

Supplementary materials.

Investigating the long-term effect of pregnancy on the course of multiple sclerosis using causal inference.

Antoine Gavoille *et al.*

List of supplementary materials :

eTable 1. Adjusted variables in the pregnancy, relapse EDSS, and censoring models used for causal inference.

eTable 2. Comparison of excluded and included patients

eTable 3. Results of the sensitivity analyses

eTable 1. Adjusted variables in the pregnancy, relapse EDSS, and censoring models used for causal inference.

Adjusted variables	Model at time t			
	Pregnancy	Relapse	EDSS	Censoring
EDSS history ^a	X		X	X
EDSS at time $t - 1$	X ^b		X ^b	X
EDSS at time t				X
Relapse history ^a	X ^c	X	X	X
Relapse at time $t - 1$	X	X	X	X
Relapse at time t			X	X
Pregnancy history ^a	X	X	X	X
Pregnancy at time $t - 1$	X	X	X	X
Pregnancy at time t		X	X	X
MS phenotype at time t	X	X	X ^d	X
Age at baseline	X ^b	X ^b	X	X
Time from MS onset to baseline	X	X	X	X
Number of children at baseline	X	X	X	X

^a History: all past values of the variable from baseline to time $t - 2$

^b Cubic spline with two knots

^c Cumulative history (sum of all the past values of the variable)

^d With additional interaction term with EDSS at time $t - 1$

EDSS: Expanded Disease Status Scale; MS: multiple sclerosis

eTable 2. Comparison of excluded and included patients

	Included patients n = 9,100	Excluded patients n = 8,463
Age at baseline (years), <i>mean (SD)</i>	33.60 (6.86)	34.98 (6.64)
Calendar year at baseline , <i>median [Q1; Q3]</i>	2009 [2004; 2013]	2005 [2000; 2010]
Disease duration at baseline (years), <i>mean (SD)</i>	4.67 (5.21)	5.43 (5.65)
EDSS at baseline , <i>mean (SD)</i>	1.81 (1.73)	2.08 (2.02)
Number of children at baseline , <i>median [Q1; Q3]</i>	1 [0; 2]	0 [0; 0]
MS phenotype at baseline , <i>n (%)</i>		
RR	8171 (89.8%)	7285 (86.1%)
SP	574 (6.3%)	773 (9.1%)
PP	355 (3.9%)	405 (4.8%)

eTable 3. Results of the sensitivity analyses

	Number of patients	Number of patient-years	Number of pregnancies	Long term effect ^a	Per-partum effect ^a	Post-partum effect ^a	Delayed effect ^a
Mean EDSS ^b							
Main analysis	9,100	73,707	2,597	0.00 [-0.16; 0.15] p=0.98	-0.06 [-0.12; -0.01] p=0.03	-0.06 [-0.14; 0.01] p=0.10	-0.03 [-0.18; 0.12] p=0.69
1) MS onset as baseline	2,095	16,846	1,043	0.18 [-0.10; 0.46] p=0.15	-0.24 [-0.70; 0.27] p=0.19	-0.42 [-1.33; 0.19] p=0.14	-0.06 [-0.82; 0.75] p=0.97
2a) First EDSS retained	9,100	73,707	2,597	0.06 [-0.06; 0.20] p=0.35	-0.08 [-0.14; -0.01] p=0.04	-0.06 [-0.13; 0.02] p=0.20	0.08 [-0.05; 0.21] p=0.17
2b) Last EDSS retained	9,100	73,707	2,597	0.10 [-0.02; 0.21] p=0.11	-0.11 [-0.17; -0.06] p<0.001	-0.04 [-0.13; 0.02] p=0.25	0.05 [-0.08; 0.18] p=0.50
3) Censoring at first missing EDSS	9,100	39,576	1,142	-0.17 [-0.61; 0.25] p=0.42	-0.16 [-0.22; -0.08] p<0.001	-0.14 [-0.25; -0.04] p=0.02	0.00 [-0.38; 0.30] p=0.80
4) Only the first pregnancy considered	9,100	73,707	2,125	0.08 [-0.04; 0.21] p=0.13	-0.12 [-0.16; -0.07] p<0.001	-0.11 [-0.18; -0.05] p<0.001	0.00 [-0.11; 0.13] p=0.84
Annual probability of relapse ^c							
Main analysis	9,100	73,707	2,597	0.95 [0.93; 1.38] p=0.50	0.80 [0.72; 0.89] p<0.001	1.34 [1.20; 1.48] p<0.001	1.10 [0.94; 1.45] p=0.21
1) MS onset as baseline	2,095	16,846	1,043	0.95 [0.79; 1.88] p=0.71	0.77 [0.43; 1.65] p=0.21	1.27 [0.64; 2.94] p=0.32	0.92 [0.29; 2.45] p=0.96
2a) First EDSS retained	9,100	73,707	2,597	0.95 [0.88; 1.37] p=0.64	0.77 [0.68; 0.85] p<0.001	1.34 [1.22; 1.48] p<0.001	1.10 [0.86; 1.45] p=0.42
2b) Last EDSS retained	9,100	73,707	2,597	0.95 [0.90; 1.4] p=0.58	0.77 [0.69; 0.85] p<0.001	1.33 [1.22; 1.46] p<0.001	1.10 [0.86; 1.42] p=0.43
3) Censoring at first missing EDSS	9,100	39,576	1,142	1.00 [0.69; 1.48] p=0.56	0.76 [0.65; 0.88] p<0.001	1.37 [1.18; 1.64] p<0.001	1.04 [0.64; 1.56] p=0.97
4) Only the first pregnancy considered	9,100	73,707	2,125	0.94 [0.86; 1.48] p=0.70	0.77 [0.68; 0.84] p<0.001	1.32 [1.17; 1.46] p<0.001	1.09 [0.86; 1.42] p=0.48

^a Causal mean difference [95% CI for the mean EDSS, and causal risk ratio [95% CI for the annual probability of relapse

^b In the last one-year period of the considered period for the long-term and delayed effects, or in the per-partum or post-partum year for the short-term effects

^c Over the whole considered period