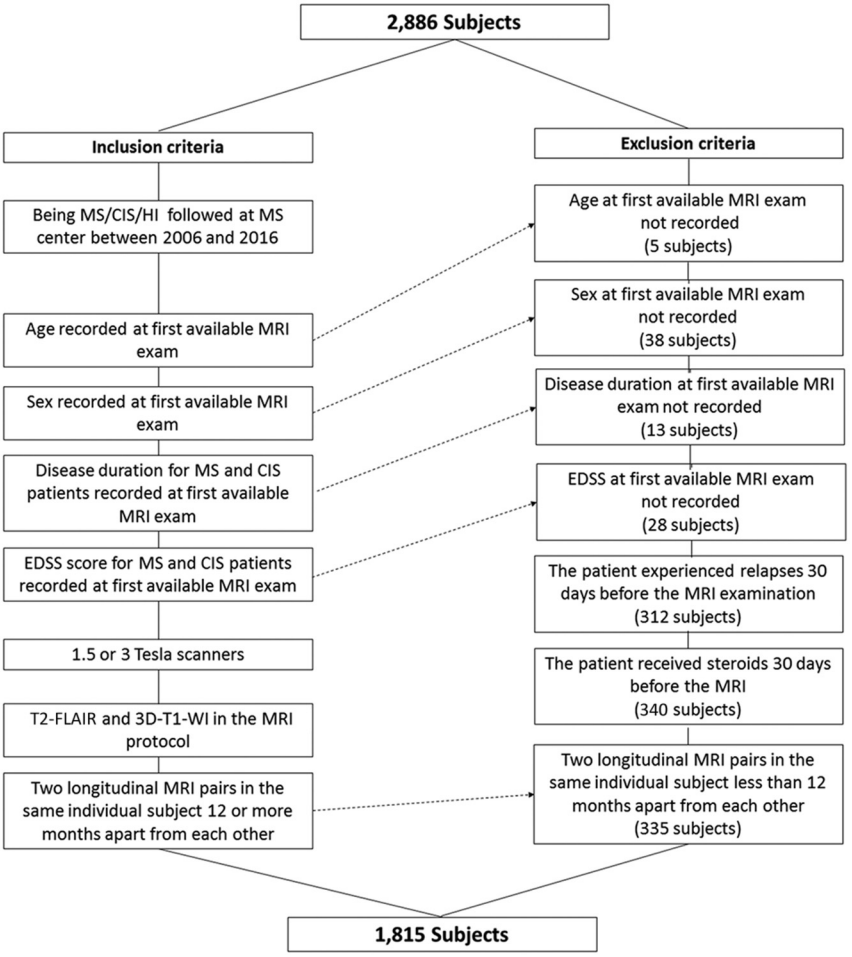
[a] Intercept as depicted in milliliters is the predicted value of the dependent variable when all the independent variables are restricted to zero. Estimate is a representation of the LVV volume increase and NBV volume decrease in milliliters per 1-unit increase of the independent measure per year (the interaction term with time). Estimate of PBVC is a representation of change in percentage per 1-unit increase of the independent measure per year (the interaction term with time). Volumetric (milliliters) data were fitted to random intercept and slope models, while PBVC models were fitted to random slope models.

On-line Table 8: Univariate linear mixed-effect models describing the longitudinal relationship between yearly change in clinical measures and lateral ventricle volume change in patients with CIS[a]

