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RESEARCH ARTICLE

Comparison of cohort and nested case-control designs for estimating the effect of time-varying drug exposure on the risk of adverse event in the presence of ties

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This article has earned an open data badge "**Reproducible Research**" for making publicly available the code necessary to reproduce the reported results. The results reported in this article could fully be reproduced.

Abstract

Cohort and nested case-control (NCC) designs are frequently used in pharmacoepidemiology to assess the associations of drug exposure that can vary over time with the risk of an adverse event. Although it is typically expected that estimates from NCC analyses are similar to those from the full cohort analysis, with moderate loss of precision, only few studies have actually compared their respective performance for estimating the effects of time-varying exposures (TVE). We used simulations to compare the properties of the resulting estimators of these designs for both time-invariant exposure and TVE. We varied exposure prevalence, proportion of subjects experiencing the event, hazard ratio, and control-to-case ratio and considered matching on confounders. Using both designs, we also estimated the real-world associations of time-invariant ever use of menopausal hormone therapy (MHT) at baseline and updated, time-varying MHT use with breast cancer incidence. In all simulated scenarios, the cohort-based estimates had small relative bias and greater precision than the NCC design. NCC estimates displayed bias to the null that decreased with a greater number of controls per case. This bias markedly increased with higher proportion of events. Bias was seen with Breslow's and Efron's approximations for handling tied event times but was greatly reduced with the exact method or when NCC analyses were matched on confounders. When analyzing the MHT-breast cancer association, differences between the two designs were consistent with simulated data. Once ties were taken correctly into account, NCC estimates were very similar to those of the full cohort analysis.

KEYWORDS

breast cancer, cohort design, nested case control design, pharmacoepidemiology, simulation study, tied events, time-varying exposure

1 | INTRODUCTION

In pharmacoepidemiology, assessing the effect of drug exposure on the risk of an adverse event is a real challenge because exposure can vary over time and its effect can be complex (Abrahamowicz et al., 2012). To account for within-subject variation in drug exposure, longitudinal data need to be collected for a cohort of individuals and time-to-event analyses are generally used to model the time-varying exposure (TVE) to drug (Pazzagli et al., 2018).

The analysis of the entire cohort using the Cox proportional hazards regression model (Cox, 1972) is the classical approach to analyze such data (Ryan & Woodall, 2005). The Cox model allows to account for change of exposure during the follow-up using time-dependent covariates (O'Quigley, 2008). Estimation is based on partial likelihood, which, at each observed event, compares the values of the covariates of the individual who experienced the event with those of all individuals at risk at that event time (Cox, 1975).

The nested case-control (NCC) study design is another widely used approach to explore the association between drug exposure and the event of interest. NCC analysis is conducted as a case-control study based on all cases (subjects who experienced the event of interest during follow-up) and a random sample of control subjects individually matched to cases on time at risk, using incidence density sampling (Lubin & Gail, 1984; Prentice & Breslow, 1978), and possibly some covariates (Breslow & Day 1987; Klein et al., 2014). The sampled controls may be selected as controls for more than one case and may later become cases. The TVE of interest, for both the case and his/her matched controls, is evaluated at the case's time of event and then compared between the case and his/her matched controls. Therefore, for each study subject, a truly TVE is assessed only at a single time point, avoiding the need for complex statistical techniques (Etminan, 2004). The NCC is an efficient sampling design that requires exposure assessment on a far smaller sample than the full cohort design (Liddell et al., 1977), which is advantageous when exposure measurements (e.g., biomarkers) are difficult to obtain for logistical and/or financial reasons. Thus, the NCC design has been used for its convenience, cost-efficiency, and analytical flexibility (Essebag et al., 2005; Langholz, 2014). One key advantage of the NCC design is, indeed, that it allows the use of matching variables other than time and therefore is effective in reducing the risk of residual confounding due to possible mismodeling of some important confounders (Etminan, 2004). Estimation in the NCC design is based on a stratified version of the partial likelihood, where for each stratum the risk set, created at the time of case's event, is limited to a case and his/her matched controls (Prentice & Breslow, 1978).

The partial likelihood used to estimate the Cox proportional hazards model depends on the ordering of events in time. Yet, due to imprecise measurement of time (e.g., in days, weeks, or months), datasets may contain several *tied* event times, that is, events that occur at the same time, which poses special problems for partial likelihood estimation (Hertz-Picciotto & Rockhill, 1997). In the presence of ties, exact expression of the partial likelihood considers all possible permutations at each time when more than one event occurs (Peto, 1972). However, this is time-consuming and there are situations in which this approach may become computationally impossible due to the large number of ties in the dataset. To overcome these computational difficulties, some approximations have been developed. Both Breslow's (1974) and Efron's (1977) approximations are much faster than the exact method for handling the ties, and both work well when ties are relatively few. However, both approximations can yield biased estimates when the average proportion of cases in the risk sets used in the analyses becomes relatively large (Allison, 2010; Borucka, 2014; Hertz-Picciotto & Rockhill, 1997), which is likely to happen in NCC studies (Farewell & Prentice, 1980).

