The case time series design – eAppendix 3
A simulation study

This simulation study evaluates the inferential performance of regression models for the *case time series* design under various data-generating scenarios, through the assessment of bias, coverage of the confidence intervals, and root mean square error (RMSE) of the estimators. The study aims, first, at testing the ability of the model in recovering the true exposure-response association under increasingly complex data settings, and second, at evaluating the four key assumptions underpinning the case time series design.

All the simulated scenarios use a common setting with 500 subjects followed up for one year between 01/01/2019 and 31/12/2019. For each scenario, $m = 50{,}000$ datasets are simulated, each including (initially) $500 \cdot 365 = 182{,}500$ observations. The inference focuses on a risk summary β, whose definition is scenario-dependent. Specifically, all the simulated cases assume a risk period lasting 10 days following the exposure, which, using a time series terminology, corresponds to a *lag period* defined over days 0-10. For most scenarios, the risk summary β represents the constant effect in each day within the risk (lag) period. In contrast, Scenario 10 illustrates more complex lag structures where the effect varies within the risk period, and here β_c quantifies the net effect cumulated across lag 0-10. The performance is assessed in terms of relative bias (%), coverage, and relative RMSE (%), defined as:

$$\text{Bias} = \frac{\left|\sum_{i=1}^{m}\left(\hat{\beta}_i - \beta\right)/m\right|}{\beta_c}$$

$$\text{Coverage} = \sum_{i=1}^{m} I\left(\left|\hat{\beta}_i - \beta\right| \leq \Phi^{-1}(1-\alpha/2) \cdot \sqrt{V\left(\hat{\beta}_i\right)}\right)/m$$

$$\text{RMSE} = \frac{\sqrt{\sum_{i=1}^{m}\left(\hat{\beta}_i - \beta\right)^2/m}}{\beta}$$

where $\hat{\beta}_i$ is the estimate at each of the $i = 1, \ldots, m$ iterations, I is an indicator function, and $\Phi^{-1}(1-\alpha)$ is the quantile function of the cumulative normal distribution related to probability $1-\alpha$, with $\alpha = 0.05$.

Each scenario is described in detail in the sections below, with additional results that complement the figures reported in Table 1 of the manuscript. The R code to fully reproduce the simulations and results in each scenario is provided in the online supplemental material, with an updated version available at the personal website (http://www.ag-myresearch.com/) and GitHub webpage (https://github.com/gasparrini/) of the author.

Part I: assessment of modelling performance

The first part of the simulation study (Scenarios 1-10) applies the case time series methodology in increasingly complex data-generating settings, simulated under the four core assumptions. The expectation is that the case time series models will produce valid estimates of risk associations in all the cases. The study covers scenarios with various definitions of the outcome, exposure, underlying baseline risks, temporal associations, and both time-invariant and time-varying confounding. Specifically:

- The outcome is represented by different quantities, such as event counts, binary indicators, or continuous measures.
- The exposure, similarly, is represented either by binary indicators of episodes or by continuous measures.
- The time-varying baseline risk is optionally included, and in this case, simulated either as shared (common) trend or alternatively as subject-specific deviations from an average trend.

- Time-invariant and time-varying confounders are optionally included, and in this case, simulated as risk factors strongly correlated with the exposure.
- The temporal association is represented either as a simple constant risk period following an exposure or by more complex lag structures.

The scenarios, summarised in Table S1 below, depict combinations of the features above, from basic data setting to situations involving more complex definitions.

Table S1. Description of the simulation scenarios with combinations of the design features.

Scenario	Outcome	Exposure	Trend	Confounder	Lag structure
Scenario 1: Basic	Count	Episode	None	None	Simple
Scenario 2: Rare outcome/exposure	Count (rare)	Episode (rare)	None	None	Simple
Scenario 3: Continuous exposure	Count	Continuous	None	None	Simple
Scenario 4: Binary outcome	Binary indicator	Continuous	None	None	Simple
Scenario 5: Continuous outcome	Continuous	Continuous	None	None	Simple
Scenario 6: Common trend	Count	Continuous	Common	None	Simple
Scenario 7: Subject-specific trend	Count	Continuous	Subject-specific	None	Simple
Scenario 8: Unobserved baseline confounder	Count	Continuous	Subject-specific	Baseline	Simple
Scenario 9: Time-varying confounder	Count	Continuous	Subject-specific	Time-varying	Simple
Scenario 10: Complex lag structure	Count	Continuous	Subject-specific	Both	Complex

