RESEARCH ARTICLE

Investigating the Long-term Effect of Pregnancy on the Course of Multiple Sclerosis Using Causal Inference

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Abstract

Background and Objectives

The question of the long-term safety of pregnancy is a major concern in patients with multiple sclerosis (MS), but its study is biased by reverse causation (women with higher disability are less likely to experience pregnancy). Using a causal inference approach, we aimed to estimate the unbiased long-term effects of pregnancy on disability and relapse risk in patients with MS and secondarily the short-term effects (during the perpartum and postpartum years) and delayed effects (occurring beyond 1 year after delivery).

Methods

We conducted an observational cohort study with data from patients with MS followed in the Observatoire Français de la Sclérose en Plaques registry between 1990 and 2020. We included female patients with MS aged 18–45 years at MS onset, clinically followed up for more than 2 years, and with ≥3 Expanded Disease Status Scale (EDSS) measurements. Outcomes were the mean EDSS score at the end of follow-up and the annual probability of relapse during follow-up. Counterfactual outcomes were predicted using the longitudinal targeted maximum likelihood estimator in the entire study population. The patients exposed to at least 1 pregnancy during their follow-up were compared with the counterfactual situation in which, contrary to what was observed, they would not have been exposed to any pregnancy. Short-term and delayed effects were analyzed from the first pregnancy of early-exposed patients (who experienced it during their first 3 years of follow-up).

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Observatoire Français de la Sclérose en Plaques (OFSEP) coinvestigators are listed in the appendix at the end of the article.

Glossary

DAG = directed acyclic graph; **EDSS** = Expanded Disease Status Scale; **IPW** = inverse probability weighting; **LTMLE** = longitudinal targeted maximum likelihood estimator; **MS** = multiple sclerosis; **OFSEP** = Observatoire Français de la Sclérose en Plaques; **PP** = primary progressive; **RR** = relapsing-remitting; **SP** = secondary progressive.

Results

We included 9,100 patients, with a median follow-up duration of 7.8 years, of whom 2,125 (23.4%) patients were exposed to at least 1 pregnancy. Pregnancy had no significant long-term causal effect on the mean EDSS score at 9 years (causal mean difference [95% CI] = 0.00 [−0.16 to 0.15]) or on the annual probability of relapse (causal risk ratio [95% CI] = 0.95 [0.93–1.38]). For the 1,253 early-exposed patients, pregnancy significantly decreased the probability of relapse during the perpartum year and significantly increased it during the postpartum year, but no significant delayed effect was found on the EDSS and relapse rate.

Discussion

Using a causal inference approach, we found no evidence of significantly deleterious or beneficial long-term effects of pregnancy on disability. The beneficial effects found in other studies were probably related to a reverse causation bias.

As multiple sclerosis (MS) frequently affects young women of childbearing age, the question of the effect of pregnancy on the course of the disease is a major concern. Approximately 25%–35% of female patients experience a pregnancy after MS onset,[1-3] and when questioned about the reasons for not wanting to become pregnant, 30%–35% of female patients report MS-related reasons, mainly due to symptoms interfering with parenting.[4,5]

Short-term effects of pregnancy on the natural course of MS have been described in several prospective observational studies: the relapse rate decreases during pregnancy and increases during the postpartum period, but the short-term progression of disability does not seem to be affected.[6] The long-term effects of pregnancy on disability progression are much more controversial. Comparing women who did or did not get pregnant after MS onset is subject to important biases, mainly a reverse causation bias, as patients with higher disability are less likely to get pregnant[4,7,8]; this bias could result in a falsely beneficial effect of pregnancy on the subsequent progression of the disease. Studies have found either a long-term beneficial effect of pregnancy[1,9-14] or no significant effect,[2,3,15-20] depending on the cohort size, methodology, and adjusted factors.

Classical statistical approaches such as multivariate analysis or propensity score fail to properly account for this bias due to the time-dependent nature of pregnancy occurrence and disability. Time-varying feedback confounding occurs when an outcome, e.g., disability, is causally affected by a past exposure, e.g., pregnancy, but also have a causal effect on the future exposure: in this case, adjustment for the outcome is necessary to account for the confounding effect of the outcome on the future exposure, but this adjustment will remove the effect of the past exposure on the outcome, which is a part of the effect of interest. The use of recent statistical methods based on the causal inference and counterfactual framework may properly account for time-dependent reverse causation, if all assumptions are met, and hence properly assess the unbiased causal effects of pregnancy on the long-term disease course.[21]

In the present study, we aimed to investigate the long-term effects of pregnancy on MS course (neurologic disability and relapse rate) using a causal inference approach. Our secondary objective was to study the short-term effects, during the perpartum year and first postpartum year, and the delayed effects, occurring more than 1 year after delivery (long-term effects being the sum of the short-term and delayed effects).

