Bias control in the analysis of case-control studies with incidence density sampling

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Abstract

Background: Previous simulation studies of the case-control study design using incidence density sampling, which required individual matching for time, showed biased estimates of association from conditional logistic regression (CLR) analysis; however, the reason for this is unknown. Separately, in the analysis of case-control studies using the exclusive sampling design, it has been shown that unconditional logistic regression (ULR) with adjustment for an individually matched binary factor can give unbiased estimates. The validity of this analytic approach in incidence density sampling needs evaluation.

Methods: In extensive simulations using incidence density sampling, we evaluated various analytic methods: CLR with and without a bias reduction method, ULR with adjustment for time in quintiles (and residual time within quintiles), and ULR with adjustment for matched sets *and* bias reduction. We re-analyzed a case-control study of *Haemophilus influenzae* type B vaccine using these methods.

Results: We found that the bias in the CLR analysis from previous studies was due to sparse data bias. It can be controlled by the bias reduction method for CLR, or by increasing the number of cases and/or controls. ULR with adjustment for time in quintiles usually gave results highly comparable to CLR, despite breaking the matches. Further adjustment for residual time trends was needed in the case of time-varying effects. ULR with adjustment for matched sets tended to perform poorly despite bias reduction.

Conclusion: Studies using incidence density sampling may be analyzed by either unconditional logistic regression with adjustment for time or conditional logistic regression, possibly with bias reduction.

Keywords: Bias reduction; Logistic regression; Incidence density sampling; Matched case-control study

Key messages:

- Case-control studies using incidence density sampling can usually be analyzed by unconditional logistic regression with adjustment for time intervals to give results highly comparable to conditional logistic regression, with added advantages.
- The bias in the conditional logistic regression analysis in some previous simulation studies of the case-control study design using incidence density sampling was due to sparse data bias, which can be controlled by a bias reduction method.
- The use of the bias reduction method cannot sufficiently control the bias when using unconditional logistic regression with adjustment for matched sets as indicator variables.

Introduction

There are three sampling designs for the implementation of case-control studies: the exclusive design (traditional design), the inclusive design, and the incidence density sampling design (1-3). The odds ratio (OR) estimates obtained from the use of different sampling designs have different interpretations (1-3). In other words, the same statistical "estimator" (method of estimation) can yield different "estimands" (target of estimation) depending on which sampling design is used (4). With the incidence density sampling design, the OR estimator estimates the incidence density ratio (IDR), also called the incidence rate ratio (IRR), for an exposed group compared to an unexposed group (2). The IDR is practically equivalent to the hazard ratio in a piecewise constant hazard model (5). Two defining characteristics of the incidence density sampling approach are individual matching for time and the possibility of a subject being sampled multiple times. In contrast, the exclusive and inclusive designs may or may not involve matching. Furthermore, the exclusive design samples a subject only once (either as a case or a control). The inclusive design samples cases and controls independently; a subject may be sampled once or twice (1-3).

In two articles that centred on the use of a weighted Cox model in case-control studies with incidence density sampling, it was shown that both the conditional logistic regression (CLR) model and the weighted Cox model over-estimated the degree of association between the exposure and the outcome (6,7). The reason for this bias was unknown. The simulations involved about 100 cases, each matched to one control (6,7). With a small sample size or a large number of parameters to estimate, the maximum (conditional) likelihood estimation method may suffer sparse data bias (8-10). This bias has recently been described as "a problem hiding in plain sight" (11). Data are said to be sparse if the total number of observations is small or if most strata

defined by categorical covariates have small number of observations, say five or fewer (12). An approximate formula that describes the bias is (13):

$$\boldsymbol{b} = E(\hat{\boldsymbol{\beta}} - \boldsymbol{\beta}) \approx p\boldsymbol{\beta}/N,$$

where $\boldsymbol{b}$, $\boldsymbol{\beta}$ and $\hat{\boldsymbol{\beta}}$ are the vectors of approximate bias, true regression coefficients, and estimator of the regression coefficients, respectively; p and N are the number of regression coefficients to be estimated and the total number of observations, respectively; $E()$ denotes expected value. That is, the size of sparse data bias in maximum likelihood estimation increases with increasing p-to-N ratio. Furthermore, since p and N must be positive, the bias and the regression coefficients have the same sign, indicating that the estimates are biased away from zero. Mathematical details on sparse data bias can be found in, e.g. (12) and (13).

Firth proposed a penalized likelihood approach for bias reduction in unconditional logistic regression (ULR-BR) (8). The penalty term $\frac{1}{2}\{\ln|I(\beta)|\}$, with $I(\beta)$ denoting the Fisher's information matrix, is added to the log-likelihood of the unconditional logistic regression model. This method was recently extended to conditional logistic regression (CLR-BR) (10).

On a separate issue, it is well-known that matching in case-control studies introduces selection bias (3,14). The conventional view is that frequency-matched and individually-matched case-control studies should be analyzed by unconditional logistic regression (ULR) and conditional logistic regression (CLR), respectively. Recently, this view has been challenged (14,15). In the context of an exclusive sampling design, in which each case was matched to a control according to a binary factor, it was demonstrated, using a hypothetical example, that ULR with adjustment for the binary factor gave an unbiased estimate of the odds ratio (15). Note that this is not the same as ULR with adjustment for matched sets as indicator variables, which is known to cause a serious bias (16). The use of ULR with covariate adjustment, if valid, is potentially more efficient because the CLR cannot include concordant sets or cases without

controls. However, it is not clear whether this approach is valid when the matching factor is time, as in the implementation of incidence density sampling.

Cox shows that grouping observations that followed a normal distribution according to the tertiles, quartiles, quintiles or sextiles retains about 79%, 86%, 90% or 92% of the information, respectively (17). The incremental gain in information retention achieved by an additional group diminishes as the number of groups increases. Some researchers suggest that a continuous variable on which cases and controls are individually matched can be grouped into broad intervals and adjusted for as indicator variables (18). Others caution that this might involve too much coarseness (14,19). Further adjustment for a linear residual term within each category may reduce the residual coarseness (14,19). In the present context, we consider the use of ULR with adjustment for time in quintiles (ULR-Q) or ULR with adjustment for time in quintiles and a linear residual term within each quintile (ULR-QL).

While ordinary ULR with adjustment for matched sets as indicator variables is known to introduce bias, whether the bias can be controlled by a bias reduction method using penalized likelihood has not been fully explored. We refer to unconditional logistic regression analysis with adjustment for matched sets as indicator variables *and* using the bias reduction method as ULR-BR. The SAS User's Guide included one simulation that compared ULR-BR and CLR in the analysis of 20 pairs of cases and controls. It claimed that the results were comparable, despite the mean of ULR-BR estimates for the log OR being higher than that of CLR (20). Another simulation study that included ULR-BR examined two scenarios: 50 cases with 50 matched controls and 20 cases with 80 matched controls (21); the degree of bias was much milder in the latter than the former. However, the study does not shed light on the method's performance in larger sample sizes.

The aims of this article are two-fold. First, to elucidate whether the unexplained bias in the previous simulations is due to sparse data. Second, to evaluate the performance of various analytic models in a broad range of scenarios that may involve both sparse data bias and bias arising from breaking the matches.

Methods

Simulations

We conducted extensive simulations using incidence density sampling. The first series replicated the previous simulations of case-control studies nested within a fixed cohort using the Gompertz distribution (6,7), but we broadened the range of the number of cases and case to control ratios. Details of the simulation procedures are provided in Online Supplementary Material 1. We also assessed the sensitivity of the results to changes to the parameters of the Gompertz distribution. Details of these procedures are provided in Online Supplementary Material 2. The previous simulations that we have replicated were motivated by studies of lung disease (outcome) in relation to a quantitative measure of smoking (exposure). Although the true $ln(\text{IDR})$, either 0.0005 or 0.001, in those simulations appeared small, it belied the true extent of the association as the numeric values and variability of the quantitative exposure were large. For easier reading, we multiplied the IDR parameters by 100 so that they represent the effect of an increase of 100 units of exposure.

We also conducted a second series of simulations in a dynamic population setting using a Weibull distribution with a decreasing hazard of disease over time. This is motivated by our experience in the studies of pediatric infectious diseases, where disease incidence tends to decline as children get older. Details of the simulation procedures for the dynamic population

setting are available in Online Supplementary Material 3. To assess the sensitivity of the results to the distribution parameters, we conducted further simulations with hazards being constant or increasing over time (Online Supplementary Material 4).

We conducted further sensitivity analyses: One series of simulations changed the linear effect of a quantitative exposure variable to a non-linear effect by using square root and logarithmic transformations of the exposure variable, and another series changed the time-constant effect to a time-varying effect; details are described in Online Supplementary Materials 5 and 6, respectively. A final series considered a scenarios of further matching on a binary covariate but omitting it in the analysis; details are described in Online Supplementary Material 7.

We used 1000 replicates in each simulation scenario. In each replicate, we applied CLR, CLR-BR, ULR-Q and ULR-BR. In a series where the ULR-Q did not perform well, we also applied ULR-QL. Details of the statistical models are provided in Online Supplementary Material 8. We reported the relative bias of the mean estimates of the ln(IDR), defined as $(\text{mean of estimated}\ \ln(\text{IDR}) - \text{true}\ \ln(\text{IDR}))/\text{true}\ \ln(\text{IDR})$, root mean square error (RMSE), and the coverage probability of the 95% Wald confidence intervals (CI).

Case study

We re-analyzed the data of a case-control study of *Haemophilus influenzae* type B (Hib) vaccine. Details of the study has been published previously (22). In brief, the study was based on surveillance for Hib disease in The Gambia, West Africa, from 1997 to 2002. Approval was obtained from the Joint Ethics Committee of the Gambian Government and the Medical Research Council (Gambia). For each Hib disease case, 10 matched controls at-risk at the same calendar time and at the same age were recruited. After exclusions of cases who did not live in

The Gambia or who had no covariate information, 46 cases and 460 controls were included in the analysis. The analysis adjusted for three socio-environmental covariates that were not criteria for matching. Exposure status was classified as vaccinated with 0, 1, 2 or 3 doses of the Hib vaccine.

We re-analyzed the full data set using the methods aforementioned, with the Wald test and Wald 95% CIs. Since the Hib study individually matched for both time and age, without assuming the same age pattern of disease at different times, we controlled for time in quintiles, age in quintiles and their interaction terms (24 degrees of freedom in total) in the ULR-Q approach. In addition, for each case we randomly selected 1, 2 and 4 controls and applied the same analytic methods.

Results

Simulation: Fixed cohort

Based on the same population size as in the previous simulation by Leffondre et al. (7), there were 102 pairs of cases and controls on average. Halving, doubling and quadrupling the population size changed the average number of case-control pairs to 51, 204 and 407, respectively.

(Figure 1 here)

The upper-left panel of Figure 1 shows the relative bias in the design of one control per case. Using CLR, the relative bias in our re-run of the simulation with about 100 cases was +7.9%, which is similar to the relative bias of +8.7% in Table 2 of Leffondre et al. (7). The relative bias increased to +12.4% if the number of case-control pairs was reduced by half. Conversely, the relative bias decreased to 1.3% as the number of case-control pairs increased to

about 400. In contrast, CLR-BR had close to zero relative bias across all four settings. With about 50 and 100 cases, ULR-Q had relative bias slightly higher than CLR. Relative bias in ULR-Q and CLR were approximately equivalent when there were about 200 and 400 cases. ULR-BR clearly over-estimated ln(IDR).

The other panels in Figure 1 show the relative bias in the scenarios of the case to control ratio being 1:2, 1:4 and 1:10. It should be noted that the range on the y-axis is narrower for scenarios in the lower row of panels compared with the upper row of panels. Overall, as the ratio of controls to cases increased, the relative bias decreased. At 1:10, even ULR-BR had relative bias similar to the CLR. As the number of cases or the ratio of controls to cases increased, the RMSE of all four methods decreased. When there were 4 or 10 controls per case, all four methods had similar RMSE. With 1 or 2 controls per case, ULR-BR tended to have larger RMSE, while the other three methods were similar in this regard. Among the 16 scenarios examined, ULR-BR had the largest RMSE in 13 scenarios. Further details of the simulation results are available in Online Supplementary Material 1.

Figure 2 shows the coverage probability of the 95% CIs. The upper-left panel are the results for the scenario of case to control ratio being 1:1. The ULR-BR deviated from the target of 95% by about +3% and -2% when the average number of cases were 50 and 400, respectively. In no scenario did the other three methods deviate from the 95% target by over 2%.

(Figure 2 here)

The other three panels of Figure 2 show the 95% CI coverage probability in the scenarios with case to control ratio being 1:2, 1:4 and 1:10. The results did not change much as compared to those of 1:1 ratio. The main difference was that, with more than one control per case, ULR-BR had coverage probability similar to the other three methods.

In further simulations with different parameters for the Gompertz distribution, the findings were similar (see Online Supplementary Materials 2 for details).

Figure 3 shows the exposure distributions of the cases and controls in the setting of 50:50 and 400:400 observations. The upper left panel of Figure 1 showed that CLR and ULR-Q gave relative bias of 12% and 15% in the 50:50 setting, respectively, while both of them were approximately unbiased in the 400:400 setting. King and Zeng give a heuristic explanation of the sparse data bias (23): The degree of overlapping of the exposure distributions between the cases and controls determines the odds ratio estimate. Since small samples tend to miss the true minimum and maximum exposure level in the population, the sample tends to over- and under-estimate the minimum and maximum, respectively. Similarly, percentiles near the minimum and maximum also tend to be over- and under-estimated, respectively. This reduces the overlap of the exposure distributions between the cases and controls and leads to an over-estimation of the strength of association. This pattern of lesser exposure distribution overlap when sample size is smaller can also be seen in Figure 3. For example, in the 50:50 setting, the maximum and 98th percentile of exposure distribution (averaged over 1000 replicates) in the controls correspond to the 97th and 93rd percentiles in the cases. But for the 400:400 setting, the maximum and 98th percentile of exposure distribution correspond to the 99th and 94th percentiles in the cases. Hence the overlap of the exposure distributions is lesser in the 50:50 than the 400:400 setting.

(Figure 3 here)

Simulation: Dynamic population

The upper-left panel of Figure 4 presents the relative bias in the design with one control per case. With only 50 cases, the relative bias of the CLR estimates was about 97%. CLR-BR, ULR-Q and

ULR-BR showed 13%, 30% and 49% relative bias, respectively. The relative biases approached zero when the number of cases increased to 100 or more, with the exception of ULR-BR which remained high.

(Figure 4 here)

The other panels in Figure 4 show the relative bias in the scenarios of case to control ratio of 1:2, 1:4 and 1:10. It is important to note that the range of the y-axis is not the same for the four panels. Overall, as the number of controls per case increased, the relative bias decreased. With the number of cases ≥ 200 and ≥ 2 controls per case, all four methods gave similar estimates. CLR had the largest RMSE in 10 of the 16 scenarios. Details of the simulation results are available in Online Supplementary Material 3.

Figure 5 shows the coverage probability of the 95% CIs. The upper-left panel are the results for the scenario of case to control ratio being 1:1. ULR-Q deviated from the 95% target by at most 1.1%. The other three methods had coverage probability of about 3% to 4% higher than the nominal level when the number of cases was 50. As the number of cases increased, they converged to close to the target level, but ULR-BR tended to have higher coverage probability than the others.

(Figure 5 here)

The other three panels of Figure 5 show the 95% CI coverage probability in the scenarios with case to control ratios of 1:2, 1:4 and 1:10. The results do not change much as compared to those of the 1:1 ratio. The main difference was that, with case to control ratio of 1:10, the ULR-BR had coverage probability lower than those of the other three methods and the nominal level of 95%.

In further simulations with hazards being constant or increasing over time, the findings remained similar to the aforementioned simulations (see Online Supplementary Materials 4 for details).

Insensitivity assessment: Non-linear effects, time-varying effects, and omitted variable

In the scenarios of non-linear effects (either square root or logarithm form), the performance of the methods remained similar to their performance in the scenarios of linear effects (see Online Supplementary Materials 5 for details). There is more relative bias for all methods under the scenarios with logarithm than square root form of non-linearity. But the relative performance of the methods and the similarity in performance between CLR-BR, CLR and ULR-Q are as described above.

In the scenarios of time-varying effects, the performance of CLR and CLR-BR were similar to their performance under time-constant effects (Figures 6 and 7). ULR-BR frequently suffered non-convergence, especially for 1:1 and 1:2 case to control ratios (up to over 900 failures out of 1000 replicates). Therefore we do not show the results in the Figures. ULR-Q gave a relative bias between 12% and 15% (Figure 6). Its 95% CI coverage dropped below 90% in most scenarios (details not shown). It also had the largest RMSE in 10 of the 16 scenarios.

We included an additional analysis of ULR-QL, as proposed by Greenland and his colleagues for unconditional logistic regression when breaking the matches (14,19). The performance of ULR-QL clearly improves over ULR-Q. As sample size increases, the relative bias approaches zero. Importantly, the 95% CI coverage remained close to the nominal level in all cases (Figures 6 and 7; further details in Online Supplementary Material 6).

(Figure 6 here)

(Figure 7 here)

In analysis where a binary matching variable is omitted from the analytic models, ULR-Q shows a bias towards the null value (Online Supplementary Material 7). This is expected as it has been discussed in epidemiology text books, e.g. (18). ULR-BR's bias away from the null value is now less serious, as compared with the findings shown in Figure 1. This indicates that the two sources of bias, one arising from adjustment for matched sets as indicator variables and another arising from omitting a matching factor in the analysis, may cancel out to some extent but the former remains dominant in the scenarios examined.

Case study: Hib vaccine

Table 1 shows the Hib vaccination status of the 46 cases and their 460 individually matched controls. As shown in the original publication on the Hib study, conditional logistic regression analysis with adjustment for socio-environmental covariates gave estimates of protective efficacy (PE = 1 – IDR) of 38% for one dose and 94% for two and 94% for three doses of Hib vaccine (22).

(Table 1 here)

Table 2 shows the results of the re-analysis of the Hib vaccine study. In the re-analysis of the full dataset (10 controls per case), all four analytic methods rejected the null hypotheses of no association between Hib disease and receipt of two or three doses of Hib vaccines (each $P<0.01$). On the other hand, none of the four methods rejected the null hypothesis of no association between Hib disease and one dose of Hib vaccine (each $P>0.10$).

(Table 2 here)

In the analysis of partial data, for which we chose 1, 2 or 4 controls per case, randomly selected from the 10 controls available, the results obtained were approximately similar to those

from the full dataset. However, in the analysis of data with two randomly selected controls per case, the CLR estimate for three doses of Hib vaccine was zero and the 95% CI was from zero to positive infinity. In this analysis, it happened that all four controls that were chosen for the two cases with three doses of the Hib vaccine were concordant with the case for vaccination status. As such, the CLR gave a point estimate of zero and a very large SE. In contrast, CLR-BR rejected the null hypothesis of no association (P=0.037) and gave an estimate of 0.032 (95% CI: 0.001, 0.818). ULR-BR and ULR-Q did not reject the null hypothesis but they gave upper bounds of 95% CIs that were only slightly above 1.0.

Discussion

The incidence density sampling design is an important approach for epidemiological investigation of incidence rate ratios. It is also a natural choice for the studies of dynamic populations, which require matching for time (24). Although it is widely used, this sampling design appears to be relatively less well understood than the exclusive sampling design, as has been revealed by a literature review (1). Furthermore, some researchers may advocate exclusive sampling over incidence density sampling without a clear scientific rationale (25). Wider appreciation of the rationale for using the incidence density sampling design, and of the methods of analysis that should be used, is needed. Findings from previous simulations of case-control studies with incidence density sampling indicated bias, but the reason was not known. It is important to clarify whether the bias arises from incidence density sampling itself, from the way the data is analyzed, or from some other reason.

Our simulations demonstrated that CLR analysis of case-control studies based on incidence density sampling is asymptotically valid; as sample size increases the IDR estimate is

consistent with the true value and the coverage of the confidence interval is close to the nominal level. The bias shown in previous simulation studies was due to sparse data. Our simulations demonstrated that the bias in the IDR estimate could be prevented by increasing the number of cases, increasing the number of controls per case, using a bias reduction method, or a combination of them.

It may be practically difficult to increase the number of cases due to the rareness of some outcomes, such as the case in the Hib disease example. However, the choice of case to control ratio is usually controllable and the choice of analytic method is always controllable. With approximately 50 cases and a 1:1 or 1:2 case to control ratio, analysis by CLR can give a relative bias that may not be ignorable. The practical importance of a given degree of bias depends on its context. In some instances, the tolerance for bias may be small. For example, in non-inferiority studies of immunization, the non-inferiority margin can be very small and even a mild degree of bias may lead to a different conclusion (26).

For studies with the number of cases below 200 and case to control ratio not higher than 1:2, we recommend the use of conditional logistic regression with bias reduction. While we have focused on bias reduction based on the Firth-type penalization in this article, we recognize that there are other bias reduction methods and software to implement them (11,21,27). Further research on their performance in incidence density sampling would be useful. For Firth-type penalization, Sun et al. provided an R function for the implementation of CLR-BR (10), but it only allows up to two exposure variables (https://www.stat.tamu.edu/~sinha/research.html; accessed on 3 April 2018). Based on their codes and with permission, we have created an R function for CLR-BR without a limit on the number of exposure variables (R function, example R codes and example data file available as Online Supplementary Materials 9-11).