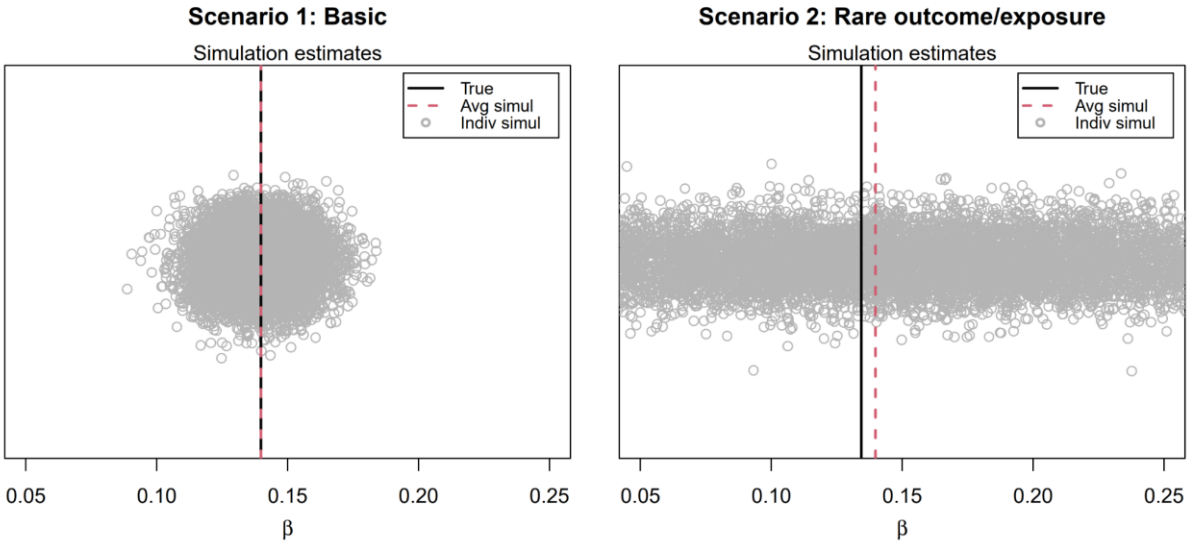
Scenario 1: Basic

In this first scenario, the exposure x is defined as a binary indicator of multiple episodes, randomly occurring in 10% of the 365 days of follow-up for each subject. Each exposure episode is associated with an increase in risk for an outcome event, which is assumed constant over the 0-10 risk period. The risk summary is represented by the relative risk (RR) of experiencing an outcome event in each of the 11 days within the risk period, with $\mathrm{RR} = \exp(\beta) = 1.15$. The outcome is represented as counts of repeated events y randomly sampled from a multinomial distribution, with the number of occurrences per subject varying randomly in the range 5-20. This feature simulates subject-specific constant baseline risks varying across the 500 subjects. No trend, either common or subject-specific, and time-varying confounders are included.

The case time series analysis is performed using a fixed-effects Poisson model, which corresponds to a conditional Poisson regression. The model includes a single term, defined by the cumulated exposure x_c, representing the sum of the exposure episodes in the same day and previous 10 days (lag 0-10). Subject-specific intercept terms ξ_i are included to model differential baseline risks. It is worth noting that, in these settings, the case time series design resembles a standard self-controlled case series (SCCS), although with the follow-up split into equally-spaced time intervals. However, the case time series data setting allows modelling multiple exposure episodes with potentially overlapping risk periods, through the computation of cumulative effects.

Results reported in the manuscript indicate no bias and perfect coverage for the estimate of the risk summary β. Figure S1 (left panel) confirms these findings, displaying the distribution of the 50,000 estimates $\hat{\beta}_i$ together with their average and the true effect β.

Figure S1. Estimates of $\log(\mathrm{RR}) = \beta$ from the case time series models applied in Scenario 1 (left panel) and Scenario 2 (right panel). The graphs report the true simulated association (black line), the average estimate of the 50,000 iterations (red line), and the estimates of the individual iterations (grey dots). A small bias in noticeable in Scenario 2. The individual estimates are scattered across the *y*-axis to show the distributions. The range of the x-axis in the right panel only includes a subset of the individual estimates.



Scenario 2: Rare outcome/exposure

Scenario 2 repeats the simulations from the previous scenario but in the case of rare outcome events and exposure episodes. Specifically, the same settings are used, but simulating only 1 to 5 exposure episodes and 1 to 3 outcome events per subject. The same fixed-effects Poisson regression model of Scenario 1 is used.

Results are reported in Figure S1 (right panel), with the distribution of the 50,000 estimates $\hat{\beta}_i$ within the same range as the previous scenarios. Note that the estimates cover a wider range when compared to Scenario 1, indicating the much lower precision due to the rare occurrence of exposure episodes and outcome events. More importantly, the plot confirms the small bias, with an underestimation of 4.5% (see Table 1 in the manuscript), which is consistent with the asymptotic bias of maximum likelihood estimators in this extreme scenario. This phenomenon was previously described in the SCCS literature and defined algebraically.[1] Specifically, the bias originates from the extreme unbalance between the expected events in the risk and control periods, and quickly reduces to negligible values when increasing the number of outcome events and/or the exposure episodes, as in Scenario 1. However, the bias is small even in this extreme scenario, and the case time series model maintains a nominal coverage (see Table 1 in the manuscript).