It is generally admitted that estimates obtained from NCC analyses are similar to those obtained from analysis of the entire cohort, with only a moderate loss of precision (Breslow et al., 1983; Essebag et al., 2005; Liddell et al., 1977). However, to our knowledge, only one study relied on simulations to systematically evaluate and compare their respective performance for estimating the effect of TVE (Austin et al., 2012). In contrast with the previous findings of NCC and whole cohort analyses yielding similar estimates, the authors reported potentially important biases in NCC analyses with TVE that increased with the proportion of uncensored events (Austin et al., 2012).

The aim of this study was to further investigate the performances of cohort and NCC approaches for estimating the association between exposure and the risk of adverse event and the potential for bias in the latter analyses, in particular for a TVE. Special attention was paid to the presence, frequency, and handling of ties, as they can greatly influence the results (Allison, 2010; Farewell & Prentice, 1980).

This article is organized as follows: first, we describe the simulation study that was conducted to assess and compare the properties of the NCC versus cohort-based estimators for both a time-invariant exposure and a simple TVE. Then, we present the results of a real-world case study, where we apply these designs to estimate the risk of invasive breast cancer associated with ever use of menopausal hormone therapy (MHT) in a large cohort of French women with long follow-up (Fournier et al., 2014). Finally, we conclude with a discussion and recommendations.

2 | SIMULATION STUDY

2.1 | Methods

We performed two simulation studies, one focusing on a time-invariant binary exposure and another on a simple binary change-of-state TVE, such as treatment initiation during the follow-up. For each simulation, we considered 18 alternative scenarios that differed with respect to (i) value of "true" hazard ratio (HR), (ii) proportion of exposed subjects, and (iii) incidence rate for the outcome of interest. For each scenario, we generated 1000 independent random samples, each representing a hypothetical cohort of $N = 5000$ subjects followed for up to 2 years (730 days).

2.1.1 | Data generation

For simulations with time-invariant exposure, individual exposure status $A(i)$, $i = 1,\ldots,N$ was generated as a binary variable (1 = exposed vs. 0 = unexposed) from a Bernoulli distribution of a prespecified probability $p(i)$ of exposure and kept unchanged throughout the follow-up period. For TVE, the current exposure status $A(i,t)$ at time t was assumed to change from "unexposed" to "exposed" at most once during follow-up. Thus, for each exposed subject i, we generated his/her individual time of change $\tau(i)$ from a uniform distribution $[0;T]$, where T = maximum follow-up duration for the entire cohort. Then, we set $A(i,t) = 0$ for $0 < t < \tau(i)$, and $A(i,t) = 1$ for $t \geq \tau(i)$. We considered two sets of simulations. For the first set, no covariates were generated and, thus, no adjusting or additional matching was considered in the analyses. For the second set of simulations, we added two potential confounders: a binary indicator for male sex ($SEX \sim$ Bernoulli (0.4)) and age in years as a continuous variable ($AGE \sim \mathcal{U}[40,\ 65]$). In this case, we assumed that the probability $p(i)$ of being ever exposed during the 2-year follow-up depended on these two fixed-in-time covariates, according to the following equation: $\text{logit}\,(p(i)) = \alpha + \log(2) \times SEX(i) + \frac{\log(2)}{10} \times AGE(i)$, where α was derived from the logit of the target proportion of exposed minus $\log(2) \times \text{mean}(SEX) + \frac{\log(2)}{10} \times \text{mean}(AGE)$. Then we assumed that the risk of event depended on these two covariates (with log(HR) = log(2) for male sex and $\frac{\log(2)}{10}$ per year of age) in addition to either time-invariant or TVE.

We used the permutational algorithm (Sylvestre & Abrahamowicz, 2008), specifically designed and validated to simulate event times conditional on time-varying effects and/or exposure/covariates, and the corresponding *permalgo* function in R (Sylvestre et al., 2015) to generate event times, conditional on exposure (for simulations without covariates) and covariates (for simulations with covariates), as well as random times of right censoring. We assumed an exponential distribution, with a constant hazard rate, for generating event times, and a uniform distribution to generate censoring times assumed to reflect random losses to follow-up, with additional administrative censoring of all subjects who remained at risk at two years of follow-up. Our unit time for analysis was 1 day so that event and censoring times were rounded up to the nearest day. For each set of simulations and each of the two exposure types, in the data-generating model we assumed two values of "true" HR: 2 and 1.25 (exposed vs. unexposed). Across the 18 simulated scenarios, we then varied combinations of the expected proportions of subjects who: (i) were exposed (0.10, 0.25, and 0.50) and (ii) experienced an uncensored event (0.05, 0.10, and 0.25) during the 2 years of follow-up. The latter incidence was approximately controlled by adjusting the hazard rate λ of the exponential distribution used for generating event times.

2.1.2 | Analyses of simulated data

Simulated data were analyzed using two alternative approaches: one corresponding to a full cohort design and another assuming an NCC study was embedded in the same cohort.