Methods

Patients

Data were extracted from the French MS registry, the Observatoire Français de la Sclérose en Plaques (OFSEP),[22] on December 15, 2020. The OFSEP is a national prospective registry that collects clinical data from patients with MS in expert centers in France (~ 69,000 patients in December 2020). Data are retrospectively collected at the time of the first visit and prospectively thereafter. For each patient, clinical and imaging data are collected during routine follow-up visits, usually once a year, using a dedicated software, the European Database on Multiple Sclerosis.[23] These data include a systematic question regarding the number of children and their date of birth.

Inclusion criteria were as follows: (1) female patients with a diagnosis of MS according to the current criteria at the time of diagnosis, i.e., either Poser or McDonald criteria (2001 or 2010),[24-26] (2) aged 18–45 years at MS onset, and (3) with a

clinical evaluation occurring after January 1, 1990. Patients with a clinical follow-up lasting less than 2 years, with less than 3 Expanded Disease Status Scale (EDSS) measurements, or with missing data regarding the number of children or their date of birth were excluded. All MS phenotypes were considered: relapsing-remitting (RR), secondary progressive (SP), and primary progressive (PP).

Standard Protocol Approvals, Registrations, and Patient Consents

Patients registered in the OFSEP (clinicaltrials.gov [NCT02889965]) provided written informed consent for participation. In accordance with the French legislation, the OFSEP was approved by both the French data protection agency (Commission nationale de l'informatique et des libertés; authorization request 914066v3) and a French ethics committee (Comité de Protection des Personnes: reference 2019-A03066-51), and the present study was declared in conformity with the MR-004 (Méthodologie de référence 004).

Data Collection and Structuring in 1-Year Time Periods

For each patient, baseline was defined as the time of the first available EDSS measurement occurring after January 1, 1990. Time was divided into 1-year periods from baseline to the last available clinical evaluation. For patients who got pregnant at least once, baseline was set back in time to ensure that their first delivery date coincided with the start of a new period, so that the perpartum and postpartum periods occurred in 2 distinct (and consecutive) periods. Periods were analyzed until less than 50% of the patients were still being followed.

Neurologic disability was assessed by the EDSS[27] measured at each visit by the neurologist in charge of the patient. EDSS measurements performed within less than 30 days after a relapse were not retained. If more than 1 EDSS measurement was made during the same 1-year period, the lowest score was retained. For 1-year periods with no EDSS score available, the last value was used if measurements were available for at least one of the last three 1-year periods, or the patient was censored at the time of the first missing value if more than 3 consecutive yearly measurements were missing.

At baseline, the disease duration (delay since MS onset), age, and number of children were calculated. EDSS score, the number of relapse occurrence, and MS phenotype (RR, SP, or PP) were reported for each 1-year period. Pregnancies occurring during the first 1-year period were not considered because reverse causation could not be corrected due to the absence of prior EDSS measurement; thus, pregnancy effects were analyzed starting from the second 1-year period. The study design, with an example of structuring the data into 1-year periods, is depicted in Figure 1.

Outcomes

The main outcome was the mean EDSS score in the last 1-year period, and the secondary outcome was the annual probability of relapse (probability of experiencing at least 1 relapse during the 1-year period) over all the periods.

Counterfactual Definition of the Causal Effect of Pregnancy

To determine the long-term causal effect of pregnancy in a counterfactual framework, we considered the contrast between 2 situations: the observed situation (in which patients might become pregnant during each 1-year period) and the counterfactual situation (in which, contrary to the facts, none of the patients became pregnant). Based on the hypotheses detailed below and assuming that there was no other confounding factor, the causal inference approach was able to provide an unbiased estimate of the outcomes in the counterfactual situation without pregnancy. Thus, the contrast between this counterfactual estimate without pregnancy and the one from the observed situation with pregnancy corresponded to the long-term causal effect of pregnancy on the considered outcome (i.e., "what would have been the EDSS course of patients who did experience one or more pregnancies if they had not"). This analysis can be viewed as an emulated randomized trial comparing patients exposed vs nonexposed to pregnancy, as if the exposure was randomly allocated between 2 comparable groups, except that the control group was not actually observed and their outcomes must be estimated counterfactually.