Whether individually matched case-control studies can be analyzed by ULR has been debated for a long time. It is increasingly recognized that breaking the matches for broad matching factors such as gender and use of ULR to adjust for the factors is a valid analytic approach (14,15). However, the discussion and evaluation to-date focuses on the exclusive sampling design and case-control studies nested within defined cohorts (28,29). The incidence density sampling design requires matching for a continuous factor, time. We have evaluated a strategy of using unconditional logistic regression with adjustment for quintiles of time. This method usually performed well and gave results highly comparable to those obtained from CLR. Breaking the matches appears to be a valid option. It is possible to consider further adding a linear trend within each group to account for residual time trends (14,19). In our simulation with time-varying effects, the adjustment for time in quintiles was not sufficient. The addition of the residual terms proposed by Greenland and colleagues (14,19) provided accurate results in terms of relative bias and coverage probability. Although ULR-Q performed well in many scenarios, it does not always work. This modelling method should be used judiciously.

Furthermore, when the number of controls per case is not large, such as the 1:2 scenario in the analysis of the partial data from the Hib study, concordance in exposure status between cases and matched controls may occur. This causes the matched sets to become non-informative and the estimate of standard error to become very large. The bias reduction method, or breaking the matches, can give more sensible confidence intervals.

A limitation of our study is that we have not examined the performance of profile (penalized) likelihood-based CI, which can have better performance than Wald CI in some situations such as when there is a very strong degree of association (21,30) but can be demanding in computation time (31).

While there is no debate that the (inappropriate) use of ULR with adjustment for matched set indicators generates substantial bias, whether this bias can be controlled by any bias reduction method has been unclear. In our analyses, it did not work well except in some scenarios when the number of controls per case was large.

In conclusion, the bias shown in the previous simulation studies was due to sparse data. It was not an inherent problem in incidence density sampling or conditional logistic regression. The application of a bias reduction method for conditional logistic regression analysis is recommended when case to control ratio is 1:2 or smaller or number of cases is 100 or smaller. The breaking of matches is possible in incidence density sampling, but it requires judicious use of analytic methods and preferably with large numbers of cases and controls.

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Conflict of interest

The authors declare that they have no conflict of interest with respect to this research study and paper.

Contributors

YBC conceived the study, designed the study, interpreted the findings, and wrote the first and final version of the article. XM implemented the simulation and data analysis, interpreted the findings and critically reviewed and revised the draft article. KFL, JL and PM participated in the design of the study, interpreted the findings and critically reviewed and revised the draft article. All authors approved the final version and agreed to be accountable for all aspects of the work.

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Table 1. Hib Vaccination Status in a Case-Control Study of Hib Disease in The Gambia, 1997-2002

			Cases			
			0 dose	1 dose	2 doses	3 doses
		No. of cases / No. of controls	29	13	2	2
Controls	0 dose	232	202	30	0	0
	1 dose	101	53	43	3	2
	2 doses	72	26	35	6	5
	3 doses	55	9	22	11	13

Table 2. Analysis of a Case-control Study of Hib Vaccination and Hib Disease in The Gambia, 1997-2002

Case to control ratio	Models [c]	1 dose		2 doses		3 doses	
		IDR	(95% CI)	IDR	(95% CI)	IDR	(95% CI)
1:10 [a]	CLR	0.622	(0.245, 1.577)	0.060	(0.010, 0.376)	0.056	(0.008, 0.384)
	CLR-BR	0.640	(0.264, 1.555)	0.078	(0.015, 0.405)	0.068	(0.012, 0.374)
	ULR-BR	0.644	(0.271, 1.531)	0.082	(0.018, 0.372)	0.067	(0.012, 0.385)
	ULR-Q	0.733	(0.320, 1.680)	0.085	(0.016, 0.459)	0.094	(0.016, 0.556)
1:1 [b]	CLR	0.504	(0.090, 2.815)	0.101	(0.004, 2.301)	0.024	(0.001, 0.774)
	CLR-BR	0.604	(0.144, 2.528)	0.227	(0.022, 2.326)	0.077	(0.006, 0.952)
	ULR-BR	0.593	(0.089, 3.964)	0.185	(0.008, 4.404)	0.048	(0.003, 0.938)
	ULR-Q	0.473	(0.128, 1.755)	0.254	(0.025, 2.629)	0.044	(0.004, 0.475)
1:2 [b]	CLR	0.823	(0.290, 2.337)	0.117	(0.012, 1.152)	0.000	(0.000, ∞)
	CLR-BR	0.848	(0.321, 2.240)	0.183	(0.027, 1.217)	0.032	(0.001, 0.818)
	ULR-BR	0.855	(0.257, 2.846)	0.171	(0.024, 1.207)	0.023	(0.000, 1.172)
	ULR-Q	0.962	(0.351, 2.642)	0.134	(0.021, 0.844)	0.127	(0.015, 1.055)
1:4 [b]	CLR	0.824	(0.290, 2.343)	0.041	(0.005, 0.351)	0.055	(0.005, 0.612)
	CLR-BR	0.846	(0.317, 2.260)	0.063	(0.010, 0.403)	0.084	(0.010, 0.692)
	ULR-BR	0.826	(0.277, 2.458)	0.058	(0.009, 0.360)	0.076	(0.008, 0.694)
	ULR-Q	1.007	(0.400, 2.536)	0.083	(0.015, 0.469)	0.164	(0.025, 1.059)

[a] Full dataset with 10 controls per case

[b] Partial data with 1, 2 or 4 controls randomly selected from the 10 controls for each case

[c] CLR: conditional logistic regression; CLR-BR: conditional logistic regression with bias-reduction; ULR-BR unconditional logistic regression with adjustment for matched set indicators and bias-reduction; ULR-Q unconditional logistic regression with adjustment for quintiles of time, age and their interactions.

Legends to Figures

Figure 1. Relative bias in relation to the average number of cases, case to control ratio and analytic methods under a simulation setting of a fixed cohort. CLR: conditional logistic regression; CLR-BR: conditional logistic regression with bias reduction; ULR-BR: unconditional logistic regression with adjustment for match set indicators and bias reduction; ULR-Q: unconditional logistic regression with adjustment for quintiles of time.

Figure 2. Coverage probability of 95% CI in relation to the average number of cases, case to control ratio and analytic methods under a simulation setting of a fixed cohort. CLR: conditional logistic regression; CLR-BR: conditional logistic regression with bias reduction; ULR-BR: unconditional logistic regression with adjustment for match set indicators and bias reduction; ULR-Q: unconditional logistic regression with adjustment for quintiles of time.

Figure 3. Comparison of exposure distribution among cases and controls in 50 cases and 50 controls and in 400 cases and 400 controls.

Figure 4. Relative bias in relation to the average number of cases, case to control ratio and analytic methods under a simulation setting of a dynamic population. CLR: conditional logistic regression; CLR-BR: conditional logistic regression with bias reduction; ULR-BR: unconditional logistic regression with adjustment for match set indicators and bias reduction; ULR-Q: unconditional logistic regression with adjustment for quintiles of time.

Figure 5. Coverage probability of 95% CI in relation to the average number of cases, case to control ratio and analytic methods under a simulation setting of a dynamic population. CLR: conditional logistic regression; CLR-BR: conditional logistic regression with bias reduction; ULR-BR: unconditional logistic regression with adjustment for match set indicators and bias reduction; ULR-Q: unconditional logistic regression with adjustment for quintiles of time.

Figure 6. Relative bias in relation to the average number of cases, case to control ratio and analytic methods under time-varying effects. CLR: conditional logistic regression; CLR-BR: conditional logistic regression with bias reduction; ULR-Q: unconditional logistic regression with adjustment for quintiles of time; ULR-QL: unconditional logistic regression with adjustment for quintiles of time and residual time within each quintile.

Figure 7. Coverage probability of 95% CI in relation to the average number of cases, case to control ratio and analytic methods under time-varying effects. CLR: conditional logistic regression; CLR-BR: conditional logistic regression with bias reduction; ULR-QL: unconditional logistic regression with adjustment for quintiles of time and residual time within each quintile.

Online Supplementary Material 1.

Simulation settings and procedures and results: Fixed cohort

1. Settings and procedures

The simulation of the population data and the permutation algorithm in step (13) follow the appendix in Leffondré et al. [6], except the use of N not equal to 1000.

(A) Generation of the population data with population size N = 500, 1000, 2000, or 4000

(1) Generate N survival ages T^* from a marginal Gompertz distribution with shape parameter $\alpha = 0.2138$, and scale parameter $\lambda = 7 \times 10^{-8}$.

(2) Generate N censoring ages C from a uniform distribution $U(35, 69.5)$, such that the censoring rate is around 90%.

(3) Denote $t = \min(T^*, C)$ and $d = I_{\{T^* \leq C\}}$.

(4) Sort the N tuples (t_i, d_i) such that $t_i < t_{i+1},\ i = 1, \dots, N$.

(5) For each subject j $(j = 1, \dots, N)$, the age at exposure initiation A_j is generated from lognormal distribution with mean 2.75 and SD 0.25 (both on log-scale), such that the expectation of A is 16 and its standard deviation is 4. Subjects are unexposed if $A_j > t_j$.

(6) Define risk indicator matrix for subject j at t_i, $Y_j(t_i) = I_{\{i \leq j\}}$.

(7) The initial intensity of exposure IA_j at the age of exposure initiation A_j is generated from lognormal distribution with mean 3.06 and SD 0.56 (both on log-scale), such that the expectation of IA is 25 and its standard deviation is 15.

(8) Defined age interval in 10-years bands: $(0,10], (10, 20], (20, 30]$ … … , $(60,70]$.

(9) Consider two patterns of change of exposure intensity: increasing or decreasing. Within each scenario, all subjects had the same pattern.

(9.1) For increasing intensity pattern, the percentage of increase in intensity at each predefined age interval generated from lognormal distributions with mean 0.4 and SD 0.085. That is, average rate of increase on log-scale in intensity is 40%.

(9.2) For decreasing intensity pattern, the percentage of decrease in intensity at each predefined age interval generated from lognormal distributions with mean 0.1 and SD 0.075, i.e. average rate of decrease on log-scale in intensity is 10%.

(10) Current intensity $IA_j(t_i)$ is calculated as a step function over duration of exposure $(A_j, t_i],\ i = 1, \dots, j$, with jumps only at the predefined age.

(11) Duration gap $G_j(t_i)$ between two consecutive times starting from A_j ending with t_j:

$G_j(t_i) = 0\ if\ t_i < A_j\ and\ t_i > t_j;\ t_i - A_j\ if\ t_{i-1} < A_j < t_i;\ t_i - t_{i-1}\ if\ A_j < t_{i-1} < t_i$.

(12) The value of the cumulative exposure $E_j(t_i)$, which is an N×N matrix, is calculated as $E_j(t_i) = \sum_{l=1}^{i} IA_j(t_l) \times G_j(t_l)$.

(13) Permutational algorithm: Starting from the earliest observed time t_1, randomly assign each consecutive survival status tuple $(t_i, d_i),\ i = 1, \dots, N$ to a vector of current covariate values $E_j(t_i), j = 1, \dots, N$.

(a) If $d_i = 1$ (i.e. if t_i represents an event time), covariate vectors are sampled with probabilities based on the partial likelihood of the Cox model. Accordingly, for an subject j at t_i, this probability is defined as $Prob_j(t_i) = \frac{\exp(\beta E_j(t_i))}{\sum_{s \in R_i} \exp(\beta E_s(t_i))}$, where R_i is the risk set at t_i, which excluded those subjects who had been selected for earlier time. We considered the true regression parameter values $\beta = 0.05, 0.1$, which represents the effect of 100 units of cumulative exposure.

(b) If $d_i = 0$, assign a subject who is censored at time t_i by simple random sampling from the risk set R_i with equal probability.

(B) Case-control study design using incidence density sampling

On average, within a population of size N, the parameter setting gave rise to approximately N/10 cases. Case to control ratio was 1:M, with M = 1, 2, 4 or 10.

(1) All the subjects who had an event are selected as cases.

(2) For each case, we randomly selected M control(s) with replacement among subjects still at risk at the age (time) of the case's diagnosis. Cumulative exposure intensity was ascertained at this time.

(3) Following the incidence density sampling approach, a subject could serve as a control for different cases, and a case could be selected as a control for an earlier case.

(C) Implementation and presentation

We ran 1000 replications for each scenario, then calculated the mean $\bar{\beta}$ over the 1000 estimates $\hat{\beta}_k$ as the estimator of the true value β, where k = 1,2, …, 1000. The relative bias was then calculated as $(\bar{\beta} - \beta)/\beta$. We compared the average of the 1000 standard errors $\widehat{SE}_k$ (ASE) to the empirical standard deviation (ESD) of the 1000 estimates $\hat{\beta}_k$. The coverage probability was estimated as the proportion of samples for which the 95% confidence interval (CI), $\hat{\beta}_k \pm 1.96\widehat{SE}_k$, included the true value β. We also report the root mean square error (RMSE) calculated as $\sqrt{\sum_{k=1}^{1000}(\hat{\beta}_k - \beta)^2 /1000}$.

2. Simulation results

Table 1. Time decreasing exposure intensity and 1:1 case-control ratio

Population size	Average no. of cases	True parameter	Method	Relative bias (%)	ASE/ESD[†]	CP (%)[††]	RMSE $\times 10^{-3}$
500	51	0.05	CLR	+12.4	0.98	96.7	42
			CLR-BR	+2.7	1.00	96.2	38
			ULR-BR	+32.2	1.18	98.4	47
			ULR-Q	+14.5	1.00	96.6	41
	51	0.1	CLR	+8.1	0.97	96.0	49
			CLR-BR	-0.5	1.00	94.9	45
			ULR-BR	+13.8	1.33	99.4	41
			ULR-Q	+9.9	0.99	96.1	45
1000	102	0.05	CLR	+7.9[*]	0.97	95.9	29
			CLR-BR	+2.8	0.98	95.8	28
			ULR-BR	+30.7	1.13	96.8	36
			ULR-Q	+8.9	0.96	95.7	29
	102	0.1	CLR	+6.8[**]	0.92	95.3	36
			CLR-BR	+2.5	0.94	94.3	34
			ULR-BR	+15.0	1.33	98.9	30
			ULR-Q	+6.9	0.94	94.5	33
2000	204	0.05	CLR	+4.3	1.01	94.9	20
			CLR-BR	+1.7	1.01	94.7	19
			ULR-BR	+29.2	1.16	94.7	27
			ULR-Q	+4.3	1.01	94.6	19
	204	0.1	CLR	+4.4	1.02	96.4	23
			CLR-BR	+2.3	1.03	96.3	22
			ULR-BR	+15.3	1.38	97.8	22
			ULR-Q	+3.6	1.04	96.4	20
4000	407	0.05	CLR	+1.3	0.97	94.9	14
			CLR-BR	-0.05	0.98	94.8	14
			ULR-BR	+27.2	1.11	92.8	21
			ULR-Q	+1.0	0.98	94.4	14
	407	0.1	CLR	+0.8	0.99	95.3	16
			CLR-BR	-0.3	0.99	94.4	16
			ULR-BR	+13.1	1.26	96.2	17
			ULR-Q	+0.3	0.99	95.0	15

[†] Average standard error (ASE) divided by empirical standard deviation (ESD) of estimates.

[††]Coverage probability of 95% confidence intervals.

[*] Relative bias was +8.7% and [**] +4.8% in Table 2 of Leffondré et al.[6]

Table 2. Time-increasing exposure intensity and 1:1 case to control ratio

Population size	Average no. of cases	True parameter	Method	Relative bias (%)	ASE/ESD[†]	CP (%)[††]	RMSE $\times 10^{-3}$
500	51	0.05	CLR	+9.5	0.92	95.7	33
			CLR-BR	+0.1	0.95	93.5	31
			ULR-BR	+20.4	1.23	99.1	32
			ULR-Q	+11.6	0.94	95.2	32
	51	0.1	CLR	+7.2	0.95	96.0	41
			CLR-BR	-1.0	1.00	95.4	37
			ULR-BR	+3.4	1.46	99.7	25
			ULR-Q	+7.5	0.98	96.6	36
1000	102	0.05	CLR	+5.9*	0.96	95.8	21
			CLR-BR	+1.2	0.98	94.9	20
			ULR-BR	+21.9	1.21	98.5	23
			ULR-Q	+6.5	0.96	95.2	21
	102	0.1	CLR	+4.8**	0.92	96.1	29
			CLR-BR	+0.8	0.95	95.1	27
			ULR-BR	+3.4	1.41	99.2	17
			ULR-Q	4.1	0.95	94.5	25
2000	204	0.05	CLR	+4.3	0.99	94.9	14
			CLR-BR	+2.0	1.00	94.8	14
			ULR-BR	+21.7	1.23	96.6	17
			ULR-Q	+3.5	1.01	96.2	13
	204	0.1	CLR	+2.9	1.02	96.4	18
			CLR-BR	+0.9	1.03	96.0	17
			ULR-BR	+3.1	1.42	99.2	10
			ULR-Q	+1.4	1.03	96.0	15
4000	407	0.05	CLR	+0.8	0.99	95.0	9
			CLR-BR	-0.3	0.98	94.8	9
			ULR-BR	+17.6	1.21	94.8	12
			ULR-Q	+0.1	0.99	94.8	9
	407	0.1	CLR	+0.6	0.99	94.6	12
			CLR-BR	-0.3	1.00	93.9	12
			ULR-BR	-0.2	1.32	99.2	5
			ULR-Q	-1.1	0.99	94.7	10

[†] Average standard error divided by empirical standard deviation of estimates

[††]Coverage probability of 95% confidence intervals.

[*] Relative bias was +4.5% and [**] +5.1% in Table 2 of Leffondré et al.[6]

Table 3. Time-decreasing exposure intensity and 1:2 case to control ratio

Population size	Average no. of cases	True parameter	Method	Relative bias (%)	ASE/ESD[†]	CP (%)[††]	RMSE $\times 10^{-3}$
500	51	0.05	CLR	+8.9	0.99	97.1	34
			CLR-BR	+5.0	1.00	96.8	32
			ULR-BR	+18.8	1.10	97.7	37
			ULR-Q	+10.8	1.00	96.4	34
	51	0.1	CLR	+6.0	0.95	95.9	40
			CLR-BR	+1.7	0.96	95.7	37
			ULR-BR	+13.3	1.07	96.8	41
			ULR-Q	+8.2	0.95	94.5	39
1000	102	0.05	CLR	+3.1	0.99	95.7	23
			CLR-BR	+1.2	0.99	95.8	22
			ULR-BR	+14.4	1.09	96.4	26
			ULR-Q	+3.5	1.00	95.7	23
	102	0.1	CLR	+3.2	1.00	95.7	26
			CLR-BR	+1.1	1.00	95.4	25
			ULR-BR	+12.4	1.10	96.0	29
			ULR-Q	+3.8	0.98	94.8	25
2000	204	0.05	CLR	+2.6	1.03	96.3	16
			CLR-BR	+1.6	1.03	96.3	15
			ULR-BR	+14.8	1.12	96.1	19
			ULR-Q	+2.5	1.04	96.1	15
	204	0.1	CLR	+1.7	1.00	95.4	18
			CLR-BR	+0.6	1.00	95.2	18
			ULR-BR	+11.7	1.10	94.9	22
			ULR-Q	+1.2	1.00	95.6	17
4000	407	0.05	CLR	+0.05	0.95	93.9	12
			CLR-BR	-0.5	0.95	93.8	12
			ULR-BR	+12.4	1.03	93.4	15
			ULR-Q	-0.2	0.95	93.6	12
	407	0.1	CLR	+0.1	0.96	95.0	13
			CLR-BR	-0.5	0.96	95.3	13
			ULR-BR	+10.5	1.05	90.4	17
			ULR-Q	-0.4	0.95	93.8	13

[†] Average standard error divided by empirical standard deviation of estimates

[††]Coverage probability of 95% confidence intervals.