In the absence of covariates, data from the entire cohort were analyzed using a conventional univariate unadjusted Cox proportional hazards model with either time-invariant $A(i)$ or time-varying $A(i,t)$ exposure, depending on the structure of the simulated data. Log-HR estimates for exposure, together with a 95% confidence interval (CI), were obtained using the *coxph* function from the *survival* package in R, with Efron's approximation for handling ties (Efron, 1977). This method is recommended because it is faster than the exact method (Borucka, 2014) and more accurate than Breslow's approximation (Hertz-Picciotto & Rockhill, 1997).

To perform analyses according to the NCC design, first all "cases" (subjects who had the event during the follow-up) and their corresponding event times were identified in the cohort generated for a given simulated sample. We then used either

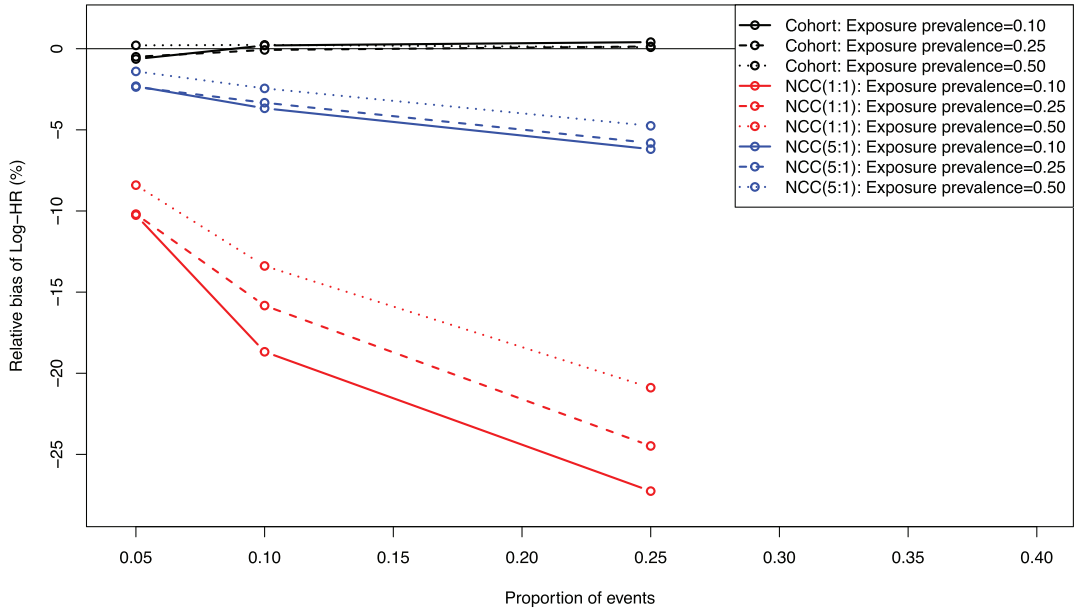

FIGURE 1 Relative bias of log-HR from full cohort and NCC (for one and five controls per case) analyses with Efron's approximation for handling tied events: time-invariant exposure and true hazard ratio of 2.

1:1 or 5:1 control-to-case matching. For 5:1 matching, the controls were selected in a nested manner, such that the control selected in 1:1 matching was among the five selected controls. We implemented incidence density sampling by randomly selecting controls from each case's risk set (subjects in the cohort who remain at risk, i.e., event-free, until the time at which this particular case experienced the event) using the *ccwc* function in *Epi* package in R. This function groups all cases who experienced the event of interest at the same time, and their respective controls in the same stratum, therefore generating ties in those strata where two or more cases had the same event time.

To handle ties within the strata, in three alternative analyses of the same dataset, we used the exact method (Peto, 1972) as well as the Breslow (1974) and the Efron (1977) approximations. As the fourth analytical method, we modified the *ccwc* function so that cases who experienced the event at the same time were allocated to separate strata, ensuring that each stratum included only a *single* case and, thus, avoiding ties. This approach, referred to as the "modified *ccwc* approach" in the remainder of the paper, is described in Supporting Information Appendix 1. The NCC samples with either one or five controls per case were analyzed using conditional logistic regression to estimate the association between exposure and the occurrence of the event of interest, by conditioning on the matched sets. Log-odds ratio estimates for conditional logistic regression, equivalent to log-HR (Prentice & Breslow, 1978), were obtained using the *clogit* function from the *survival* package in R.

For the second set of simulations considering confounders, data from the entire cohort were analyzed using the Cox model adjusted for sex and age (grouped into five classes of 5 years each) with Efron's approximation. We considered NCC analyses with Efron's approximation either adjusted for or matched on sex and age (categorized into five classes of 5 years each).

In all scenarios, we compared the performance of each analytical approach with respect to estimated log-HR for exposure, across the 1000 samples simulated for a given scenario, using: (i) relative and absolute bias, (ii) average standard error estimator (SEE), that is, the observed standard deviation of the 1000 estimates, (iii) root mean square error (RMSE), and (iv) coverage probability of the 95% CI.