Scenario 3: Continuous exposure

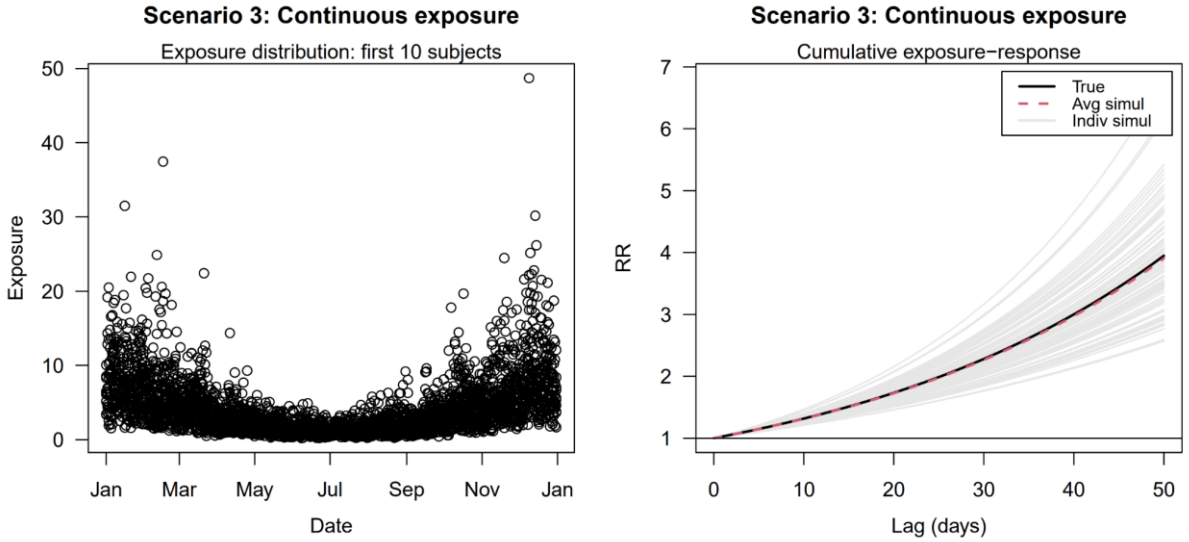
This scenario replicates Scenario 1, although using a continuous exposure instead of a binary indicator for exposure episodes. Specifically, a subject-specific exposure is simulated through the following function:

$$e(t) = \exp\big(\cos(2\pi/365 \cdot t) + 1 + v_{\rho\sigma}(t)\big)$$

where t is time defined as the day of the year (from 1 to 365), and $v_{\rho\sigma}$ is an auto-correlated random error simulated from a normal distribution with mean 0, standard deviation $\sigma = 0.5$, and correlation $\rho = 0.5$ (see also the related R script). This function defines an exposure variable x with strong seasonal distribution, as displayed in Figure S2 (left panel) with data simulated for the first 10 subjects. The exposure is associated with an increase in risk for an outcome event, with a constant relative risk (RR) of $\exp(\beta) = 1.0025$ for a unit increase in x in each day within the 0-10 risk period. Again, 5-20 occurrences of the repeated outcome events are sampled for each subject. The same fixed-effects Poisson regression model is used to estimate the association, although this time using as the single term the continuous measure of x_c cumulated across the 0-10 lag period.

Table 1 in the main manuscript confirms that the case time series models keep their optimal inferential properties in the analysis of continuous exposures. The flexible parameterization of the temporal effect of the exposure in the case time series design allows the derivation of more complex effect summaries. For instance, $\mathrm{RR} = \exp(\beta \cdot 11 \cdot x)$ represents the effect cumulated across the 11 days of the 0-10 lag period, and it can be

interpreted as the increase in risk at the end of the risk period associated to a single exposure episode x. This summary is displayed graphically in Figure S2 (right panel), which illustrates the cumulative exposure-response association across the exposure range. The graph confirms the absence of bias in the case time series model.



Scenario 4: Binary outcome

This scenario replicates Scenario 3, but by simulating an outcome represented by a binary indicator instead than by an event count. This means that the outcome measures presence/absence and not the number of events in each time unit. In most situations, the difference is subtle, but it implies different modelling choices, as described below. The scenario simulates the same continuous exposure with a seasonal distribution as in the previous case, and the same risk summary is represented by $\beta = \log(1.0025)$. However in this case $\exp(\beta)$ represents an odds ratio (OR) of a positive outcome and not a RR. The outcome is simulated from a Bernoulli distribution with probability $p = \exp(\alpha_b + \beta x_c)/\big(1 + \exp(\alpha_b + \beta x_c)\big)$, where $\alpha_b = \log(p_b/(1 - p_b))$, p_b is a baseline probability of 0.1, and $\exp(\beta x_c)$ is the OR associated with the number of exposure episodes x_c cumulated within the lag period.

