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Does live birth reduce the rate of multiple sclerosis? Removing immortal time bias by alignment of time zero and exposure

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Does live birth reduce the rate of multiple sclerosis? Removing immortal time bias by alignment of time zero and exposure.

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Data and computing code availability: This study is based on Danish nationwide registry data, which are protected by Danish law and EU General Data Protection Regulation (GDPR) and therefore cannot be shared publicly. Access to these data is available to qualified researchers through the secure research servers hosted by Statistics Denmark, contingent on project approval and full compliance with Danish and EU data-protection requirements. R code is openly available at the GitHub [link].

ABSTRACT

Background: Studies of pregnancy and multiple sclerosis report inconsistent associations suggesting a protective effect or no association. This study evaluates whether temporal misalignment between the start of follow-up (time zero) and exposure can explain the protective association between live birth and multiple sclerosis onset reported in some earlier studies.

Methods: Using Danish population-based registry data, we assessed how different analytic strategies influence the estimated live birth-multiple sclerosis association. We reproduced two approaches used in prior literature: (i) fixing live birth exposure status at 15 years old (time zero); and (ii) treating live birth as a time-varying exposure. Additionally, we used (iii) the clone-censor-weight method to align time zero with exposure and remove immortal time bias.

Results: When fixing live birth status at 15 years, we observed a protective association between live birth and multiple sclerosis (adjusted HR 0.30 [95% CI 0.28;0.33]). The association attenuated to the null, when live birth was treated as a time-varying exposure (adjusted HR 0.98 [95% CI 0.89;1.07]). Following the clone-censor-weight approach, the estimated effect yielded no association either (weighted HR 1.06 [95% CI 0.76;1.70]).

Conclusions: The protective association reported in prior studies is plausibly explained by immortal time bias. The live birth-multiple sclerosis association represents a case of temporal overlap between exposure and outcome, but the underlying issue applies broadly across epidemiological research. Aligning time zero with exposure and securing temporality is essential when temporal misalignment distorts effect estimates and hinders causal inference.

Keywords: Live birth; Multiple Sclerosis; Immortal Time Bias; Clone Censor Weight Approach; Register-based; Denmark.

1 Introduction

In the 1840s, William Farr observed that certain professions appeared to have longer life expectancies. He later recognised that this likely reflected a selection mechanism, as individuals had to survive long enough to enter those professions in the first place [1]. Farr had identified the core of what we now call *immortal time bias*.

In time-to-event analysis, valid causal inference requires that the cause precede its effect [2]. The prospective study design supports this by anchoring follow-up at the moment of exposure and continuing until the outcome is observed, the person is censored, or the study ends. A structural problem, however, arises when the beginning of follow-up (*time zero*) and exposure do not coincide [3,4]: the interval between the two is, by definition, event-free among those who are eventually exposed, artificially inflating their apparent survival [3]. Immortal time bias emerges from exactly this misalignment: exposed individuals accumulate event-free (i.e. "immortal") time that is not caused by any biological mechanism but rather a product of the study design itself, which becomes stronger with increasing temporal overlap between the exposure and outcome windows.

The question of how live birth affects women's risk of developing the chronic autoimmune disease multiple sclerosis (MS) illustrates immortal time bias particularly well. MS typically onsets between ages 20 and 50 (mean age: 39.3) [5], which overlaps almost perfectly with the reproductive years during which live births occur. The excess MS incidence among women compared to men has prompted hypotheses that female reproductive factors may play an important role, including higher age at first childbirth and lower parity [6–11], potentially contributing to rising MS rates [12]. Figure 1 illustrates how women who remain event-free long enough to have a live birth accumulate immortal time, while women who are diagnosed with MS before they have a live birth are classified as unexposed. This unequally distributed immortal time across exposure groups may distort the comparison between groups and result in spurious associations.

