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

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Contribution of causal inference to the analysis of the long-term effect of pregnancy on the course of multiple sclerosis

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Number of characters in title: 111

Abstract Word count: 349

Word count of main text: 3617

References: 37

Figures: 4

Tables: 2

Supplemental: STROBE reporting guidelines

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Search Terms: [359] All CBMRT, [41] Multiple sclerosis, [54] Cohort studies

Acknowledgements: This study was conducted using data from the OFSEP, which is supported by a grant provided by the French State and handled by the Agence Nationale de la Recherche, within the framework of the Investments for the Future program, under the reference ANR-10-COHO-002, by the Eugène Devic EDMUS Foundation against multiple sclerosis and by the ARSEP Foundation. We thank Hélène Boyer (Direction de la Recherche en Santé, Hospices Civils de Lyon) for her help in manuscript preparation.

Study Funding: The authors report no targeted funding

Disclosures: Antoine Gavoille Declare no conflicts of interest related to this work; Fabien Rollot Declare no conflicts of interest related to this work; Romain Casey Declare no conflicts of interest related to this work; Debouverie Marc Declare no conflicts of interest related to this work; Le Page Emmanuelle Declare no conflicts of interest related to this work; Ciron Jonathan Consulting and lecturing fees, travel grants from Biogen, Novartis, Merck, Teva, Sanofi-Genzyme, Roche, BMS-Celgene and Alexion ; De Sèze Jerome Consulting and lecturing fees, travel grants and unconditional research support from Biogen, Genzyme, Novartis, Roche, Sanofi Aventis and Teva Pharma.; Ruet Aurelie Consultancy fees, speaker fees, research grants (non personal), or honoraria approved by the institutions from Novartis, Biogen Idec, Genzyme, Medday, Roche, Teva and Merck.; Maillart Elisabeth Consulting and lecturing fees from Alexion, Biogen, BMS, Merck Serono, Novartis, Roche, Sanofi, Teva Pharmaceuticals, and Ad Scientiam and research support from Biogen, Novartis and Roche; Labauge Pierre Consulting and lecturing fees, travel grants and unconditional research support from Biogen, Genzyme, Novartis, Merck Serono, Roche, and Teva Pharma; Zephir Helene Consulting or lectures, and invitations for national and international congresses from Biogen, Merck, Teva, Sanofi-Genzyme, Novartis and Bayer, as well as research support from Teva and Roche, and academic research grants from Académie de Médecine, LFSEP, FHU Imminent and ARSEP Foundation; Papeix Caroline Declare no conflicts of interest related to this work; Defer Gilles Consulting and lecturing fees for Biogen, BMS, Novartis, Genzyme, Merck-Serono, Roche and Teva and funding for travel from Merck Serono, Biogen, Sanofi-Genzyme, Novartis and Teva. Institution granted for research supporting from Merck Serono, Biogen, Genzyme and Novartis.; Lebrun-Frénay Christine Fees for consulting or lectures from Novartis, Genzyme, Roche.; Moreau Thibault Fees as scientific adviser from Biogen, Medday, Novartis, Genzyme, Sanofi.; Laplaud David Axel Served on scientific advisory boards for Roche, Sanofi, Novartis, medday, Merck and Biogen, received conference travel support and/or speaker honoraria from Novartis, Biogen, Roche, Sanofi, Celgene and Merck and received research support from Fondation ARSEP and Agence Nationale de la Recherche.; Berger Eric Honoraria and consulting fees from Novartis, Sanofi Aventis, Biogen, Genzyme, Roche and Teva Pharma.; Stankoff Bruno Consulting and lecturing fees, travel grants from Biogen Idec, Merck-Serono, Novartis, Genzyme, and unconditional research support from Merck-Serono, Genzyme, and Roche.; Clavelou Pierre Consulting and lecturing fees, travel grants and unconditional research support from Actelion, Biogen, Genzyme, Novartis, Medday, Merck Serono, Roche, and Teva Pharma; Thouvenot Eric Consulting and lecturing fees, travel grants or unconditional research support from the following pharmaceutical companies: Actelion, Biogen, Celgene, Genzyme, Merck Serono, Novartis, Roche, Teva pharma; has a patent pending for biomarkers of neurodegeneration and neuroregeneration and a patent pending for a diagnosis method of multiple sclerosis (EP18305630.8) ; and received academic research support from PHRC and ARSEP Foundation; Heinzlef Olivier Consulting and lecturing fees from Bayer Schering, Merck, Teva, Genzyme, Novartis, Almirall and biogenidec, travel grants from Novartis, Teva, Genzyme, Merck Serono and Biogen Idec and research support from Roche, Merck and Novartis; Pelletier Jean Fees as scientific adviser and travel grants from Biogen, Merck-Serono, Novartis,from Biogen, Medday, Novartis, Genzyme, Roche, Sanofi, Teva and unconditional research support from Merck-Serono and Roche.; Al-Khedr Abdullatif Declare no conflicts of interest related to this work; Casez Olivier Funding for travel and honoraria from Biogen, Merck Serono, Novartis, Sanofi-Genzyme and Roche.; Bourre Bertrand Served on scientific advisory board for Biogen, Genzyme, Merck Serono, Novartis, Roche and received funding for travel and honoraria from Biogen Idec, Merck Serono, Novartis, Sanofi-Genzyme, Roche and Teva; Cabre Philippe Declare no conflicts of interest related to this work; Wahab Abir Received expert testimony from Roche and travel grants from Biogen.; Magy Laurent Declare no conflicts of interest related to this work; Camdessanché Jean-Philippe Consulting and lecturing fees from Akcea, Alnylam, Biogen, CSL-Behring, Genzyme, Grifols, Laboratoire Français des Biotechnologies, Natus, Novartis, Pfizer, Pharmalliance, Teva, SNF-Floerger; travel grants from Biogen, CSL-Behring, Genzyme, Laboratoire Français des Biotechnologies, Merck-Serono, Novartis, Pfizer, Teva.; Maurousset Aude Received funding for travel from Merck Serono, Teva, Novartis, Sanofi-Genzyme, Biogen and Roche. Served on scientific advisory board for Roche. Received honoria from Biogen,