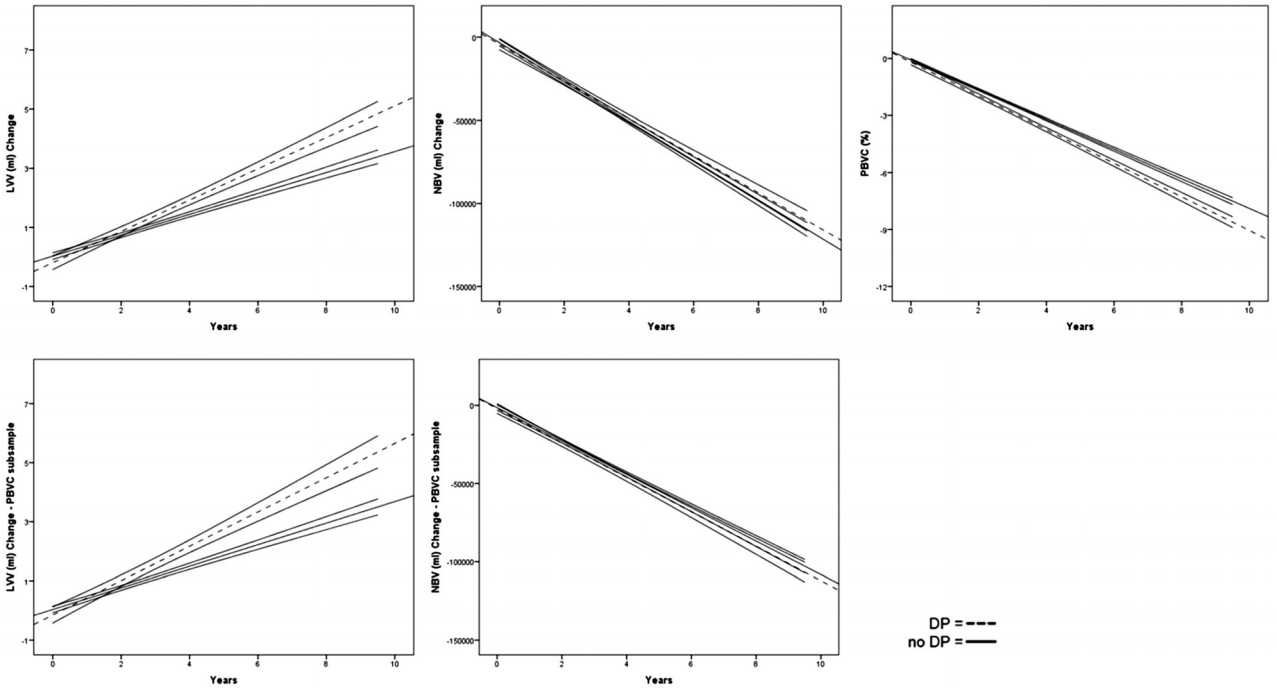
	LVV (mL) PBVC Subsample (*n* = 93)		NBV (mL) PBVC Subsample (*n* = 93)	
Patients with CIS	**Est**	***P* Value**	**Est**	***P* Value**
Intercept	16.149		579.736	
DDY	0.019	.003	−0.783	.0001
Intercept	15.813		1580.549	
EDSS	0.168	.0001	−4.304	.0001
Intercept	15.991		1580.364	
MSSS	0.102	.0001	−2.421	.0001
CDMS-intercept				
No	16.008		1588.063	
Yes	0.297	.0001	−10.487	.0001
Difference	0.371	.0001	−9.109	.0001
	+0.074 (24.9%)	.264	+1.378 (13.1%)	.395

Note:—Est indicates estimate; DDY, disease duration.

[a] Intercept as depicted in milliliters is the predicted value of the dependent variable when all the independent variables are restricted to zero. Estimate is a representation of the LVV volume increase and NBV volume decrease in milliliters per 1-unit increase of the independent measure per year (the interaction term with time). Estimate of PBVC is a representation of change in percentage per 1-unit increase of the independent measure per year (the interaction term with time). Volumetric (milliliters) data were fitted to random intercept and slope models, while PBVC models were fitted to random slope models.



ON-LINE FIGURE 1. Flow chart of inclusion and exclusion criteria.



ON-LINE FIGURE 2. Change in brain volume measures in patients with multiple sclerosis who did or did not reach disability progression during the follow-up. In the *upper row* are shown changes in milliliters in LVV (*left*), NBV (*middle*), and PBVC (*right*). In the *lower row* are shown changes in milliliters in LVV (*left*) and NBV (*middle*) in a subsample of patients who had available PBVC between the first MR imaging and the most recent follow-up in patients. *Middle lines* represent DP and no-DP; *outside lines* are 95% confidence intervals.