

RESEARCH

Open Access



The hazard of using the Poisson model to cope with immortal time bias in the case of time-varying hazard

Federico Rea^{1,2*}, Gabriella Morabito^{1,2}, Giovanni Corrao^{1,2} and Anna Cantarutti^{1,2}

Abstract

Background A time-dependent analysis, usually by means of Poisson and Cox regression models, can be applied to prevent immortal time bias. However, the use of the Poisson model requires the assumption that the event rate is constant over time. This study aims to assess the potential consequences of using the Poisson model to cope with immortal time bias on estimating the exposure-outcome relationship in the case of time-varying risks.

Methods A simulation study was carried out. Survival times were assumed to follow a Weibull distribution, and the Weibull parameters were chosen to identify three different scenarios: the hazard of the event is constant, decreases, or increases over time. A dichotomous time-varying exposure in which patients can change at most once from unexposed to exposed was considered. The Poisson model was fitted to estimate the exposure-outcome association.

Results Small changes in the outcome risk over time (as denoted by the shape parameter of the Weibull distribution) strongly affected the exposure-outcome association estimate. The estimated effect of exposure was always lower and greater than the true exposure effect when the event risk decreases or increases over time, and this was the case irrespective of the true exposure effect. The bias magnitude was positively associated with the prevalence of and time to exposure.

Conclusions Biased estimates were obtained from the Poisson model to cope with immortal time. In settings with a time-varying outcome risk, the model should adjust for the trend in outcome risk. Otherwise, other models should be considered.

Keywords Immortal time bias, Poisson model, Cox Model, Time-varying risk, Simulation study

Introduction

Immortal time bias is a source of systematic uncertainty that can affect observational studies in which exposure can change during the follow-up [1]. It refers to a period during which the outcome cannot occur because of the exposure definition. For example, in pharmacoepidemiology studies, if a cohort of patients is followed from the hospital discharge and the exposure is a drug prescription, the time until the prescription is defined as immortal because exposed individuals have to survive until the treatment definition is fulfilled [2]. If this unexposed

*Correspondence:

Federico Rea
federico.rea@unimib.it

¹ National Centre for Healthcare Research & Pharmacoepidemiology, at the University of Milano-Bicocca, Milan, Italy

² Department of Statistics and Quantitative Methods, Laboratory of Healthcare Research & Pharmacoepidemiology, Unit of Biostatistics, Epidemiology and Public Health, University of Milano-Bicocca, 8, Edificio U7, Milan 20126, Italy



© The Author(s) 2024. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.

period is not correctly managed in the design or analysis, biased results will be obtained.

Albeit this bias was identified decades ago [3], it occurs frequently even now in many fields [4–7]. Several approaches have been proposed to prevent immortal time bias [8], including the adoption of a time-dependent analysis, the analysis of only subjects who have survived until a pre-defined time point (i.e. the so-called “landmark analysis”), and a time-matched analysis in which, for each exposed subject, an individual not (yet) exposed on that date is identified. To properly classify the immortal person-time by using a time-varying exposure, Poisson and Cox regression models can be used [9]. Although the Poisson regression model is frequently applied [10–14], its use requires the assumption that the event rate is constant over time [15], and, thus, the same during the exposed and unexposed periods. This principle, known as exchangeability, is an essential conditional for observing unbiased associations [16]. However, suppose the exposure follows a specific trend (e.g., all patients are unexposed at the start of the study and can switch to exposure during follow-up), and the risk of the outcome increases (or decreases) over time. In that case, the baseline risks are non-exchangeable, and thus confounding affects the measure of the exposure-outcome relation. To handle time-varying outcome risk when using the Poisson model, appropriate intervals of follow-up time in which the event rate is approximately constant should be identified.

With these premises, a simulation study was carried out to assess the potential consequences of using the Poisson model to cope with immortal time bias on estimating the exposure-outcome relationship without taking into account the time-varying outcome risk. By considering a dichotomous time-varying exposure in which patients can change at most once from unexposed to exposed, the exposure-outcome relationship estimate was investigated by (i) modifying the baseline risk over time, (ii) changing the true exposure effect, and (iii) varying the prevalence of and time to exposure. Finally, the association between antibiotics use during pregnancy and the risk of short-term neonatal outcomes was investigated using data from the Lombardy Region.