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Title:

Contribution of causal inference to the analysis of the long-term effect of pregnancy on the course of multiple sclerosis

Word count: 3086 *(< 4500 words, ≤ 7 tables/figures)*

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Keywords: multiple sclerosis; pregnancy; disability; long-term effect; causal inference

List of abbreviations:

DAG: directed acyclic graph

EDMUS: European Database on Multiple Sclerosis

EDSS: Expanded Disease Status Scale

ICE: iterative conditional expectation

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

Abstract: 350 words *< 350 words*

Background and objectives: As multiple sclerosis (MS) mostly affects young women, the question of the long-term safety of pregnancy is a major concern, but its study is biased by reverse causation (women with higher disability are less likely to experience pregnancy).We aimed to estimate the unbiased long-term effects of pregnancy on disability and relapse risk in MS patients using a causal inference approach, and secondarily to distinguish the short-term effects (during the per-partum period and the post-partum year) from the delayed effects (occurring beyond one year after delivery).

Methods: We conducted an observational cohort study with data from MS patients followed in the OFSEP registry between 1990 and 2020. We included MS female patients aged between 18 to 45 years at MS onset, clinically followed-up for more than 2 years and with ≥3 Expanded Disease Status Scale (EDSS) measurements available. Outcomes were the mean EDSS at the end of follow-up and the annual probability of relapse during follow-up. The patients exposed to at least one pregnancy during their follow-up were compared to the counterfactual situation in which they were not exposed to pregnancy, according to a counterfactual definition of causality. Short-term and delayed effects were analyzed in early-exposed patients, who experienced pregnancy during their first three years of follow-up.

Results: Out of 12,066 eligible patients, 9,100 patients were included. The median follow-up duration was 7.8 years, and 2,125 (23.4%) were exposed to at least one pregnancy. There was no significant long-term causal effect of pregnancy on the mean EDSS at 9 years (causal mean difference [95% CI] = 0.00 [-0.16; 0.15]), nor on the annual probability of relapse

(causal risk ratio [95% CI] = 0.95 [0.93; 1.38]). For the 1,253 early-exposed patients, the probability of relapse was significantly lower with pregnancy during the per-partum year and significantly higher during the post-partum year, but no significant delayed effect was found on 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 are probably related to a reverse causation bias.

INTRODUCTION

As multiple sclerosis (MS) mostly affects young women of childbearing age, the question of the impact 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 post-partum period, but the short-term progression of disability is not affected.[6] Long-term impacts 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. Classical statistical approaches such as multivariate analysis or propensity score fail to properly account for this bias due to the time-dependent nature of the exposure and outcome variables, and 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. The use of recent statistical methods based on the causal inference and counterfactual framework may properly account for time-dependent reverse causation, 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 (neurological disability and relapse rate) using a causal inference approach. Our secondary objective was to distinguish within the long-term effects the short-term effects

(during the per-partum year and first post-partum year) from the delayed effects (occurring more than one year after delivery).

METHODS

Patients

Data were extracted from the French MS registry, the *Observatoire Français de la Sclérose en Plaques* (OFSEP),[22] on December 15, 2020. 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 (EDMUS).[23] These data include a systematic question regarding the number of children and their date of birth.

Inclusion criteria were: 1) female patients with a diagnosis of MS according to current criteria at the time of diagnosis, i.e. either Poser or McDonald criteria (2001 or 2010),[24–26] 2) aged 18 to 45 years at MS onset, 3) with a clinical evaluation occurring after January 1, 1990, and 4) with a clinical follow-up of more than 2 years including at least 3 Expanded Disease Status Scale (EDSS) measurements. All MS phenotypes were considered: relapsing-remitting (RR), secondary progressive (SP), and primary progressive (PP). Patients with missing data regarding the number of children or their date of birth were excluded.

Legal

Patients registered in the OFSEP (clinicaltrials.gov [NCT02889965]) provided written informed consent for participation. In accordance with the French legislation, 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 conformed with the MR-004 (*Méthodologie de référence 004*).

Data collection and structuring in one-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 one-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 per-partum and post-partum periods occurred in two distinct (and consecutive) periods. Periods were analyzed until less than 50% of the patients were still being followed.

Neurological 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 one EDSS measurement was made during a same one-year period, the lowest score was retained. For one-year periods with no EDSS score available, the last value was used if measurements were available for at least one of the last 3 one-year periods, or the patient was censored 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, the number of relapse occurrence, and MS phenotype (RR, SP, or PP) were reported for each one-year period. Pregnancies occurring during the first one-year period were not considered because the reverse causation bias could not be corrected due to the absence of prior EDSS measurement. The study design, with an example of structuring the data into one-year periods, is depicted in Figure 1.