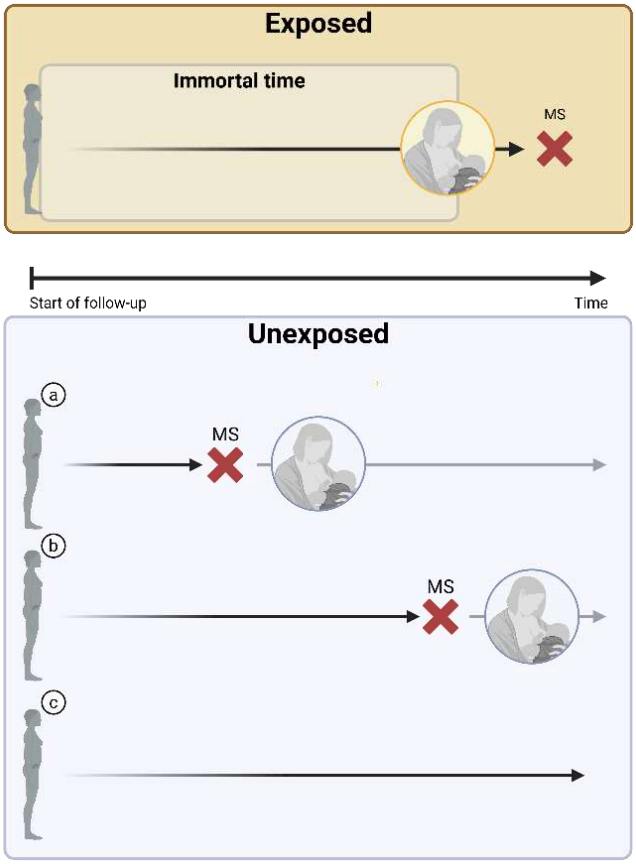


Figure 1: Illustration of immortal time bias using live birth and MS as examples. In the exposed group (yellow box), the 'immortal' follow-up time between the start of follow-up and exposure is marked in gray. Women diagnosed with MS before achieving a live birth are assigned to the unexposed group (blue box). Woman a and b illustrate that the earlier the outcome, the shorter the window to become exposed. Created in BioRender. Pociot, F. (https://BioRender.com/dmuy1yo) is licensed under CC BY 4.0.

Live birth is a composite exposure reflecting reproductive decision-making, parity, fertility, health, offspring viability, etc., which can and have been studied independently to address corresponding hypotheses about their effect on MS. A British cohort study found no association between live birth and MS onset [13], a Danish register-based cohort study found parity compared to nulliparity related to reduced risk of MS, however, with evidence against a biological effect of pregnancy [14]. Case-control studies of age-matched women with and without MS have generally reported reduced odds of MS among women with live births [6–8,15,16]. Some have attributed this finding to reverse causality from pre-clinical MS stages rather than a true

biological effect [8,9] – a concern they have attempted to circumvent by imposing a quarantine period, excluding births within a defined window before MS diagnosis, with a suggested waning effect as the quarantine extends further from diagnosis [6,8,14].

To assess how misalignment between time zero and exposure may distort the estimated effect of live birth on MS onset and explain conflicting results from prior studies, we conduct three analytical approaches: (i) fixing live birth status at baseline, (ii) treating live birth as a time-varying exposure, and (iii) using cloning-censoring-weighting. The first two approximate approaches used in prior studies, while the latter approximates a design formally aligning time zero and removing immortal time bias.

2 Material and methods

2.1 Study population and data sources

Using the nationwide Danish population registries [17] we established a cohort of 481,673 women (472,566 complete cases) born between 1975 and 1990. In accordance with prior literature, women were followed from the age of 15 years for any first live birth and MS diagnosis (International Classification of Diseases (ICD)-8 codes: 34000, 34001, 34008, 34009, and ICD-10 codes G35, G359, G359A, G359B, G359C) in the Danish Medical Birth Register [18] and the Danish National Patient Register [19], respectively. Women whose first live birth (n=37), MS diagnosis (n=16), or death (n=4699) occurred before age 15 were excluded.