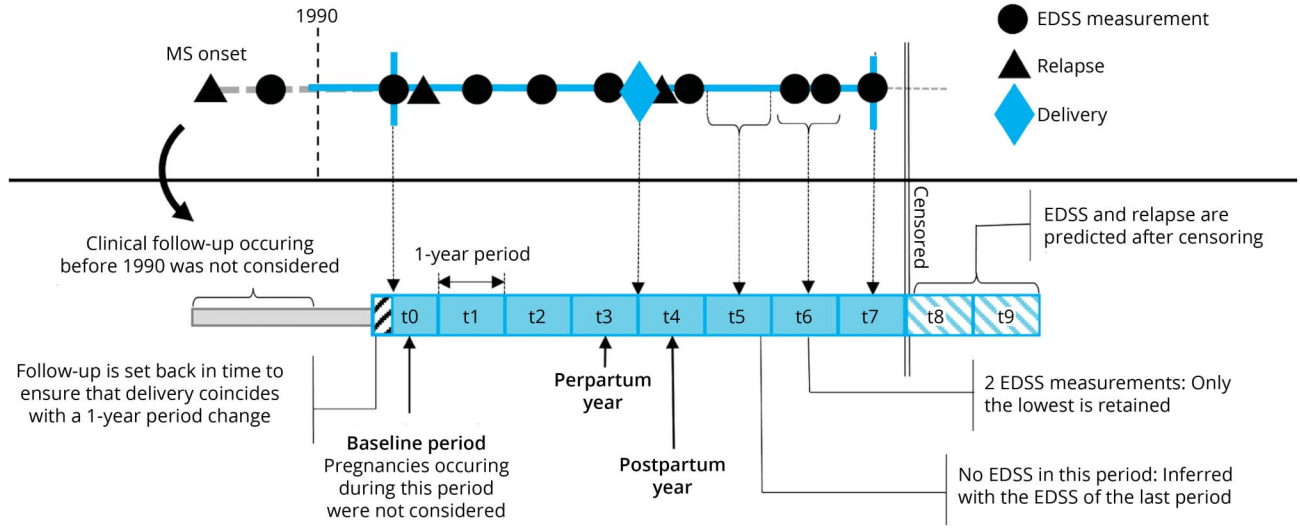
To distinguish the long-term effects into short-term and delayed effects, a focus was made on the first pregnancy of patients early exposed to pregnancy (i.e., within the first 3 years of follow-up) by removing the follow-up data prior to the year before pregnancy to ensure that the period of their pregnancy coincided with the first 1-year period of the study. The perpartum effect was defined as the contrast between observed and counterfactual situations in the year before delivery, the postpartum effect as the contrast in the year following delivery, and the delayed effect as the contrast over the remaining follow-up duration, beyond 1 year after delivery. For this analysis, in the counterfactual situation, subsequent pregnancies occurring after the first considered pregnancy remained as observed.

The results were presented as causal mean differences in the last 1-year period (observed mean – counterfactual mean) for the EDSS score and as causal risk ratios over all 1-year periods (observed proportion/counterfactual proportion) for the probability of relapse. For all analyses, the entire population was studied in the statistical models: unexposed patients provide information to estimate the counterfactual outcomes in exposed patients. Only in a second step, the calculation of counterfactual and observed outcomes was restricted to the population exposed to at least 1 pregnancy during their follow-up.

Theoretical Assumptions for Causal Inference

The causal inference methodology is based on theoretical assumptions about the causal relationship between the different

Figure 1 Study Design: Data Structuring



Example of structuring of the follow-up into 1-year periods for a patient exposed to a pregnancy. EDSS = Expanded Disease Status Scale; MS = multiple sclerosis.

variables investigated, synthesized in a causal Directed Acyclic Graph (DAG; Figure 2). We hypothesized that pregnancy P influenced the risk of relapse R and the accumulation of disability D during the same period (perpartum effect: $P_t \rightarrow R_t$ and $P_t \rightarrow D_t$), the following period (postpartum effect $P_t \rightarrow R_{t+1}$ and $P_t \rightarrow D_{t+1}$), and all subsequent periods (delayed effects $P_t \rightarrow R_{t+2}$, $R_{t+3}, \ldots$ and $P_t \rightarrow D_{t+2}$, $D_{t+3}, \ldots$). Other assumptions were that disability and relapses affected all the subsequent probabilities of pregnancy (reverse causation effect $R_t \rightarrow P_{t+1}$, $P_{t+2}, \ldots$ and $D_t \rightarrow P_{t+1}$, $P_{t+2}, \ldots$), that the occurrence of relapse affected the accumulation of disability during the same period ($R_t \rightarrow D_t$) and the subsequent periods ($R_t \rightarrow D_{t+1}, \ldots$), that pregnancy probability, relapse risk, and disability were affected by their history, and that MS phenotype and baseline confounders affected the probability of pregnancy, the relapse risk, and the disability accumulation at each time.

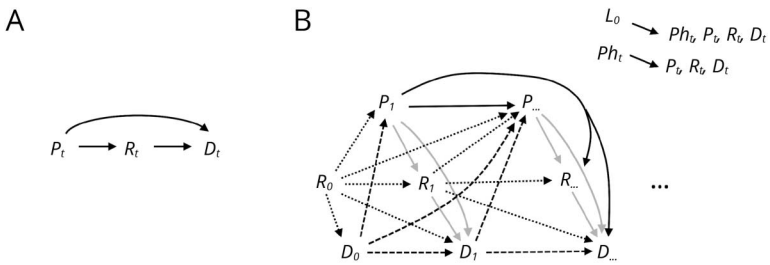
Censoring

Censoring due to lost to follow-up or death was handled with the same causal inference approach, simply by considering the censoring as an exposure and providing a counterfactual estimate in the absence of censoring (i.e., "what would have been the EDSS course if no patient had been censored").