Table 4. Time-increasing exposure intensity and 1:2 case to control ratio

Population size	Average no. of cases	True parameter	Method	Relative bias (%)	ASE/ESD[†]	CP (%)[††]	RMSE $\times 10^{-3}$
500	51	0.05	CLR	+7.9	0.98	96.5	25
			CLR-BR	+3.7	0.99	97.1	24
			ULR-BR	+17.1	1.10	97.2	28
			ULR-Q	+9.6	0.99	96.2	25
	51	0.1	CLR	+5.0	0.96	95.1	32
			CLR-BR	+0.7	0.98	94.7	30
			ULR-BR	+9.7	1.09	97.7	31
			ULR-Q	+6.2	0.98	96.2	29
1000	102	0.05	CLR	+3.7	0.97	95.5	17
			CLR-BR	+1.6	0.98	94.9	16
			ULR-BR	+14.2	1.08	96.5	19
			ULR-Q	+3.9	0.97	94.9	17
	102	0.1	CLR	+2.0	1.04	95.9	19
			CLR-BR	-0.05	1.05	95.9	19
			ULR-BR	+8.4	1.15	97.4	21
			ULR-Q	+1.9	1.03	96.4	18
2000	204	0.05	CLR	+1.8	1.01	96.4	11
			CLR-BR	+0.7	1.02	96.2	11
			ULR-BR	+13.0	1.11	95.5	13
			ULR-Q	+1.4	1.01	96.2	11
	204	0.1	CLR	+1.5	1.02	96.0	14
			CLR-BR	+0.5	1.03	95.7	13
			ULR-BR	+8.0	1.12	95.4	15
			ULR-Q	+0.3	1.00	95.4	13
4000	407	0.05	CLR	+0.4	0.98	94.4	7
			CLR-BR	-0.1	0.98	94.2	7
			ULR-BR	+11.7	1.07	92.7	10
			ULR-Q	-0.3	0.97	94.7	7
	407	0.1	CLR	+0.1	0.97	95.1	10
			CLR-BR	-0.4	0.98	94.6	10
			ULR-BR	+6.3	1.05	93.2	11
			ULR-Q	-1.4	0.98	93.7	9

[†] Average standard error divided by empirical standard deviation of estimates

[††]Coverage probability of 95% confidence intervals.

Table 5. Time-decreasing exposure intensity and 1:4 case to control ratio

Population size	Average no. of cases	True parameter	Method	Relative bias (%)	ASE/ESD[†]	CP (%)[††]	RMSE $\times 10^{-3}$
500	51	0.05	CLR	+4.3	0.93	95.5	31
			CLR-BR	+4.1	0.94	95.4	30
			ULR-BR	+7.5	0.99	95.7	32
			ULR-Q	+5.5	0.93	94.7	31
	51	0.1	CLR	+4.2	0.97	96.4	32
			CLR-BR	+2.2	0.98	96.5	31
			ULR-BR	+6.9	1.03	96.6	33
			ULR-Q	+5.7	0.97	96.1	32
1000	102	0.05	CLR	+3.0	0.98	95.6	20
			CLR-BR	+2.9	0.98	95.6	20
			ULR-BR	+6.4	1.02	96.2	21
			ULR-Q	+3.2	0.97	95.0	20
	102	0.1	CLR	+2.6	0.95	94.3	23
			CLR-BR	+1.5	0.96	94.0	22
			ULR-BR	+6.2	1.00	95.1	24
			ULR-Q	+2.4	0.96	94.5	22
2000	204	0.05	CLR	+0.2	0.97	94.5	14
			CLR-BR	+0.1	0.97	94.4	14
			ULR-BR	+3.6	1.01	95.0	15
			ULR-Q	+0.2	0.97	94.6	14
	204	0.1	CLR	+0.4	0.98	94.8	15
			CLR-BR	-0.1	0.98	94.8	15
			ULR-BR	+4.5	1.02	96.1	16
			ULR-Q	+0.01	0.99	94.6	15
4000	407	0.05	CLR	+0.8	0.97	94.8	10
			CLR-BR	+0.7	0.96	94.8	10
			ULR-BR	+4.3	1.00	95.4	11
			ULR-Q	+0.4	0.96	94.2	10
	407	0.1	CLR	+0.5	0.98	95.1	11
			CLR-BR	+0.2	0.98	95.0	11
			ULR-BR	+4.8	1.03	94.9	12
			ULR-Q	-0.2	0.98	95.0	11

[†] Average standard error divided by empirical standard deviation of estimates

[††]Coverage probability of 95% confidence intervals.

Table 6. Time-increasing exposure intensity and 1:4 case to control ratio

Population size	Average no. of cases	True parameter	Method	Relative bias (%)	ASE/ESD[†]	CP (%)[††]	RMSE $\times 10^{-3}$
500	51	0.05	CLR	+5.0	0.94	95.1	22
			CLR-BR	+3.6	0.94	94.7	21
			ULR-BR	+8.1	0.99	95.9	23
			ULR-Q	+6.3	0.92	95.0	23
	51	0.1	CLR	+3.7	0.97	95.8	26
			CLR-BR	+1.4	0.98	95.1	25
			ULR-BR	+6.0	1.03	96.3	26
			ULR-Q	+4.3	0.97	94.8	24
1000	102	0.05	CLR	+2.8	0.98	94.8	14
			CLR-BR	+2.1	0.98	94.6	14
			ULR-BR	+6.6	1.03	95.9	15
			ULR-Q	+2.8	0.98	95.6	14
	102	0.1	CLR	+2.5	0.95	95.0	18
			CLR-BR	+1.3	0.96	95.1	17
			ULR-BR	+5.7	1.00	95.2	18
			ULR-Q	+2.0	0.94	94.1	17
2000	204	0.05	CLR	+0.5	1.03	95.6	9
			CLR-BR	+0.1	1.03	95.6	9
			ULR-BR	+4.7	1.07	97.1	10
			ULR-Q	+0.3	1.02	95.4	9
	204	0.1	CLR	+0.6	0.97	94.2	12
			CLR-BR	+0.01	0.98	94.5	12
			ULR-BR	+4.1	1.02	95.3	13
			ULR-Q	-0.6	0.97	94.3	11
4000	407	0.05	CLR	+1.2	0.97	94.5	6
			CLR-BR	+0.9	0.97	94.4	6
			ULR-BR	+5.7	1.01	93.9	7
			ULR-Q	+0.3	0.97	94.7	6
	407	0.1	CLR	+0.6	0.98	95.0	8
			CLR-BR	+0.3	0.98	94.6	8
			ULR-BR	+4.1	1.02	93.3	9
			ULR-Q	-1.0	0.99	94.9	7

[†] Average standard error divided by empirical standard deviation of estimates

[††]Coverage probability of 95% confidence intervals.

Table 7. Time decreasing exposure intensity and 1:10 case to control ratio

Population size	Average no. of cases	True parameter	Method	Relative bias (%)	ASE/ESD[†]	CP (%)[††]	RMSE $\times 10^{-3}$
500	51	0.05	CLR	+2.7	0.97	95.7	26
			CLR-BR	+5.1	0.97	95.9	26
			ULR-BR	+2.9	0.96	95.3	26
			ULR-Q	+3.2	0.97	95.7	27
	51	0.1	CLR	+2.4	1.00	96.1	26
			CLR-BR	+2.1	1.00	96.3	25
			ULR-BR	+2.1	0.99	95.9	26
			ULR-Q	+3.0	0.99	96.1	26
1000	102	0.05	CLR	-0.5	0.96	94.8	19
			CLR-BR	+0.8	0.96	94.5	18
			ULR-BR	-1.0	0.94	93.8	18
			ULR-Q	-0.5	0.95	94.8	19
	102	0.1	CLR	+1.1	0.99	95.3	18
			CLR-BR	+0.9	0.99	95.5	18
			ULR-BR	+1.0	0.97	94.3	19
			ULR-Q	+0.8	0.99	95.2	18
2000	204	0.05	CLR	+1.4	0.98	93.7	13
			CLR-BR	+2.1	0.98	93.7	13
			ULR-BR	+0.6	0.96	93.0	13
			ULR-Q	+1.1	0.99	93.3	13
	204	0.1	CLR	+1.2	0.98	94.2	13
			CLR-BR	+1.1	0.98	94.3	13
			ULR-BR	+1.3	0.97	93.8	13
			ULR-Q	+0.7	0.99	94.1	13
4000	407	0.05	CLR	+0.7	0.98	94.8	9
			CLR-BR	+1.1	0.98	94.6	9
			ULR-BR	-0.2	0.95	93.9	9
			ULR-Q	+0.3	0.98	95.1	9
	407	0.1	CLR	+0.8	0.98	94.1	9
			CLR-BR	+0.7	0.98	94.1	9
			ULR-BR	+1.0	0.97	94.0	9
			ULR-Q	+0.1	0.98	94.2	9

[†] Average standard error (ASE) divided by empirical standard deviation (ESD) of estimates.

[††]Coverage probability of 95% confidence intervals.

Table 8. Time-increasing exposure intensity and 1:10 case to control ratio

Population size	Average no. of cases	True parameter	Method	Relative bias (%)	ASE/ESD[†]	CP (%)[††]	RMSE $\times 10^{-3}$
500	51	0.05	CLR	+3.5	0.99	95.7	18
			CLR-BR	+4.3	0.99	95.6	18
			ULR-BR	+3.3	0.99	95.2	18
			ULR-Q	+3.4	0.99	95.5	18
	51	0.1	CLR	+2.7	0.98	95.5	21
			CLR-BR	+1.8	0.98	95.9	20
			ULR-BR	+2.6	0.98	95.1	21
			ULR-Q	+2.5	0.98	95.9	20
1000	102	0.05	CLR	+0.8	1.00	95.7	12
			CLR-BR	+1.1	1.00	95.6	12
			ULR-BR	+0.5	0.98	94.9	12
			ULR-Q	+0.3	1.00	95.3	12
	102	0.1	CLR	+1.2	0.97	94.6	14
			CLR-BR	+0.8	0.97	95.1	14
			ULR-BR	+1.5	0.96	94.3	14
			ULR-Q	+0.2	0.97	95.0	14
2000	204	0.05	CLR	+1.4	0.99	94.5	8
			CLR-BR	+1.5	0.99	94.5	8
			ULR-BR	+1.2	0.98	94.3	8
			ULR-Q	+0.7	1.00	94.8	8
	204	0.1	CLR	+1.2	0.98	94.8	10
			CLR-BR	+1.0	0.98	94.8	10
			ULR-BR	+1.9	0.97	94.5	10
			ULR-Q	-0.1	0.99	94.4	9
4000	407	0.05	CLR	+0.9	0.97	94.4	6
			CLR-BR	+0.9	0.97	94.5	6
			ULR-BR	+0.9	0.96	93.8	6
			ULR-Q	+0.01	0.98	94.4	5
	407	0.1	CLR	+0.7	0.98	95.4	7
			CLR-BR	+0.6	0.98	95.6	6
			ULR-BR	+1.4	0.97	94.4	7
			ULR-Q	-0.8	0.98	94.4	6

[†] Average standard error divided by empirical standard deviation of estimates

[††]Coverage probability of 95% confidence intervals.

Online Supplementary Material 2.

Further simulation settings and results: Fixed cohort

1. Variation in settings and procedures

Other than the modifications described below, the simulation settings and procedures are the same as those described in Online Supplementary Material 1.

(A) Generation of the population data with population size N = 1000

(1)Generate N survival ages T^* from a marginal Gompertz distribution with scale parameter $\lambda = 1.4 \times 10^{-6}$ and shape parameter $\alpha = 0.2138$ such that the censoring rate is about 50%, and scale parameter $\lambda = 7 \times 10^{-8}$ and shape parameter $\alpha = 0.32$ such that the censoring rate is about 30%.

(2)Consider a decreasing intensity pattern, in which the percentage of decrease in intensity at each predefined age interval generated from lognormal distributions with mean 0.1 and SD 0.075, i.e. average rate of decrease on log-scale in intensity is 10%.

(3)Considered the true regression parameter values $\beta = 0.05$, which represents the effect of 100 units of cumulative exposure.

(B) Case-control study design using incidence density sampling

We randomly select 50, 100, 200 or 400 cases.

2. Simulation results in figures

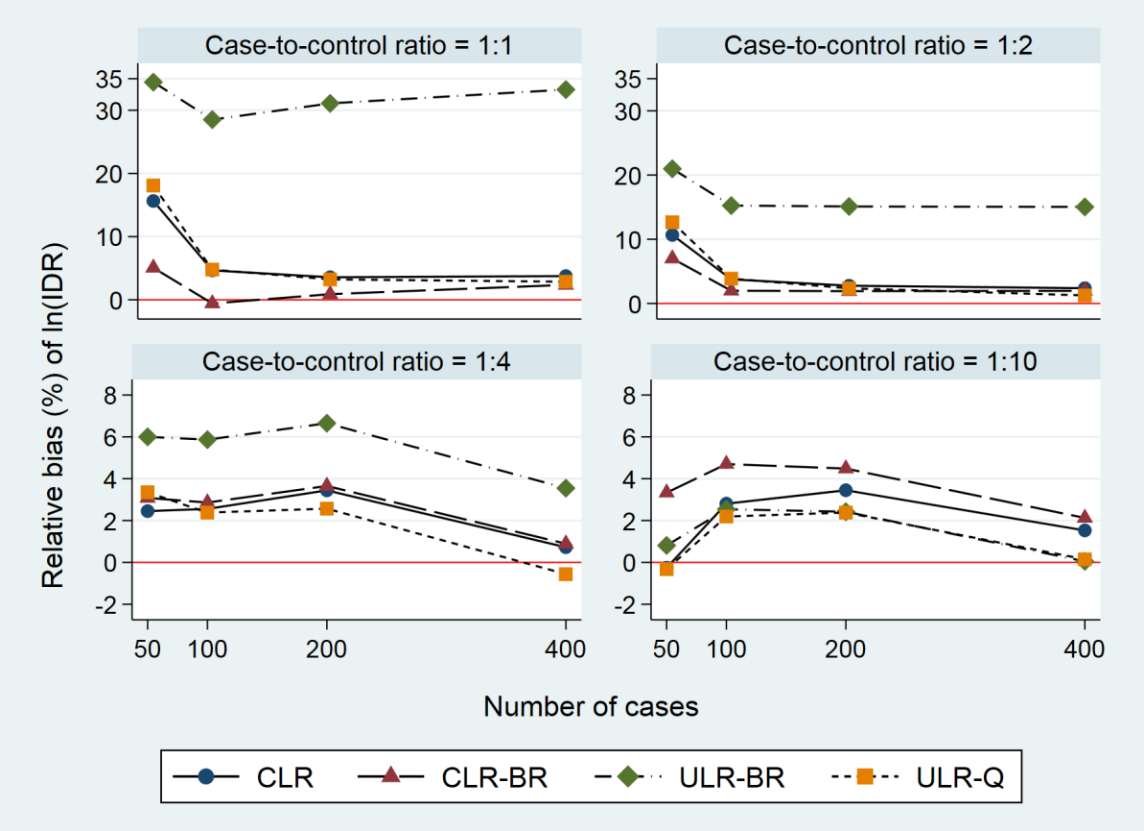

Figure 1. Relative bias of ln(IDR) in relation to the number of cases, case to control ratio and analytic methods under a simulation setting with $\lambda = 1.4 \times 10^{-6}$, $\alpha = 0.2138$, and censoring rate about 50%.

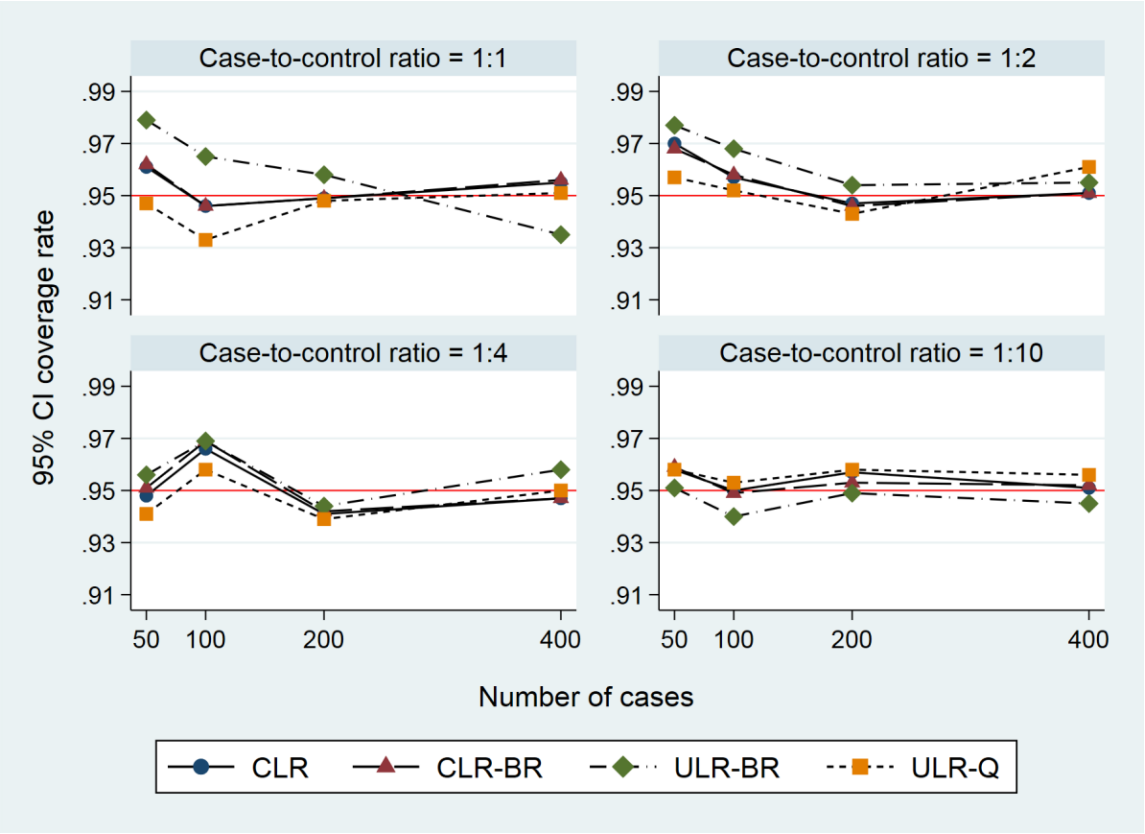

Figure 2. Coverage probability of 95% CI in relation to the number of cases, case to control ratio and analytic methods under a simulation setting with $\lambda = 1.4 \times 10^{-6}$, $\alpha = 0.2138$, and censoring rate about 50%.

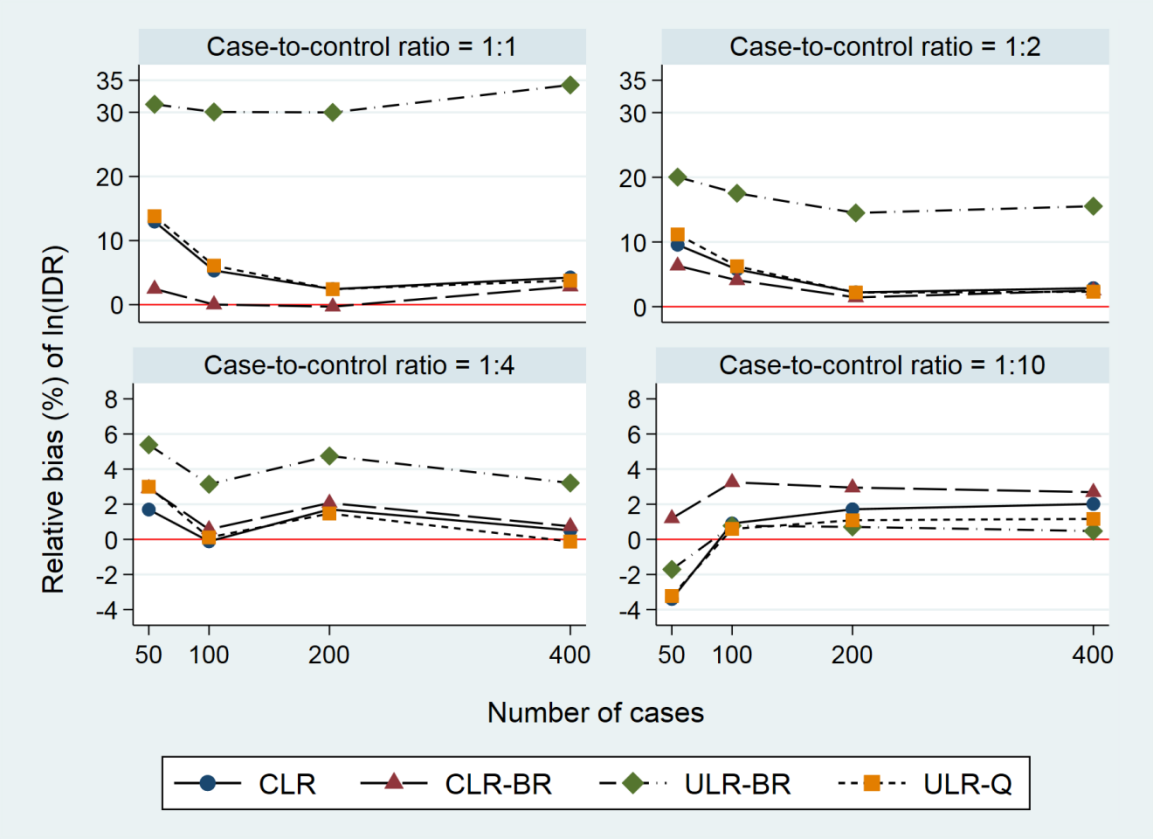

Figure 3. Relative bias of ln(IDR) in relation to the number of cases, case to control ratio and analytic methods under a simulation setting with $\lambda = 7 \times 10^{-8}$, $\alpha = 0.32$, and censoring rate about 30%.