The hypothesised relationship between first live birth and MS diagnosis is depicted in Figure 2. Information on the identified confounders was obtained from Statistics Denmark's data portal [20]. Highest attained education was categorised according to Statistics Denmark's Classification System for Education [21], and migration background indicated whether the woman was born in Denmark and whether either parent immigrated to Denmark.

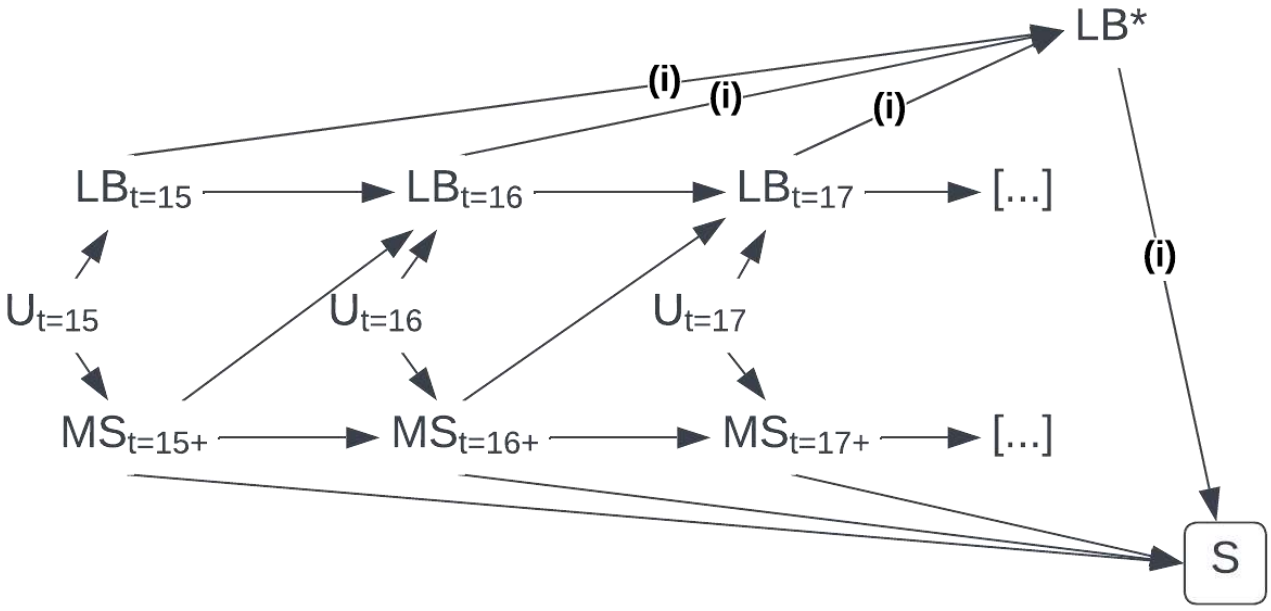


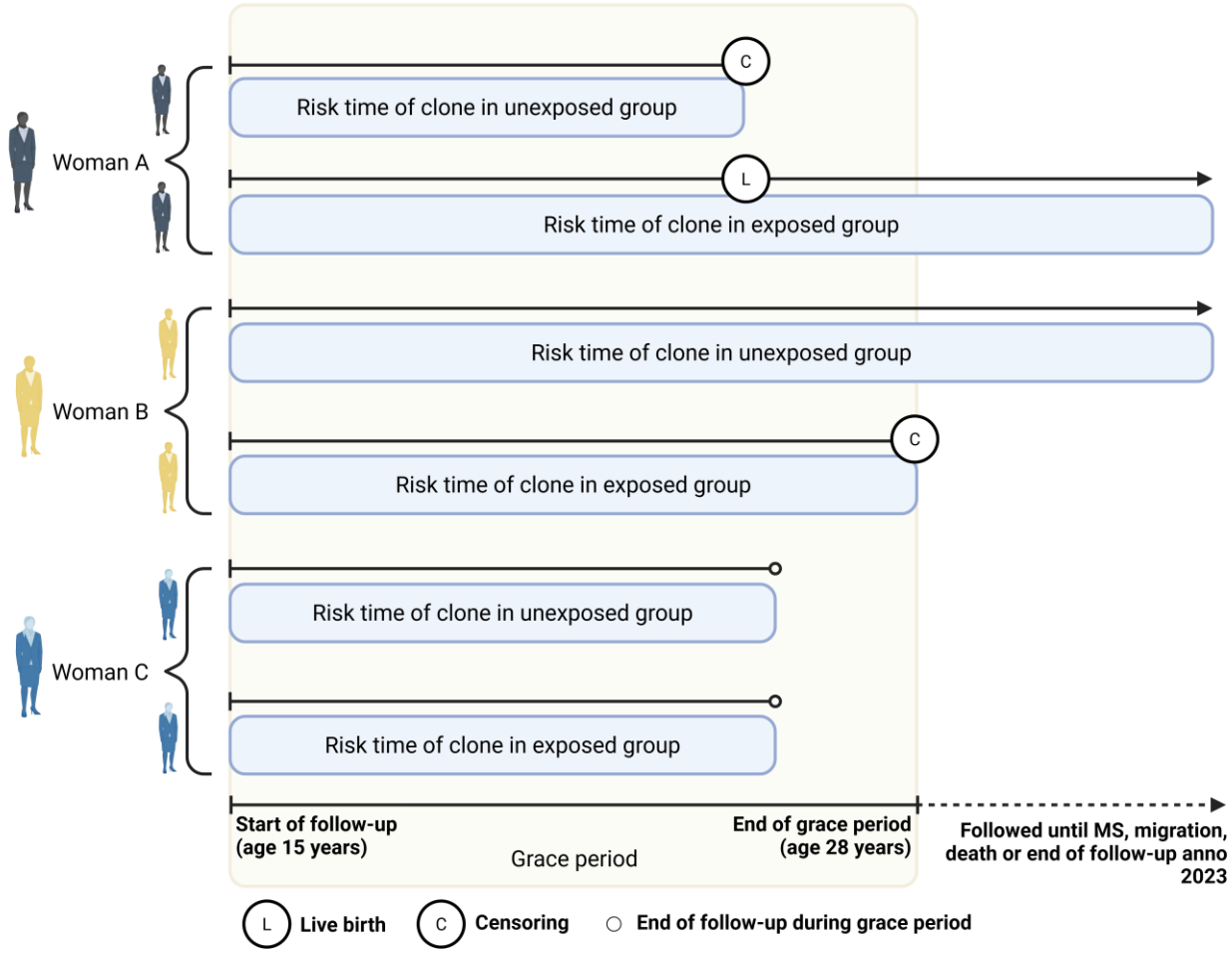
Figure 2: Directed acyclic graph (DAG) illustrating immortal time bias. LB_t denotes live birth status at time t, and MS_{t+} denotes multiple sclerosis status in the interval]t; t+1]. Arrows from MS_{t+} towards LB_{t+1} indicate that live birth is conditional on having no prior MS. LB denotes time-fixed live birth status (analytical approach (i) in our study). S denotes sample selection, and the arrows from MS_{t+} towards S indicate that women who have a live birth at a specific time must have no prior MS (i.e. selection). According to the DAG, this selection over time induces collider-stratification bias, which leads to creating spurious associations between live birth status and any possible MS at future time points. C: measured baseline confounders such as birth year, highest attained education, and migration background; and U_t: unmeasured confounders, possibly time-varying. Note, conditioning on confounders does not remove the immortal time bias due to selecting women conditionally on MS status over time.*