Methods

Survival and exposure times

This study was based on simulations. To simulate survival times in the setting of time-varying hazard, event times were assumed to follow a Weibull distribution. The Weibull is a common time-to-event distribution characterized by two parameters: λ (scale) and ν (shape). When $\nu < 1$, the hazard of the event decreases over time; when $\nu > 1$, the hazard of the event increases over time; when

$\nu = 1$, the hazard of the event is constant over time, and the Weibull distribution reduces to an exponential distribution. In our analyses, survival times were censored after five time units.

We consider only one type of time-varying exposure, i.e. a dichotomous time-varying exposure in which patients can change at most once from unexposed to exposed. To simulate the exposure status, exposure times were initially assumed to follow a Uniform distribution from 0 to 10. In further analyses, we modified the way to generate the exposure status (see below). If the exposure time was less than the survival time, the patient was considered exposed from the former time, and a new event time was simulated. The exposure effect was assumed to be constant over time. The true risk ratio of outcome in relation to exposure was denoted by RR_T .

Main scenarios

To assess the validity of estimates from the Poisson model, Weibull parameters were arbitrarily chosen as follows to identify three different scenarios:

- scenario A (the hazard of the event is constant over time): $\lambda = 0.1$ and $\nu = 1$;
- scenario B (the hazard of the event decreases over time): $\lambda = 0.75$ and $\nu = 0.33$;
- scenario C (the hazard of the event increases over time): $\lambda = 1e-05$ and $\nu = 7$.

For each scenario, 1,000 samples of size 10,000 were drawn. A Poisson regression model was used to assess the exposure effect by estimating the risk ratio of outcome in relation to exposure (denoted by RR_p). For each scenario, the median of estimated risk ratios of the 1,000 samples were calculated.

Varying the parameter values

To investigate the ability of the Poisson model to obtain unbiased results in different settings, three analyses were performed.

First, to evaluate the validity of estimates according to the trend of the outcome hazard, simulations were carried out by varying the Weibull distribution parameters from scenario A to scenarios B and C as follows:

- from A to B: $\lambda = 0.75$ and $\nu \in (0.1, 1)$,
- from A to C: $\lambda = 0.1$ and $\nu \in (1, 3)$.

In this analysis, the exposure effect was set to $RR_T = 0.75$.

Second, to verify how the exposure effect affects the estimates of the Poisson model, the exposure effect (RR_T) was made to vary from 0.5 to 2.

Finally, to assess the impact of exposure time and prevalence on the results, we changed the way to generate exposure status. To explore the influence of exposure prevalence, we set it to 15%, 25%, and 40%. With this aim, exposure status was simulated for each patient from a Binomial distribution with the abovementioned probabilities. In addition, to investigate the impact of exposure time, the mean time to exposure was made to vary from 0 to 5 time units. Exposure times were simulated from a Gamma distribution with scale parameter equal to 0.1 and shape parameter from 0 to 50. In this analysis, the exposure effect was set to $RR_T=0.75$.

In all analyses, we assumed no confounding between exposure and outcome.

Statistical analyses were performed within the R software environment. The base code used for the present study is reported in the [Supplementary Material 1](#).

Real-world data

To investigate a real-world scenario in pregnancy, the healthcare utilization databases of the Lombardy Region (Italy) were analysed to identify all deliveries between 2007 and 2017. Antibiotics dispensed during the third trimester of pregnancy as well as neonatal outcomes (low birth weight and small for gestational age) were assessed. Women were defined as exposed to antibiotics use after the date of the first drug dispensing. More details on these data and on the criteria for selecting the study cohort are available in previous studies [17, 18]. The Poisson and the Cox models were fitted to estimate the exposure-outcomes associations.