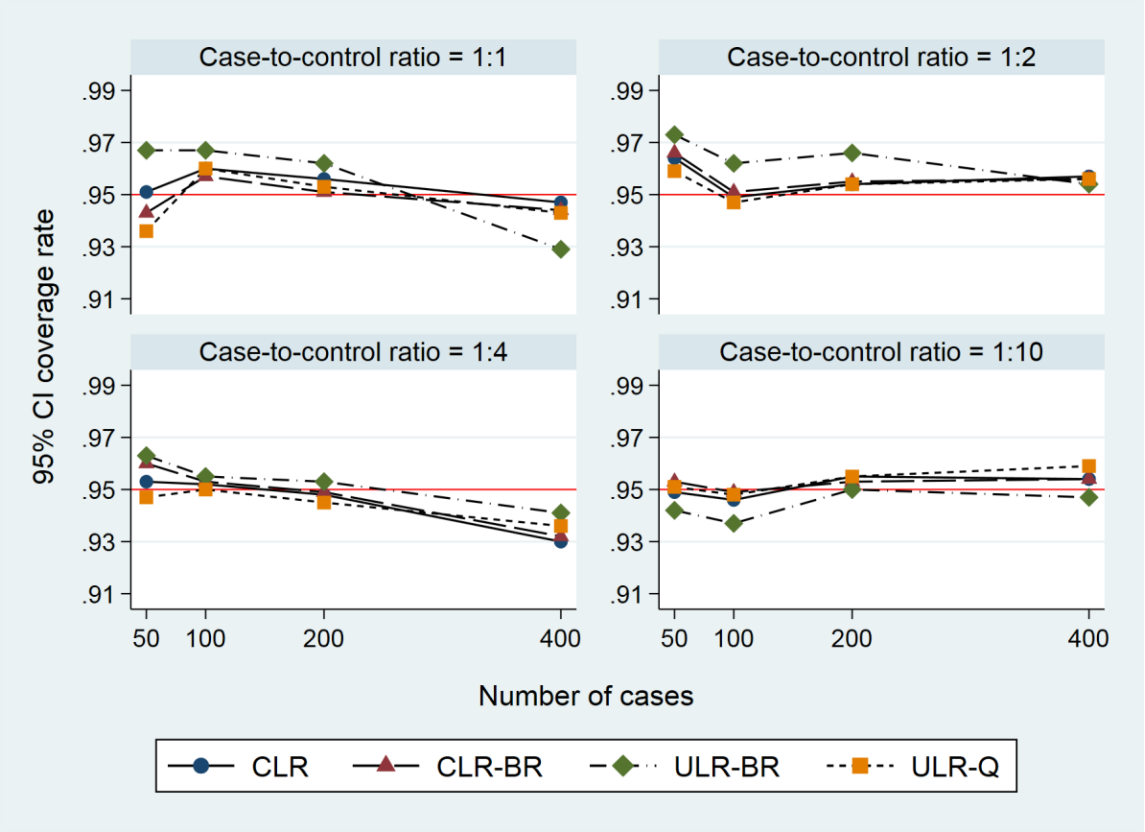

Figure 4. Coverage probability of 95% CI in relation to the number of cases, case to control ratio and analytic methods under a simulation setting with with $\lambda = 7 \times 10^{-8}$, $\alpha = 0.32$, and censoring rate about 30%.

3. Simulation results in tables

Table 1. Time decreasing exposure intensity with censoring rate about 50% and 1:1 case to control ratio

Population size	No. of cases	True parameter	Method	Relative bias (%)	ASE/ESD†	CP (%)††	RMSE $\times 10^{-3}$
1000	50	0.05	CLR	+15.6	0.93	96.1	52
			CLR-BR	+5.1	0.96	96.2	47
			ULR-BR	+34.5	1.10	97.9	59
			ULR-Q	+18.1	0.92	94.7	52
	100	0.05	CLR	+4.7	0.94	94.6	35
			CLR-BR	-0.6	0.95	94.6	34
			ULR-BR	+28.5	1.08	96.5	43
			ULR-Q	+4.8	0.95	93.3	34
	200	0.05	CLR	+3.6	0.99	94.9	25
			CLR-BR	+0.9	0.99	94.9	24
			ULR-BR	+31.1	1.10	95.8	33
			ULR-Q	+3.2	0.99	94.8	24
	400	0.05	CLR	+3.8	1.00	95.5	18
			CLR-BR	+2.4	1.00	95.6	18
			ULR-BR	+33.3	1.10	93.5	28
			ULR-Q	+2.9	1.00	95.1	18

† Average standard error (ASE) divided by empirical standard deviation (ESD) of estimates.

†† Coverage probability of 95% confidence intervals.

Table 2. Time-decreasing exposure intensity with censoring rate about 50% and 1:2 case to control ratio

Population size	No. of cases	True parameter	Method	Relative bias (%)	ASE/ESD†	CP (%)††	RMSE $\times 10^{-3}$
1000	50	0.05	CLR	+10.7	0.98	97.0	40
			CLR-BR	+7.0	0.98	96.8	38
			ULR-BR	+21.0	1.08	97.7	44
			ULR-Q	+12.7	0.97	95.7	40
	100	0.05	CLR	+3.8	0.99	95.7	28
			CLR-BR	+2.0	0.99	95.8	27
			ULR-BR	+15.2	1.08	96.8	31
			ULR-Q	+3.9	0.99	95.2	27
	200	0.05	CLR	+2.8	0.97	94.7	21
			CLR-BR	+1.9	0.97	94.6	20
			ULR-BR	+15.1	1.05	95.4	24
			ULR-Q	+2.4	0.97	94.3	20
	400	0.05	CLR	+2.4	0.99	95.1	15
			CLR-BR	+2.0	0.98	95.1	15
			ULR-BR	+15.0	1.06	95.5	19
			ULR-Q	+1.3	1.00	96.1	15

† Average standard error divided by empirical standard deviation of estimates.

†† Coverage probability of 95% confidence intervals.

Table 3. Time-decreasing exposure intensity with censoring rate about 50% and 1:4 case to control ratio

Population size	No. of cases	True parameter	Method	Relative bias (%)	ASE/ESD†	CP (%)††	RMSE $\times 10^{-3}$
1000	50	0.05	CLR	+2.5	0.95	94.8	35
			CLR-BR	+3.1	0.95	95.1	33
			ULR-BR	+6.0	1.01	95.6	36
			ULR-Q	+3.4	0.95	94.1	35
	100	0.05	CLR	+2.6	1.00	96.6	24
			CLR-BR	+2.9	1.00	96.9	23
			ULR-BR	+5.9	1.04	96.9	25
			ULR-Q	+2.4	1.00	95.8	24
	200	0.05	CLR	+3.4	0.92	94.1	19
			CLR-BR	+3.7	0.92	94.2	19
			ULR-BR	+6.7	0.96	94.4	20
			ULR-Q	+2.6	0.93	93.9	19
	400	0.05	CLR	+0.7	0.98	94.7	13
			CLR-BR	+0.9	0.98	94.7	13
			ULR-BR	+3.5	1.02	95.8	14
			ULR-Q	-0.6	0.99	95.0	13

† Average standard error divided by empirical standard deviation of estimates.

†† Coverage probability of 95% confidence intervals.

Table 4. Time decreasing exposure intensity with censoring rate about 50% and 1:10 case to control ratio

Population size	No. of cases	True parameter	Method	Relative bias (%)	ASE/ESD†	CP (%)††	RMSE $\times 10^{-3}$
1000	50	0.05	CLR	-0.3	0.98	95.8	31
			CLR-BR	+3.3	0.98	95.9	30
			ULR-BR	+0.8	0.97	95.1	30
			ULR-Q	-0.3	0.98	95.8	31
	100	0.05	CLR	+2.8	0.96	95.0	22
			CLR-BR	+4.7	0.96	94.9	22
			ULR-BR	+2.5	0.94	94.0	22
			ULR-Q	+2.2	0.97	95.3	22
	200	0.05	CLR	+3.4	0.97	95.7	16
			CLR-BR	+4.5	0.97	95.3	16
			ULR-BR	+2.4	0.94	94.9	16
			ULR-Q	+2.4	0.98	95.8	16
	400	0.05	CLR	+1.5	0.98	95.1	12
			CLR-BR	+2.1	0.98	95.2	12
			ULR-BR	+0.1	0.95	94.5	12
			ULR-Q	+0.1	0.99	95.6	12

† Average standard error (ASE) divided by empirical standard deviation (ESD) of estimates.

†† Coverage probability of 95% confidence intervals.

Table 5. Time decreasing exposure intensity with censoring rate about 30% and 1:1 case to control ratio

Population size	No. of cases	True parameter	Method	Relative bias (%)	ASE/ESD†	CP (%)††	RMSE $\times 10^{-3}$
1000	50	0.05	CLR	+13.0	0.86	95.1	61
			CLR-BR	+2.5	0.88	94.3	56
			ULR-BR	+31.3	1.02	96.7	69
			ULR-Q	+13.8	0.88	93.6	59
	100	0.05	CLR	+5.3	0.98	96.0	37
			CLR-BR	+0.0	0.99	95.7	35
			ULR-BR	+30.1	1.11	96.7	46
			ULR-Q	+6.1	0.98	96.0	37
	200	0.05	CLR	+2.4	0.99	95.6	26
			CLR-BR	-0.3	0.99	95.1	26
			ULR-BR	+30.0	1.10	96.2	35
			ULR-Q	+2.4	0.99	95.3	26
	400	0.05	CLR	+4.2	1.00	94.7	19
			CLR-BR	+2.8	1.00	94.4	19
			ULR-BR	+34.3	1.10	92.9	29
			ULR-Q	+3.8	1.01	94.3	19

† Average standard error (ASE) divided by empirical standard deviation (ESD) of estimates.

†† Coverage probability of 95% confidence intervals.

Table 6. Time-decreasing exposure intensity with censoring rate about 30% and 1:2 case to control ratio

Population size	No. of cases	True parameter	Method	Relative bias (%)	ASE/ESD†	CP (%)††	RMSE $\times 10^{-3}$
1000	50	0.05	CLR	+9.6	0.97	96.4	44
			CLR-BR	+6.3	0.98	96.6	41
			ULR-BR	+20.0	1.08	97.3	48
			ULR-Q	+11.2	0.97	95.9	44
	100	0.05	CLR	+5.8	0.94	94.9	32
			CLR-BR	+4.1	0.94	95.1	31
			ULR-BR	+17.5	1.03	96.2	36
			ULR-Q	+6.2	0.94	94.7	32
	200	0.05	CLR	+2.2	1.00	95.4	21
			CLR-BR	+1.4	1.00	95.5	21
			ULR-BR	+14.5	1.09	96.6	25
			ULR-Q	+2.2	1.01	95.4	21
	400	0.05	CLR	+2.9	1.01	95.7	16
			CLR-BR	+2.5	1.01	95.6	16
			ULR-BR	+15.5	1.09	95.4	19
			ULR-Q	+2.3	1.02	95.6	16

† Average standard error divided by empirical standard deviation of estimates

†† Coverage probability of 95% confidence intervals.

Table 7. Time-decreasing exposure intensity with censoring rate about 30% and 1:4 case to control ratio

Population size	No. of cases	True parameter	Method	Relative bias (%)	ASE/ESD†	CP (%)††	RMSE $\times 10^{-3}$
1000	50	0.05	CLR	+1.7	0.95	95.3	39
			CLR-BR	+2.9	0.95	96.0	37
			ULR-BR	+5.4	1.01	96.3	39
			ULR-Q	+3.0	0.95	94.7	39
	100	0.05	CLR	-0.1	0.98	95.2	27
			CLR-BR	+0.6	0.98	95.3	26
			ULR-BR	+3.1	1.02	95.5	28
			ULR-Q	+0.1	0.98	95.0	27
	200	0.05	CLR	+1.7	0.98	94.8	19
			CLR-BR	+2.1	0.98	94.9	19
			ULR-BR	+4.7	1.02	95.3	20
			ULR-Q	+1.5	0.98	94.5	19
	400	0.05	CLR	+0.5	0.96	93.0	15
			CLR-BR	+0.7	0.96	93.2	15
			ULR-BR	+3.2	1.00	94.1	15
			ULR-Q	-0.1	0.97	93.6	15

† Average standard error divided by empirical standard deviation of estimates

†† Coverage probability of 95% confidence intervals.

Table 8. Time decreasing exposure intensity with censoring rate about 30% and 1:10 case to control ratio

Population size	No. of cases	True parameter	Method	Relative bias (%)	ASE/ESD†	CP (%)††	RMSE $\times 10^{-3}$
1000	50	0.05	CLR	-3.4	0.95	94.9	35
			CLR-BR	+1.2	0.96	95.3	33
			ULR-BR	-1.7	0.94	94.2	33
			ULR-Q	-3.2	0.96	95.1	35
	100	0.05	CLR	+0.9	0.99	94.6	24
			CLR-BR	+3.2	0.99	94.9	24
			ULR-BR	+0.8	0.96	93.7	23
			ULR-Q	+0.6	0.99	94.8	24
	200	0.05	CLR	+1.7	0.98	95.5	18
			CLR-BR	+2.9	0.98	95.3	17
			ULR-BR	+0.7	0.95	95.0	17
			ULR-Q	+1.1	0.98	95.5	17
	400	0.05	CLR	+2.0	1.00	95.4	13
			CLR-BR	+2.7	1.00	95.4	13
			ULR-BR	+0.5	0.96	94.7	13
			ULR-Q	+1.2	1.00	95.9	13

† Average standard error (ASE) divided by empirical standard deviation (ESD) of estimates.

†† Coverage probability of 95% confidence intervals.

Online Supplementary Material 3.

Simulation settings and procedures and results: Dynamic population

1. Settings and procedures

(A) Generation of the dynamic population with population size 1,000

(1) Generate a population with 80% of its members under observation since time 0 and 20% new members with entry times that following uniform distribution $U(0,1)$.
(2) Generate N survival ages T^* from a marginal Weibull distribution with shape parameter $\gamma = 0.5$, and scale parameter $\lambda = 0.5$.
(3) Generate censoring ages C such that 50% of the population have exit times that follows a uniform distribution $U(1,2)$ and the other 50% remain under observation till end of study at time 2.
(4) Denote $t = \min(T^*, C)$ and $d = I_{\{T^* \le C\}}$.
(5) Sort the N tuples (t_i, d_i) such that $t_i < t_{i+1},\ i = 1, \dots, N-1$.
(6) Generate time at exposure initiation A_j such that 2/3 of the population have A_j being a time-varying covariate that follows a uniform distribution $U(0,2)$; the other 1/3 of the population remain exposure-free through-out, $A_j = \infty$.
(7) Define a covariate matrix with element $E_j(t_i) = 0\ if\ t_i < A_j,\ E_j(t_i) = 1\ if\ t_i \ge A_j$, at each time $t_i,\ i = 1, \dots, N$ for all subjects $(j = 1, \dots, N)$.
(8) Permutational algorithm:
Starting from the earliest observed time t_1, randomly assign each consecutive survival status tuple $(t_i, d_i),\ i = 1, \dots, N$ to a vector of current covariate values $E_j(t_i), j = 1, \dots, N$.
   (a) If $d_i = 1$ (i.e. t_i represents an event time), covariate vectors are sampled with probabilities based on the partial likelihood of the Cox model. Accordingly, for an subject j at t_i, this probability is defined as $Prob_j(t_i) = \frac{\exp(\beta E_j(t_i))}{\sum_{s \in R_i} \exp(\beta E_s(t_i))}$, where R_i is the risk set at t_i, which excluded those subjects who had been selected for earlier time. We considered the true regression parameter value $\beta = -0.3$.
   (b) If $d_i = 0$, assign a subject who is censored at time t_i by simple random sampling from the risk set R_i with equal probability.

(B) Case-control study design using incidence density sampling

Case to control ratio was 1: M, with M = 1, 2, 4 or 10.

(9) We randomly select 50, 100, 200 or 400 events as cases.

(10) For each case, we randomly selected M control(s) among subjects still at risk at the time of the case's diagnosis. Exposure status was ascertained at this time.

(11) Following the incidence density sampling approach, a subject could serve as a control more than once, and a case could be selected as a control for an earlier case.

2. Simulation results

Table 1. Dynamic population and 1:1 case to control ratio

Population size	No. of cases	True parameter	Method	Relative bias (%)	ASE/ESD †	CP (%)††	RMSE
1000	50	-0.3	CLR	+97.2	71.1	98.8	3.03
			CLR-BR	+12.9	0.91	97.7	0.72
			ULR-BR	+49.2	1.06	97.8	0.95
			ULR-Q	+30.2	5.86	96.1	1.63
	100	-0.3	CLR	+3.9	0.97	96.0	0.51
			CLR-BR	-2.4	0.97	95.7	0.47
			ULR-BR	+30.5	1.07	97.7	0.63
			ULR-Q	+1.1	0.97	94.9	0.49
	200	-0.3	CLR	+4.5	0.97	95.2	0.34
			CLR-BR	+1.5	0.97	95.4	0.33
			ULR-BR	+35	1.06	96.3	0.45
			ULR-Q	+3.0	0.98	95.0	0.34
	400	-0.3	CLR	-2.7	1.00	95.5	0.23
			CLR-BR	+4.0	1.00	95.6	0.23
			ULR-BR	+27.7	1.08	96.2	0.32
			ULR-Q	-4.9	1.02	96.0	0.23

† Average standard error divided by empirical standard deviation of estimates.

†† Coverage probability of 95% confidence intervals.

Table 2. Dynamic population and 1:2 case to control ratio

Population size	No. of cases	True parameter	Method	Relative bias (%)	ASE/ESD†	CP (%)††	RMSE
1000	50	-0.3	CLR	+30.8	12.3	96.8	1.08
			CLR-BR	+0.5	0.96	96.2	0.60
			ULR-BR	+13.7	1.07	98.1	0.66
			ULR-Q	+27.9	2.43	96.2	0.98
	100	-0.3	CLR	-3.4	1.03	95.8	0.41
			CLR-BR	-11.1	1.03	95.5	0.39
			ULR-BR	+0.8	1.14	97.9	0.42
			ULR-Q	+5.1	1.04	95.9	0.40
	200	-0.3	CLR	-0.2	1.00	95.8	0.29
			CLR-BR	-4.1	1.01	95.7	0.29
			ULR-BR	+5.5	1.10	96.8	0.31
			ULR-Q	-2.6	1.02	95.6	0.28
	400	-0.3	CLR	-1.2	1.01	96.1	0.20
			CLR-BR	+3.0	1.01	96.1	0.20
			ULR-BR	+6.2	1.10	97.4	0.22
			ULR-Q	+3.2	1.02	96.2	0.20

† Average standard error divided by empirical standard deviation of estimates.

†† Coverage probability of 95% confidence intervals.

Table 3. Dynamic population and 1:4 case to control ratio

Population size	No. of cases	True parameter	Method	Relative bias (%)	ASE/ESD†	CP (%)††	RMSE
1000	50	-0.3	CLR	+44.0	20.0	97.2	1.33
			CLR-BR	+0.7	0.99	96.2	0.54
			ULR-BR	+4.6	1.04	97.0	0.53
			ULR-Q	+34.4	2.96	97.3	1.05
	100	-0.3	CLR	+12.8	0.92	94.6	0.42
			CLR-BR	+3.0	0.93	94.2	0.40
			ULR-BR	+4.1	0.96	95.0	0.40
			ULR-Q	+11.4	0.92	94.9	0.41
	200	-0.3	CLR	+2.2	0.99	95.5	0.27
			CLR-BR	-2.3	0.99	95.8	0.27
			ULR-BR	+2.0	1.02	96.8	0.26
			ULR-Q	+0.2	1.00	95.9	0.26
	400	-0.3	CLR	-0.6	1.04	95.6	0.18
			CLR-BR	+2.7	1.04	95.6	0.18
			ULR-BR	+3.0	1.07	95.9	0.18
			ULR-Q	-2.5	1.05	95.7	0.18

† Average standard error divided by empirical standard deviation of estimates.

†† Coverage probability of 95% confidence intervals.

Table 4. Dynamic population and 1:10 case to control ratio

Population size	No. of cases	True parameter	Method	Relative bias (%)	ASE/ESD†	CP (%)††	RMSE
1000	50	-0.3	CLR	+61.0	19.6	96.5	1.47
			CLR-BR	+9.2	0.95	95.9	0.54
			ULR-BR	+9.5	0.90	94.3	0.52
			ULR-Q	+54.1	3.59	96.5	1.27
	100	-0.3	CLR	+7.2	0.99	95.4	0.36
			CLR-BR	+3.3	1.00	95.1	0.35
			ULR-BR	-4.6	0.94	94.1	0.34
			ULR-Q	+5.5	1.00	95.4	0.36
	200	-0.3	CLR	+4.3	1.00	95.2	0.25
			CLR-BR	-0.7	1.00	94.8	0.25
			ULR-BR	-3.1	0.94	93.2	0.24
			ULR-Q	+2.3	1.01	95.5	0.25
	400	-0.3	CLR	+3.1	0.99	94.4	0.18
			CLR-BR	+0.7	1.00	94.8	0.18
			ULR-BR	+2.2	0.93	93.3	0.17
			ULR-Q	+1.0	1.01	95.0	0.17

† Average standard error divided by empirical standard deviation of estimates.