2.2 | Results in the absence of covariates

2.2.1 | Results for a time-invariant exposure

The results of simulations for a time-invariant exposure and HR = 2 are presented in Figure 1 and Table 1. Figure 1 compares the relative bias of log-HR estimates obtained from the entire cohort and NCC analyses with Efron's approximation for

TABLE 1 Simulations results of the full cohort (with Efron's method) and nested case-control (for one and five controls per case with the exact method, Breslow's and Efron's approximations, and modified ccwc approach) analyses for time-invariant exposure and true hazard ratio of 2

Study design	5% events: Relative bias (%) (absolute bias)	SEE	RMSE	CP (%)	10% events: Relative bias (%) (absolute bias)	SEE	RMSE	CP (%)	25% events: Relative bias (%) (absolute bias)	SEE	RMSE	CP (%)
10% subjects exposed												
Full cohort	**−0.636** (0.004)	0.167	0.166	95.3	**0.200** (0.001)	0.116	0.113	95.5	**0.406** (0.003)	0.076	0.076	95.4
NCC (1:1) B	−16.227 (0.112)	0.242	0.249	93.1	−28.039 (0.194)	0.153	0.231	80.5	−41.119 (0.285)	0.090	0.292	4.6
NCC (1:1) Ef	**−10.256** (0.071)	0.244	0.251	93.8	**−18.677** (0.129)	0.155	0.194	87.6	**−27.263** (0.189)	0.091	0.205	45.7
NCC (1:1) Ex	3.326 (0.023)	0.278	0.293	94.7	1.309 (0.009)	0.191	0.194	95.2	0.878 (0.006)	0.125	0.124	94.6
NCC (1:1)*	3.059 (0.021)	0.279	0.284	95.3	1.105 (0.008)	0.192	0.188	96.2	1.135 (0.008)	0.127	0.129	94.0
NCC (5:1) B	−4.120 (0.029)	0.188	0.181	95.1	−6.987 (0.048)	0.127	0.129	95.5	−11.896 (0.082)	0.081	0.111	84.2
NCC (5:1) Ef	**−2.311** (0.016)	0.188	0.184	95.0	**−3.673** (0.025)	0.128	0.128	95.4	**−6.190** (0.043)	0.081	0.092	91.6
NCC (5:1) Ex	−0.022 (0.000)	0.193	0.189	95.1	0.274 (0.002)	0.134	0.131	95.3	0.610 (0.004)	0.088	0.089	95.4
NCC (5:1)*	−0.591 (0.004)	0.193	0.188	95.9	0.614 (0.004)	0.134	0.126	96.0	1.062 (0.007)	0.088	0.087	95.2
25% subjects exposed												
Full cohort	**−0.498** (0.003)	0.130	0.129	95.4	**−0.076** (0.001)	0.090	0.089	95.8	**0.137** (0.001)	0.058	0.057	96.0
NCC (1:1) B	−15.659 (0.109)	0.181	0.195	93.2	−24.881 (0.172)	0.116	0.197	72.8	−38.109 (0.264)	0.068	0.269	0.2
NCC (1:1) Ef	**−10.193** (0.071)	0.182	0.187	94.0	**−15.829** (0.110)	0.117	0.154	86.1	**−24.480** (0.170)	0.068	0.181	28.4
NCC (1:1) Ex	0.481 (0.003)	0.202	0.201	95.3	1.209 (0.008)	0.139	0.136	95.9	0.550 (0.004)	0.090	0.088	94.8
NCC (1:1)*	1.640 (0.011)	0.203	0.200	96.1	0.731 (0.005)	0.140	0.139	95.1	0.887 (0.006)	0.091	0.091	95.7
NCC (5:1) B	−3.948 (0.027)	0.143	0.144	95.4	−6.259 (0.043)	0.098	0.102	94.0	−10.972 (0.076)	0.061	0.095	77.8
NCC (5:1) Ef	**−2.361** (0.016)	0.143	0.145	95.4	**−3.328** (0.023)	0.098	0.098	95.0	**−5.812** (0.040)	0.061	0.073	91.0
NCC (5:1) Ex	−0.472 (0.003)	0.146	0.147	94.9	0.046 (0.000)	0.101	0.099	96.1	0.100 (0.001)	0.066	0.065	94.3
NCC (5:1)*	−0.007 (0.000)	0.146	0.146	95.5	0.319 (0.002)	0.101	0.101	95.2	0.188 (0.001)	0.066	0.065	96.2
50% subjects exposed												
Full cohort	**0.207** (0.001)	0.135	0.137	94.8	**0.235** (0.002)	0.093	0.091	94.8	**0.089** (0.001)	0.059	0.059	95.5
NCC (1:1) B	−13.234 (0.092)	0.177	0.192	92.6	−21.738 (0.151)	0.115	0.180	76.0	−33.994 (0.236)	0.067	0.242	2.8
NCC (1:1) Ef	**−8.408** (0.058)	0.177	0.187	93.9	**−13.388** (0.093)	0.116	0.143	88.8	**−20.890** (0.145)	0.068	0.158	42.1
NCC (1:1) Ex	−0.345 (0.002)	0.190	0.194	94.9	−0.110 (0.001)	0.130	0.126	95.9	−0.227 (0.002)	0.082	0.081	95.1
NCC (1:1)*	0.557 (0.004)	0.191	0.198	93.9	−0.523 (0.004)	0.131	0.130	95.6	0.277 (0.002)	0.084	0.083	95.8
NCC (5:1) B	−2.741 (0.019)	0.144	0.146	94.9	−4.922 (0.034)	0.098	0.099	94.5	−9.192 (0.064)	0.061	0.087	82.5
NCC (5:1) Ef	**−1.397** (0.010)	0.144	0.147	94.5	**−2.446** (0.017)	0.098	0.097	95.4	**−4.752** (0.033)	0.061	0.070	91.5
NCC (5:1) Ex	0.093 (0.001)	0.146	0.149	94.0	0.292 (0.002)	0.101	0.098	96.0	0.119 (0.001)	0.064	0.065	94.9
NCC (5:1)*	0.342 (0.002)	0.146	0.147	94.9	0.221 (0.002)	0.101	0.100	95.3	−0.046 (0.000)	0.064	0.065	94.7