Outcomes

The main outcome was the mean EDSS in the last one-year period and the secondary outcome was the annual probability of relapse (probability of experiencing at least one relapse during the one-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 two situations: the observed situation (in which patients might become pregnant during each one-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. non-exposed to pregnancy, as if the exposure was randomly allocated between two 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 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 one-year period of study. The per-partum effect was

defined as the contrast between observed and counterfactual situations in the year before delivery, the post-partum effect as the contrast in the year following delivery, and the delayed effect as the contrast over the remaining follow-up duration, beyond one year after delivery.

The results were presented as causal mean differences in the last one-year period (*observed mean – counterfactual mean*) for the EDSS and as causal risk ratios over all one-year periods (*observed proportion/counterfactual proportion*) for the probability of relapse. The calculation of counterfactual and observed outcomes was restricted to the population exposed to at least one 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 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 (per-partum effect: $P_t \rightarrow R_t$ and $P_t \rightarrow D_t$), the following period (post-partum effect $P_t \rightarrow R_{t+1}$ and $P_t \rightarrow D_{t+1}$) and all subsequent periods (delayed effects $P_t \rightarrow R_{t+2}, R_{t+3}$, ... and $P_t \rightarrow D_{t+2}, D_{t+3}$, ...). Other assumptions were that disability and relapses affected all the subsequent probabilities of pregnancy (reverse-causation effect $R_t \rightarrow P_{t+1}, P_{t+2}$, ... and $D_t \rightarrow P_{t+1}, P_{t+2}$, ...), that the occurrence of relapse affected the accumulation of disability during the same period ($R_t \rightarrow D_t$) and the subsequent periods ($R_t \rightarrow D_{t+1}$, ...), that pregnancy probability, relapse risk, and disability were affected by their past 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 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 lost to follow-up*").

Statistical analysis

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 one-year period, EDSS was modelled 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 and MS phenotype. The results provided by the two combined algorithms in LTMLE, inverse probability weighting (IPW),[29–31] and iterative conditional expectation (ICE),[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.

Confidence intervals were obtained by bootstrapping over 1000 resamples. P-values less than 0.05 were considered statistically significant. All analyses were performed using the R software, version 4.0.3,[34] and *ltmle* package[35] for causal inference.

RESULTS

Out of 12,066 eligible patients, 2,966 patients were excluded due to missing data regarding the number of children or their date of birth, resulting in a total of 9,100 patients included. The median [Q1-Q3] follow-up duration was 7.8 [5.3-12.0] years.

During their follow-up, 2,125 (23.4%) patients experienced at least one pregnancy, corresponding to a total of 2,597 observed pregnancies. At baseline, patients exposed to at least one pregnancy were younger (mean age: 27.7 versus 35.4 years for unexposed patients, Wilcoxon test $p < 0.001$), had a shorter disease duration (median delay since diagnosis: 1.1 versus 3.6 years, Wilcoxon test $p < 0.001$), and a lower EDSS (median: 1.0 versus 1.5, Wilcoxon test $p < 0.001$; Table 1). The probability of pregnancy was negatively correlated with the EDSS in the previous year (odds ratio per 1 point increase in EDSS [95% CI] = 0.85 [0.83; 0.87], $p < 0.001$, 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 one 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 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: the mean EDSS 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; 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 per-partum effect was analyzed during the first year, the post-partum effect during the second year, and the delayed effect over the remaining 5 years (Figure 4).

Regarding the short-term effects, the mean EDSS was significantly but slightly lower in the situation with pregnancy during the per-partum year: it was 1.34 without pregnancy and 1.28 with pregnancy (mean causal difference [95% CI] = -0.06 [-0.12; -0.01], p = 0.03); but this difference was no longer significant during the post-partum year (mean causal difference [95% CI] = -0.06 [-0.14; 0.01], p = 0.10). The probability of relapse during the per-partum 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 post-partum 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 effect on the mean EDSS during the last period (mean causal difference [95% CI] = -0.03 [-0.18; 0.12], p = 0.69), nor 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).

DISCUSSION

In the present study, using a causal inference approach to account for the time-dependent reverse causation bias between pregnancy and neurological 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 impact of pregnancy on disability and relapse risk was observed only in the short-term, during the per-partum and the first post-partum years, with no significant delayed effect on the disease course beyond one 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% confidence interval (upper bound of +0.15 mean EDSS difference) and of 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 per-partum period and 34% higher during the post-partum period. This effect on the relapse risk led to differences in disability in the short term: during the per-partum period, disability was reduced, but this difference had low clinical relevance and disappeared during the post-partum year, meaning that the higher relapse risk during the post-partum period "compensated" for the beneficial effect observed during the per-partum 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 EDSS 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 of Ramagopalan *et al.*[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] Zuluaga *et al.*[3] and Andersen *et al.*[20] have used a methodology closer to ours, considering pregnancy as a time-dependent exposure and using a propensity score for the probability of experiencing at least one pregnancy over the entire follow-up, and have found no significant effect of pregnancy (whereas a protective effect was found by Zuluaga *et al*. when pregnancy was considered as a time-fixed covariable[3]). None of these studies have applied a fully adequate methodology to correct for the time-dependent confounding relationship between neurological 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 impact MS through different mechanisms. On the short term, the hormonal and immunological changes occurring during pregnancy and the post-partum 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. The potential long-term impact of pregnancy might result from a punctual change during the short-term period of pregnancy with no further delayed effect, or from a modification of the disease severity that might be delayed, occurring distantly after pregnancy, and change the disability trajectory. We found no evidence for a delayed effect of pregnancy on the EDSS course nor on the relapse probability.