Differently from all the other scenarios, the data are fitted using a fixed-effects logistic regression, simply

Figure S2. Left panel: distribution of the continuous exposure along the year for the first 10 subjects, simulated in one of the 50,000 iteration of Scenario 3, and then Scenarios 4-9 and 13. Right panel: Overall cumulative association representing the cumulative risk across the 0-10 risk period simulated in Scenario 3, with the true RR linear in the log scale (black line), the average estimate (red line), and the estimates of the first 100 iterations (grey lines).

replacing the Poisson with a binomial family. Results are reported in Table 1 of the main manuscript, and they demonstrate the ability of the case time series model in providing correct point estimates and coverage when analysing associations with binary outcome indicators that follow a Bernoulli distribution. It is worth noting that, in these data settings characterised by outcomes different from event counts, neither the SCCS nor the case-crossover (CC) designs are applicable.

Scenario 5: Continuous outcome

Similarly to the previous scenario, this simulation exercise replicates the settings of Scenario 3, with the only change being the outcome definition, this time represented by a continuous quantity instead of event counts. Specifically, a unit increase in exposure x is associated with an increase of $\beta = 0.01$ in a continuous outcome y, constant within the risk period 0-10. The outcome series y is simulated as the sum of three components: a subject-specific baseline randomly sampled from a uniform distribution between 50 and 150, the increase

associated with the exposure, and a random error simulated from a normal distribution with mean 0 and standard deviation of 20. The distribution of the outcome simulated for five subjects is displayed in Figure S3 (left panel).

Similarly to Scenario 4 and differently from the other previous scenarios, the case time series model is performed using a fixed-effects regression model that assumes a different distribution, specifically using a Gaussian family. This allows modelling additive relationships under the assumption of normally distributed errors. As in the case of binary outcomes in Scenario 4, it is worth noting that neither the SCCS nor the CC designs are applicable here. Results are reported in Figure S3 (right panel), which similarly to the same panel in Figure S2 displays the cumulative exposure-response association represented by $\beta \cdot 11 \cdot x$ across the exposure range. As above, the graph confirms the absence of bias in the case time series model for modelling relationships between a continuous exposure and a continuous outcome.

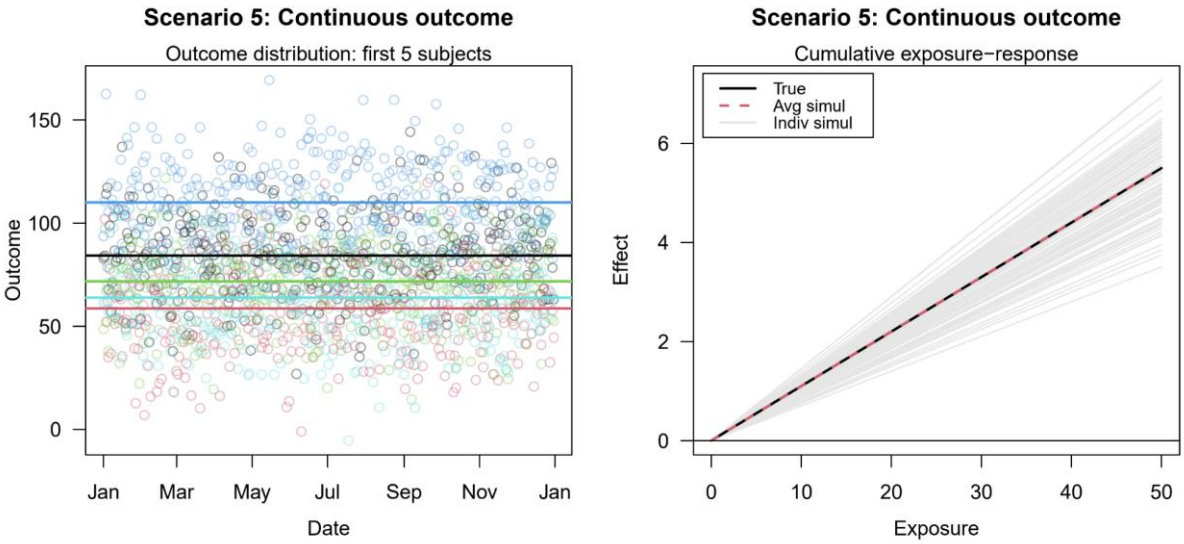


Figure S3. Left panel: distribution of the continuous outcome along the year for the first 5 subjects (in different colours), simulated in one of the 50,000 iteration of Scenario 5, together with the averages indicating differential baseline risks. Right panel: cumulative association representing the net effect across the 0-10 risk period simulated in Scenario 5, with the true linear relationship (black line), the average estimate (red line), and the estimates of the first 100 iterations (grey lines).