Sensitivity Analyses

Sensitivity analyses were performed to explore the robustness of the results to the assumptions made during the data structuring: (1) considering MS onset as the baseline

Figure 2 Causal DAG



P_t: Occurrence of a pregnancy at time t
R_t: Occurrence of ≥1 relapse at time t
D_t: Disability (EDSS) at time t
L_0: Baseline covariates affecting all subsequent variables: Disease duration, age, number of children
Ph_t: MS phenotype at time t, affecting all variables at the same time (pregnancy, relapse, and disability)

Causal DAG representing the main assumptions about the relationship between pregnancy P, relapse R, and disability D within the same 1-year period t (A) and between different 1-year periods (B). DAG = directed acyclic graph; EDSS = Expanded Disease Status Scale; MS = multiple sclerosis.

(excluding all patients whose clinical follow-up began after MS onset), (2) retaining the first or the last EDSS value if multiple measurements were made during the same 1-year period, (3) censoring patients at the first missing EDSS measurement, and (4) considering only the first pregnancy of patients (with subsequent pregnancies, for which delivery may not coincide with a 1-year period change, remaining as observed in the counterfactual situation).

Statistical Analyses

Counterfactual estimates were obtained with the longitudinal targeted maximum likelihood estimator (LTMLE),[28] a doubly robust approach based on an outcome model and an exposure model, used to determine counterfactual outcome values at each time by changing the exposure for its counterfactual value of interest. For each 1-year period, the EDSS was modeled using a linear regression and the probabilities of relapse, pregnancy, and censoring using logistic regressions. All models were adjusted for their causal variables according to the DAG and for baseline covariates (disease duration, age, and number of children) and MS phenotype. Longitudinal weights for each patient were obtained by the product of their pregnancy and censoring weights over time. The results provided by the 2 combined algorithms in LTMLE, inverse probability weighting (IPW),[29-31] and iterative conditional expectation[32] were explored separately to ensure double robustness. An IPW method[33] was conducted separately with the same censoring model as the LTMLE to obtain the observed outcomes corrected for censoring. All models used are described in eTable 1, links.lww.com/WNL/C573.

CIs were obtained by bootstrapping over 1,000 resamples, clustered by the patient and exposed/unexposed group, using the percentile method. p Values less than 0.05 were considered statistically significant. All analyses were performed using R software, version 4.0.3,[34] and ltmle package[35] for causal inference.

Data Availability

Anonymized data will be made available on reasonable request by any qualified investigator.

Results

Of the 15,494 female patients younger than 45 years at the start of their follow-up in the OFSEP database at the time of data extraction, 5,497 had less than 2 years of follow-up or 3 measurements of the EDSS, and 2,966 had missing data regarding the number of children or their date of birth, resulting in a total of 9,100 patients included. Excluded patients had a slightly longer disease duration at the start of follow-up, higher EDSS score, and were from an older epoch (eTable 2, links.lww.com/WNL/C573).

The median [Q1-Q3] follow-up duration was 7.8 [5.3–12.0] years; thus, data were analyzed for up to 8 years (nine 1-year periods), for a total of 73,707 patient-years. During their follow-up, 2,125 (23.4%) patients experienced at least 1 pregnancy, corresponding to a total of 2,597 observed pregnancies. At baseline, patients exposed to at least 1 pregnancy were younger (mean age: 27.7 vs 35.4 years for unexposed patients, mean difference [95% CI]: −7.7 [−7.9 to −7.4]), had a shorter disease duration (median delay since diagnosis: 1.1 vs 3.6 years, mean difference [95% CI]: −3.0 [−3.2 to −2.8]), and a lower EDSS score (median: 1.0 vs 1.5, mean difference [95% CI]: −0.7 [−0.7 to −0.6]; Table 1). The probability of pregnancy was lower in patients with a higher EDSS score in the previous period (OR per 1-point increase in the EDSS score [95% CI] = 0.85 [0.83–0.87], mixed-effect model adjusted for age and patient and weighted for censoring); this suggested the presence of a reverse causation bias.

Long-term Causal Effects of Pregnancy

The long-term causal effect of pregnancy was calculated for the 2,125 patients exposed to 1 or more pregnancies during their follow-up, over the 9 one-year periods for which data were available for at least 50% of patients. The courses of the EDSS and probability of relapse with and without pregnancy overlapped throughout the whole follow-up (Figure 3). There was no significant long-term causal effect of pregnancy on the mean EDSS score: the mean EDSS score increased from 1.29 at baseline to 1.91 at 9 years, both in the observed and in the counterfactual situation (causal mean difference [95% CI] = 0.00 [−0.16 to 0.15], p = 0.98). Pregnancy also had no significant causal effect on the annual probability of relapse over the follow-up; the probability was 35.5% in the observed situation and 37.4% in the counterfactual situation (causal risk ratio [95% CI] = 0.95 [0.93–1.38], p = 0.50; Table 2).

Short-term and Delayed Causal Effects of Pregnancy

The study of short-term and delayed effects of pregnancy was conducted in 1,253 (13.8%) patients early exposed to pregnancy during their first 3 years of follow-up. At least 50% of them were followed for 7 years: the perpartum effect was analyzed during the first year, the postpartum effect during the second year, and the delayed effect over the remaining 5 years (Figure 4).