†† Coverage probability of 95% confidence intervals.

Online Supplementary Material 4.

Further simulation settings and procedures: Dynamic population

1. Variation in settings and procedures

Other than the modifications described below, the simulation settings and procedures are the same as those described in Online Supplementary Material 3.

(A) Generation of the dynamic population with population size N=1000

(1) Generate N survival ages T^* from a marginal Weibull distribution with shape parameter $\gamma = 1$ which leads to a constant hazard over time or $\gamma = 1.5$ which leads to an increasing hazard over time and scale parameter $\lambda = 0.5$.

2. Simulation results in figures

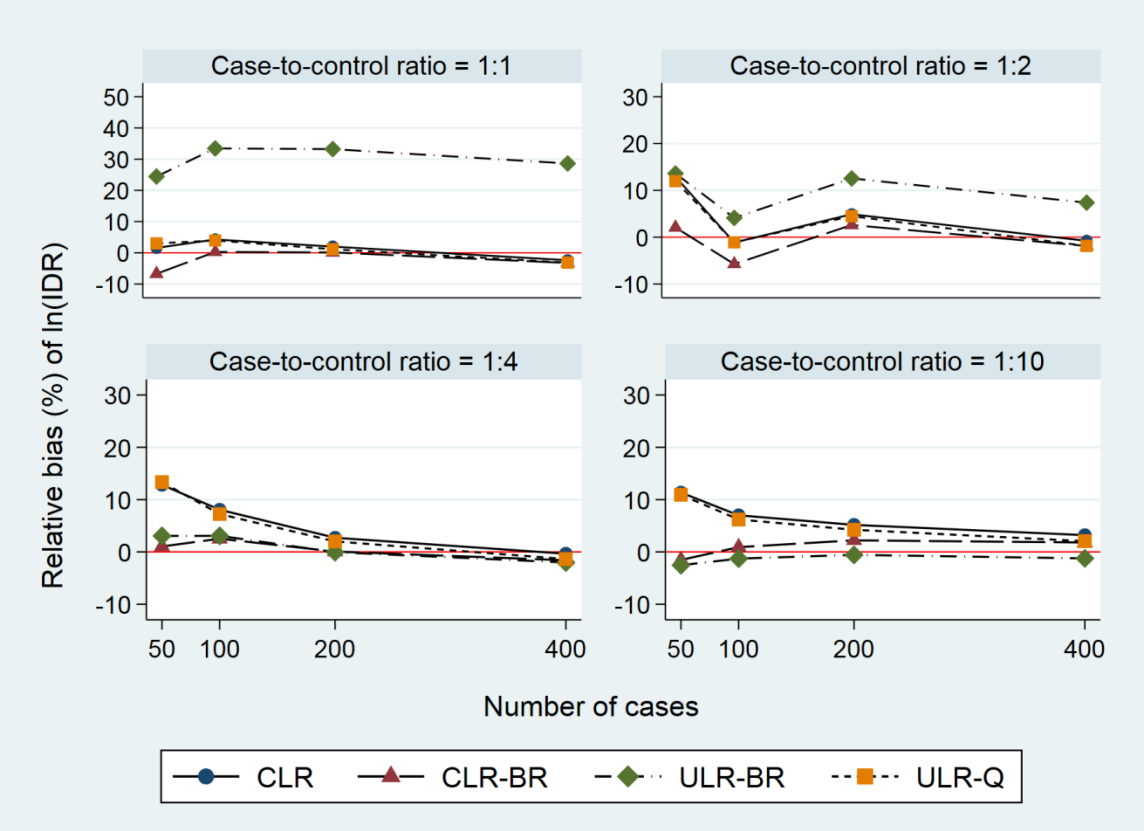

Figure 1. Relative bias of ln(IDR) in relation to the number of cases, case to control ratio and analytic methods under a simulation setting of a dynamic population with constant hazard.

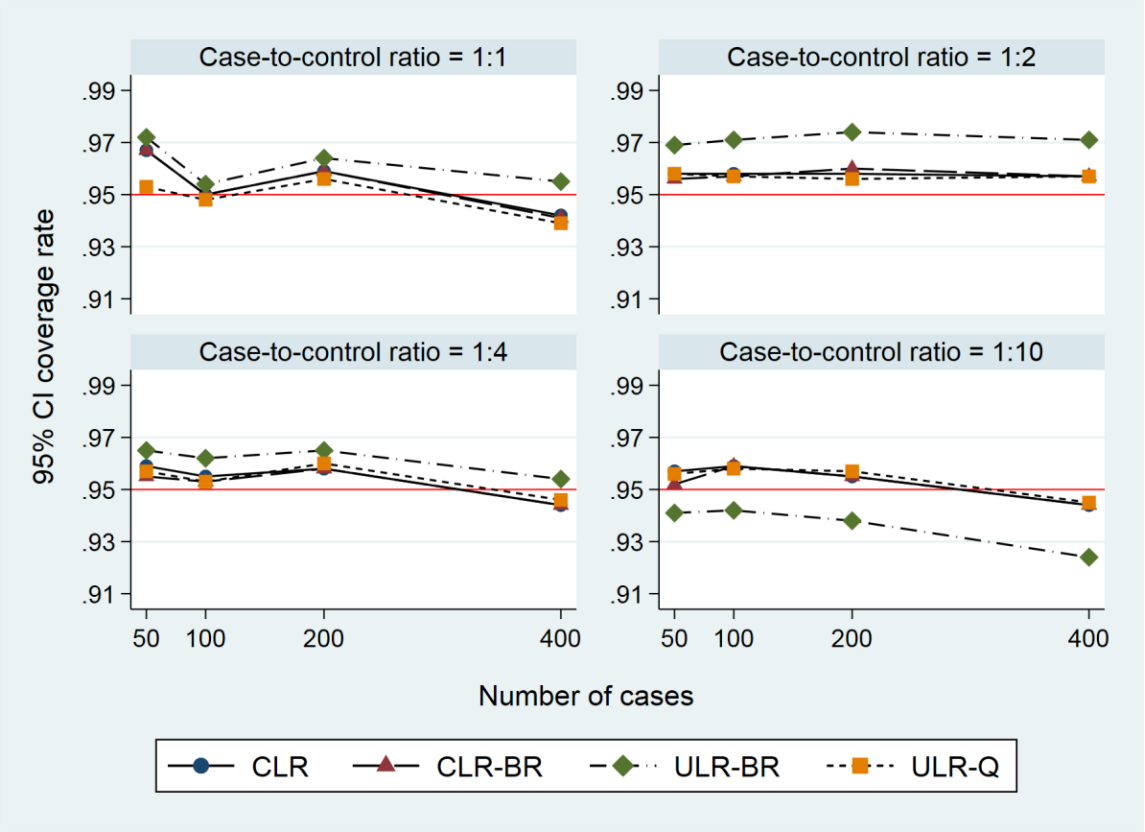

Figure 2. Coverage probability of 95% CI in relation to the number of cases, case to control ratio and analytic methods under a simulation setting of a dynamic population with constant hazard.

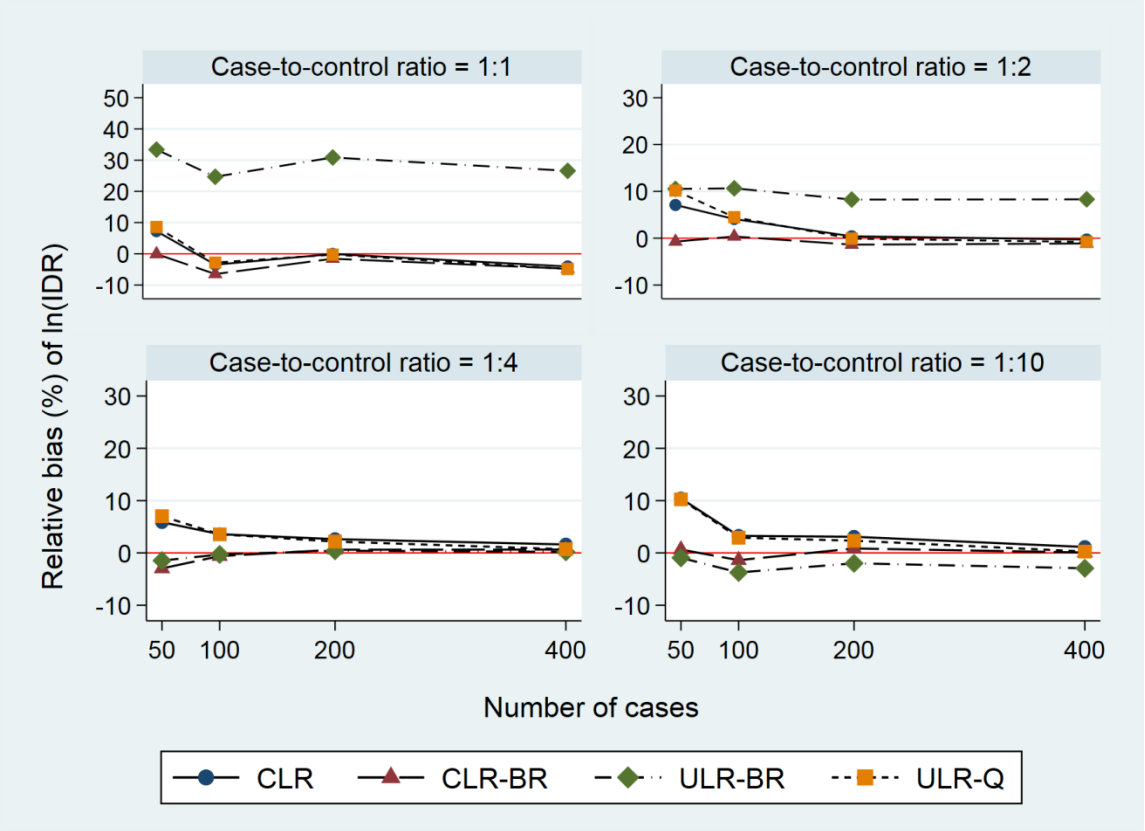

Figure 3. Relative bias of ln(IDR) in relation to the number of cases, case to control ratio and analytic methods under a simulation setting of a dynamic population with increasing hazard.

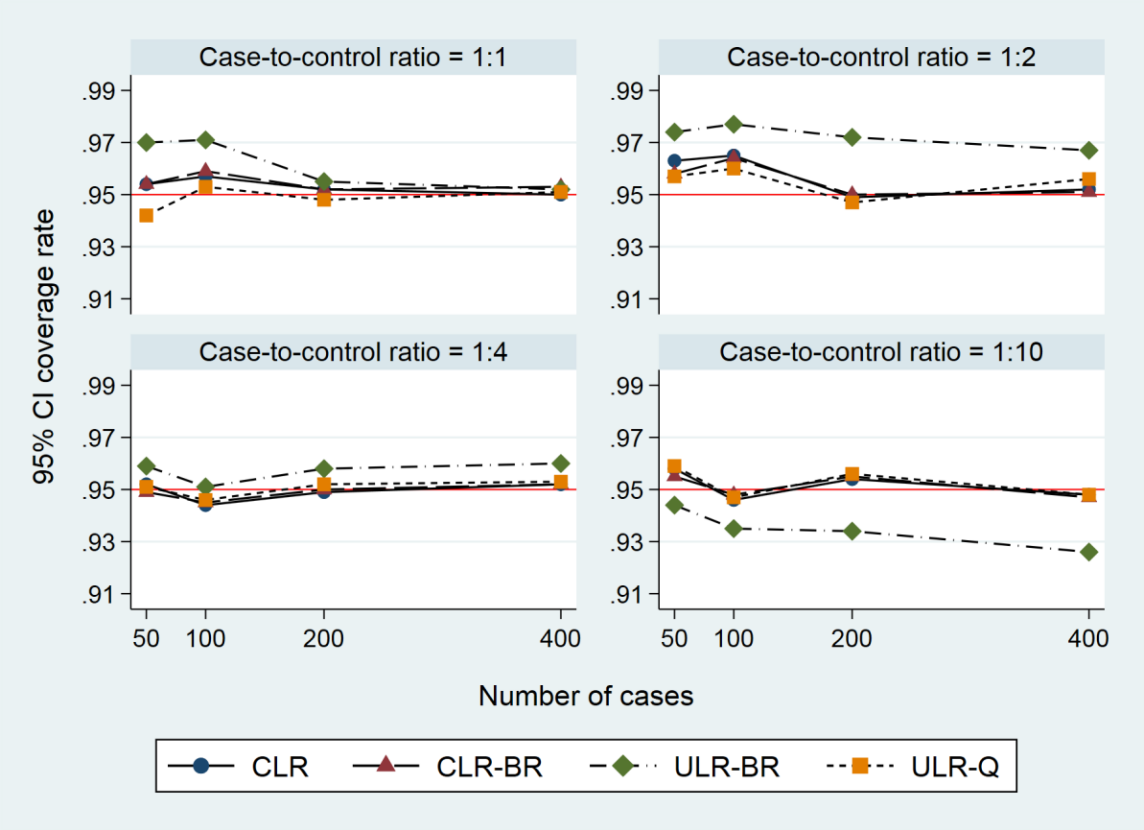

Figure 4. Coverage probability of 95% CI in relation to the number of cases, case to control ratio and analytic methods under a simulation setting of a dynamic population with increasing hazard.

3. Simulation results in tables

Table 1. Dynamic population with constant hazard and 1:1 case to control ratio

Population size	No. of cases	True parameter	Method	Relative bias (%)	ASE/ESD†	CP (%)††	RMSE
1000	50	-0.3	CLR	+1.6	0.96	96.7	0.60
			CLR-BR	-6.7	0.98	96.7	0.54
			ULR-BR	+24.4	1.09	97.2	0.72
			ULR-Q	+3.0	0.96	95.3	0.59
	100	-0.3	CLR	+4.3	0.97	95.0	0.40
			CLR-BR	+0.3	0.98	95.0	0.39
			ULR-BR	+33.4	1.07	95.4	0.52
			ULR-Q	+3.9	0.98	94.8	0.39
	200	-0.3	CLR	+2.0	1.00	95.9	0.27
			CLR-BR	+0.1	1.00	95.9	0.27
			ULR-BR	+33.2	1.08	96.4	0.37
			ULR-Q	+1.2	1.01	95.6	0.27
	400	-0.3	CLR	-2.4	0.99	94.2	0.19
			CLR-BR	-3.3	0.99	94.1	0.19
			ULR-BR	+28.6	1.06	95.5	0.26
			ULR-Q	-3.1	0.99	93.9	0.19

† Average standard error divided by empirical standard deviation of estimates.

†† Coverage probability of 95% confidence intervals.

Table 2. Dynamic population with constant hazard and 1:2 case to control ratio

Population size	No. of cases	True parameter	Method	Relative bias (%)	ASE/ESD†	CP (%)††	RMSE
1000	50	-0.3	CLR	+12.9	0.93	95.8	0.53
			CLR-BR	+2.1	0.94	95.6	0.50
			ULR-BR	+13.6	1.04	96.9	0.54
			ULR-Q	+12.0	0.94	95.8	0.52
	100	-0.3	CLR	-1.1	0.99	95.8	0.34
			CLR-BR	-5.7	0.99	95.7	0.33
			ULR-BR	+4.1	1.09	97.1	0.36
			ULR-Q	-1.1	0.99	95.7	0.34
	200	-0.3	CLR	+4.9	1.00	95.8	0.23
			CLR-BR	+2.6	1.01	96.0	0.23
			ULR-BR	+12.5	1.10	97.4	0.25
			ULR-Q	+4.5	1.01	95.6	0.23
	400	-0.3	CLR	-0.8	0.99	95.7	0.17
			CLR-BR	-1.9	0.99	95.7	0.17
			ULR-BR	+7.4	1.08	97.1	0.18
			ULR-Q	-1.9	1.00	95.7	0.16

† Average standard error divided by empirical standard deviation of estimates.

†† Coverage probability of 95% confidence intervals.

Table 3. Dynamic population with constant hazard and 1:4 case to control ratio

Population size	No. of cases	True parameter	Method	Relative bias (%)	ASE/ESD†	CP (%)††	RMSE
1000	50	-0.3	CLR	+12.8	0.98	95.9	0.45
			CLR-BR	+1.0	1.00	95.5	0.43
			ULR-BR	+3.1	1.04	96.5	0.43
			ULR-Q	+13.3	0.98	95.7	0.46
	100	-0.3	CLR	+8.1	0.99	95.5	0.31
			CLR-BR	+2.5	1.00	95.3	0.31
			ULR-BR	+3.1	1.03	96.2	0.30
			ULR-Q	+7.2	0.99	95.3	0.31
	200	-0.3	CLR	+2.7	1.01	95.8	0.21
			CLR-BR	+0.1	1.01	95.8	0.21
			ULR-BR	+0.0	1.04	96.5	0.21
			ULR-Q	+2.0	1.02	96.0	0.21
	400	-0.3	CLR	-0.3	0.98	94.4	0.15
			CLR-BR	-1.6	0.98	94.4	0.15
			ULR-BR	-2.0	1.01	95.4	0.15
			ULR-Q	-1.4	0.99	94.6	0.15

† Average standard error divided by empirical standard deviation of estimates.

†† Coverage probability of 95% confidence intervals.

Table 4. Dynamic population with constant hazard and 1:10 case to control ratio

Population size	No. of cases	True parameter	Method	Relative bias (%)	ASE/ESD†	CP (%)††	RMSE
1000	50	-0.3	CLR	+11.4	0.99	95.7	0.42
			CLR-BR	-1.5	1.00	95.2	0.41
			ULR-BR	-2.5	0.94	94.1	0.39
			ULR-Q	+10.9	0.99	95.6	0.42
	100	-0.3	CLR	+7.0	1.00	95.9	0.29
			CLR-BR	+0.9	1.01	95.9	0.29
			ULR-BR	-1.3	0.94	94.2	0.28
			ULR-Q	+6.2	1.01	95.8	0.29
	200	-0.3	CLR	+5.2	1.01	95.5	0.20
			CLR-BR	+2.2	1.01	95.5	0.20
			ULR-BR	-0.6	0.94	93.8	0.19
			ULR-Q	+4.2	1.02	95.7	0.20
	400	-0.3	CLR	+3.2	0.97	94.4	0.15
			CLR-BR	+1.8	0.97	94.4	0.15
			ULR-BR	-1.2	0.90	92.4	0.14
			ULR-Q	+2.1	0.97	94.5	0.15

† Average standard error divided by empirical standard deviation of estimates.

†† Coverage probability of 95% confidence intervals.

Table 5. Dynamic population with increasing hazard and 1:1 case to control ratio

Population size	No. of cases	True parameter	Method	Relative bias (%)	ASE/ESD†	CP (%)††	RMSE
1000	50	-0.3	CLR	+7.3	0.94	95.4	0.56
			CLR-BR	-0.1	0.95	95.4	0.52
			ULR-BR	+33.4	1.05	97.0	0.69
			ULR-Q	+8.6	0.94	94.2	0.55
	100	-0.3	CLR	-3.5	0.98	95.7	0.36
			CLR-BR	-6.5	0.98	95.9	0.35
			ULR-BR	+24.7	1.07	97.1	0.47
			ULR-Q	-2.8	0.98	95.3	0.36
	200	-0.3	CLR	+0.0	0.98	95.2	0.25
			CLR-BR	-1.6	0.98	95.2	0.25
			ULR-BR	30.9	1.06	95.5	0.34
			ULR-Q	-0.3	0.99	94.8	0.25
	400	-0.3	CLR	-4.1	1.00	95.0	0.17
			CLR-BR	-4.8	1.00	95.3	0.17
			ULR-BR	+26.6	1.07	95.2	0.24
			ULR-Q	-4.9	1.01	95.1	0.17

† Average standard error divided by empirical standard deviation of estimates.

†† Coverage probability of 95% confidence intervals.

Table 6. Dynamic population with increasing hazard and 1:2 case to control ratio

Population size	No. of cases	True parameter	Method	Relative bias (%)	ASE/ESD†	CP (%)††	RMSE
1000	50	-0.3	CLR	+7.1	0.99	96.3	0.45
			CLR-BR	-0.7	0.99	95.8	0.43
			ULR-BR	+10.5	1.10	97.4	0.47
			ULR-Q	+10.2	0.97	95.7	0.46
	100	-0.3	CLR	+4.1	0.99	96.5	0.31
			CLR-BR	+0.4	0.99	96.4	0.30
			ULR-BR	+10.7	1.09	97.7	0.33
			ULR-Q	+4.5	0.99	96.0	0.31
	200	-0.3	CLR	+0.4	1.01	94.9	0.21
			CLR-BR	-1.4	1.01	95.0	0.21
			ULR-BR	+8.3	1.10	97.2	0.23
			ULR-Q	-0.1	1.02	94.7	0.21
	400	-0.3	CLR	-0.3	1.02	95.2	0.15
			CLR-BR	-1.1	1.02	95.1	0.15
			ULR-BR	+8.3	1.11	96.7	0.16
			ULR-Q	-0.8	1.02	95.6	0.15

† Average standard error divided by empirical standard deviation of estimates.