Some limitations should be noted. Although we accounted for the main hypothetical confounders of the relationship between pregnancy and disease course (reverse causation with

disability and age), residual confounding may still exist as a consequence of the observational nature of our study. Furthermore, 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 two models was misspecified). A division into one-year time periods was probably too broad and potentially implied reverse causation relationship within one-year periods between pregnancy, disability and relapse occurrence, but the data collection, primarily the EDSS measurements, did not enable a structuring of the analysis into shorter time periods. Also, 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 one value was missing so the measurement was quickly corrected for the following period. Finally, we only considered the occurrence of a pregnancy as the exposure, but a desire of 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).

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 in a balanced way, 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 counselling.

Acknowledgment:

This study was conducted using data from the OFSEP, which is supported by a grant provided by the French State and handled by the Agence Nationale de la Recherche, within the framework of the Investments for the Future program, under the reference ANR-10-COHO-002, by the Eugène Devic EDMUS Foundation against multiple sclerosis and by the ARSEP Foundation.

We thank Hélène Boyer (Direction de la Recherche en Santé, Hospices Civils de Lyon) for her help in manuscript preparation.

Contributions:

AG designed the study; all authors collected the data; AG and FS performed the statistical analysis; AG drafted the manuscript; AG, SV, FR, RC, and FS interpreted the data and reviewed the manuscript; AG had full access to all the data and takes responsibility for the integrity of data and the accuracy of the data analysis.

Funding*: This study received no funding.*

Conflicts of interest:

Name	*Disclosures*
Antoine Gavoille	*Declare no conflicts of interest related to this work*
Fabien Rollot	*Declare no conflicts of interest related to this work*
Romain Casey	*Declare no conflicts of interest related to this work*
Debouverie Marc	*Declare no conflicts of interest related to this work*
Le Page Emmanuelle	*Declare no conflicts of interest related to this work*
Ciron Jonathan	Consulting and lecturing fees, travel grants from Biogen, Novartis, Merck, Teva, Sanofi-Genzyme, Roche, BMS-Celgene and Alexion
De Sèze Jerome	Consulting and lecturing fees, travel grants and unconditional research support from Biogen, Genzyme, Novartis, Roche, Sanofi Aventis and Teva Pharma.
Ruet Aurelie	Consultancy fees, speaker fees, research grants (non personal), or honoraria approved by the institutions from Novartis, Biogen Idec, Genzyme, Medday, Roche, Teva and Merck.
Maillart Elisabeth	Consulting and lecturing fees from Alexion, Biogen, BMS, Merck Serono, Novartis, Roche, Sanofi, Teva Pharmaceuticals, and Ad Scientiam and research support from Biogen, Novartis and Roche
Labauge Pierre	Consulting and lecturing fees, travel grants and unconditional research support from Biogen, Genzyme, Novartis, Merck Serono, Roche, and Teva Pharma
Zephir Helene	Consulting or lectures, and invitations for national and international congresses from Biogen, Merck, Teva, Sanofi-Genzyme, Novartis and Bayer, as well as research support from Teva and Roche, and academic research grants from Académie de Médecine, LFSEP, FHU Imminent and ARSEP Foundation
Gout Olivier	*Declare no conflicts of interest related to this work*
Defer Gilles	Consulting and lecturing fees for Biogen, BMS, Novartis, Genzyme, Merck-Serono, Roche and Teva and funding for travel from Merck Serono, Biogen, Sanofi-Genzyme, Novartis and Teva. Institution granted for research supporting from Merck Serono, Biogen, Genzyme and Novartis.
Lebrun-Frénay Christine	Fees for consulting or lectures from Novartis, Genzyme, Roche.
Moreau Thibault	Fees as scientific adviser from Biogen, Medday, Novartis, Genzyme, Sanofi.
Laplaud David Axel	Served on scientific advisory boards for Roche, Sanofi, Novartis, medday, Merck and Biogen, received conference travel support and/or speaker honoraria from Novartis, Biogen, Roche, Sanofi, Celgene and Merck and received research support from Fondation ARSEP and Agence Nationale de la Recherche.
Berger Eric	Honoraria and consulting fees from Novartis, Sanofi Aventis, Biogen, Genzyme, Roche and Teva Pharma.
Stankoff Bruno	Consulting and lecturing fees, travel grants from Biogen Idec, Merck-Serono, Novartis, Genzyme, and unconditional research support from Merck-Serono, Genzyme, and Roche.
Clavelou Pierre	Consulting and lecturing fees, travel grants and unconditional research support from Actelion, Biogen, Genzyme, Novartis, Medday, Merck Serono, Roche, and Teva Pharma
Thouvenot Eric	Consulting and lecturing fees, travel grants or unconditional research support from the following pharmaceutical companies: Actelion, Biogen, Celgene, Genzyme, Merck Serono, Novartis, Roche, Teva pharma; has a patent pending for biomarkers of neurodegeneration and neuroregeneration and a patent pending for a diagnosis method of multiple sclerosis (EP18305630.8) ; and received academic research support from PHRC and ARSEP Foundation
Heinzlef Olivier	Consulting and lecturing fees from Bayer Schering, Merck, Teva, Genzyme, Novartis, Almirall and biogenidec, travel grants from Novartis, Teva, Genzyme, Merck Serono and Biogen Idec and research support from Roche, Merck and Novartis
Pelletier Jean	Fees as scientific adviser and travel grants from Biogen, Merck-Serono, Novartis,from