Note: Results in bold are those displayed in Figure 1.Abbreviations: B, Breslow; CP, Coverage probability; Ef, Efron, Ex, exact; NCC, nested case-control; RMSE, root mean square error; SEE, average standard error estimator.

*Modified *ccwc* approach.

Results in bold are those displayed in Figure 1.

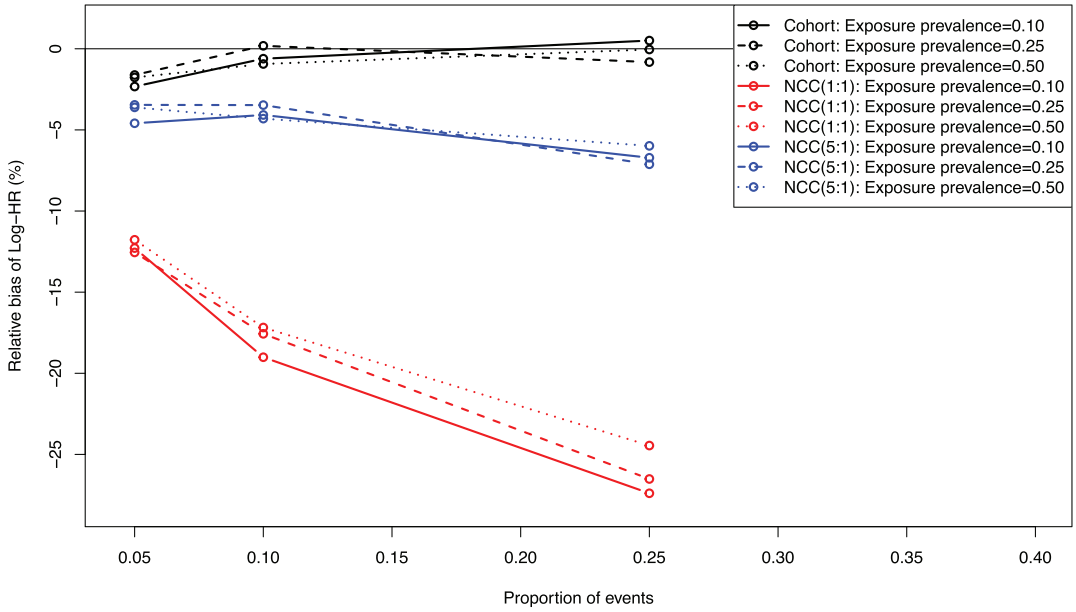

FIGURE 2 Relative bias of log-HR from full cohort and NCC (for one and five controls per case) analyses with Efron's approximation for handling tied events: time-varying exposure and true hazard ratio of 2.

handling ties. The frequency of ties was correlated to the proportion of uncensored events: from 15% to 53% in median for, respectively, 5–25% of subjects who experienced an event regardless of exposure prevalence (see Table A.1 in Supporting Information Appendix 2).

In all scenarios, the log-HR estimates were unbiased (relative bias < 1%) for the cohort design. In contrast, the log-HR estimates for the NCC design displayed systematic, often important, bias to the null with Efron's approximation and even more so with Breslow's approximation. This bias was much more pronounced with 1:1 matching than 5:1 matching (e.g., maximal relative bias of 27% for one control versus 6% for five controls with Efron's approximation; Figure 1). This bias increased markedly with higher proportion of events (e.g., for 10% exposed subjects, relative bias was 10%, 19%, and 27% for, respectively, 5%, 10%, and 25% subjects who experienced an event; Figure 1). Moreover, bias decreased slightly with increasing proportion of exposed subjects (e.g., for 25% of subjects who experienced an event, relative bias was 27%, 24%, and 21% for, respectively, 10%, 25%, and 50% of exposed subjects; Figure 1). These biases were almost entirely eliminated when using the exact method for handling ties (Peto, 1972) or the modified *ccwc* approach (maximal relative bias of only 1% for both methods vs. 41% and 27% for Breslow's and Efron's approximations, respectively; Table 1).