2.2 Analytical strategy

We implemented two analytical approaches applied in the existing literature. (i) We defined live birth as a fixed binary exposure at cohort entry (age 15 years) whenever a woman had a live birth registered before MS diagnosis, censoring, or end of follow-up; thereby mimicking misalignment between time zero and exposure as typically done in case-control studies where future information is used to classify exposure at time zero (e.g. classifying exposure as: "before potential MS, did she ever experience pregnancy?" and assigning that

status at time zero). (ii) We included live birth as a time-varying exposure, allowing each woman's exposure status to switch at the moment of her first live birth, thereby removing the immortal time window, as the pre-exposure risk time no longer contributed to the exposed group but to the unexposed group. Thus, any MS that occurred during follow-up was attributed to the correct corresponding exposure group. For this reason, early works in other epidemiological fields recommend this time-dependent model to address immortal time bias [4,22]. For both analytical approaches, we estimated crude and adjusted hazard ratios (HRs) for MS diagnosis with 95% confidence intervals (CI) in Cox regression models with age as the underlying time scale for women without and with live birth. Adjusted analyses included birth year, highest attained education, and migration background.

Despite the fact that the time-dependent model attempts to eliminate immortal time bias, interpreting its HR estimates is complicated by their non-collapsibility nature and because they inform on the association between MS onset and live birth *whenever it may occur* – that is, without an explicit exposure assessment period and time zero [23]. To address this issue, we applied the clone-censor-weight approach (iii), which has recently been popularised to address immortal time bias and align time zero [23–26]. Here, we approximated and contrasted two counterfactual scenarios: one where all women were to give live birth within a defined exposure time window (so-called *grace period*); the other where all women were to give no live birth during that same exposure grace period. To do so, we initially cloned each observation from the observational data and allocated one clone to the exposed group, the other to the unexposed group (Figure 3; persons A and B are both cloned). Because the exposed and unexposed groups were identical at baseline, the groups were thus artificially fully exchangeable and confounding-free [24–26]. All groups were followed in parallel throughout a grace period, in which exposure was accepted. Whenever an individual's exposure status was no longer compatible with the exposure status of the assigned group, she was censored (Figure 3, Person A's one clone is censored in the unexposed group when she had a live birth). An individual with end of follow-up before the grace period, and with no exposure, remained uncensored and contributed to the observed follow-up in both the exposed and non-exposed groups (Figure 3, both clones for Person C remain uncensored) until her follow-up ended (which we assumed to be non-informative).



153

154 *Figure 3: Illustration of the clone-censor-weight approach. One clone of each individual is assigned to the*
155 *exposed group, another to the unexposed group. Follow-up begins at cohort entry (left), continues through the*
156 *grace period during which live birth is accepted as exposure, and ends with MS diagnosis, migration, death,*
157 *or end of follow-up (right), whichever comes first. During the grace period, a clone is censored if its exposure*
158 *status is no longer compatible with its assigned group (person A at timepoint C). This informed censoring is*
159 *accounted for by upweighting uncensored women to recover the censored at each event throughout the grace*
160 *period. Created in BioRender. Pociot, F. (https://BioRender.com/dmuy1yo) is licensed under CC BY 4.0.*

161 We set the grace period to 28 years, taking equally into account the highest age quartiles for the first live
162 birth (30.0 years) and the lowest age quartile at diagnosis of MS (26.0 years). Censoring women whenever
163 they were no longer compatible with their assigned exposure group introduced selection bias since the

probability of censoring in each exposure group was not random and likely depended on individual characteristics. Thus, even though the initial cloning step artificially removed confounding, the censoring step merely shifted this bias towards selection. To compensate, we estimated the inverse individual probabilities of remaining uncensored at each event time during the grace period, using a Cox regression model including variables assumed to be associated with censoring. Importantly, the model was run separately for the two groups in case of interactions between covariates and exposure groups. The inverse probabilities of remaining uncensored were used to up-weight uncensored women to recover censored observations in the same group and sustain exchangeability of the two groups throughout the grace period [24–26]. Using the weighted data, we contrasted the two exposure groups and estimated the marginal HR for MS diagnosis; 95% CIs were obtained via bootstrapping. To overcome computational power issues, we specifically used the *bags of little bootstraps* approach, which combines subsampling and bootstrapping to provide valid inference while substantially reducing memory requirements [27]. All analyses were conducted using R version 4.3.1.