Results

Main scenarios

The survival curves estimated by means of the Kaplan-Meier method of the three scenarios are reported in Fig. 1. In scenario A, the outcome risk is constant;

therefore, the proportion of patients who experienced the event is steady over time. Scenario B, in which the outcome risk decreases over time, is characterized by a higher proportion of patients who experienced the outcome at the beginning of follow-up. Finally, in scenario C, because the outcome risk increases over time, the number of patients who experienced the outcome quickly rises at the end of follow-up.

Varying the baseline risk over time

Figure 2 shows the risk ratio estimated by the Poisson model (RR_p) by varying the shape parameter of the Weibull distribution (i.e. by moving from scenario A to one of the other scenarios). Small changes in the shape parameter strongly affected the exposure-outcome association estimate, both towards scenarios B and C. For example, RR_p drops to 0.51 when $v=0.7$ and 0.22 when $v=0.3$ (Fig. 2, left panel). Conversely, RR_p increases to 1.08 when $v=1.6$ and 1.61 when $v=2.6$ (Fig. 2, right panel).

Varying the exposure effect

The influence of the RR_T on the RR_p is reported in Fig. 3. In scenario A, the exposure-outcome association estimate from the Poisson model is always equal to the true exposure effect (Fig. 3, left panel). Conversely, the RR_p is always lower and greater than the RR_T in scenarios B and C, respectively, and the extent of the difference between the estimate and true effect is quite constant for each value of RR_T on the logarithmic scale (Fig. 3, central and right panel).

Varying the prevalence of and time to exposure

Figure 4 shows the impact of the exposure time and prevalence. The difference between RR_T and RR_p is greatest when the mean exposure time and prevalence are high. For example, in scenario B, RR_p is 0.27 (exposure

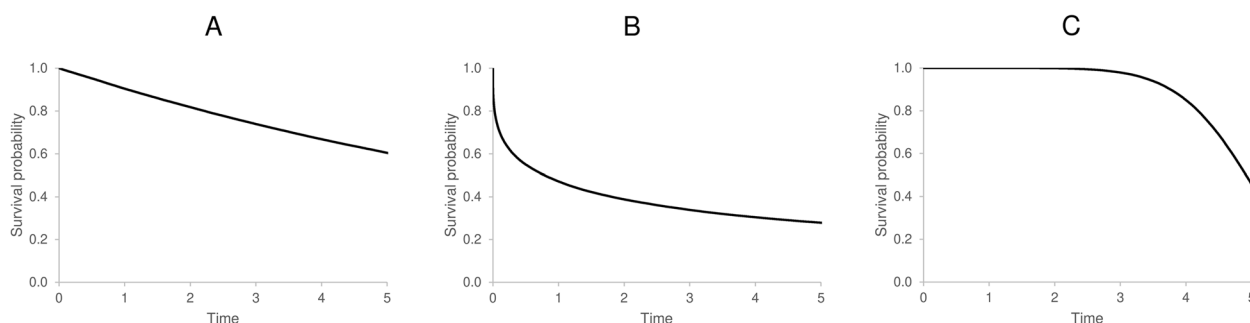


Fig. 1 Kaplan–Meier curves of survival according to the three main scenarios Scenario A, in which the outcome hazard is constant over time, was obtained by assuming that survival times followed a Weibull distribution with $\lambda=0.1$ and $v=1$. Scenario B, in which the outcome hazard decreases over time, was obtained by assuming that survival times followed a Weibull distribution with $\lambda=0.75$ and $v=0.33$. Scenario C, in which the outcome hazard increases over time, was obtained by assuming that survival times followed a Weibull distribution with $\lambda=1e-05$ and $v=7$