Regarding the short-term effects, the mean EDSS score was significantly but slightly lower in the situation with pregnancy during the perpartum year: it was 1.34 without pregnancy and 1.28 with pregnancy (mean causal difference [95% CI] = −0.06 [−0.12 to −0.01], p = 0.03), but this difference was no longer significant during the postpartum year (mean causal difference [95% CI] = −0.06 [−0.14 to 0.01], p = 0.10). The probability of relapse during the perpartum year was significantly higher without pregnancy (32.9%) than with pregnancy (26.3%; causal risk ratio [95% CI] = 0.80 [0.72–0.89], p < 0.001). It was significantly lower during the postpartum year without pregnancy (27.9%) than with pregnancy (37.3%; causal risk ratio [95% CI] = 1.34 [1.20–1.48], p < 0.001; Table 2). For the delayed effects, pregnancy had no significant

Table 1 Description of the Cohort Population

	Total	Exposure to ≥1 pregnancy during follow-up	
	N = 9,100	No (n = 6,975)	Yes (n = 2,125)
Patients characteristics			
Age at MS onset (y), mean (± SD)	28.9 (±6.5)	30.0 (±6.7)	25.4 (±4.5)
Age at baseline (y), mean (± SD)	33.6 (±6.9)	35.4 (±6.4)	27.7 (±4.6)
Calendar year of the start of the follow-up (y), median [Q1-Q3]	2009 [2004–2013]	2009 [2004–2013]	2008 [2004–2012]
Disease duration at baseline (y), median [Q1–Q3]	2.7 [0.5–7.6]	3.6 [0.8–8.8]	1.1 [0.0–3.9]
Duration of follow-up (y), median [Q1–Q3]	7.8 [5.3–12.0]	7.6 [5.1–11.8]	8.5 [5.9–12.4]
MS phenotype at baseline, n (%)			
RR	8,171 (89.8%)	6,083 (87.2%)	2,088 (98.3%)
SP	574 (6.3%)	558 (8.0%)	16 (0.8%)
PP	355 (3.9%)	334 (4.8%)	21 (1.0%)
EDSS score at baseline, median [Q1–Q3]	1.5 [0.0–3.0]	1.5 [0.0–3.0]	1.0 [0.0–2.0]
EDSS score at the end of follow-up, median [Q1–Q3][a]	2.0 [1.0–4.0]	2.5 [1.0–5.0]	1.5 [1.0–2.5]
Change in the EDSS score between baseline and end of follow-up, n (%)[a]			
Stable	2,162 (24.0%)	1,474 (21.9%)	688 (29.9%)
Worsened	5,340 (59.1%)	4,162 (61.8%)	1,178 (51.2%)
Improved	1,529 (17.0%)	1,095 (16.3%)	434 (18.9%)
No. of pregnancies during follow-up, n (%)			
0	6,975 (76.6%)	6,975 (100.0%)	0 (0.0%)
1	1,682 (18.4%)	0 (0.0%)	1,682 (79.1%)
2	414 (4.6%)	0 (0.0%)	414 (19.5%)
3	29 (0.1%)	0 (0.0%)	29 (1.4%)
Follow-up information			
No. of 1-y periods of follow-up	n = 73,707	n = 55,841	n = 17,866
With missing EDSS measurement, n (%)	13,474 (18.3%)	10,005 (17.9%)	3,469 (19.4%)
With 2 or more consecutive missing EDSS measurements, n (%)	2,197 (3.0%)	1,512 (2.7%)	685 (3.8%)
With more than 1 discordant EDSS measurement, n (%)	12,278 (20.4%)	9,600 (20.9%)	2,678 (18.6%)
With more than 1 discordant EDSS by more than 1 point, n (%)	3,086 (5.1%)	2,338 (5.1%)	748 (5.2%)
Delay between 2 consecutive EDSS measurements (mo), median [Q1–Q3]	6.1 [3.3–10.1]	6.1 [3.3–10.0]	6.1 [3.3–10.3]

EDSS = Expanded Disease Status Scale; MS = multiple sclerosis; PP = primary progressive; Q1-Q3 = interquartile range; RR = relapsing-remitting; SP = secondary progressive.
[a] Weighted by inverse probability of censoring.

effect on the mean EDSS score during the last period (mean causal difference [95% CI] = −0.03 [−0.18 to 0.12], $p = 0.69$) or on the probability of relapse during the follow-up (causal risk ratio [95% CI] = 1.10 [0.94–1.45], $p = 0.21$; Table 2).