3 Results

Women with no live birth at baseline more often had longer education (long educational level: 35.0% vs. 19,6%) and were more often labelled as "immigrants" (5.3% vs. 3.5%) or "descendants" (3.3% vs. 2.4%) in the Danish registries compared to women with a live birth (Table 1). Following the clone-censor-weight approach, women with no live birth within the grace period from 15 to 28 years more often had longer education (long educational level: 29.0% vs. 16,0%) and were less often those labelled as "immigrants" (3.6% vs. 5.0%) (Table 2).

Table 3 shows the results of our three main analyses. In the analysis with registered live birth as a fixed exposure (i), we found pregnancy to be associated with a 70% decreased hazard of MS diagnosis after adjusting for birth year, highest attained education, and migration background (adjusted HR 0.30, 95% CI [0.28;0.33]). Treating live birth as a time-varying exposure (ii) led to no association with MS (adjusted HR 0.98, 95% CI [0.89;1.07]). Lastly, correcting for the temporal misalignment at time zero using the clone-

censor-weight approach (iii) led to no association between live birth and MS onset (weighted HR 1.06, 95% CI [0.76;1.70], Table 3).

4 Discussion

Our results demonstrate that immortal time bias could reasonably explain the conflicting findings from previous studies showing either a protective association or no association between live birth and MS diagnosis. The misalignment between time zero and exposure, which arises from fixing exposure status at baseline, can distort the estimated effect of live birth on MS onset, leading to a spurious protective association. We did not observe any association between live birth and MS onset when live birth was included as a time-varying exposure, nor did we when we aligned time zero and exposure status using cloning-censoring-weighting.

The difference in effect estimates and study designs complicate direct comparison of our results with prior results. The protective effect observed when we allow the temporal misalignment between time zero and exposure is consistent with findings from several other studies. However, prior studies have interpreted the apparent protective effects differently. The majority of studies conducted sensitivity analyses excluding pregnancies that were timed close to an MS diagnosis, showing that the apparent protective association was driven by livebirths closest to an MS diagnosis. Magyari et al. (2013) found reduced odds of MS among women who had given birth within the five years preceding clinical onset, with no discernible effect of earlier births [6]. Gasperi et al. (2022), Salehi et al. (2018), and Ponsonby et al. (2012) similarly found that women with a live birth had significantly lower odds of developing MS or having their first clinical demyelinating event - a neurologic episode, also called an attack - compared to women without a pregnancy [7,15,16]. All three studies interpreted the reduced odds as a protective effect of childbirth on MS risk. Even though Nielsen et al. (2011) and Hedström et al. (2013) reported a strikingly similar pattern of protective effect of childbirth on MS [8,14], Nielsen et al. (2011) and Hedström et al. (2013) interpreted this pattern as evidence of reverse causality [8,14]. When we addressed immortal time bias by including live birth as a time-varying exposure, the estimates reduced to no association. When further securing temporality and aligning time zero with exposure by conducting the clone-censor-weight approach, our results showed again no effect of live birth on MS. The same finding was shown by Villard-Mackintosh and Vessey (1993), who

examined the effect of oral contraceptives and parity on MS onset rates in a cohort of 17032 married women aged 25 to 39 between 1968 and 1974 in Britain [13]. Villard-Mackintosh and Vessey (1993) found no apparent effect of parity on MS onset rates.