†† Coverage probability of 95% confidence intervals.

Table 7. Dynamic population with increasing hazard and 1:4 case to control ratio

Population size	No. of cases	True parameter	Method	Relative bias (%)	ASE/ESD†	CP (%)††	RMSE
1000	50	-0.3	CLR	+5.9	1.00	95.2	0.40
			CLR-BR	-3.0	1.01	94.9	0.39
			ULR-BR	-1.5	1.05	95.9	0.38
			ULR-Q	+7.0	1.00	95.1	0.41
	100	-0.3	CLR	+3.6	0.97	94.4	0.29
			CLR-BR	-0.6	0.97	94.5	0.29
			ULR-BR	-0.3	1.01	95.1	0.28
			ULR-Q	+3.6	0.97	94.6	0.29
	200	-0.3	CLR	+2.6	1.00	94.9	0.20
			CLR-BR	+0.6	1.00	95.0	0.20
			ULR-BR	+0.4	1.04	95.8	0.19
			ULR-Q	+2.2	1.00	95.2	0.20
	400	-0.3	CLR	+1.6	1.00	95.2	0.14
			CLR-BR	+0.6	1.00	95.2	0.14
			ULR-BR	+0.2	1.03	96.0	0.14
			ULR-Q	+0.7	1.01	95.3	0.14

† Average standard error divided by empirical standard deviation of estimates.

†† Coverage probability of 95% confidence intervals.

Table 8. Dynamic population with increasing hazard and 1:10 case to control ratio

Population size	No. of cases	True parameter	Method	Relative bias (%)	ASE/ESD†	CP (%)††	RMSE
1000	50	-0.3	CLR	+10.4	0.98	95.8	0.39
			CLR-BR	+0.6	0.99	95.5	0.38
			ULR-BR	-0.9	0.93	94.4	0.36
			ULR-Q	+10.3	0.98	95.9	0.39
	100	-0.3	CLR	+3.3	0.98	94.6	0.27
			CLR-BR	-1.4	0.98	94.8	0.27
			ULR-BR	-3.7	0.92	93.5	0.26
			ULR-Q	+2.9	0.98	94.7	0.27
	200	-0.3	CLR	+3.1	1.00	95.4	0.19
			CLR-BR	+0.9	1.00	95.5	0.19
			ULR-BR	-2.0	0.93	93.4	0.18
			ULR-Q	+2.3	1.00	95.6	0.19
	400	-0.3	CLR	+1.1	0.99	94.8	0.13
			CLR-BR	+0.1	0.99	94.7	0.13
			ULR-BR	-2.9	0.92	92.6	0.13
			ULR-Q	+0.3	0.99	94.8	0.13

† Average standard error divided by empirical standard deviation of estimates.

†† Coverage probability of 95% confidence intervals.

Online Supplementary Material 5.

Further simulation settings and results: Two non-linear forms (square root and logarithm)

1. Variation in settings and procedures

Other than the modifications described below, the simulation settings and procedures are the same as those described in Online Supplementary Material 1.

(A) Generation of the population data with population size N = 500, 1000, 2000 or 4000

(1) Denote $t = \min(T^*, C)$ and $d = I_{\{T^* \leq C\}}$, let $\bar{t}$ be the mean of t when $d = 1$.
(2) Consider a decreasing intensity pattern, in which the percentage of decrease in intensity at each predefined age interval generated from lognormal distributions with mean 0.1 and SD 0.075, i.e. average rate of decrease on log-scale in intensity is 10%.
(3) Permutational algorithm: Starting from the earliest observed time t_1, randomly assign each consecutive survival status tuple $(t_i, d_i),\ i = 1, \dots, N$ to a vector of current covariate values $E_j(t_i), j = 1, \dots, N$.
    (a) If $d_i = 1$ (i.e. if t_i represents an event time), covariate vectors are sampled with probabilities based on the partial likelihood of the Cox model. Accordingly, for an subject j at t_i, this probability is defined as $Prob_j(t_i) = \frac{\exp(\eta_{ij})}{\sum_{s \in R_i} \exp(\eta_{is})}$, where R_i is the risk set at t_i, which excluded those subjects who had been selected for earlier time. We refer to $\eta_{ij} = \beta\sqrt{E_j(t_i)/100}$ and $\eta_{ij} = \beta \ln\big(E_j(t_i)/100 + 1\big)$ as non-linear forms 1 and 2, respectively. The true parameter value $\beta = 0.05$.
    (b) If $d_i = 0$, assign a subject who is censored at time t_i by simple random sampling from the risk set R_i with equal probability.

(B) Presentation of findings

Coverage probabilities of 95% CI that drop below the range of y-axis 0.9 to 1.0 are not shown in the figures. These details are shown in tables.

2. Simulation results in figures

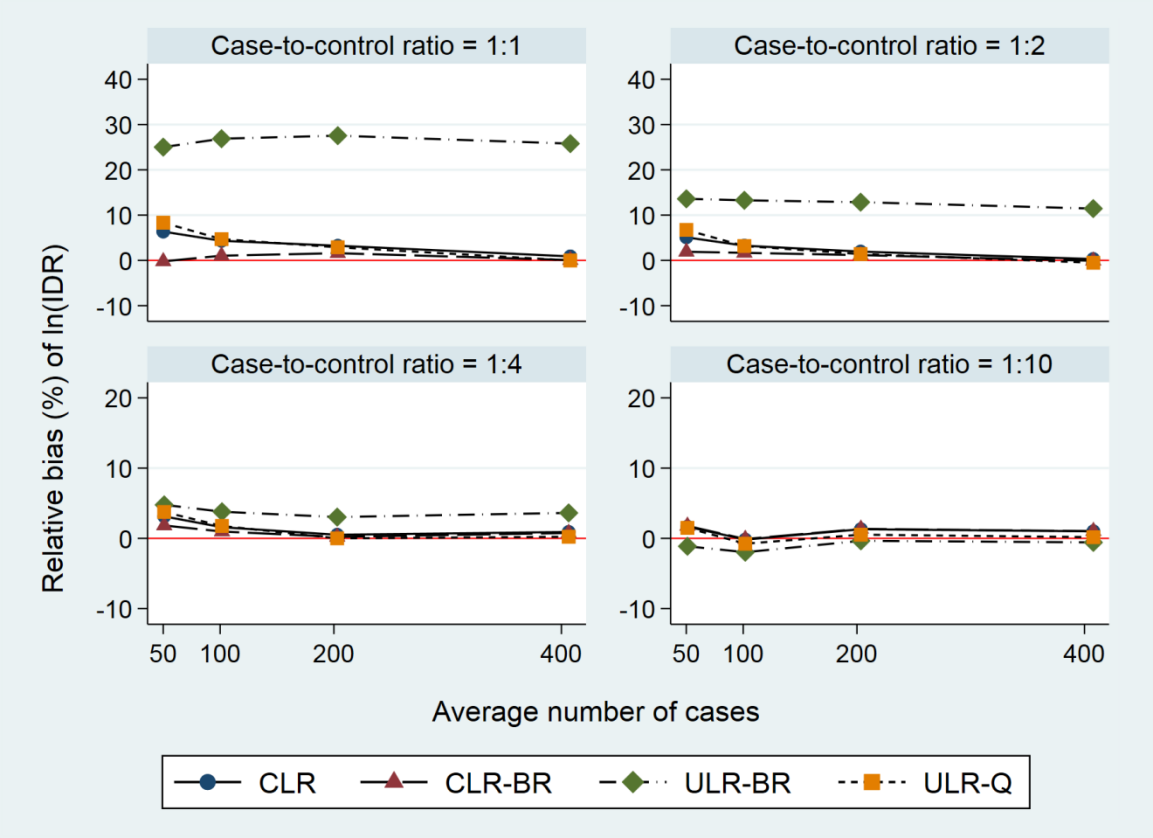

Figure 1. Relative bias of ln(IDR) in relation to the number of cases, case to control ratio and analytic methods under a simulation setting of a fix population with non-linear form 1 (square root).

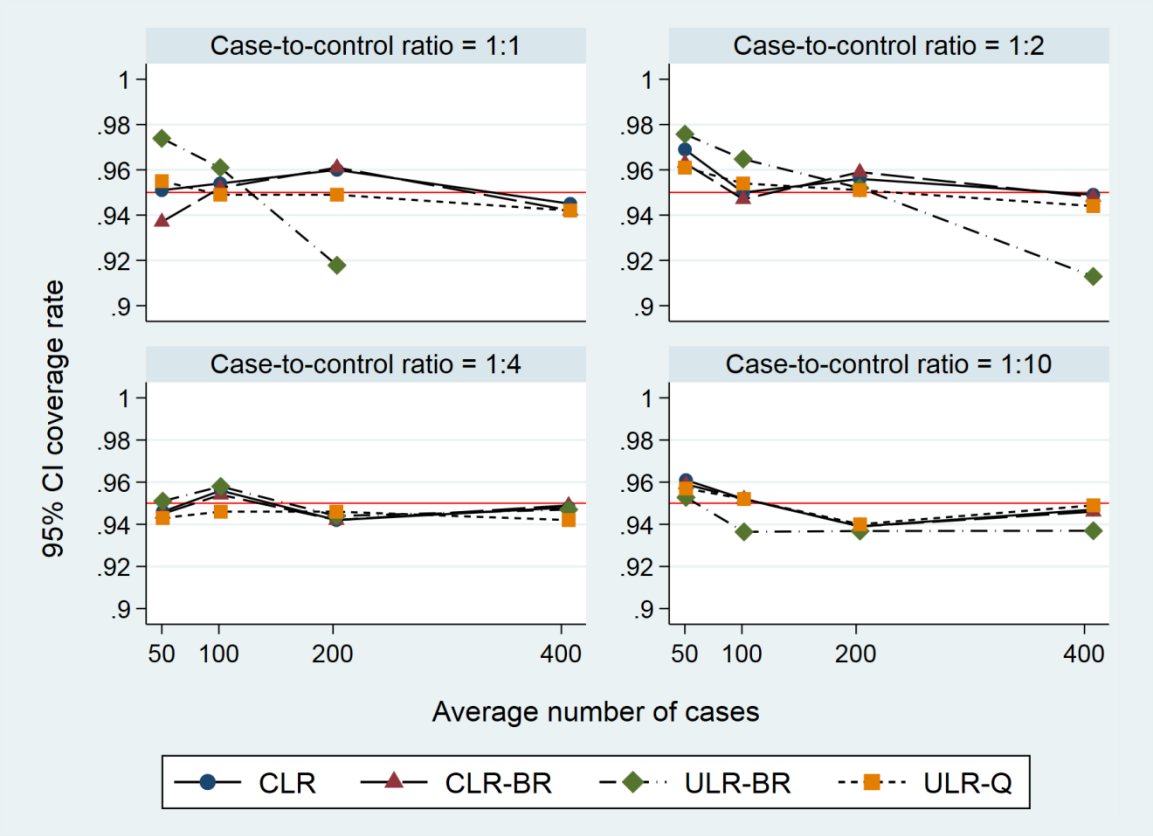

Figure 2. Coverage probability of 95% CI in relation to the number of cases, case to control ratio and analytic methods under a simulation setting of a fix population with non-linear form 1 (square root).

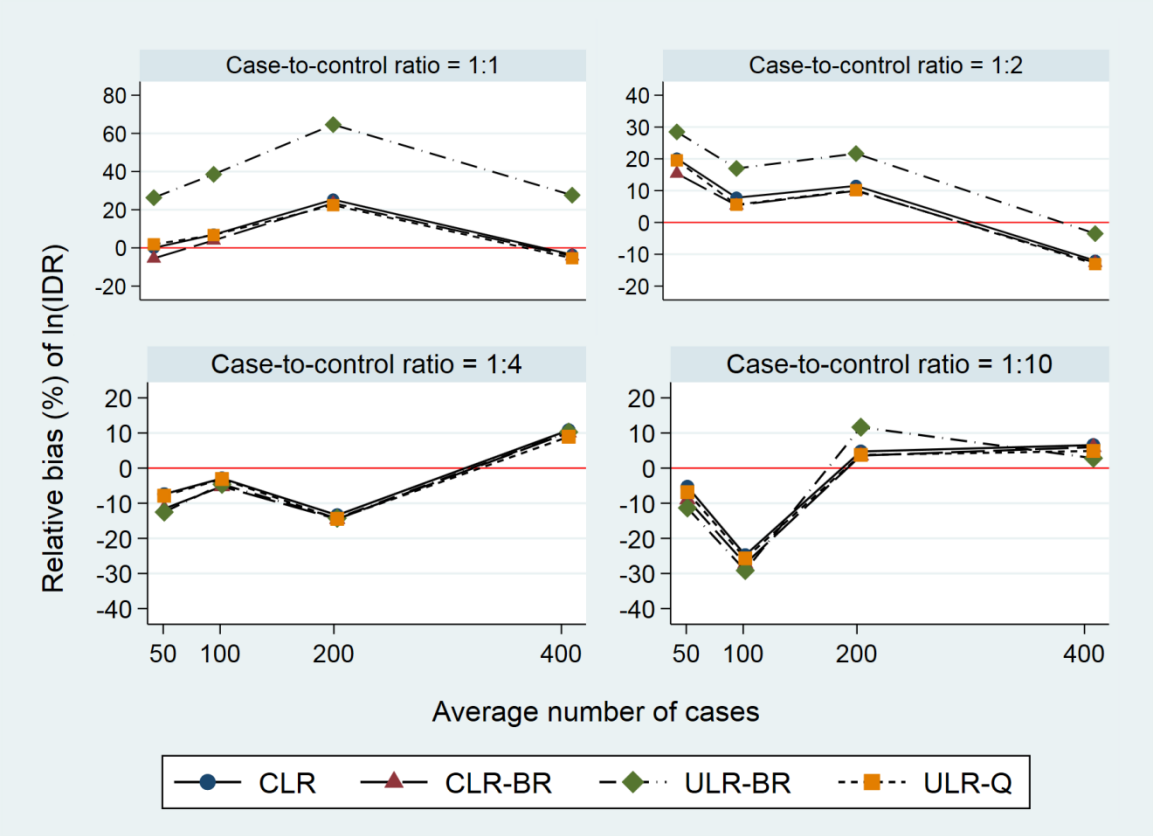

Figure 3. Relative bias of ln(IDR) in relation to the number of cases, case to control ratio and analytic methods under a simulation setting of a fix population with non-linear form 2 (logarithm).

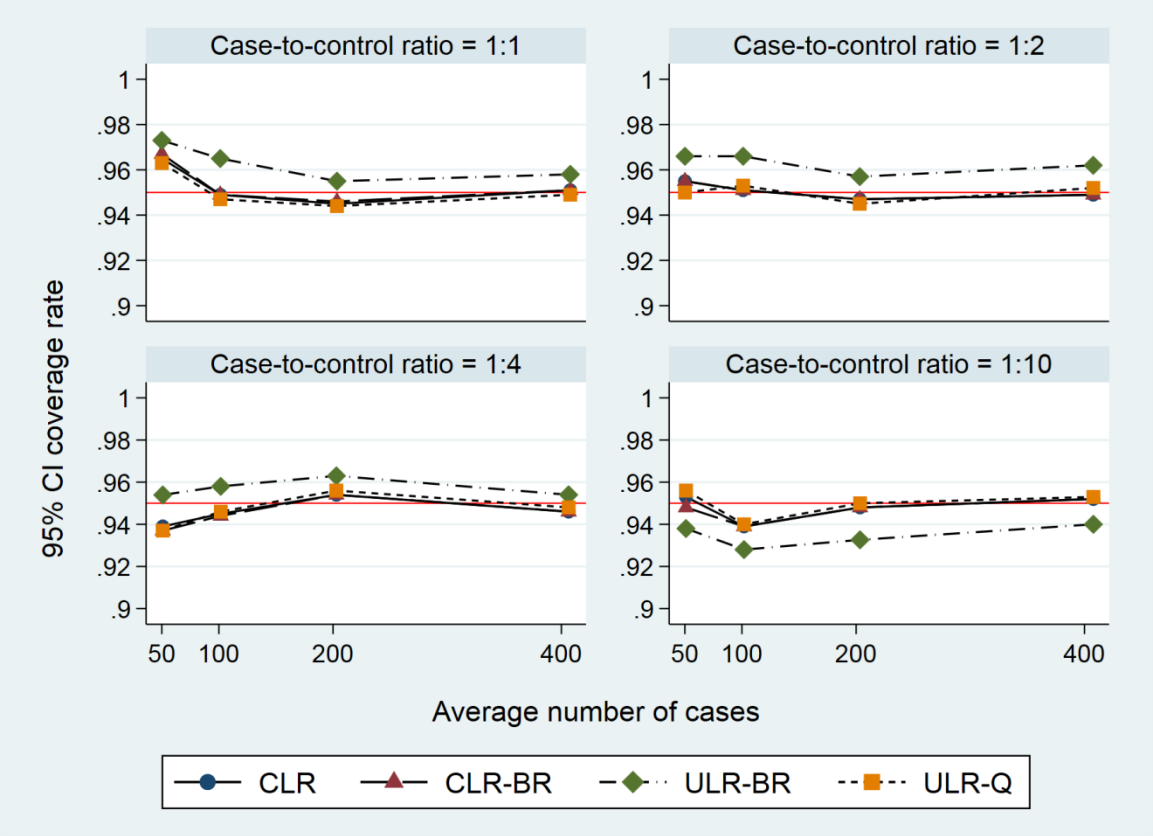

Figure 4. Coverage probability of 95% CI in relation to the number of cases, case to control ratio and analytic methods under a simulation setting of a fix population with non-linear form 2 (logarithm).

3. Simulation results in tables

Table 1. Non-linear form 1 (square root) and 1:1 case to control ratio

Population size	Average no. of cases	True parameter	Method	Relative bias (%)	ASE/ESD†	CP (%)††	RMSE $\times 10^{-3}$
500	51	0.05	CLR	+6.4	0.93	95.1	29
			CLR-BR	-0.2	0.95	93.7	27
			ULR-BR^	+25.0	1.14	97.4	32
			ULR-Q	+8.3	0.95	95.5	27
1000	102	0.05	CLR	+4.3	0.96	95.4	19
			CLR-BR	+1.0	0.97	95.2	18
			ULR-BR^	+26.9	1.14	96.1	25
			ULR-Q	+4.7	0.96	94.9	18
2000	204	0.05	CLR	+3.2	1.03	96.0	13
			CLR-BR	+1.6	1.03	96.1	12
			ULR-BR^	+27.6	1.20	91.8	19
			ULR-Q	+2.9	1.02	94.9	12
4000	407	0.05	CLR	+0.9	0.95	94.5	9
			CLR-BR	+0.1	0.95	94.2	9
			ULR-BR^	+25.8	1.10	83.9	17
			ULR-Q	+0.0	0.96	94.2	9

† Average standard error (ASE) divided by empirical standard deviation (ESD) of estimates.

†† Coverage probability of 95% confidence intervals.

^ The number of replicates which did not converge up 100 iterations in the settings with population size 500 to 4,000 were 4, 1, 2 and 1, respectively.

Table 2. Non-linear form 1 (square root) and 1:2 case to control ratio

Population size	Average no. of cases	True parameter	Method	Relative bias (%)	ASE/ESD†	CP (%)††	RMSE $\times 10^{-3}$
500	51	0.05	CLR	+5.1	1.00	96.9	22
			CLR-BR	+1.9	1.01	96.3	21
			ULR-BR^	+13.6	1.11	97.6	24
			ULR-Q	+6.7	0.99	96.1	22
1000	102	0.05	CLR	+3.3	0.99	95.0	15
			CLR-BR	+1.7	0.99	94.7	15
			ULR-BR^	+13.3	1.09	96.5	18
			ULR-Q	+3.2	1.01	95.4	15
2000	203	0.05	CLR	+1.9	0.99	95.6	11
			CLR-BR	+1.2	0.99	95.9	11
			ULR-BR^	+12.9	1.08	95.2	13
			ULR-Q	+1.4	1.00	95.1	10
4000	407	0.05	CLR	+0.3	0.97	94.9	8
			CLR-BR	-0.1	0.97	94.8	8
			ULR-BR^	+11.4	1.05	91.3	10
			ULR-Q	-0.5	0.96	94.4	8

† Average standard error (ASE) divided by empirical standard deviation (ESD) of estimates.

†† Coverage probability of 95% confidence intervals.

^ The number of replicates which did not converge up to 100 iterations in the settings with population size 500 to 4,000 were 10, 7, 1 and 1, respectively.

Table 3. Non-linear form 1 (square root) and 1:4 case to control ratio

Population size	Average no. of cases	True parameter	Method	Relative bias (%)	ASE/ESD†	CP (%)††	RMSE $\times 10^{-3}$
500	51	0.05	CLR	+3.1	0.95	94.6	20
			CLR-BR	+1.8	0.95	94.5	19
			ULR-BR	+4.8	0.99	95.1	20
			ULR-Q	+3.8	0.95	94.3	20
1000	102	0.05	CLR	+1.6	0.98	95.6	13
			CLR-BR	+1.0	0.98	95.4	13
			ULR-BR^	+3.8	1.01	95.8	14
			ULR-Q	+1.8	0.97	94.6	13
2000	203	0.05	CLR	+0.5	0.98	94.2	9
			CLR-BR	+0.2	0.98	94.2	9
			ULR-BR	+3.0	1.01	94.4	10
			ULR-Q	+0.0	0.98	94.6	9
4000	406	0.05	CLR	+0.9	1.00	94.8	7
			CLR-BR	+0.8	1.00	94.9	7
			ULR-BR^	+3.6	1.02	94.7	7
			ULR-Q	+0.2	0.99	94.2	7

† Average standard error (ASE) divided by empirical standard deviation (ESD) of estimates.