In all scenarios, the full cohort-based estimates displayed systematically smaller variance than those of the NCC design (SEEs in Table 1). As expected, precision generally improved in both designs as the proportion of events, exposure prevalence, and (for NCC analyses) the number of controls per case increased. Precision from the NCC analysis with the exact method or modified *ccwc* approach was systematically lower than that from the NCC analysis with Breslow's or Efron's approximation. Consequently, the bias–variance trade-off was in favor of the exact method or modified *ccwc* approach only for greater proportion of events, that is, 25% and perhaps 10% (Table 1). In all scenarios, coverage probability of the cohort design maintained nominal levels (0.95) while that of the NCC design was lower than nominal, especially for Breslow's and Efron's approximations with higher proportions of events (scenarios for which considerable biases were observed).

Simulation results for HR = 1.25 were globally similar to those for HR = 2: although somewhat reduced in magnitude, underestimation bias increasing with higher proportion of events was again seen in NCC analyses using Efron's or Breslow's approximation. However, because their bias was smaller, the bias–variance trade-off became more favorable to these two approximation methods with HR = 1.25 (data not shown).

2.2.2 | Results for a TVE

Results for a TVE were similar to those obtained for a fixed exposure, whether HR = 2 or HR = 1.25. The results of the simulations for TVE and HR = 2 are presented in Figure 2 and Table 2. The relative biases of estimates obtained from

TABLE 2 Simulations results of the full cohort (with Efron method) and nested case-control (for one and five controls per case with exact method, Breslow and Efron's approximations, and modified ccwc approach) analyses for time-varying exposure and true hazard ratio of 2

Study design	5% events: Relative bias (%) (absolute bias)	SEE	RMSE	CP (%)	10% events: Relative bias (%) (absolute bias)	SEE	RMSE	CP (%)	25% events: Relative bias (%) (absolute bias)	SEE	RMSE	CP (%)
10% subjects exposed												
Full cohort	**−2.328** (0.016)	0.226	0.226	96.1	**−0.611** (0.004)	0.157	0.146	96.9	**0.506** (0.004)	0.104	0.100	96.7
NCC (1:1) B	−18.475 (0.128)	0.331	0.318	95.9	−28.404 (0.197)	0.210	0.258	89.5	−41.108 (0.285)	0.123	0.297	29.2
NCC (1:1) Ef	**−12.283** (0.085)	0.335	0.328	95.2	**−19.010** (0.132)	0.213	0.232	92.4	**−27.395** (0.190)	0.125	0.218	70.6
NCC (1:1) Ex	2.200 (0.015)	0.385	0.390	96.0	2.265 (0.016)	0.265	0.264	96.0	1.689 (0.012)	0.174	0.168	96.0
NCC (1:1)*[a]	2.188 (0.015)	0.385	0.383	96.1	2.061 (0.014)	0.266	0.265	95.5	1.602 (0.011)	0.175	0.182	94.7
NCC (5:1) B	−6.503 (0.045)	0.256	0.259	94.7	−7.464 (0.052)	0.174	0.164	96.7	−12.415 (0.086)	0.111	0.130	92.0
NCC (5:1) Ef	**−4.591** (0.032)	0.256	0.264	94.1	**−4.080** (0.028)	0.174	0.165	96.5	**−6.716** (0.047)	0.111	0.116	95.3
NCC (5:1) Ex	−2.263 (0.016)	0.263	0.271	93.7	−0.003 (0.000)	0.183	0.172	96.1	0.127 (0.001)	0.121	0.116	96.5
NCC (5:1)*	−1.924 (0.013)	0.263	0.259	95.8	−0.526 (0.004)	0.183	0.173	96.8	0.481 (0.003)	0.121	0.123	95.7
25% subjects exposed												
Full cohort	**−1.616** (0.011)	0.163	0.170	94.2	**0.183** (0.001)	0.113	0.113	95.1	**−0.820** (0.006)	0.074	0.074	94.5
NCC (1:1) B	−18.136 (0.126)	0.232	0.252	92.4	−26.770 (0.186)	0.148	0.223	79.6	−39.979 (0.277)	0.087	0.284	4.0
NCC (1:1) Ef	**−12.551** (0.087)	0.234	0.251	93.0	**−17.568** (0.122)	0.150	0.186	88.3	**−26.514** (0.184)	0.088	0.200	45.9
NCC (1:1) Ex	−0.552 (0.004)	0.263	0.279	93.8	1.085 (0.008)	0.182	0.185	94.9	−0.093 (0.001)	0.119	0.116	95.6
NCC (1:1)*	0.992 (0.007)	0.265	0.273	94.2	2.183 (0.015)	0.183	0.187	95.4	−0.482 (0.003)	0.120	0.119	94.7
NCC (5:1) B	−5.158 (0.036)	0.182	0.189	94.3	−6.632 (0.046)	0.123	0.127	94.0	−12.451 (0.086)	0.078	0.112	84.5
NCC (5:1) Ef	**−3.458** (0.024)	0.182	0.191	94.3	**−3.471** (0.024)	0.124	0.125	94.9	**−7.119** (0.049)	0.079	0.091	90.8
NCC (5:1) Ex	−1.344 (0.009)	0.186	0.195	94.3	0.226 (0.002)	0.129	0.129	94.5	−0.887 (0.006)	0.085	0.083	94.4
NCC (5:1)*	−1.313 (0.009)	0.186	0.192	94.3	0.074 (0.001)	0.129	0.132	94.6	−1.081 (0.007)	0.085	0.087	94.1
50% subjects exposed												
Full cohort	**−1.766** (0.012)	0.143	0.147	94.0	**−0.938** (0.007)	0.099	0.099	94.3	**−0.044** (0.000)	0.064	0.066	94.6
NCC (1:1) B	−17.164 (0.119)	0.196	0.217	91.7	−25.875 (0.179)	0.127	0.210	72.6	−37.784 (0.262)	0.074	0.268	2.3
NCC (1:1) Ef	**−11.772** (0.082)	0.198	0.211	92.6	**−17.178** (0.119)	0.128	0.171	85.7	**−24.454** (0.170)	0.075	0.184	37.3
NCC (1:1) Ex	−1.807 (0.013)	0.218	0.221	94.7	−1.127 (0.008)	0.150	0.151	94.2	−0.543 (0.004)	0.097	0.099	94.4
NCC (1:1)*	−0.228 (0.002)	0.220	0.220	95.7	−0.444 (0.003)	0.152	0.151	94.8	−0.233 (0.002)	0.098	0.097	95.7
NCC (5:1) B	−5.204 (0.036)	0.157	0.159	93.9	−7.162 (0.050)	0.107	0.115	92.9	−10.977 (0.076)	0.067	0.100	79.4
NCC (5:1) Ef	**−3.611** (0.025)	0.157	0.160	93.8	**−4.305** (0.030)	0.107	0.111	94.1	**−5.983** (0.041)	0.067	0.081	89.2
NCC (5:1) Ex	−1.843 (0.013)	0.160	0.162	93.7	−1.079 (0.007)	0.111	0.112	95.0	−0.287 (0.002)	0.072	0.074	94.4
NCC (5:1)*	−2.668 (0.018)	0.160	0.165	94.2	−1.209 (0.008)	0.111	0.108	95.8	−0.235 (0.002)	0.072	0.074	94.6