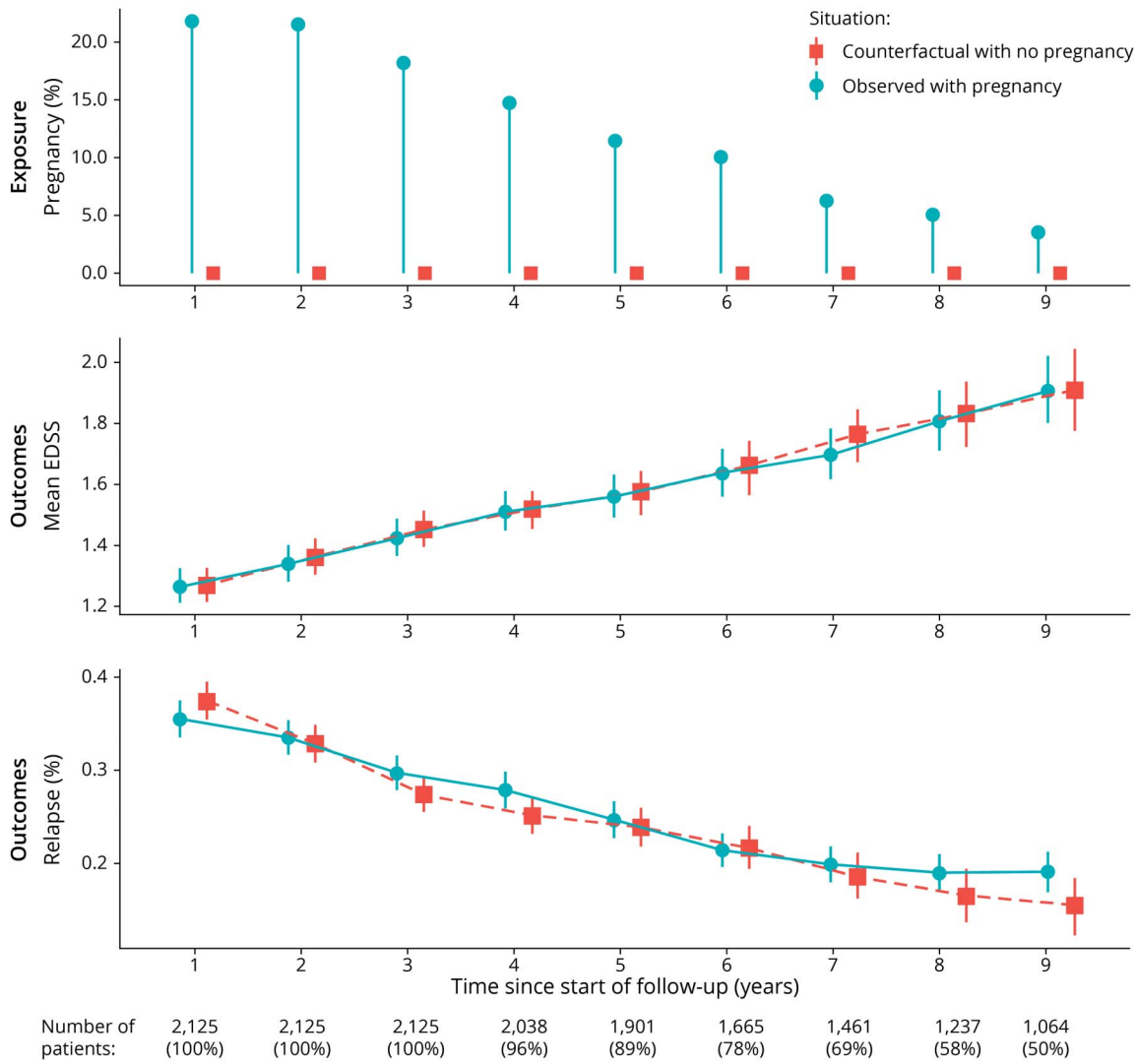
Sensitivity Analyses

Sensitivity analyses were consistent with the main results with small difference in magnitude or statistical power (eTable 3, links.lww.com/WNL/C573).

Discussion

In the present study, using a causal inference approach to account for the time-dependent reverse causation between pregnancy and neurologic disability in women with MS, we found no significant long-term causal effect of pregnancy on the disability accumulation, assessed using the EDSS. Our secondary results were also in favor of the absence of long-term effect on the relapse risk. An effect of pregnancy on disability and relapse risk

Figure 3 Long-term Effects of Pregnancy



Mean EDSS score, annual probability of relapse, and proportion of patients exposed to pregnancy in the observed situation and the counterfactual situation without pregnancy in the exposed population. EDSS = Expanded Disease Status Scale.

was observed only in the short term, during the perpartum and the first postpartum years, with no significant delayed effect on the disease course beyond 1 year after delivery.

Our results regarding the long-term effects of pregnancy on MS course are reassuring, and they were obtained with sufficient statistical power to exclude a clinically pertinent deleterious effect in view of the 95% CI (upper bound of +0.15 mean EDSS difference) and the large number of patients included, over substantial follow-up durations. The short-term effects of pregnancy found herein were concordant with published results,[6] as the risk of relapse was 20% lower during the perpartum period and 34% higher during the postpartum period. This effect on the relapse risk led to differences in disability in the short term: during the perpartum period, disability was reduced, but this difference had low clinical relevance and disappeared during the postpartum year, meaning that the higher relapse risk during the postpartum period compensated for the beneficial effect observed during the perpartum period.