	Biogen, Medday, Novartis, Genzyme, Roche, Sanofi, Teva and unconditional research support from Merck-Serono and Roche.
Al-Khedr Abdullatif	*Declare no conflicts of interest related to this work*
Casez Olivier	Funding for travel and honoraria from Biogen, Merck Serono, Novartis, Sanofi-Genzyme and Roche.
Bourre Bertrand	Served on scientific advisory board for Biogen, Genzyme, Merck Serono, Novartis, Roche and received funding for travel and honoraria from Biogen Idec, Merck Serono, Novartis, Sanofi-Genzyme, Roche and Teva
Cabre Philippe	*Declare no conflicts of interest related to this work*
Wahab Abir	Received expert testimony from Roche and travel grants from Biogen.
Magy Laurent	*Declare no conflicts of interest related to this work*
Camdessanché Jean-Philippe	Consulting and lecturing fees from Akcea, Alnylam, Biogen, CSL-Behring, Genzyme, Grifols, Laboratoire Français des Biotechnologies, Natus, Novartis, Pfizer, Pharmalliance, Teva, SNF-Floerger; travel grants from Biogen, CSL-Behring, Genzyme, Laboratoire Français des Biotechnologies, Merck-Serono, Novartis, Pfizer, Teva.
Maurousset Aude	Received funding for travel from Merck Serono, Teva, Novartis, Sanofi-Genzyme, Biogen and Roche. Served on scientific advisory board for Roche. Received honoria from Biogen, Novartis, and Roche.
Bakchine Serge	*Declare no conflicts of interest related to this work*
Ben Nasr Haifa	Honoraria and consulting fees from Novartis, Genzyme and Roche, research supports from Biogen and Novartis and travel grants from Genzyme, Novartis and Roche
Dimitri Boulos Dalia	*Declare no conflicts of interest related to this work*
Hankiewicz Karolina	*Declare no conflicts of interest related to this work*
Neau Jean-Philippe	*Declare no conflicts of interest related to this work*
Pottier Corinne	*Declare no conflicts of interest related to this work*
Nifle Chantal	*Declare no conflicts of interest related to this work*
Muriel Rabilloud	*Declare no conflicts of interest related to this work*
Fabien Subtil	*Declare no conflicts of interest related to this work*
Vukusic Sandra	Grants, personal fees and non-financial support from Biogen, grants and personal fees from Geneuro, grants, personal fees and non-financial support from Genzyme, grants and personal fees from Medday, grants, personal fees and non-financial support from Merck-Serono, grants, personal fees and non-financial support from Novartis, grants, personal fees and non-financial support from Roche, grants, personal fees and nonfinancial support from Sanofi, personal fees from Teva

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Tables

Table 1. Baseline characteristics

	Total	Exposure to ≥ 1 pregnancy during follow-up	
	n = 9,100	**No** n = 6,975	**Yes** n = 2,125
Age at MS onset (years), *mean (± SD)*	28.9 (± 6.5)	30.0 (± 6.7)	25.4 (± 4.5)
Age at baseline (years), *mean (± SD)*	33.6 (± 6.9)	35.4 (± 6.4)	27.7 (± 4.6)
Disease duration at baseline (years), *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 (years), *median [Q1-Q3]*	7.8 [5.3 - 12.0]	7.6 [5.1 - 11.8]	8.5 [5.9 - 12.4]
EDSS at baseline, *median [Q1-Q3]*	1.5 [0.0 - 3.0]	1.5 [0.0 - 3.0]	1.0 [0.0 - 2.0]
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%)
Number 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%)

EDSS: Expanded Disease Status Scale; MS: multiple sclerosis; PP: primary progressive; Q1-Q3: interquartile range; RR: relapsing-remitting; SD: standard deviation; SP: secondary progressive.

Table 2. Long-term, short-term, and delayed causal effects of pregnancy on the mean EDSS 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					
Patients with at least one pregnancy				n = 2,125	
Number of one-year periods until 50% of patients were lost to follow-up				9	
Long term effect	Mean EDSS [b]	1.91	1.91	0.00 [-0.16; 0.15]	NS
	Annual probability of relapse [c]	35.5%	37.4%	0.95 [0.93; 1.38]	NS
Contrast between the observed situation with pregnancy and the counterfactual without pregnancy in the early-exposed population					
Patients with at least one pregnancy during the first 3 years of follow-up				n = 1,253	
Number of one-year periods until 50% of patients were lost to follow-up				7	
Per-partum effect	Mean EDSS [b]	1.28	1.34	-0.06 [-0.12; -0.01]	0.03
	Annual probability of relapse [c]	26.3%	32.9%	0.80 [0.72; 0.89]	< 0.001
Post-partum effect	Mean EDSS [b]	1.40	1.46	-0.06 [-0.14; 0.01]	NS
	Annual probability of relapse [c]	37.3%	27.9%	1.34 [1.20; 1.48]	< 0.001
Delayed effect	Mean EDSS [b]	1.89	1.92	-0.03 [-0.18; 0.12]	NS
	Annual probability of relapse [c]	26.3%	23.9%	1.10 [0.94; 1.45]	NS

[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

CI: confidence interval; EDSS: Expanded Disease Status Scale; NS: not significant.

Figures

Figure 1. Study design: example of structuring of the follow-up into one-year periods for a patient exposed to a pregnancy.

EDSS: Expanded Disease Status Scale; MS: multiple sclerosis

Figure 2. Causal DAG representing the main assumptions about the relationship between pregnancy P, relapse R, and disability D within a same one-year period t (A) and between different one-year periods (B).