Scenario 6: Common trend

All the previous scenarios assume that the variation in risk within each individual is only due to the time-varying exposure and that the underlying baseline risk is in fact constant. This scenario depicts a more complex setting, with a common trend across the year that is shared by the 500 subjects. Given the strong seasonal distribution of the exposure, this trend needs to be adjusted for in order to obtain valid estimates of the association. The seasonal trend is simulated with the following function:

$$s(t) = \exp(\gamma_1 \sin(p_1 \pi/365 \cdot t) + \gamma_1 \cos(p_2 \pi/365 \cdot t))$$

where γ_1-γ_2 and p_1-p_2 are parameters of the sine and cosine terms, respectively, defining their amplitude and frequency. At each iteration, each parameter in the two pairs are sampled from a uniform distribution in the ranges -0.2 to 0.2, and -4 to 4, respectively, thus producing different common seasonal risk trends. Figure S4 (left panel) illustrates a random sample of seven iterations, showing shared trends with different peak/trough times, and either flat or strong.

The scenario replicates the repeated outcome events, continuous exposure, and constant risk period following exposure over lag 0-10 of Scenario 3. The same fixed-effects Poisson regression model is applied, but this time including a cyclic B-spline of the day of the year with 6 degrees of freedom (df) and a linear term for time to adjust for the seasonal and long-term trends. Results in the main manuscript (Table 1) indicate that the case

time series model is able to retrieve the true net risk with no bias and nominal confidence intervals, although with a higher root mean square error (RMSE), indicating a loss of precision due to the adjustment for the underlying trend.

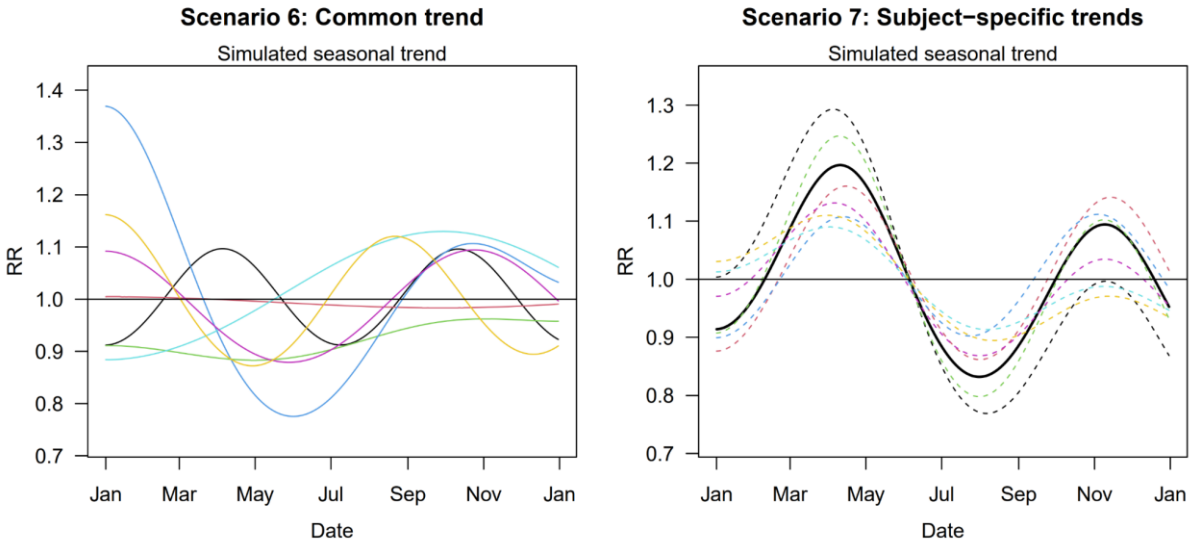


Figure S4. Left panel: common (shared) trend simulated in seven iterations (in different colours) in Scenarios 6-9, showing various shapes and strengths. Right panel: deviations (coloured dashed lines) from the common trend (continuous black line) for seven random subjects simulated in a single iteration in Scenarios 7-10, showing subject-specific trends.

Scenario 7: Subject-specific trend

This scenario makes the simulation setting even more complex by relaxing the assumptions of a common seasonal trend. An average baseline risk is first simulated as in Scenario 6 by randomly sampling the γ_1-γ_2 and p_1-p_2 parameters at each iteration. However, each parameter is then perturbed in each subject with a random amount independently sampled from a normal distribution with mean 0 and standard deviation 0.05, thus allowing subject-specific deviations. An example of a single iteration is depicted in Figure S4 (right panel), displaying the average and subject-specific trends.

The same fixed-effects Poisson regression of Scenario 6 is applied, but this time adding a stratification of the follow-up period, defining intercepts $\xi_{i(k)}$ at subject/month instead of subject-only level. These additional terms, not directly estimated but treated as nuisance parameters, allow subject-specific monthly deviations on top of the average trend captured by the cyclic B-splines. Again, the simulation results demonstrate that the case time series model can produce unbiased point estimates and confidence intervals. There is a further increase in RMSE due to the additional complexity of adjusting for the trends.

Scenario 8: Unobserved baseline confounder

This scenario introduces further complexities in the simulation setting by adding a risk factor z_f that varies across subjects but it is constant (fixed) in time. This is simulated independently for each subject by sampling a value from a uniform distribution between 0 and 100. A correlation with the continuous exposure x defined in Scenario 3 is then imposed by multiplying the latter by $z_f/50$, thus doubling the original exposure for a subject with $z_f = 100$. This creates a correlation between x and z_f, with a Pearson coefficient r of approximately 0.45. The risk factor z_f is assumed to be associated with a varying baseline risk, by setting the repeated events per subject as the rounded integer of $z_f/5 + 1$ instead of a random number between 5 and 20 as in the previous scenarios.