The results of other observational studies investigating long-term effects of pregnancy on disability are discordant depending on the methodology used.[1-3,9-19] A majority of them used a Cox survival model and considered the time to reach a level of an EDSS score of 4 or 6 or the time to SP transition as outcome. The age at MS onset is a major confounder in the relationship between pregnancy and disability: while in the study.[2] including more than 2,000 patients, the beneficial effect of pregnancy shown in univariate analyses was no longer significant after adjustment on the age at MS onset, other studies have found a protective effect of pregnancies despite adjustment for age.[1,9,12-14] Two studies[3,20] have used a methodology closer to ours, considering pregnancy as a time-dependent exposure and using a

Table 2 Long-term, Short-term, and Delayed Causal Effects of Pregnancy on the Mean EDSS Score and the Annual Probability of Relapse

		Observed situation with pregnancies	Counterfactual situation without pregnancy	Causal effect of pregnancy (95% CI)[a]	*p* Value
Contrast between the observed situation with pregnancy and the counterfactual without pregnancy in the exposed population					
Long-term effect	Mean EDSS score[b]	1.91	1.91	0.00 (−0.16 to 0.15)	0.98
	Annual probability of relapse[c]	35.5%	37.4%	0.95 (0.93 to 1.38)	0.50
Contrast between the observed situation with pregnancy and the counterfactual without pregnancy in the early-exposed population					
Perpartum effect	Mean EDSS score[b]	1.28	1.34	−0.06 (−0.12 to −0.01)	0.03
	Annual probability of relapse[c]	26.3%	32.9%	0.80 (0.72 to 0.89)	<0.001
Postpartum effect	Mean EDSS score[b]	1.40	1.46	−0.06 (−0.14 to 0.01)	0.10
	Annual probability of relapse[c]	37.3%	27.9%	1.34 (1.20 to 1.48)	<0.001
Delayed effect	Mean EDSS score[b]	1.89	1.92	−0.03 (−0.18 to 0.12)	0.69
	Annual probability of relapse[c]	26.3%	23.9%	1.10 (0.94 to 1.45)	0.21

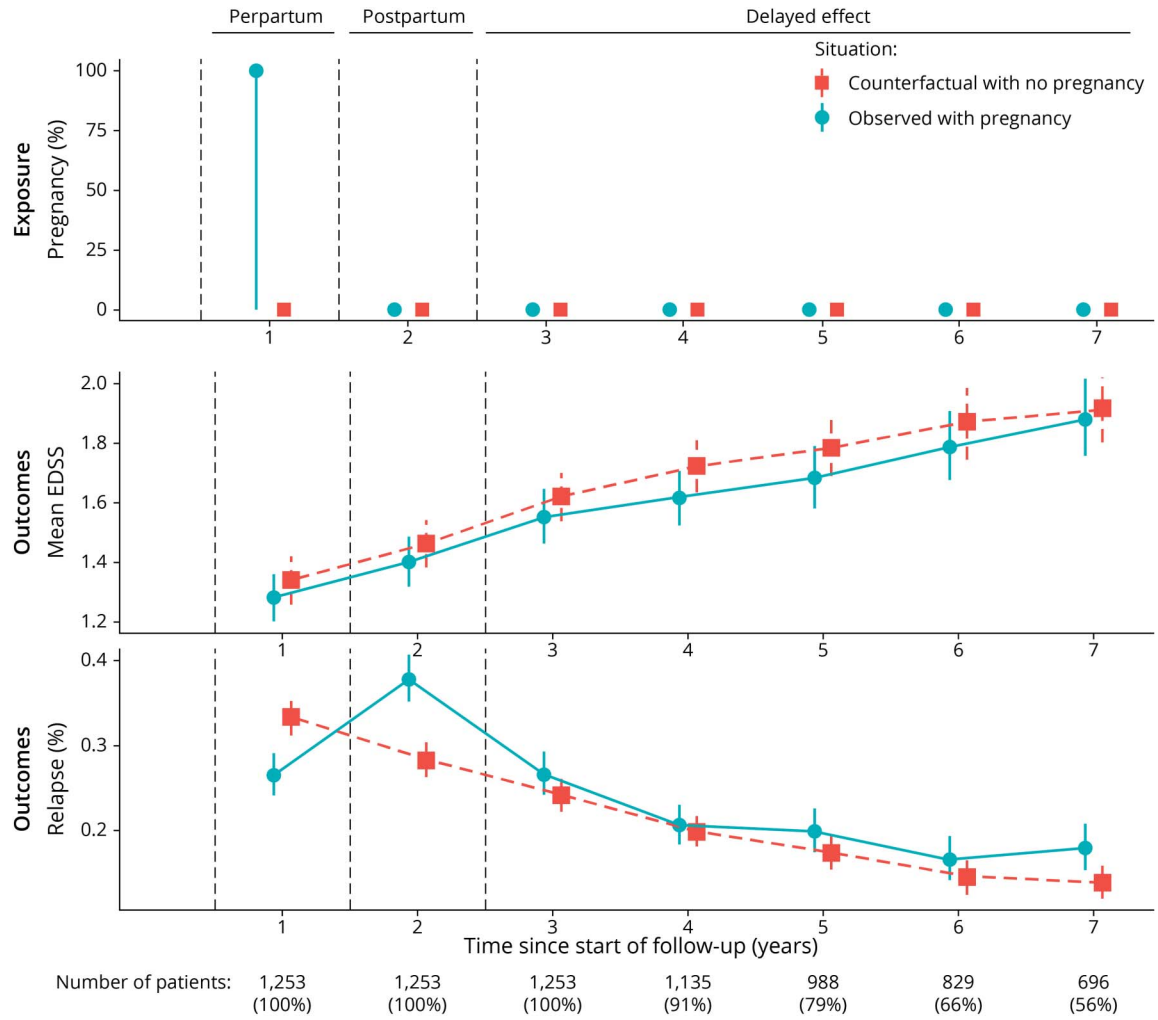
Abbreviation: EDSS = Expanded Disease Status Scale.
[a] Causal mean difference (95% CI) for the mean EDSS score and causal risk ratio (95% CI) for the annual probability of relapse.
[b] In the last 1-year period of the considered period for the long-term and delayed effects or in the perpartum or postpartum year for the short-term effects.
[c] Over the whole considered period.