Note: Results in bold are those displayed in Figure 2.Abbreviations: B, Breslow; CP, coverage probability; Ef, Efron; Ex, exact; NCC, nested case-control; RMSE, root mean square error; SEE, average standard error estimator.

*Modified *ccwc* approach.

full cohort and NCC analyses with Efron's approximation for handling ties are shown in Figure 2. The frequency of ties was comparable to that observed with a fixed exposure across all nine scenarios (Table A.2 in Supporting Information Appendix 2). The cohort design yielded unbiased estimates (relative bias < 2.5%), while NCC estimates with Breslow's and Efron's approximations were again biased to the null, sometimes greatly (maximal relative bias from 27% for one control to 7% for five controls). The same trend of an increasing bias as the proportion of events increased (e.g., for 10% of exposed subjects, the bias increased from 12% to 19% and then 27% for, respectively, 5%, 10%, and 25% of subjects who experienced an event) was apparent. There was no clear trend, however, with the proportion of exposed subjects. Breslow's approximation for handling ties resulted in larger bias in the estimates from the NCC design than Efron's approximation in all scenarios (Table 2). These biases were greatly reduced when using the exact method or modified *ccwc* approach with only one case in each stratum (maximal relative bias from 41% and 27% for Breslow's and Efron's approximations, respectively, to 2% for the exact method and modified *ccwc* approach).

As expected, Table 2 shows smaller SEEs and RMSEs for the full cohort than for the NCC design in all scenarios. Predictably, precision of estimates improved for both designs as the proportion of events, exposure prevalence, and (for NCC analyses) number of controls per case increased. Similar to time-invariant exposure, for NCC analysis with Breslow's and Efron's approximations where estimates produced larger bias, RMSE was greater for higher proportion of events and one control per case and SEEs were systematically smaller than those from the NCC analysis with the exact method or modified *ccwc* approach.

Similarly to what we observed for a fixed exposure, coverage probability of the cohort design was close to 95% for all scenarios while that of the NCC design fell below nominal especially for Breslow's and Efron's approximations with higher proportions of events and subjects exposed (scenarios for which most important biases were observed).