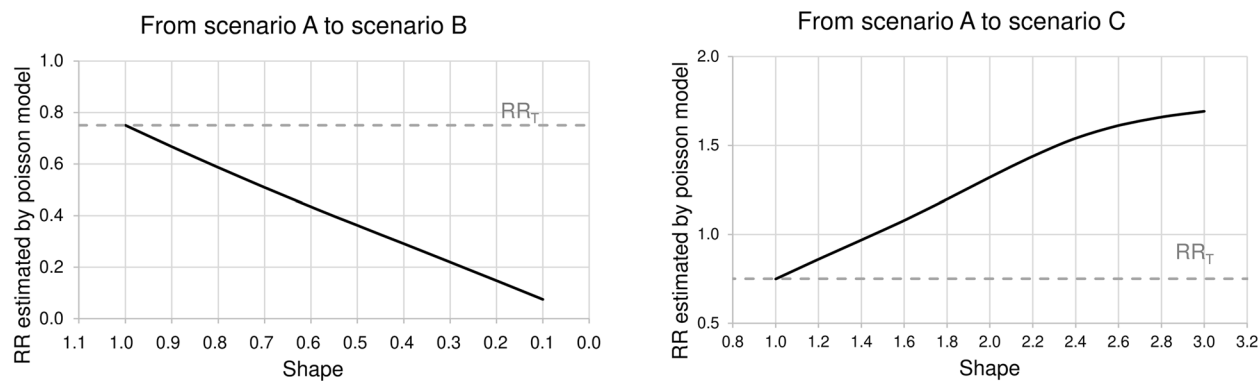


Fig. 2 Risk ratios estimated by Poisson model (RR_p) by varying the shape parameter of the Weibull distribution for generating survival times, that is by moving from scenario A to scenario B (left panel) and from scenario A to scenario C (right panel) The left panel was obtained by assuming that survival times followed a Weibull distribution with $\lambda=0.75$ and $u \in (0.1,1)$. The right panel was obtained by assuming that survival times followed a Weibull distribution with $\lambda=0.1$ and $u \in (1,3)$. The true exposure effect (RR_T) was set to 0.75

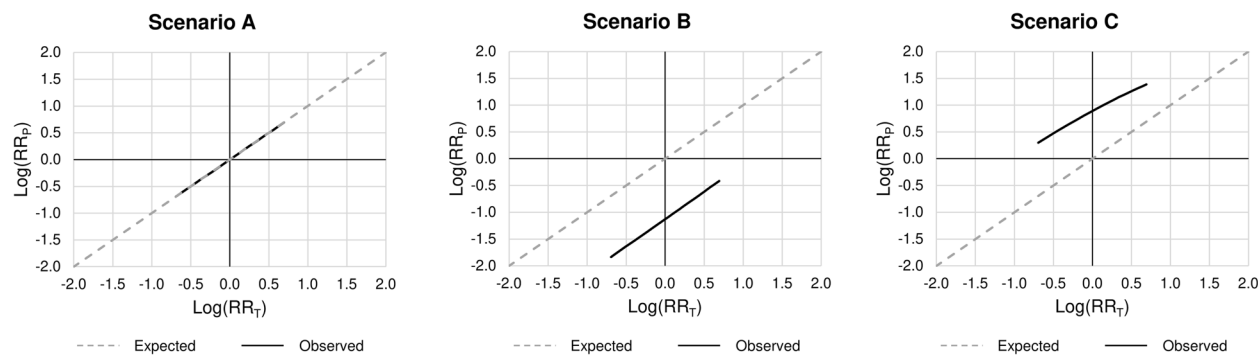


Fig. 3 Risk ratios estimated by Poisson model (RR_p) by varying the true exposure effect (RR_T) according to the three main scenarios