propensity score for the probability of experiencing at least 1 pregnancy over the entire follow-up, and have found no significant effect of pregnancy (whereas a protective effect was found in the first one.[3] when pregnancy was considered as a time-fixed covariable). None of these studies have applied a fully adequate methodology to correct for the time-dependent confounding relationship between neurologic disability and pregnancy probability; therefore, reverse causation bias is likely to be present in all of them. By using a causal inference approach with a counterfactual framework, particularly well-suited to the analysis of longitudinal data, we were able to explicitly correct for this bias and highlight the reasons underlying the falsely positive effects of pregnancy found in some studies.

Pregnancy might affect MS through different mechanisms. In the short term, the hormonal and immunologic changes occurring during pregnancy and the postpartum period have been shown to directly affect disease activity (through an estrogen increase and a shift toward an anti-inflammatory Th2 environment),[36,37] and a part of the short-term effect might be mediated by the interruption of disease-modifying therapies. Potential delayed effects of pregnancy, occuring distantly from the delivery, might be related to long-lasting biological changes (immunological or hormonal) affecting disease severity, and resulting in a change in the disability trajectory. We found no evidence for a delayed effect of pregnancy on the EDSS course or the relapse probability.

Some limitations should be noted. Although we accounted for the main hypothetical confounders of the relationship between pregnancy and disease course (age and reverse causation with disability), residual confounding due to unmeasured confounders may still exist as a consequence of the observational nature of our study (e.g., body mass index and smoking). Treatment was initially considered in the causal reasoning: based on the assumptions that the treatment decision is causally affected by past pregnancy, disability, and relapses and has a causal effect on future disability and relapse risk, it was only a mediator of the effect of pregnancy on disability and relapse

Figure 4 Short-term and Delayed Effects of Pregnancy



Mean EDSS score, annual probability of relapse, and proportion of patients exposed to pregnancy in the observed situation with pregnancies and in the counterfactual situation without pregnancy in the early-exposed population: perpartum effect (first year), postpartum effect (second year), and delayed effect (remaining 5 years of follow-up). EDSS = Expanded Disease Status Scale.

and had no confounding effect, so it was not necessary to account for treatment in the causal models. Furthermore, a causal inference method relies on an outcome model and an exposure model, and a misspecification of both of these models may have led to a biased estimate of counterfactual outcome (but the doubly robust approach theoretically provided an unbiased estimate even if only one of these 2 models was misspecified). A division into 1-year time periods was probably too broad and potentially implied reverse causation relationship within 1-year periods between pregnancy, disability, and relapse occurrence, but the data collection, primarily the EDSS measurements, did not enable structuring of the analysis into shorter time periods. In addition, as an observational registry study, there may be measurement errors related to data collection or data structuring into 1-year periods. Missing EDSS measurements had to be inferred from the last available value, this concerned 18.3% of time periods, but in 15.3% of the cases, only 1 value was missing, so the measurement was quickly corrected for the following period, and sensitivity analysis found no difference when censoring at the first missing EDSS value. Finally, we only considered the occurrence of pregnancy as the exposure, but a desire for pregnancy may also affect a patient's disease course, e.g., by influencing the treatment choice during the preconception period (but we could not account for this as information regarding pregnancy desire was not available).

In conclusion, using a causal inference approach, we found no evidence of a significantly deleterious or beneficial causal long-term effect of pregnancy on disability. Pregnancy significantly affected relapse risk and disability in the short term, with a decrease in perpartum and an increase in postpartum, leading to an overall balanced and neutral effect, but we did not identify a significant delayed effect on the future disability trajectory and relapse probability. This

provides additional reassuring information for family planning counseling.

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