The case time series analysis is performed first using the same fixed-effects Poisson regression model of Scenario 7, without including the risk factor z_f. The results indicate no bias, thus demonstrating how the case time series, similarly to other self-matched methods, can control by design for unobserved baseline confounders that do not vary within the follow-up period.

Scenario 9: Time-varying confounder

This scenario follows the previous example by simulating an additional risk factor, which however is defined as a term z_v that varies both between and between subjects. This time-varying variable is simulated by perturbing the continuous exposure x defined in Scenario 3 with a random amount sampled from a normal distribution with mean 0 and standard deviation 3. This creates a strong correlation between the two terms x and z_v, with a Pearson coefficient r of approximately 0.80. The risk factor z_v is assumed to have an independent effect on the outcome, simulated as a same-day RR of $\exp(0.01) \cong 1.01$ for a unit increase.

The case time series analysis is performed first using the same fixed-effects Poisson regression model of Scenarios 7 and 8, although in this case adding z_v as a simple linear term with no lag. The results suggest no evidence bias, thus demonstrating how the case time series design provides a way to effectively control for confounding from measurable time-varying factors if their risk associations are appropriately specified in the regression model.

Scenario 10: Complex lag structure

The previous scenarios assume a simple temporal relationship with a constant risk across the pre-defined period of 10 days. This scenario uses a combination of the settings of Scenarios 7-9, but it describes a more complex temporal dependency by assigning different weights to each lag ℓ in the interval 0-10 through the function:

$$w(\ell) = \phi_{2,2}(\ell)$$

where $\phi_{m,s}$ is a normal density function with mean m and standard deviation s. This choice defines a lag structure with an initial increase in risk, a peak after 2 days, and then an attenuation until the effect disappears after about 8 days (see Figure S5). The weights are then re-calibrated to produce lag-specific effects β_ℓ, with $\sum \beta_\ell = \beta_c$ and $\mathrm{RR} = \exp(\beta_c)$. In order to produce comparable risk estimates as the previous scenarios with constant risk across lags, the cumulative risk is simulated as $\beta_c = \log(1.0025) \cdot 11$. This net risk summary is the focus of the inferential assessment using the measures or bias, coverage, and RMSE defined at the beginning of the document. In addition, in these most complex scenarios, both unobserved time-invariant and observed time-varying risk factors simulated following the same definition of Scenarios 8 and 9, respectively, plus the same subject-specific trends described in Scenario 7.

The case time series analysis is performed using a model similar to the fixed-effects Poisson regression of Scenario 9, but this time including a *distributed lag model* (DLM) to describe more flexibly the complex lag structure associated with the exposure.[2] This term is parameterized by a *cross-basis*, a bi-dimensional function expressed in the spaces of the exposure and lag. Specifically, the exposure-response is modelled using a simple linear function, while a natural cubic spline with three equally-spaced knots a lags 2.5, 5.0, and 7.5 is applied to model the lag-response association that describes the temporal structure.

Results reported in the main manuscript (Table 1) indicate unbiased point estimates and confidence intervals for the log cumulative risk β_c. Figure S5 confirms the findings across the lag-response space, showing that the case time series model is capable of retrieving complex lagged associations through the application of sophisticated time series techniques based on DLMs. It is worth noting that this complex temporal relationship is reliably estimated even in the presence of strong baseline and temporal confounding from time-invariant and time-varying risk factors, in addition to subject-specific trends, all of which are appropriately controlled for either by design or by including related terms in the regression model.

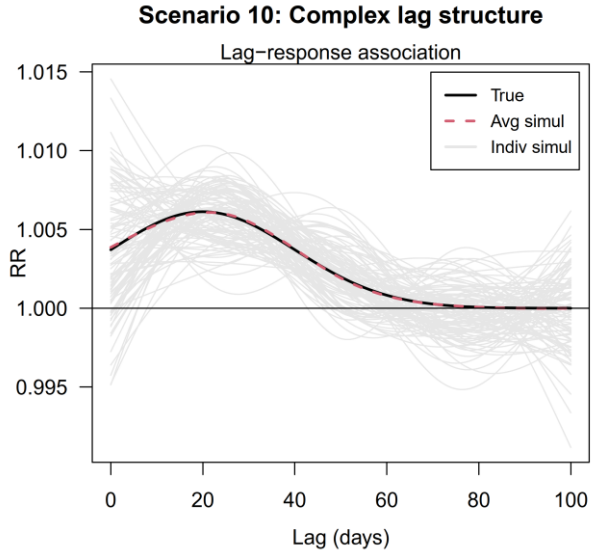


Figure S5. Complex lag structures simulated in Scenario 10. The graph shows the lag-response associations with the varying pattern of lag-specific RR, with the true simulated association (black line), the average estimate (red line), and the estimates of the first 100 iterations (grey lines). The estimates of the lag-response curve in this scenario is adjusted for additional time-invariant and time-varying confounder, in addition to underlying trends in risk.