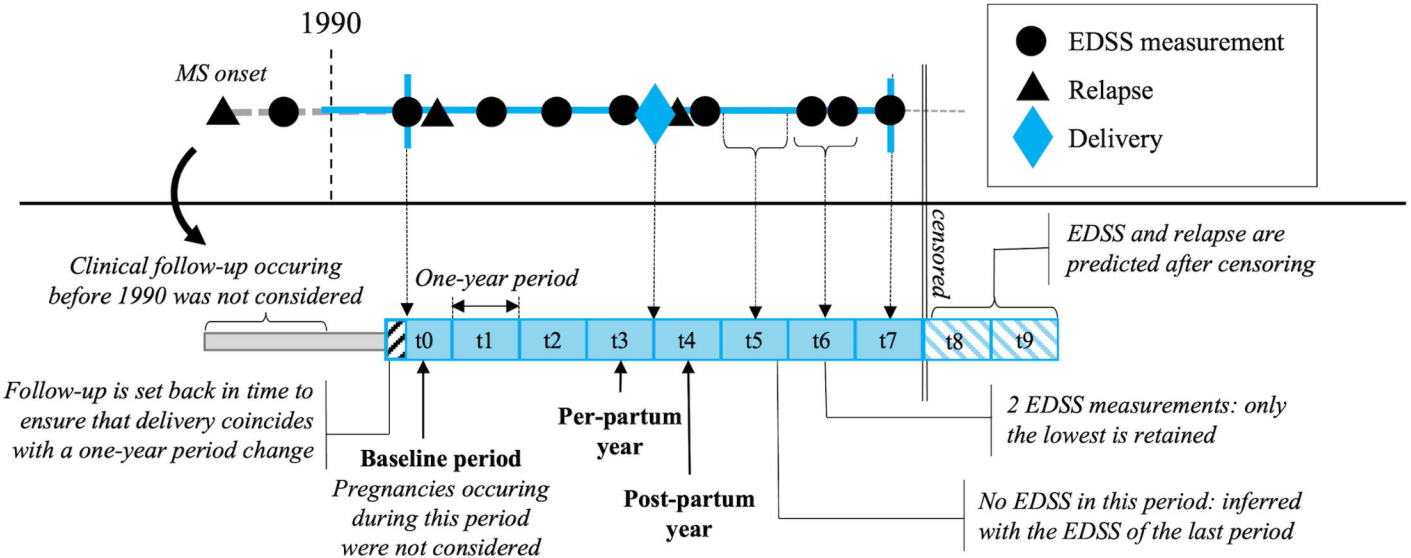
DAG: directed acyclic graph; EDSS: Expanded Disease Status Scale; MS: multiple sclerosis

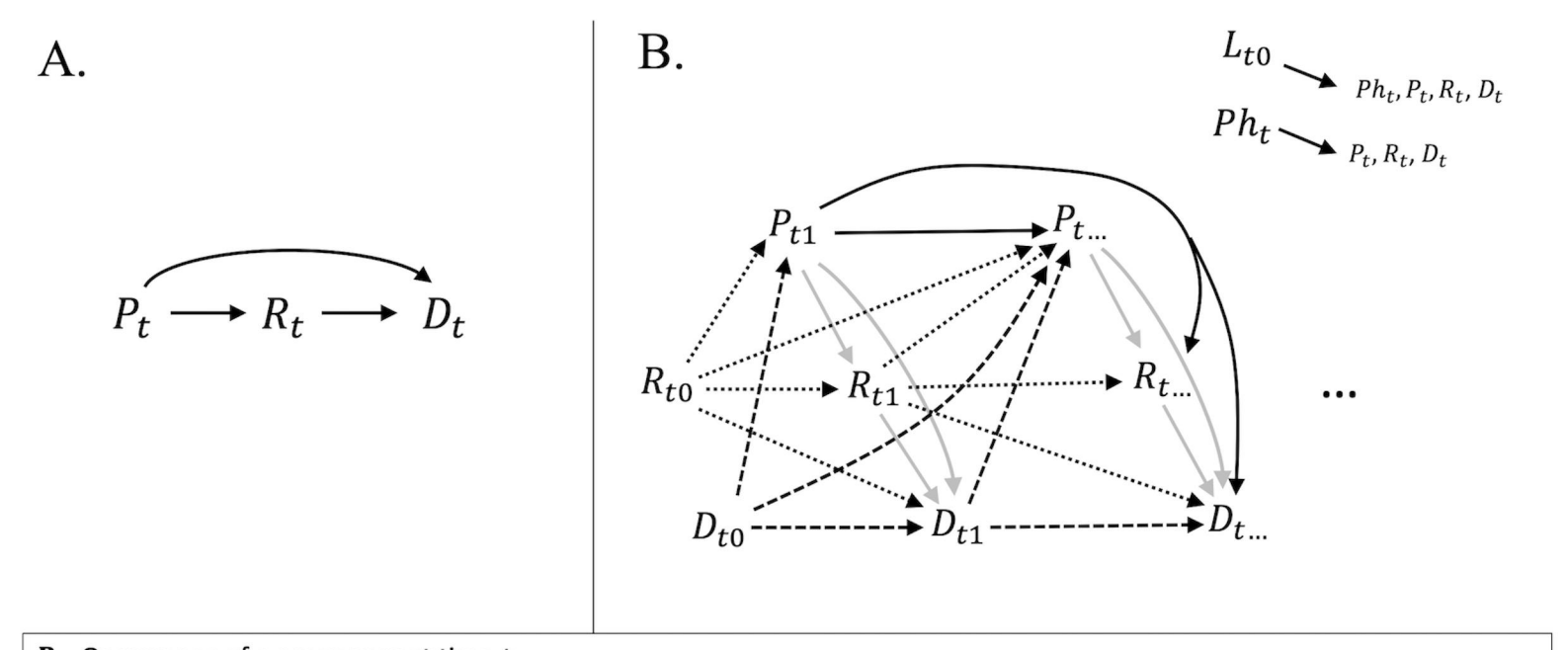
Figure 3. Mean EDSS, annual probability of relapse, and proportion of patients exposed to pregnancy in the observed situation and the counterfactual situation without pregnancy, in the exposed population.