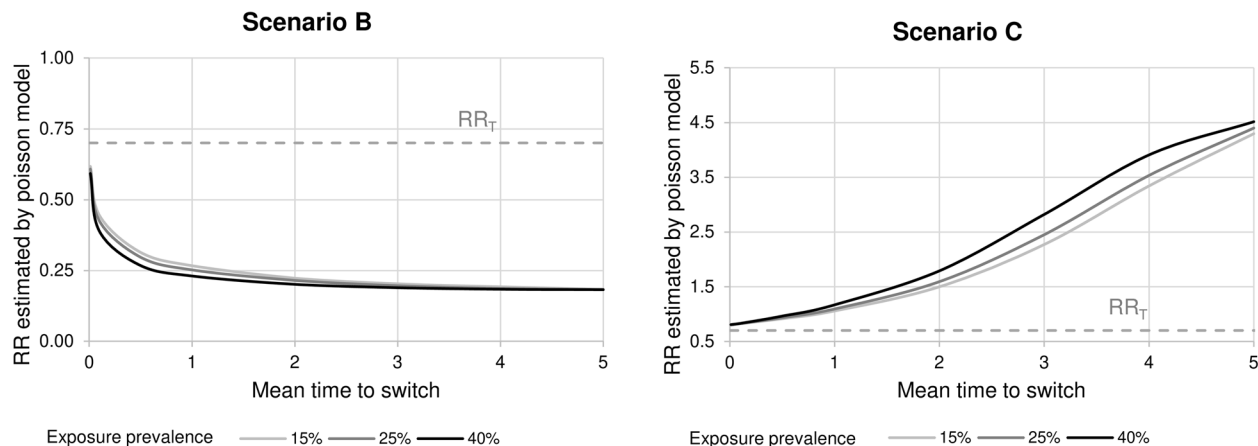


Fig. 4 Risk ratios estimated by Poisson model (RR_p) by varying the time to and prevalence of exposure Exposure status was simulated for each patient from a Binomial distribution with the following probabilities: 0.15, 0.25, and 0.40. Exposure times were then simulated from a Gamma distribution with scale parameter equal to 0.1 and shape parameter from 0 to 50. The true exposure effect (RR_T) was set to 0.75

prevalence = 15%) and 0.23 (40%) when the mean of time to exposure is 1 (Fig. 4, left panel), whereas, in scenario C, RR_p is 2.27 (exposure prevalence = 15%) and 2.82 (40%) when the mean of time to exposure is 3 (Fig. 4, right panel).

Real-world data

The survival curves of the neonatal outcomes are reported in Supplementary Figure S1 (Supplementary Material 2). These outcomes occurred at the end of follow-up, as observed in the scenario C. Supplementary Table S1 (Supplementary Material 2) shows the association estimates between antibiotics use and neonatal outcomes according to the Poisson and Cox models. According to the Poisson model, antibiotics use was associated with a significantly greater risk of neonatal outcomes (low birth weight: +57%; small for gestational age: +73%). There was no association between antibiotics use and small for gestational age according to the Cox model, while a slightly increased risk was observed for low birth weight (+11%).

Discussion

This simulation study shows the hazard of fitting the Poisson model to deal with immortal time bias in settings where the outcome risk varies over time and without taking into account this trend. Five main findings were provided. First, the estimate of the exposure-outcome association is already biased after minor changes in the trend of the outcome risk (as denoted by the shape parameter of the Weibull distribution). Second, the bias introduced using the Poisson model is not marginal since the exposure effect may be amplified, reduced, masked, or even reversed. Third, the direction of the bias is predictable. Indeed, the RR_p is always lower and greater than the RR_T when the event risk decreases or increases over time, respectively. Fourth, this was the case irrespective of the true exposure effect. Finally, the bias magnitude is positively associated with the prevalence of and time to exposure.

According to a meta-analysis of randomised controlled trials [19], antibiotics use is not associated with the risk of low birth weight and small for gestational age. Our real-world study in pregnancy shows that the estimates from the Poisson model suggested a non-marginal increased risk of neonatal outcomes among drug users (>50%). Conversely, the Cox model showed no association between drug use and small for gestational age, whereas a significantly slight increased risk for low birth weight was observed, probably due to residual confounding [17]. Because the trend in the outcomes risk followed that of scenario C in our simulations, the overestimation

of the exposure-outcome estimate by the Poisson model was expected.

In several settings, the outcome risk might vary over time. For example, the risk of several adverse events (including death and hospital admission) is higher just after a cardiovascular event [20], a fracture [21], and a transplant [22]. Otherwise, the risk of some maternal outcomes is higher at the end of the follow-up in pregnancy studies [23]. In addition, studies investigating lifetime survival are also characterized by an increased outcome risk over time [24]. In all these circumstances, the Poisson model wrongly estimates the true causal relationship between exposure and outcome. To obtain unbiased estimated, the model should adjust for the trend in outcome risk by identifying intervals of follow-up time in which the event rate is constant; however, the choice of the number of intervals as well as the position of the endpoints of each interval could be challenging [25]. Alternatively, other models, including the Cox model in which the outcome risk is left unspecified [18], should be considered.