Part II: assessment of underlying assumptions

In contrast to the previous nine scenarios, the second part of the simulation study (Scenarios 11-14) illustrates basic data settings, where however each of the four assumptions that underpin the case time series design is in turn violated (Table S2). It is expected that when data are simulated in scenarios where one of the assumptions does not hold, the inferential performance is affected, with the occurrence of biases in point estimates or wrong coverage of the confidence intervals.

Table S1. Description of simulation scenarios where each of the assumptions of the case time series design are violated.

Scenario	Outcome	Exposure	Trend	Lag structure	Confounder
Scenario 11: Outcome-dependent risk	Count	Episode	None	Simple	None
Scenario 12: Outcome-dependent follow-up	Count	Episode	None	Simple	None
Scenario 13: Outcome-dependent exposure	Count	Episode	None	Simple	None
Scenario 14: Variation in baseline risk	Count	Continuous	None	Simple	None

Scenario 11: Outcome-dependent risk

This is the first of four scenarios illustrating examples where one of the underlying assumptions of the case time series design does not hold. In particular, this scenario depicts a complex form of dependency within the series y, where the occurrence of an outcome event modifies the risk of future outcomes.[3] The example uses the same basic setting of Scenario 1, with the sampling of 5-20 *potential* outcome events per subject. However, each event carries a risk of 0.2 that future events are not occurring. This situation can arise, for instance, in the presence of a risk of death related to the outcome of interest, or because the subject changes status and his/her outcome cannot be recorded. An example is illustrated in Figure S6 (left panel), with 10 subjects for whom the risk of any future outcome can vanish after a given outcome event. Note that the subjects are still under follow-up, differently from the following scenario.

The same fixed-effects Poisson model is used to estimate the parameter β representing the risk associated with the exposure. As shown in Table 1 in the main manuscript, however, the estimates are affected by a noticeable negative bias. The mechanism can be explained by the fact that exposures episodes occurring after the change of status are not anymore associated with an increased risk. An extreme case of this situation is represented by the analysis of non-recurrent outcomes, which must be rare in the population of interest for avoiding the bias described here, as previously discussed in the literature of other self-matched designs.[4-6]

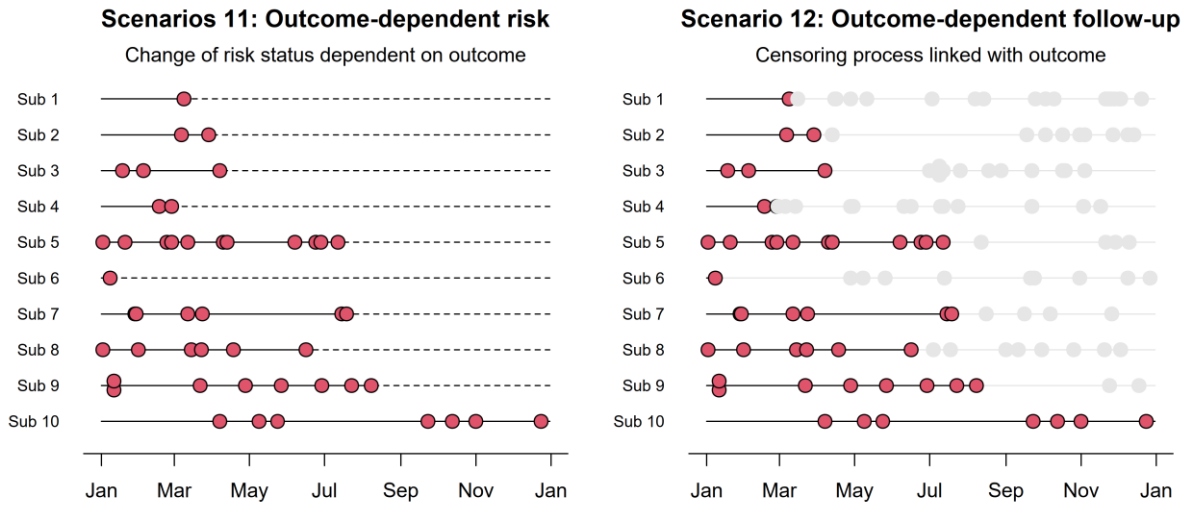


Figure S6. Graphical representation of data simulated in Scenarios 11 and 12, with the follow-up period (black lines) and outcome events (red circles) of 10 subjects. Left panel: an example of data with outcome-dependent risk simulated in Scenario 11, where each subject has a probability of 0.2 of switching to a no-risk status after each event. Right panel: the same example for Scenario 12, where the same process leads instead to censoring. Note that in the first example the follow-up continues (dashed lines) with no recorded outcome events, while in the second example the follow-up stops and the time (grey line) and potential outcomes (grey circles) do not occur.