EDSS: Expanded Disease Status Scale

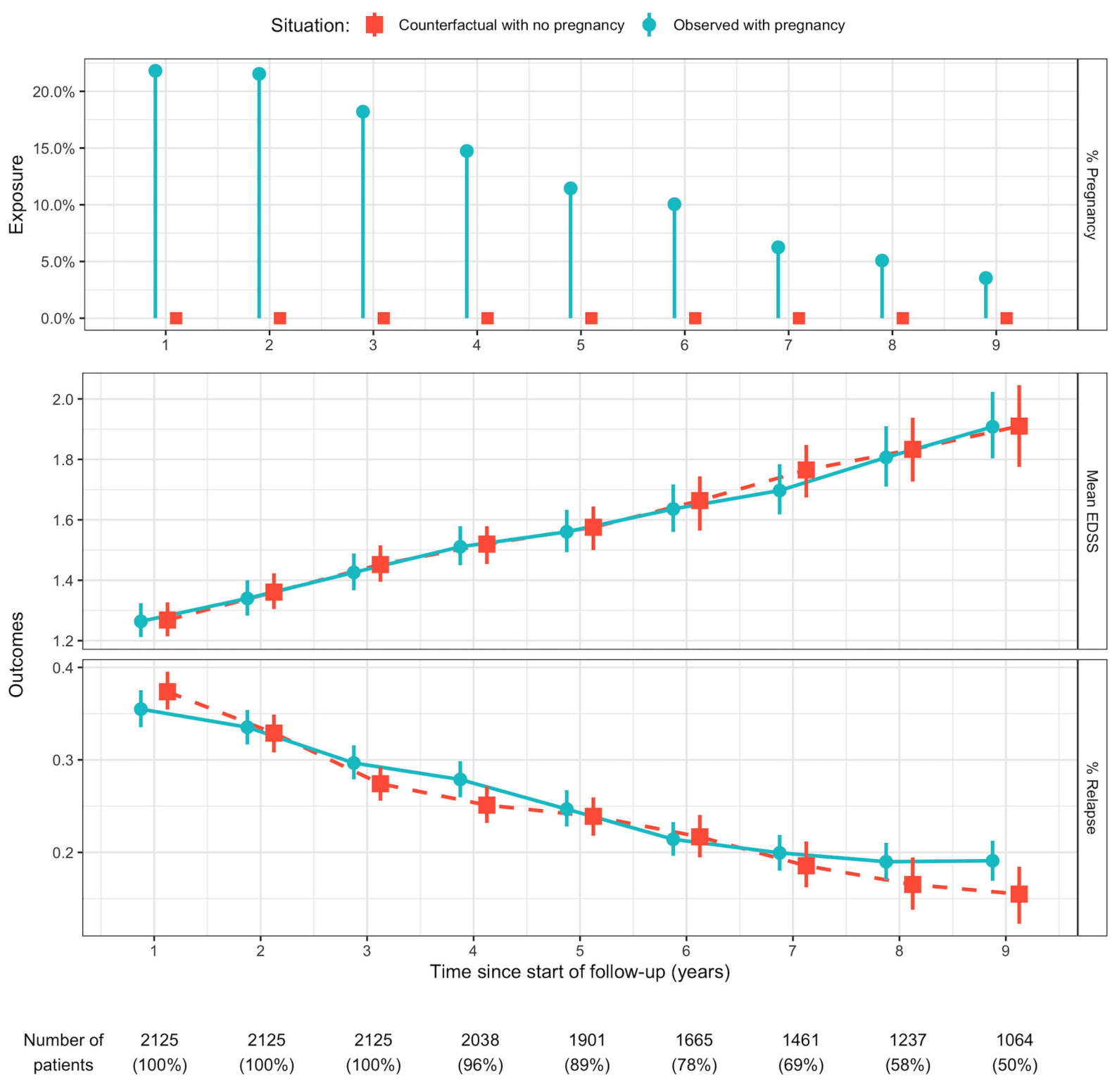
Figure 4. Mean EDSS, annual probability of relapse, and proportion of patients exposed to pregnancy in the observed situation with pregnancies and in the counterfactual situation without pregnancy, in the early-exposed population: per-partum effect (first year), post-partum effect (second year), and delayed effect (remaining 5 years of follow-up).