Some limitations of the present study should be declared. First, the simulations were carried out by selecting one distribution for the survival times (i.e. the Weibull distribution) and changing the parameters in a small range of values (arbitrarily chosen to obtain three scenarios and to show the impact on the exposure-outcome estimate). Therefore, our simulations did not account for all possible scenarios. However, the study aimed to point out the risk of using the Poisson model in settings of time-varying hazards rather than to quantify the bias in several situations. Second, data were simulated assuming no confounding between exposure and outcome, and the impact of adjusting for covariates was not explored. Third, we also assumed that the exposure effect was fixed over time. Fourth, we investigated only one type of dichotomous time-varying exposure (allowing only one switch from unexposed to exposed), which does not cover different exposure patterns occurring in clinical practice. Finally, more complex real-world scenarios, such as competing risks, were not explored in our study. All these topics should be investigated in future studies.

In conclusion, the Poisson model provides biased estimates when outcome risk varies over time. In settings with a dichotomous time-varying exposure, the exposure-outcome association estimate is lower and greater than the true risk ratio when the outcome risk decreases or increases over time, respectively. Therefore, a careful assessment of intervals of follow-up time in which the outcome risk is constant is essential to fit the Poisson model.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12874-024-02396-y>.

Supplementary Material 1.

Supplementary Material 2.

Acknowledgements

Not applicable.

Authors' contributions

F.R. conceived of the idea for the paper and wrote the first draft. F.R. and G.M. conducted the analysis. All authors contributed to the interpretation of the findings. All authors critically revised the paper for intellectual content and approved the final version of the manuscript.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

Giovanni Corrao received research support from the European Community (EC), the Italian Medicines Agency (AIFA), Italian Ministry of Health, and the Italian Ministry of Education, University and Research (MIUR). He took part to a variety of projects that were funded by pharmaceutical companies (i.e., Novartis, GSK, Roche, AMGEN, BMS, and Servier). He also received honoraria from Roche as a member of its Advisory Board. Other authors have no disclosures.