†† Coverage probability of 95% confidence intervals.

^ The number of replicates which did not converge up to 100 iterations is 1 and 1, respectively.

Table 4. Non-linear form 1 (square root) and 1:10 case to control ratio

Population size	Average no. of cases	True parameter	Method	Relative bias (%)	ASE/ESD†	CP (%)††	RMSE $\times 10^{-3}$
500	51	0.05	CLR	+1.7	0.99	96.1	17
			CLR-BR	+1.8	0.99	95.9	17
			ULR-BR^	-1.1	0.96	95.3	17
			ULR-Q	+1.5	0.99	95.7	17
1000	102	0.05	CLR	-0.2	0.96	95.2	12
			CLR-BR	-0.1	0.96	95.2	12
			ULR-BR^	-2.0	0.93	93.6	12
			ULR-Q	-0.8	0.97	95.2	12
2000	203	0.05	CLR	+1.3	1.00	93.9	8
			CLR-BR	+1.3	1.00	93.9	8
			ULR-BR^	-0.4	0.96	93.7	8
			ULR-Q	+0.5	1.00	94.0	8
4000	408	0.05	CLR	+1.0	0.98	94.7	6
			CLR-BR	+1.0	0.98	94.6	6
			ULR-BR^	-0.6	0.94	93.7	6
			ULR-Q	+0.2	0.99	94.9	6

† Average standard error (ASE) divided by empirical standard deviation (ESD) of estimates.

†† Coverage probability of 95% confidence intervals.

^ The number of replicates which did not converge up to 100 iterations in the settings with population size 500 to 4,000 is 26, 9, 3 and 1, respectively.

Table 5. Non-linear form 2 (logarithm) and 1:1 case to control ratio

Population size	Average no. of cases	True parameter	Method	Relative bias (%)	ASE/ESD†	CP (%)††	RMSE $\times 10^{-2}$
500	51	0.05	CLR	+0.1	0.99	96.5	34
			CLR-BR	-5.5	1.00	96.7	32
			ULR-BR	+26.3	1.10	97.3	42
			ULR-Q	+1.9	1.00	96.3	33
1000	102	0.05	CLR	+6.9	0.99	94.9	23
			CLR-BR	+3.9	0.99	94.9	22
			ULR-BR	+38.6	1.07	96.5	30
			ULR-Q	+6.8	0.99	94.7	23
2000	204	0.05	CLR	+25.3	0.97	94.5	17
			CLR-BR	+23.4	0.97	94.6	16
			ULR-BR	+64.6	1.04	95.5	22
			ULR-Q	+22.4	0.98	94.4	16
4000	407	0.05	CLR	-3.5	0.99	95.1	11
			CLR-BR	-4.3	0.99	95.1	11
			ULR-BR	+27.6	1.06	95.8	15
			ULR-Q	-5.4	1.00	94.9	11

† Average standard error (ASE) divided by empirical standard deviation (ESD) of estimates.

†† Coverage probability of 95% confidence intervals.

Table 6. Non-linear form 2 (logarithm) and 1:2 case to control ratio

Population size	Average no. of cases	True parameter	Method	Relative bias (%)	ASE/ESD†	CP (%)††	RMSE $\times 10^{-2}$
500	51	0.05	CLR	+20.1	0.98	95.5	29
			CLR-BR	+15.4	0.98	95.5	28
			ULR-BR	+28.5	1.07	96.6	31
			ULR-Q	+19.5	0.97	95.0	29
1000	102	0.05	CLR	+7.8	0.99	95.1	20
			CLR-BR	+5.4	0.99	95.1	20
			ULR-BR	+17.0	1.08	96.6	22
			ULR-Q	+5.6	0.99	95.3	20
2000	203	0.05	CLR	+11.5	0.99	94.7	14
			CLR-BR	+10.0	0.99	94.7	14
			ULR-BR	+21.7	1.07	95.7	15
			ULR-Q	+10.2	0.99	94.5	14
4000	407	0.05	CLR	-12.0	0.97	94.9	10
			CLR-BR	-12.7	0.97	94.9	10
			ULR-BR	-3.5	1.05	96.2	11
			ULR-Q	-13.1	0.97	95.2	10

† Average standard error (ASE) divided by empirical standard deviation (ESD) of estimates.

†† Coverage probability of 95% confidence intervals.

Table 7. Non-linear form 2 (logarithm) and 1:4 case to control ratio

Population size	Average no. of cases	True parameter	Method	Relative bias (%)	ASE/ESD†	CP (%)††	RMSE $\times 10^{-2}$
500	51	0.05	CLR	-7.4	0.94	93.9	27
			CLR-BR	-11.6	0.94	93.7	27
			ULR-BR^	-12.5	0.99	95.4	27
			ULR-Q	-7.9	0.94	93.7	27
1000	102	0.05	CLR	-2.9	0.97	94.5	18
			CLR-BR	-5.2	0.97	94.4	18
			ULR-BR	-4.6	1.01	95.8	18
			ULR-Q	-3.1	0.98	94.6	18
2000	203	0.05	CLR	-13.4	0.99	95.4	13
			CLR-BR	-14.5	0.99	95.4	13
			ULR-BR	-14.3	1.03	96.3	13
			ULR-Q	-14.5	1.00	95.6	12
4000	407	0.05	CLR	+10.8	0.98	94.6	9
			CLR-BR	+10.1	0.98	94.6	9
			ULR-BR	+10.3	1.02	95.4	9
			ULR-Q	+8.9	0.99	94.8	9

† Average standard error (ASE) divided by empirical standard deviation (ESD) of estimates.

†† Coverage probability of 95% confidence intervals.

^ The number of replicates which did not converge up to 100 iterations is 1.

Table 8. Non-linear form 2 (logarithm) and 1:10 case to control ratio

Population size	Average no. of cases	True parameter	Method	Relative bias (%)	ASE/ESD†	CP (%)††	RMSE $\times 10^{-2}$
500	51	0.05	CLR	-5.3	0.98	95.3	24
			CLR-BR	-8.9	0.98	94.8	24
			ULR-BR	-11.3	0.93	93.8	24
			ULR-Q	-6.9	0.99	95.6	24
1000	102	0.05	CLR	-24.8	0.96	93.9	17
			CLR-BR	-27.2	0.96	93.9	17
			ULR-BR	-29.2	0.91	92.8	17
			ULR-Q	-25.7	0.97	94.0	17
2000	203	0.05	CLR	+4.7	0.99	94.8	12
			CLR-BR	+3.6	0.99	94.8	12
			ULR-BR^	+11.6	0.93	93.3	12
			ULR-Q	+3.7	1.00	95.0	12
4000	407	0.05	CLR	+6.6	0.99	95.2	8
			CLR-BR	+6.0	0.99	95.2	8
			ULR-BR	+2.8	0.93	94.0	8
			ULR-Q	+4.9	1.00	95.3	8

† Average standard error (ASE) divided by empirical standard deviation (ESD) of estimates.

†† Coverage probability of 95% confidence intervals.

^ The number of replicates which did not converge up to 100 iterations is 5.

Online Supplementary Material 6.

Further simulation settings and results: Time--varying effect

1. Variation in settings and procedures

Other than the modifications described below, the simulation settings and procedures are the same as those described in Online Supplementary Material 1.

(A) Generation of the population data with population size N = 500, 1000, 2000 or 4000

(1) Denote $t = \min(T^*, C)$ and $d = I_{\{T^* \le C\}}$, let $\bar{t}$ be the mean of t when $d = 1$.
(2) Consider a decreasing intensity pattern, in which the percentage of decrease in intensity at each predefined age interval generated from lognormal distributions with mean 0.1 and SD 0.075, i.e. average rate of decrease on log-scale in intensity is 10%.
(3) Permutational algorithm: Starting from the earliest observed time t_1, randomly assign each consecutive survival status tuple $(t_i, d_i),\ i = 1, \dots, N$ to a vector of current covariate values $E_j(t_i), j = 1, \dots, N$.

(a) If $d_i = 1$ (i.e. if t_i represents an event time), covariate vectors are sampled with probabilities based on the partial likelihood of the Cox model. Accordingly, for an subject j at t_i, this probability is defined as $Prob_j(t_i) = \frac{\exp(\beta^*(t_i)E_j(t_i))}{\sum_{s \in R_i} \exp(\beta^*(t_i)E_s(t_i))}$, where $\beta^*(t_i) = \beta(1 + t_i - \bar{t})$, R_i is the risk set at t_i, which excluded those subjects who had been selected for earlier time. We considered the true regression parameter values $\beta = 0.05$, which represents the effect of 100 units of cumulative exposure.

(b) If $d_i = 0$, assign a subject who is censored at time t_i by simple random sampling from the risk set R_i with equal probability.

(B) Statistical models

One analytic model is added: Unconditional logistic regression analysis with adjustment for time in quintiles AND linear terms for residual time within quintiles (ULR-QL).

(C) Presentation of findings

Results on ULR-BR not shown in figures due to non-convergence in many replicates. Results on coverage probability of 95% CI of ULR-Q are not shown in figures since they drop below the y-axis range 0.9 to 1.0. All details including frequency of non-convergence are shown in tables.

2. Simulation results in figures

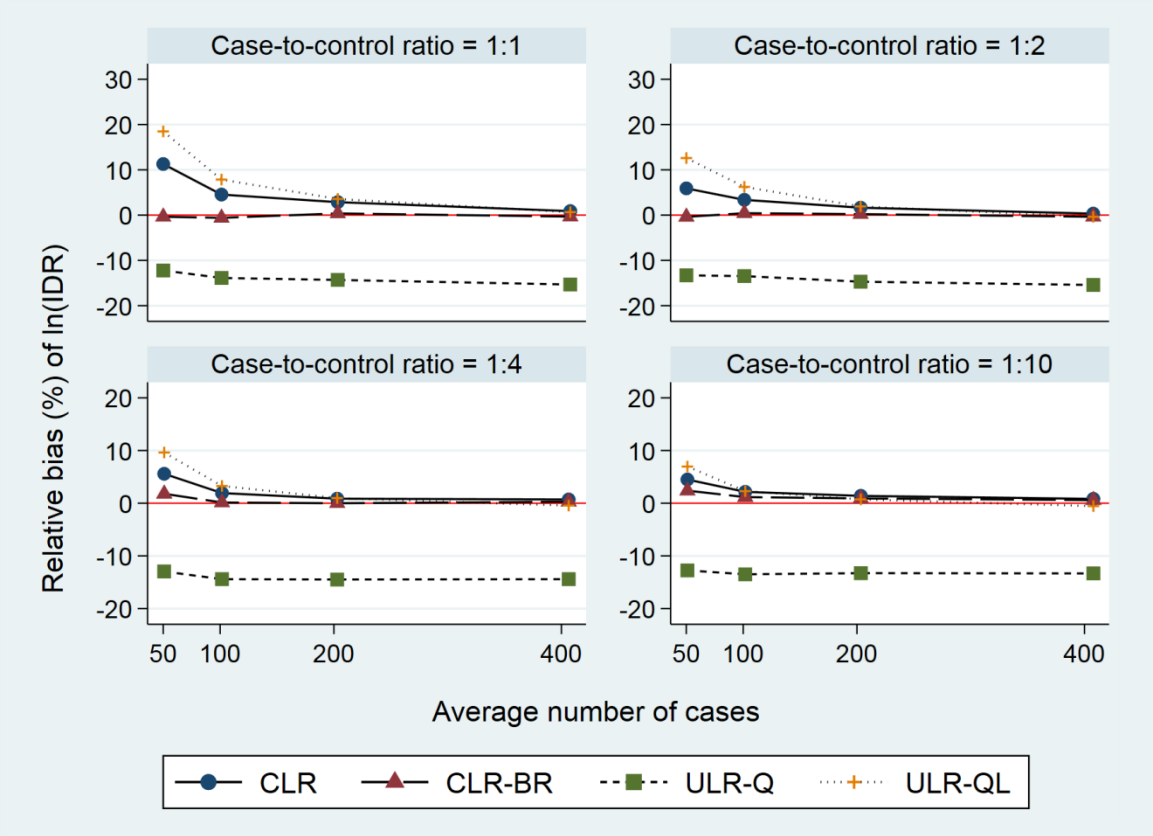

Figure 1. Relative bias of ln(IDR) in relation to the number of cases, case to control ratio and analytic methods under a simulation setting with time-varying effect.

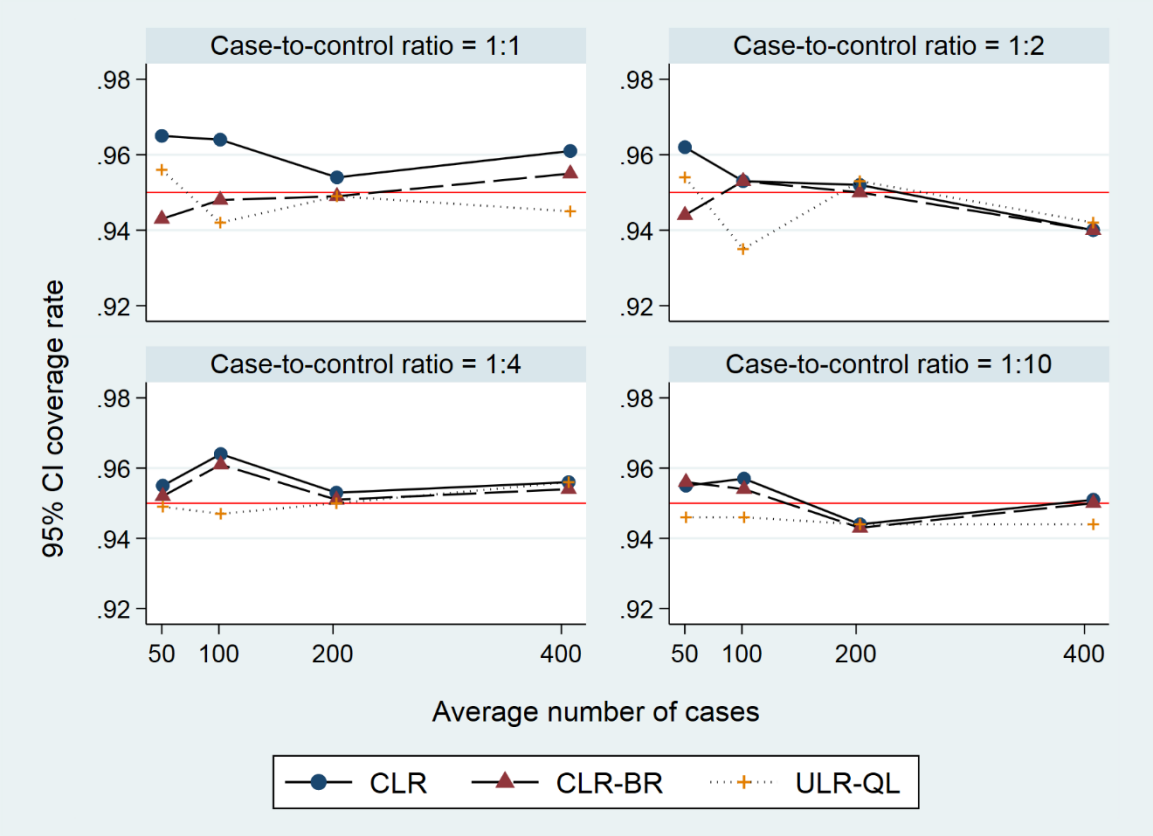

Figure 2. Coverage probability of 95% CI in relation to the number of cases, case to control ratio and analytic methods under a simulation setting with time-varying effect.

3. Simulation results in tables

Table 1. Time-varying effect and 1:1 case to control ratio

Population size	Average no. of cases	True parameter	Method	Relative bias (%)	ASE/ESD †	CP (%)††	RMSE $\times 10^{-3}$
500	51	0.05	CLR	+11.3	0.83	96.5	23
			CLR-BR	-0.4	0.98	94.3	18
			ULR-BR^	-14.8	1.51	95.1	11
			ULR-Q	-12.2	1.08	89.1	13
			ULR-QL	+18.5	0.90	95.6	19
1000	102	0.05	CLR	+4.5	0.96	96.4	13
			CLR-BR	-0.6	1.01	94.8	12
			ULR-BR^	-14.5	1.61	94.6	9
			ULR-Q	-13.9	1.09	84.9	10
			ULR-QL	+7.8	0.93	94.2	11
2000	204	0.05	CLR	+2.9	0.98	95.4	9
			CLR-BR	+0.4	1.00	94.9	8
			ULR-BR^	-14.2	1.53	88.1	8
			ULR-Q	-14.3	1.11	73.9	9
			ULR-QL	+3.6	0.98	94.9	7
4000	407	0.05	CLR	+0.9	1.00	96.1	6
			CLR-BR	-0.3	1.01	95.5	6
			ULR-BR^	-13.0	1.31	63.6	7
			ULR-Q	-15.3	1.09	50.0	8
			ULR-QL	+0.7	0.99	94.5	5

† Average standard error (ASE) divided by empirical standard deviation (ESD) of estimates.

†† Coverage probability of 95% confidence intervals.

^ The number of replicates which did not converge up to 100 iterations in the settings with population size 500 to 4,000 is 392, 595, 832 and 978, respectively.

Table 2. Time-varying effect and 1:2 case to control ratio

Population size	Average no. of cases	True parameter	Method	Relative bias (%)	ASE/ESD†	CP (%)††	RMSE $\times 10^{-3}$
500	51	0.05	CLR	+5.9	0.85	96.2	17
			CLR-BR	-0.4	0.92	94.4	15
			ULR-BR^	+0.2	1.06	97.3	11
			ULR-Q	-13.3	1.08	86.9	11
			ULR-QL	+12.6	0.90	95.4	15
1000	102	0.05	CLR	+3.4	0.97	95.3	10
			CLR-BR	+0.4	1.00	95.3	9
			ULR-BR^	+2.0	1.06	96.4	8
			ULR-Q	-13.5	1.04	80.6	9
			ULR-QL	+6.2	0.93	93.5	9
2000	203	0.05	CLR	+1.6	0.99	95.2	7
			CLR-BR	+0.2	1.00	95.0	6
			ULR-BR^	+1.7	1.08	97.3	6
			ULR-Q	-14.7	1.10	64.3	9
			ULR-QL	+1.9	0.99	95.3	6
4000	407	0.05	CLR	+0.3	0.98	94.0	5
			CLR-BR	-0.4	0.99	94.0	5
			ULR-BR^	+0.8	1.07	96.3	4
			ULR-Q	-15.4	1.06	35.9	8
			ULR-QL	-0.4	0.95	94.2	4

† Average standard error divided by empirical standard deviation of estimates.

†† Coverage probability of 95% confidence intervals.

^ The number of replicates which did not converge up to 100 iterations in the settings with population size 500 to 4,000 is 70, 93, 110 and 136, respectively.

Table 3. Time-varying effect and 1:4 case to control ratio

Population size	Average no. of cases	True parameter	Method	Relative bias (%)	ASE/ESD†	CP (%)††	RMSE $\times 10^{-3}$
500	51	0.05	CLR	+5.6	0.98	95.5	12
			CLR-BR	+1.8	1.01	95.2	11
			ULR-BR^	+3.3	1.00	95.7	11
			ULR-Q	-13.0	1.05	85.6	10
			ULR-QL	+9.6	0.92	94.9	12
1000	102	0.05	CLR	+1.9	0.99	96.4	8
			CLR-BR	+0.1	1.00	96.1	7
			ULR-BR^	+1.6	1.00	96.4	7
			ULR-Q	-14.4	1.07	73.3	9
			ULR-QL	+3.3	0.95	94.7	7
2000	203	0.05	CLR	+0.9	1.00	95.3	5
			CLR-BR	+0.0	1.01	95.1	5
			ULR-BR^	+1.5	1.01	95.7	5
			ULR-Q	-14.5	1.08	56.2	8
			ULR-QL	+1.0	0.97	95.0	5
4000	406	0.05	CLR	+0.7	0.98	95.6	4
			CLR-BR	+0.3	0.99	95.4	4
			ULR-BR^	+1.8	1.01	96.0	4
			ULR-Q	-14.4	1.12	31.8	8
			ULR-QL	-0.4	0.99	95.6	3

† Average standard error divided by empirical standard deviation of estimates.

†† Coverage probability of 95% confidence intervals.

^ The number of replicates which did not converge up to 100 iterations in the settings with population size 500 to 4,000 is 26, 32, 50 and 51, respectively.