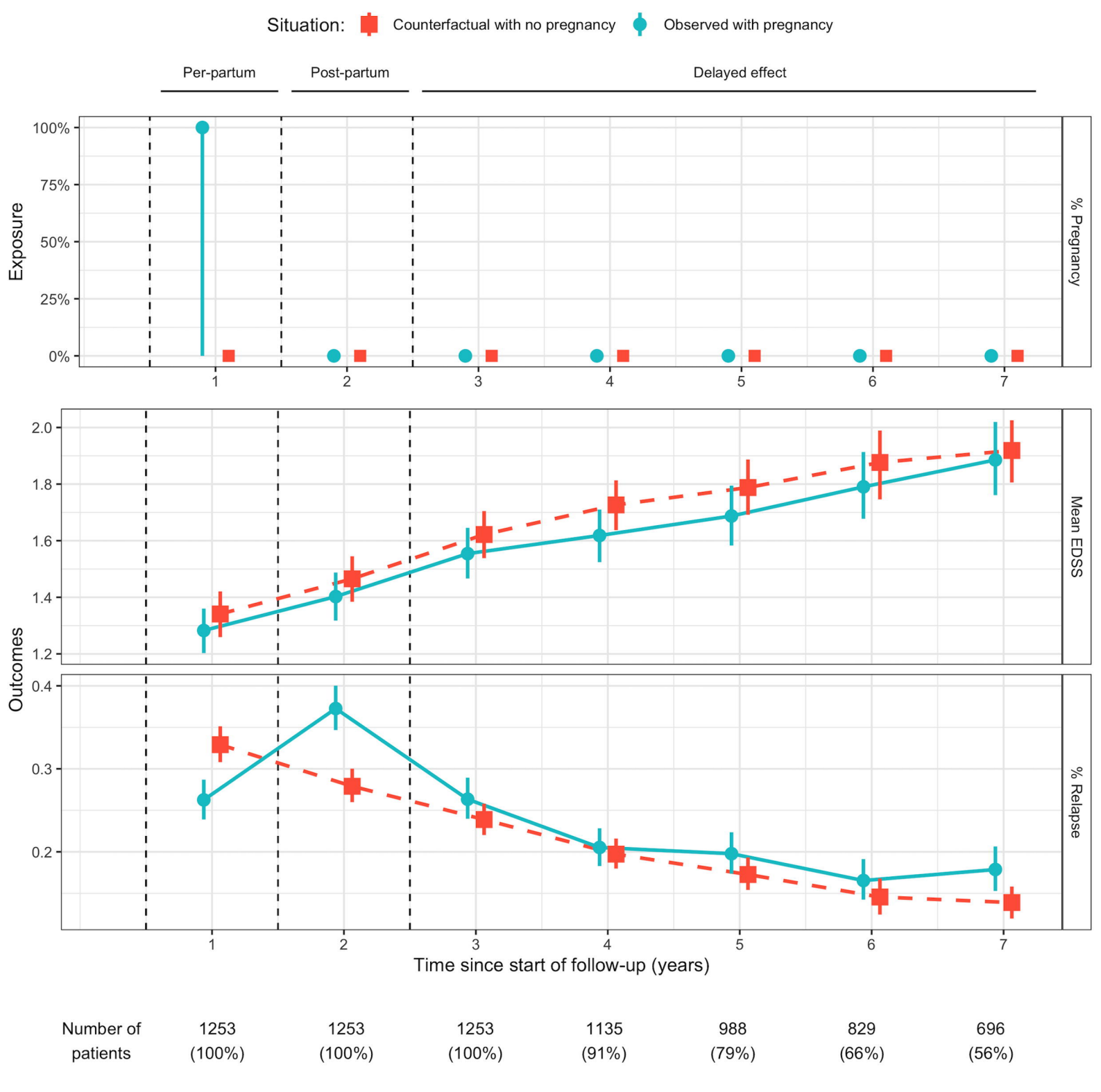
EDSS: Expanded Disease Status Scale


1990
MS onset
EDSS measurement
Relapse
Delivery
censored
EDSS and relapse are predicted after censoring
Clinical follow-up occuring before 1990 was not considered
One-year period
t0
t1
t2
t3
t4
t5
t6
t7
t8
t9
Follow-up is set back in time to ensure that delivery coincides with a one-year period change
Baseline period
Pregnancies occuring during this period were not considered
Per-partum year
Post-partum year
2 EDSS measurements: only the lowest is retained
No EDSS in this period: inferred with the EDSS of the last period



$\boldsymbol{P_t}$: Occurrence of a pregnancy at time t
$\boldsymbol{R_t}$: Occurrence of ≥ 1 relapse at time t
$\boldsymbol{D_t}$: Disability (EDSS) at time t
$\boldsymbol{L_{t0}}$: baseline covariates affecting all subsequent variables : disease duration, age, number of children
$\boldsymbol{Ph_t}$: MS phenotype at time t, affecting all variables at the same time (pregnancy, relapse, and disability)


Situation:
Counterfactual with no pregnancy
Observed with pregnancy
Exposure
20.0%
15.0%
10.0%
5.0%
0.0%
% Pregnancy
Outcomes
Mean EDSS
% Relapse
Time since start of follow-up (years)
Number of patients
2125 (100%)
2125 (100%)
2125 (100%)
2038 (96%)
1901 (89%)
1665 (78%)
1461 (69%)
1237 (58%)
1064 (50%)


Situation:
Counterfactual with no pregnancy
Observed with pregnancy
Per-partum
Post-partum
Delayed effect
Exposure
100%
75%
50%
25%
0%
% Pregnancy
Outcomes
2.0
1.8
1.6
1.4
1.2
Mean EDSS
0.4
0.3
0.2
% Relapse
1
2
3
4
5
6
7
Time since start of follow-up (years)
Number of patients
1253 (100%)
1253 (100%)
1253 (100%)
1135 (91%)
988 (79%)
829 (66%)
696 (56%)