Received: 18 December 2023 Accepted: 29 October 2024

Published online: 09 November 2024

References

1. Suissa S. Immortal time bias in pharmaco-epidemiology. *Am J Epidemiol*. 2008;167:492–9.
2. Lévesque LE, Hanley JA, Kezouh A, Suissa S. Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes. *BMJ*. 2010;340:b5087.
3. Messmer BJ, Nora JJ, Leachman RD, Cooley DA. Survival-times after cardiac allografts. *Lancet*. 1969;1:954–6.
4. Wang YB, Tan LM, Luo L, Yan S, Huang Q, Wang Y, Deng T, Shi Y, Deng Y, Jin YH. Immortal time bias exaggerates the effect of metformin on the risk of gastric cancer: a meta-analysis. *Pharmacol Res*. 2021;165: 105425.
5. Weberpals J, Jansen L, Carr PR, Hoffmeister M, Brenner H. Beta blockers and cancer prognosis - the role of immortal time bias: a systematic review and meta-analysis. *Cancer Treat Rev*. 2016;47:1–11.
6. Suissa S, Suissa K. Antifibratics and reduced mortality in idiopathic pulmonary fibrosis: immortal time bias. *Am J Respir Crit Care Med*. 2023;207:105–9.
7. Bakshi A, Suissa S. Effectiveness of aspirin in COPD: biases in the observational studies. *COPD*. 2021;18:449–55.
8. Zhou Z, Rahme E, Abrahamowicz M, Pilote L. Survival bias associated with time-to-treatment initiation in drug effectiveness evaluation: a comparison of methods. *Am J Epidemiol*. 2005;162:1016–23.
9. Suissa S. Reduced mortality with sodium-glucose cotransporter-2 inhibitors in observational studies: avoiding immortal time bias. *Circulation*. 2018;137:1432–4.
10. Komen J, Pottg rd A, Hjemdahl P, Mantel-Teeuwisse AK, Wettermark B, Hellfritsch M, Hallas J, Herings R, Smits L, Forslund T, Klungel O. Non-vitamin K antagonist oral anticoagulants, proton pump inhibitors and gastrointestinal bleeds. *Heart*. 2022;108:613–8.
11. Gronich N, Devereux SN, Lavi I, Persidis AS, Abernethy DR, Rennett G. Hypothyroidism is a risk factor for new-onset diabetes: a cohort study. *Diabetes Care*. 2015;38:1657–64.
12. Walkey AJ, Wiener RS, Ghobrial JM, Curtis LH, Benjamin EJ. Incident stroke and mortality associated with new-onset atrial fibrillation in patients hospitalized with severe sepsis. *JAMA*. 2011;306:2248–54.
13. Rossides M, Kullberg S, Di Giuseppe D, Eklund A, Grunewald J, Askling J, Arkema EV. Infection risk in sarcoidosis patients treated with methotrexate compared to azathioprine: a retrospective 'target trial' emulated with Swedish real-world data. *Respirology*. 2021;26:452–60.
14. Bastiaannet E, Sampieri K, Dekkers OM, de Craen AJ, van Herk-Sukel MP, Lemmens V, van den Broek CB, Coebergh JW, Herings RM, van de Velde CJ, Fodde R, Liefers GJ. Use of aspirin postdiagnosis improves survival for colon cancer patients. *Br J Cancer*. 2012;106:1564–70.
15. Vonesh EF, Schaubel DE, Hao W, Collins AJ. Statistical methods for comparing mortality among ESRD patients: examples of regional/inter-national variations. *Kidney Int*. 2000;57:S19–27.
16. Bours MJL. A nontechnical explanation of the counterfactual definition of confounding. *J Clin Epidemiol*. 2020;121:91–100.
17. Cantarutti A, Rea F, Franchi M, Beccalli B, Locatelli A, Corrao G. Use of antibiotic treatment in pregnancy and the risk of several neonatal outcomes: a population-based study. *Int J Environ Res Public Health*. 2021;18: 12621.
18. Corrao G, Rea F, Franchi M, Beccalli B, Locatelli A, Cantarutti A. Warning of immortal time bias when studying drug safety in pregnancy: application to late use of antibiotics and preterm delivery. *Int J Environ Res Public Health*. 2020;17: 6465.
19. Thinkhamrop J, Hofmeyr GJ, Adetoro O, Lumbiganon P, Ota E. Antibiotic prophylaxis during the second and third trimester to reduce adverse pregnancy outcomes and morbidity. *Cochrane Database Syst Rev*. 2015;2015:CD002250.
20. Rea F, Ronco R, Pedretti RFE, Merlino L, Corrao G. Better adherence with out-of-hospital healthcare improved long-term prognosis of acute coronary syndromes: evidence from an Italian real-world investigation. *Int J Cardiol*. 2020;318:14–20.
21. HEALTH Investigators. Total hip arthroplasty or hemiarthroplasty for hip fracture. *N Engl J Med*. 2019;381:2199–208.
22. Ramu B, Masotti M, Tedford RJ, Cogswell RJ. Heart transplantation in adriamycin-associated cardiomyopathy in the contemporary era of advanced heart failure therapies. *JACC Cardio Oncol*. 2021;15:294–301.
23. Lupattelli A, Corrao G, Gatti C, Rea F, Trinh NTH, Cantarutti A. Antidepressant continuation and adherence in pregnancy, and risk of antenatal hospitalization for unipolar major depressive and/or anxiety disorders. *J Affect Disord*. 2023;339:502–10.
24. Sakata R, McGale P, Grant EJ, Ozasa K, Peto R, Darby SC. Impact of smoking on mortality and life expectancy in Japanese smokers: a prospective cohort study. *BMJ*. 2012;345:e7093.
25. Demarqui FN, Loschi RH, Colosimo EA. Estimating the grid of time-points for the piecewise exponential model. *Lifetime Data Anal*. 2008;14:333–56.

Publisher's note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.