Table 4. Time-varying effect and 1:10 case to control ratio

Population size	Average no. of cases	True parameter	Method	Relative bias (%)	ASE/ESD†	CP (%)††	RMSE $\times 10^{-3}$
500	51	0.05	CLR	+4.5	0.96	95.5	10
			CLR-BR	+2.4	0.97	95.6	9
			ULR-BR^	+2.7	0.92	94.2	9
			ULR-Q	-12.8	1.04	83.4	10
			ULR-QL	+7.0	0.94	94.6	10
1000	102	0.05	CLR	+2.2	0.98	95.7	6
			CLR-BR	+1.2	0.99	95.4	6
			ULR-BR^	+1.5	0.95	93.7	6
			ULR-Q	-13.5	1.04	72.2	8
			ULR-QL	+2.3	0.97	94.6	6
2000	203	0.05	CLR	+1.4	0.97	94.4	5
			CLR-BR	+0.9	0.97	94.3	4
			ULR-BR^	+1.2	0.94	93.5	4
			ULR-Q	-13.3	1.08	54.9	7
			ULR-QL	+0.7	0.96	94.4	4
4000	408	0.05	CLR	+0.8	1.00	95.1	3
			CLR-BR	+0.6	1.00	95.0	3
			ULR-BR^	+0.9	0.96	94.5	3
			ULR-Q	-13.3	1.09	27.4	7
			ULR-QL	-0.5	0.99	94.4	3

† Average standard error (ASE) divided by empirical standard deviation (ESD) of estimates.

†† Coverage probability of 95% confidence intervals.

^ The number of replicates which did not converge up to 100 iterations in the settings with population size 500 to 4,000 is 10, 13, 10 and 7, respectively.

Online Supplementary Material 7.

Further simulation setting and results: Omitting a binary matching factor from the analysis model

1. Variation in settings and procedures

Other than the modifications described below, the simulation settings and procedures are the same as those described in Online Supplementary Material 1.

(A) Generation of the population data with population size N = 500, 1000, 2000 or 4000

(1) Consider a decreasing intensity pattern, in which the percentage of decrease in intensity at each predefined age interval generated from lognormal distributions with mean 0.1 and SD 0.075, i.e. average rate of decrease on log-scale in intensity is 10%.

(2) Generate a binary variable X_j with $Prob(X_j = 1) = 0.5, j = 1, \dots, N$.

(3) Permutational algorithm: Starting from the earliest observed time t_1, randomly assign each consecutive survival status tuple $(t_i, d_i),\ i = 1, \dots, N$ to a vector of current covariate values $E_j(t_i), j = 1, \dots, N$.

(a) If $d_i = 1$ (i.e. if t_i represents an event time), covariate vectors are sampled with probabilities based on the partial likelihood of the Cox model. Accordingly, for an subject j at t_i, this probability is defined as $Prob_j(t_i) = \frac{\exp(\eta_{ij})}{\sum_{s \in R_i} \exp(\eta_{is})}$, where $\eta_{ij} = \log(2)\, X_j + \beta(X_j + 1)E_j(t_i)$, R_i is the risk set at t_i, which excluded those subjects who had been selected for earlier time. We considered the true regression parameter values $\beta = 0.05$, which represents the effect of 100 units of cumulative exposure.

(b) If $d_i = 0$, assign a subject who is censored at time t_i by simple random sampling from the risk set R_i with equal probability.

(B) Case-control study design using incidence density sampling

For each case, we randomly selected M control(s) with replacement among subjects still at risk at the age (time) of the case's diagnosis and matching on the binary variable X of the case.

(C) Statistical modeling

One analysis model is added: unconditional logistic regression with adjustment for time in quintiles AND adjustment for the binary variable (ULR-Q*).

(D) Presentation of findings

Results on coverage probability of 95% CI of ULR-Q that drop below the y-axis range 0.9 to 1.0 are not shown in figures. The details are included in tables.

2. Simulation results in figures

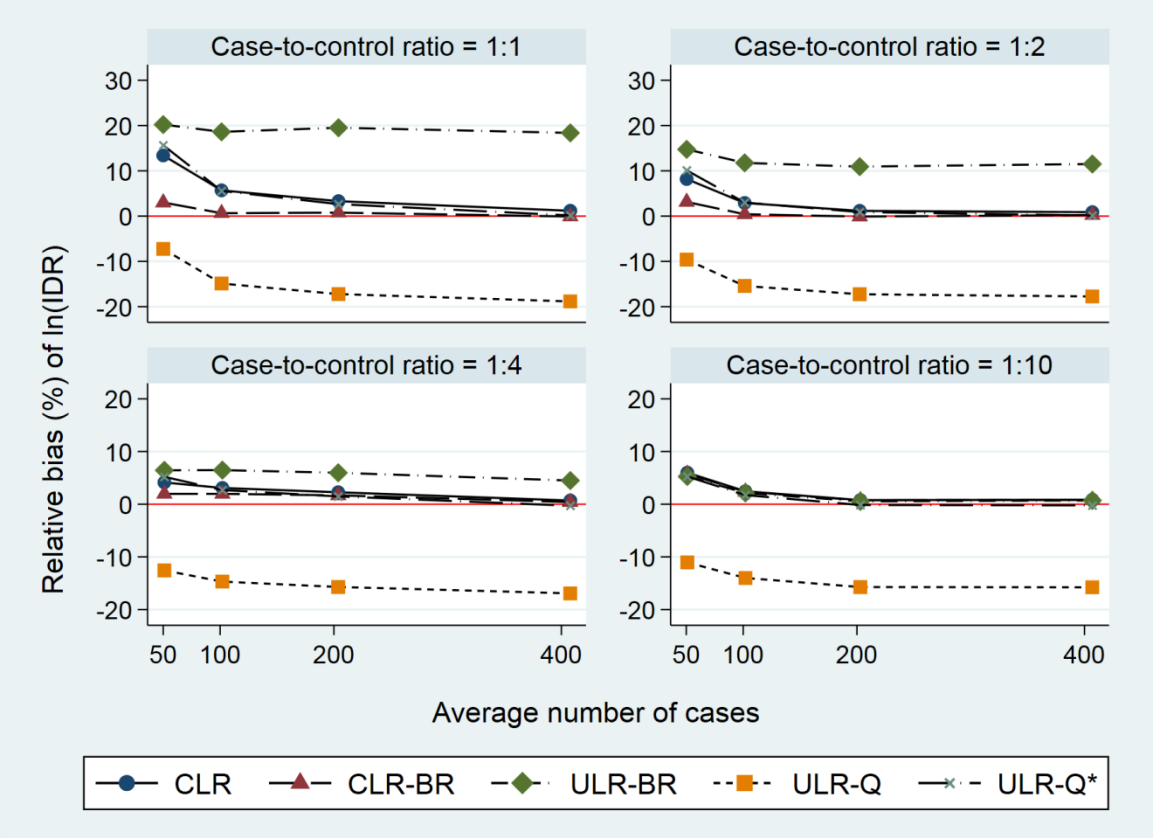

Figure 1. Relative bias of ln(IDR) in relation to the number of cases, case to control ratio and analytic methods under a setting with a binary matching variable.

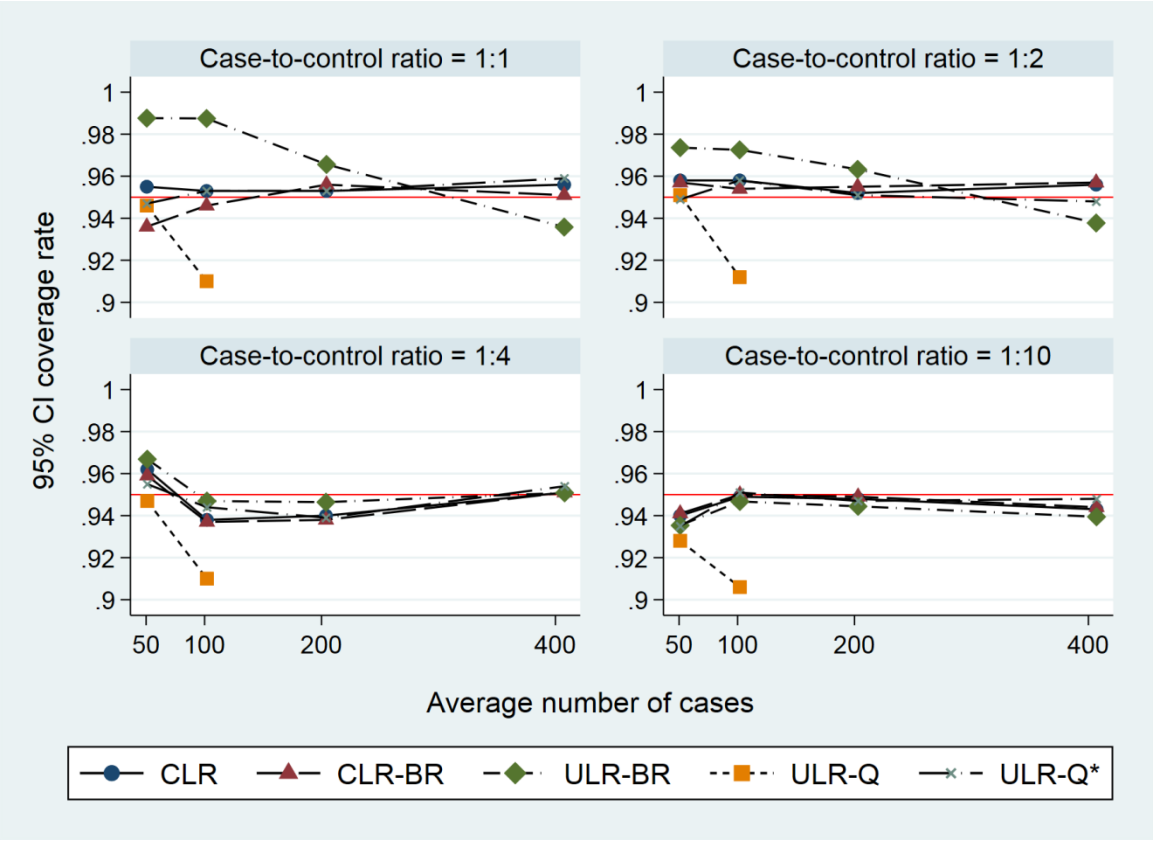

Figure 2. Coverage probability of 95% CI in relation to the number of cases, case to control ratio and analytic methods under a setting with a binary matching variable.

3. Simulation results in tables

Table 1. Setting with a binary matching variable and 1:1 case to control ratio

Population size	Average no. of cases	True parameter	Method	Relative bias (%)	ASE/ESD†	CP (%)††	RMSE $\times 10^{-3}$
500	51	0.05	CLR	+13.4	0.93	95.5	31
			CLR-BR	+3.0	0.98	93.6	28
			ULR-BR^	+20.2	1.21	98.8	29
			ULR-Q	-7.3	1.04	94.6	23
			ULR-Q*	+15.7	0.93	94.7	30
1000	102	0.05	CLR	+5.7	0.95	95.3	20
			CLR-BR	+0.6	0.97	94.6	19
			ULR-BR^	+18.6	1.20	98.8	21
			ULR-Q	-14.9	1.07	91.0	17
			ULR-Q*	+5.6	0.96	95.3	19
2000	204	0.05	CLR	+3.3	1.02	95.3	13
			CLR-BR	+0.8	1.03	95.6	13
			ULR-BR^	+19.5	1.24	96.6	16
			ULR-Q	-17.2	1.14	88.4	13
			ULR-Q*	+2.6	1.02	95.3	12
4000	407	0.05	CLR	+1.2	1.00	95.6	9
			CLR-BR	-0.1	1.00	95.1	9
			ULR-BR^	+18.4	1.21	93.6	13
			ULR-Q	-18.8	1.14	78.5	12
			ULR-Q*	+0.2	1.01	95.9	9

† Average standard error (ASE) divided by empirical standard deviation (ESD) of estimates.

†† Coverage probability of 95% confidence intervals.

^ The number of replicates which did not converge up to 100 iterations in the settings with population size 500 to 4,000 is 28, 40, 40 and 65, respectively.

Table 2. Setting with a binary matching variable and 1:2 case to control ratio

Population size	Average no. of cases	True parameter	Method	Relative bias (%)	ASE/ESD†	CP (%)††	RMSE $\times 10^{-3}$
500	51	0.05	CLR	+8.2	0.96	95.8	24
			CLR-BR	+3.1	0.98	95.7	22
			ULR-BR^	+14.7	1.09	97.4	24
			ULR-Q	-9.6	1.07	95.1	19
			ULR-Q*	+10.1	0.97	94.9	23
1000	102	0.05	CLR	+2.9	1.00	95.8	15
			CLR-BR	+0.4	1.00	95.4	15
			ULR-BR^	+11.8	1.11	97.3	17
			ULR-Q	-15.4	1.10	91.2	14
			ULR-Q*	+3.0	1.00	95.8	15
2000	204	0.05	CLR	+1.2	0.99	95.2	11
			CLR-BR	-0.1	0.99	95.5	11
			ULR-BR^	+10.9	1.08	96.3	13
			ULR-Q	-17.3	1.10	84.3	12
			ULR-Q*	+0.9	0.99	95.1	10
4000	407	0.05	CLR	+0.9	1.01	95.6	8
			CLR-BR	+0.2	1.01	95.7	7
			ULR-BR^	+11.5	1.10	93.8	10
			ULR-Q	-17.7	1.10	70.9	11
			ULR-Q*	+0.1	1.00	94.8	7

† Average standard error (ASE) divided by empirical standard deviation (ESD) of estimates.

†† Coverage probability of 95% confidence intervals.

^ The number of replicates which did not converge up to 100 iterations in the settings with population size 500 to 4,000 is 15, 16, 47 and 36, respectively.

Table 3. Setting with a binary matching variable and 1:4 case to control ratio

Population size	Average no. of cases	True parameter	Method	Relative bias (%)	ASE/ESD†	CP (%)††	RMSE $\times 10^{-3}$
500	51	0.05	CLR	+4.1	0.95	96.2	20
			CLR-BR	+2.0	0.96	95.9	19
			ULR-BR^	+6.4	1.00	96.7	20
			ULR-Q	-12.6	1.01	94.7	17
			ULR-Q*	+5.2	0.95	95.5	19
1000	102	0.05	CLR	+3.1	0.96	93.8	14
			CLR-BR	+2.0	0.96	93.7	13
			ULR-BR^	+6.5	1.01	94.7	14
			ULR-Q	-14.7	1.04	91.0	13
			ULR-Q*	+2.7	0.96	94.4	13
2000	204	0.05	CLR	+2.3	0.95	94.0	10
			CLR-BR	+1.7	0.95	93.8	10
			ULR-BR^	+6.0	0.99	94.6	10
			ULR-Q	-15.7	1.07	83.8	11
			ULR-Q*	+1.5	0.96	93.9	9
4000	407	0.05	CLR	+0.7	0.99	95.1	6
			CLR-BR	+0.4	0.99	95.1	6
			ULR-BR^	+4.5	1.04	95.1	7
			ULR-Q	-16.9	1.09	67.1	10
			ULR-Q*	-0.3	1.00	95.4	6

† Average standard error (ASE) divided by empirical standard deviation (ESD) of estimates.

†† Coverage probability of 95% confidence intervals.

^ The number of replicates which did not converge up to 100 iterations in the settings with population size 500 to 4,000 is 4, 1, 11 and 44, respectively.

Table 4. Setting with a binary matching variable and 1:10 case to control ratio

Population size	Average no. of cases	True parameter	Method	Relative bias (%)	ASE/ESD†	CP (%)††	RMSE $\times 10^{-3}$
500	51	0.05	CLR	+6.0	0.92	94.0	18
			CLR-BR	+5.7	0.92	94.1	17
			ULR-BR^	+5.3	0.92	93.5	17
			ULR-Q	-11.0	1.01	92.8	15
			ULR-Q*	+5.3	0.93	93.5	17
1000	102	0.05	CLR	+2.5	0.98	94.9	11
			CLR-BR	+2.4	0.98	95.0	11
			ULR-BR^	+2.1	0.97	94.7	11
			ULR-Q	-14.0	1.07	90.6	12
			ULR-Q*	+1.7	0.99	95.1	11
2000	204	0.05	CLR	+0.8	0.98	94.8	8
			CLR-BR	+0.7	0.98	94.9	8
			ULR-BR^	+0.5	0.97	94.4	8
			ULR-Q	-15.7	1.09	81.7	10
			ULR-Q*	-0.1	1.00	94.7	8
4000	407	0.05	CLR	+0.9	0.97	94.3	6
			CLR-BR	+0.8	0.97	94.4	6
			ULR-BR^	+0.7	0.95	93.9	6
			ULR-Q	-15.8	1.07	62.7	9
			ULR-Q*	-0.2	0.99	94.8	6

† Average standard error (ASE) divided by empirical standard deviation (ESD) of estimates.

†† Coverage probability of 95% confidence intervals.

^ The number of replicates which did not converge up to 100 iterations in the settings with population size 500 to 4,000 is 10, 5, 10 and 9, respectively.

Online Supplementary Materials 8.

Statistical models

Let E be the exposure variable of interest and β_E be its regression coefficient to be estimated. Let Y denote a binary outcome with $Y = 1$ for case and $Y = 0$ for control. Suppose there are S matched sets, each consisting of one case and M controls matched on the event time of the case.

CLR estimates β_E by maximizing the log conditional likelihood $l_{CLR}(\beta_E) = ln\big(L_{CLR}(\beta_E)\big)$, where $L_{CLR}(\beta_E)$ is (18):

$$L_{CLR}(\beta_E) = \prod_{i=1}^{S} \sum_{j=1}^{M+1} \frac{\exp(\beta_E E_{ij}) Y_{ij}}{\sum_{k=1}^{M+1} \exp(\beta_E E_{ik})}.$$

CLR-BR estimates β_E and attempts to reduce sparse data bias by maximizing a Firth-type log penalized conditional likelihood (10):

$$l_{CLR-BR}(\beta_E) = \ln(L_{CLR}(\beta_E)) + \frac{1}{2}\ln(|I_{CLR}(\beta_E)|),$$

where $I_{CLR}(\beta_E)$ is the Fisher's information matrix derived from $L_{CLR}(\beta_E)$.

Let Z_i, $i = 2, 3, \ldots S$, be a set of indicator variables that contrast matched sets 2 to S against matched set 1 as the reference. An ULR model that is known to be seriously biased for analysis of matched case-control study data is (16):

$$Prob(Y = 1|E, Z_2, \ldots, Z_S) = \frac{\exp\big(\beta_0 + \beta_E E + \sum_{i=2}^{S} \beta_{Z_i} Z_i\big)}{1 + \exp\big(\beta_0 + \beta_E E + \sum_{i=2}^{S} \beta_{Z_i} Z_i\big)},$$

whose likelihood function is:

$$L_{ULR}(\beta_E) = \prod_{i=1}^{S} \prod_{j=1}^{M+1} \frac{\exp\big(Y_{ij}(\beta_0 + \beta_E E_{ij} + \sum_{i=2}^{S} \beta_{Z_i} Z_i)\big)}{1 + \exp\big(\beta_0 + \beta_E E_{ij} + \sum_{i=2}^{S} \beta_{Z_i} Z_i\big)}.$$

ULR-BR estimates β_E and attempts to reduce sparse data bias by maximizing a Firth-type log penalized likelihood (8):

$$l_{ULR-BR}(\beta_E) = \ln(L_{ULR}(\beta_E)) + \frac{1}{2}\ln(|I_{ULR}(\beta_E)|),$$

where $I_{ULR}(\beta_E)$ is the Fisher's information matrix derived from $L_{ULR}(\beta_E)$.

ULR-Q estimates β_E by adding to the simple ULR four indicator variables that contrast the second to fifth quintiles of event time against the first quintile as the reference:

$$Prob(Y = 1|E, Q_2, Q_3, Q_4, Q_5) = \frac{\exp\left(\beta_0 + \beta_E E + \sum_{k=2}^{5} \beta_{Q_k} Q_k\right)}{1 + \exp\left(\beta_0 + \beta_E E + \sum_{k=2}^{5} \beta_{Q_k} Q_k\right)},$$

where Q_k $(k = 2, 3, 4, 5)$ is an indicator variable for the kth event time quintile.

ULR-QL estimates β_E by adding to ULR-Q a linear trend to account for residual changes over time within each time quintile:

$$Prob(Y = 1|E, Q_2, \dots, Q_5, R_1, \dots, R_5) = \frac{\exp\left(\beta_0 + \beta_E E + \sum_{k=2}^{5} \beta_{Q_k} Q_k + \sum_{l=1}^{5} \beta_{R_l} R_l\right)}{1 + \exp\left(\beta_0 + \beta_E E + \sum_{k=2}^{5} \beta_{Q_k} Q_k + \sum_{l=1}^{5} \beta_{R_l} R_l\right)},$$

where $R_l = \left(t - \bar{t}_{Q_l}\right)Q_l$, $(l = 1, 2, \dots, 5)$, t is event time and $\bar{t}_{Q_l}$ is the mean time within the lth quintile. The likelihood functions of ULR-Q and ULR-QL are straight-forward modifications of the $L_{ULR}(\beta_E)$ aforementioned by excluding the matched set indicator variables and including the appropriate covariates.