Scenario 12: Outcome-dependent follow-up

The following assumption of the case time series design states that the follow-up period must be independent of the outcome. This assumption was previously described in the context of the self-controlled case series study.[7,8] In particular, for event-type outcomes, this means that the occurrence of an event must not modify the probability of censoring the follow-up. Similarly to the previous scenario, the same settings of Scenario 1 are used to generate the complete data for the 500 subjects. However, then an artificial outcome-dependent censoring mechanism is simulated, sampling the occurrence of a censoring event on the day after an outcome with a probability of 0.2. This means that subjects have a 20% risk of having their follow-up stopped after experiencing one outcome event. An example is shown in Figure S6 (right panel), with the follow-up periods of ten subjects.

Although no other modification is applied to the data, the estimate from the fixed-effects Poisson regression model is biased upward, as shown in Table 1 of the main manuscript. Compared to Scenario 11, the direction of the bias is reversed, as potential post-event times are not always included.

Scenario 13: Outcome-dependent exposure

The third assumption listed in the manuscript dictates that a given outcome must not modify the probability distribution of the exposure x in the following period. Similarly to the previous example, this assumption was previously described in the context of the self-controlled case series study.[7,9] This scenario drops this assumption by simulating an inverse temporal relationship between exposure and outcome. The simulation setting replicates again Scenario 1, with one modification. Specifically, in addition to the usual $\mathrm{RR} = \exp(\beta_\ell) = 1.15$ that defines the increase in risk in of the 0-10 lag day following the exposure, another relationship is defined over *lead times* 1:14, meaning the series of lags from -14 to -1. This inverse temporal relationship is defined as $\mathrm{RR} = 0.60$, thus generating data where the occurrence of an outcome event is associated with a decreased probability of an exposure episode in the following two weeks.

The data are fitted fixed-effects Poisson model with a single term x_c representing the exposure cumulated within the 0-10 lag period (corresponding to the same day and 10 days before the outcome). However, the presence of an independent but unaccounted inverse temporal relationship generates an imbalance in the temporal comparison defined within the self-matched data structure. This explains the noticeable bias in the estimates, with the underestimation reported in Table 1 of the main manuscript.

Scenario 14: Variation in baseline risk

The last scenario deals with the fourth assumption of the case time series design, which states that any variation in the baseline risk within the follow-up period (or within strata of it) must be fully explained by model covariates. This assumption is the same applied within the risk sets of case-crossover design.[5,6] There are various situations where this is not the case. This scenario simulates unobserved temporal changes in baseline risk, for example, due to holiday periods where a given outcome has fewer chances to be recorded. The simulation exercise uses the same settings of Scenario 3 but including a random period of one month within May-September where the subject is at lower risk, using an RR of 0.7.

The data are fitted with the same fixed-effects Poisson model. As expected, the results in Table 1 of the main manuscript indicate a bias, with the overestimation due to unaccounted temporal differences that affect the conditional exchangeability required by the case time series design. Similar biases can arise in the presence of potentially measurable but unaccounted risk factors, for example with a modification of Scenario 9 when the time-varying variable z_v is not included in the model.

References

1. Musonda P, Hocine MN, Whitaker HJ, Farrington CP. Self-controlled case series analyses: small-sample performance. *Computational Statistics & Data Analysis*. 2008;52(4):1942-1957.
2. Gasparrini A. Modeling exposure-lag-response associations with distributed lag non-linear models. *Statistics in Medicine*. 2014;33(5):881-899.
3. Farrington CP, Hocine MN. Within-individual dependence in self-controlled case series models for recurrent events. *Journal of the Royal Statistical Society: Series C (Applied Statistics)*. 2010;59(3):457-475.
4. Whitaker HJ, Steer CD, Farrington CP. Self-controlled case series studies: Just how rare does a rare non-recurrent outcome need to be? *Biometrical Journal*. 2018;60(6):1110-1120.
5. Janes H, Sheppard L, Lumley T. Case-crossover analyses of air pollution exposure data: referent selection strategies and their implications for bias. *Epidemiology*. 2005;16(6):717-726.

6. Lu Y, Zeger SL. On the equivalence of case-crossover and time series methods in environmental epidemiology. *Biostatistics*. 2007;8(2):337-344.
7. Whitaker HJ, Ghebremichael-Weldeselassie Y, Douglas IJ, Smeeth L, Farrington CP. Investigating the assumptions of the self-controlled case series method. *Statistics in Medicine*. 2018;37(4):643-658.
8. Farrington CP, Anaya-Izquierdo K, Whitaker HJ, Hocine MN, Douglas I, Smeeth L. Self-controlled case series analysis with event-dependent observation periods. *Journal of the American Statistical Association*. 2011;106(494):417-426.
9. Farrington CP, Whitaker HJ, Hocine MN. Case series analysis for censored, perturbed, or curtailed post-event exposures. *Biostatistics*. 2009;10(1):3-16.