Our results support that the protective association may be largely attributable to immortal time bias rather than to other biases such as confounding. Indeed, the negligible difference between adjusted and unadjusted estimates obtained from the time-fixed approach (i) and the time-dependent model (ii) suggests that confounding alone plays little to no role in reducing the protective association towards the null. This explanation of apparent protective association attributable to immortal bias has been alluded to in the prior literature: for example, Nielsen et al. (2011) found that the protective effect associated with parenthood was not reproduced when MS onset was backdated by five years, suggesting that the original association was driven by factors operating close to diagnosis rather than a stable effect of earlier childbirth [14]. This concentration of the protective association in the years immediately preceding diagnosis is consistent with immortal time bias, because for a woman to be classified as exposed, she must, by definition, remain diagnosis-free until her live-birth occurs. In our study, treating live birth as a time-varying exposure (ii) and using the cloning-censoring-weighting approach (iii) yielded largely similar results. This may reflect that, in this specific context, the lack of an explicit exposure window (grace period) may not alone explain the previously claimed protective association.

Limitations of our study include those which apply more broadly to the methods we used. First, results from cloning-censoring-weighting are inherently conditional on the choice of the grace period that is used to secure temporal separation between exposure and outcome. We defined the grace period for live birth exposure as the range spanning from 15 to 28 years, and our results may not extrapolate to live birth occurring at later age. Second, once time zero and exposure were aligned and temporality was secured using the clone-censor-weight approach, we approximated a causal contrast for which effect estimates for the live birth-MS onset association are not directly comparable to prior studies due to differences in the quantity to be estimated (i.e. estimand). Here, our focus was restricted to counterfactual scenarios (i.e. “what if women were to give live birth” versus “what if they were not”) that again inherently depended on the grace period definition.

Third, the clone-censor-weight approach relies on untestable assumptions such as the absence of unmeasured confounding in the IPCW models [24,26], and it is unlikely that we accounted for all relevant variables. For example, data on use of tobacco and nicotine products, shown to have a negative effect on fertility [28] are not available from the registers.

Although applying a clone-censor-weight approach may constrain the research question to ensure a strict separation of exposure and outcome, this trade-off is warranted when temporal misalignment between time zero and exposure distorts effect estimates and hinders causal inference. Despite the fact that the clone-censor-weight approach and the time-dependent exposure model do not, strictly speaking, estimate the same statistical quantity, the concordance in their results supports that immortal time bias provides a plausible explanation for the protective association between live birth and MS onset reported by prior studies. The live birth-MS association represents an extreme instance of temporal overlap between exposure and outcome, yet the underlying problem is widely relevant across epidemiologic research.

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6 Declarations of interest

Funding
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Competing Interests
TDB, GLP, and TLN declare that they have no conflicts of interest. FP has received lecture fees to SDCC and served on advisory boards related to early detection of type 1 diabetes initiatives for Sanofi. JCA has served as Medical Science Liaison for Sanofi.

Author Contributions
All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Tine Dreier Bille, Gitte Lindved Petersen, and Tri-Long Nguyen. The first draft of the manuscript was written by Tine Dreier Bille, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval
This study was performed in line with the principles of the Declaration of Helsinki. Approval for use of data sources for research purposes was granted by the data responsible institute in the Capital Region of Denmark (approval no. p-2024-17478) in accordance with the Danish Data Protection Act and the General Data Protection Regulation.

Consent to participate
Ethical committee approval or patient consent is not required for register-based studies that are performed for the sole purpose of statistics and scientific research in Denmark.

Consent to publish
Ethical committee approval or patient consent is not required for register-based studies that are performed for the sole purpose of statistics and scientific research in Denmark.

Table 1 Baseline characteristics shown as counts with percent of total (categorical variables) and medians with interquartile ranges (IQR, continuous variables) among women without and with live birth.

	Without live birth	**With live birth**
Total	144,236 (29.9%)	337,437 (70.1%)
Migration background		
Danish ethnicity	125,169 (86.8%)	317,451 (94.1%)
Immigrant	7,707 (5.3%)	11,821 (3.5%)
Descendant	4,705 (3.3%)	8,118 (2.4%)
Missing	*6,655*	*47*
Educational level		
Primary	18,991 (17.7%)	31,952 (9.5%)
Secondary	36,666 (34.1%)	113,035 (33.5%)
Short	7,227 (6.7%)	19,461 (5.8%)
Medium	35,927 (33.4%)	106,363 (31.5%)
Long	37,605 (35.0%)	66,103 (19.6%)
Missing	*7,820*	*523*
Parental multiple sclerosis (MS) diagnosis		
Maternal MS	1,068 (0,8%)	2,567 (0,8%)
Paternal MS	557 (0,4%)	1,394 (0,4%)
Missing	*7,336*	*255*
Age in years at first live birth, median [IQR]		27.4 [24.6;30.0]

Table 2. Baseline characteristics, shown as counts with percent of total (categorical variables) and medians with interquartile ranges (IQR, continuous variables), among women in the exposed and non-exposed groups, stratified by uncensored and censored status, respectively, without and with live birth. Each patient contributes one clone to the unexposed group and one clone to the exposed group, so that each clone group sums to N = 472,566 complete cases. The number of uncensored observations summed across the two groups, however, exceeds the total N because women who were diagnosed with MS (or censored for other reasons) during the grace period without having had a live birth remained uncensored in both groups. In contrast, women with a live birth within the grace period are uncensored only in the exposed group, and women who survived the grace period without a live birth are uncensored only in the unexposed group.

	Unposed		**Exposed**	
	Uncensored	Censored during grace period	Uncensored	Censored during grace period
Total	305,912	166,654	231,342	241,224
Migration background				
Danish ethnicity	286,912 (94.0%)	154,615 (93.0%)	212,407 (92.0%)	229,120 (95.0%)
Immigrant	11,036 (3.6%)	7,334 (4.4%)	11,661 (5.0%)	6,709 (2.8%)
Descendant	7,964 (2.6%)	4,705 (2.8%)	7,274 (3.1%)	5,395 (2.2%)
Educational level				
Primary	26,246 (8.6%)	24,428 (15.0%)	30,584 (13.0%)	20,090 (8.3%)
Secondary	79,868 (26.0%)	69,627 (42.0%)	84,380 (36.0%)	65,115 (27.0%)
Short	18,417 (6.0%)	8,248 (4.9%)	11,651 (5.0%)	15,014 (6.2%)
Medium	93,672 (31.0%)	48,466 (29.0%)	67,294 (29.0%)	74,844 (31.0%)
Long	87,709 (29.0%)	15,885 (9.5%)	37,433 (16.0%)	66,161 (27.0%)
Parental multiple sclerosis (MS) diagnosis				
Maternal MS	2,298 (0.8%)	1,329 (0.8%)	1,789 (0.8%)	1,838 (0.8%)
Paternal MS	1,246 (0.4%)	702 (0.4%)	953 (0.4%)	995 (0.4%)

Birth year, median [IQR]	1982 [1978;1987]	1982 [1978;1986]	1982 [1978;1986]	1983 [1978;1987]

Table 3 Estimated effect of live birth on multiple sclerosis onset using three different analytical approaches. Results are from crude and adjusted Cox proportional hazards models.

	N events	**Person-years at risk**	**Crude HR [95% CI]**	**N events**	**Person-years at risk**	**Adjusted[a] HR [95% CI]**
i) Fixing exposure at baseline						
No registered live birth	1,269	5,820,974	1 [reference]	1,266	5,477,530	1 [reference]
Registered live birth	1,356	12,095,551	0.33 [0.31;0.36]	1,354	12,070,662	0.30 [0.28;0.33]
ii) Treating exposure as time-varying						
No registered live birth	1,269	5,820,974	1 [reference]	1,266	5,477,530	1 [reference]
Registered live birth	1,356	12,095,551	0.97 [0.94;1.13]	1,354	12,070,662	0.98 [0.89;1.07]

	Weighted HR [95% CI]
iii) Alignment of time-zero and exposure status	
No registered live birth	1 [reference]
Registered live birth	1.06 [0.76;1.70]

[a]Adjusted for birth year, highest attained education, and migration background.