2.3 | Results in the presence of confounders

2.3.1 | Results for a time-invariant exposure

The results of simulations for the sex- and age-adjusted cohort analyses and the NCC analyses either adjusted for or matched on these two covariates, for a time-invariant exposure and HR = 2 are presented in Table 3. The cohort analyses were slightly biased (bias increasing with the proportion of exposed), due to residual confounding induced by slight mis-specification of the age effect because data were generated with age as a continuous variable but analyzed with age as a categorical variable. As expected, we observed substantial relative bias (increasing as the proportion of events increased) in adjusted NCC analyses, while bias was markedly reduced in matched NCC analyses. Matching on covariates markedly reduced the number of strata with tied events. For example, with 25% events, a median number of 1265 events was observed but only 600 strata were formed when matching on time at risk only (Table A.1 in Supporting Information Appendix 2) instead of 1143 strata when matching also on covariates (Table A.3 in Supporting Information Appendix 3).

2.3.2 | Results for a TVE

Results for a TVE were similar to those obtained for a fixed exposure, with HR = 2 (Table A.4 in Supporting Information Appendix 4). The cohort design yielded unbiased estimates (relative bias < 2%), while adjusted NCC estimates were again greatly biased to the null. However, there was no bias in matched NCC estimates except for NCC (1:1) and 25% events (Table A.4 in Supporting Information Appendix 4). The number of strata with tied events for simulated data with matching on covariates was comparable to that observed with a fixed exposure across all nine scenarios (Tables A.5 in Supporting Information Appendix 4 and Table A.3 in Supporting Information Appendix 3, respectively) and markedly lower than that of simulated data without matching on covariates (Table A.2 in Supporting Information Appendix 2).

3 | REAL DATA APPLICATION

3.1 | Population and methods

To compare the estimates obtained from the two study designs using real-world data, we examined the risk of breast cancer associated with ever use of MHT in the French E3N women cohort (*Étude Épidémiologique auprès de Femmes de*

TABLE 3 Simulations results of the full cohort analysis with adjustment for sex and age and nested case-control analyses (for one and five controls per case) with adjustment for or matching on sex and age, with Efron's approximation, for time-invariant exposure and true hazard ratio of 2

Study design	5% events: Relative bias (%) (absolute bias)	SEE	RMSE	CP (%)	10% events: Relative bias (%) (absolute bias)	SEE	RMSE	CP (%)	25% events: Relative bias (%) (absolute bias)	SEE	RMSE	CP (%)
10% subjects exposed												
Full cohort Adj	0.311 (0.002)	0.150	0.150	94.8	0.305 (0.002)	0.105	0.106	95.5	0.698 (0.005)	0.070	0.070	95.7
NCC (1:1) Adj	−17.298 (0.120)	0.238	0.251	93.7	−26.870 (0.186)	0.148	0.229	78.0	−36.555 (0.253)	0.086	0.263	11.1
NCC (1:1) Ma	−0.850 (0.006)	0.238	0.232	95.5	−2.135 (0.015)	0.163	0.157	95.2	−7.244 (0.050)	0.104	0.112	92.5
NCC (5:1) Adj	−1.951 (0.014)	0.177	0.172	96.1	−5.521 (0.038)	0.120	0.128	94.0	−9.757 (0.068)	0.076	0.100	86.1
NCC (5:1) Ma	0.311 (0.002)	0.171	0.171	95.7	0.026 (0.000)	0.119	0.118	95.8	−0.674 (0.005)	0.079	0.078	94.9
25% subjects exposed												
Full cohort Adj	1.911 (0.013)	0.132	0.136	94.1	1.941 (0.013)	0.091	0.093	95.0	1.466 (0.010)	0.058	0.058	94.5
NCC (1:1) Adj	−12.404 (0.086)	0.196	0.204	94.0	−20.081 (0.139)	0.123	0.178	81.7	−30.018 (0.208)	0.070	0.218	13.4
NCC (1:1) Ma	1.030 (0.007)	0.195	0.201	94.9	−1.716 (0.012)	0.133	0.132	95.2	−4.936 (0.034)	0.083	0.087	93.1
NCC (5:1) Adj	−0.384 (0.003)	0.149	0.155	94.7	−2.440 (0.017)	0.101	0.103	94.5	−6.665 (0.046)	0.062	0.078	88.6
NCC (5:1) Ma	1.919 (0.013)	0.146	0.148	94.0	1.390 (0.010)	0.100	0.102	94.8	0.150 (0.001)	0.064	0.064	95.4
50% subjects exposed												
Full cohort Adj	2.805 (0.019)	0.148	0.150	94.6	1.985 (0.014)	0.101	0.103	94.6	1.651 (0.011)	0.063	0.064	94.9
NCC (1:1) Adj	−6.380 (0.044)	0.204	0.200	95.4	−13.666 (0.095)	0.130	0.158	89.8	−22.172 (0.154)	0.074	0.170	45.2
NCC (1:1) Ma	1.301(0.009)	0.204	0.210	95.1	−0.749 (0.005)	0.138	0.137	95.0	−3.624 (0.025)	0.085	0.087	94.1
NCC (5:1) Adj	1.248 (0.009)	0.161	0.160	94.7	−1.455 (0.010)	0.108	0.108	94.9	−4.140 (0.029)	0.066	0.073	92.5
NCC (5:1) Ma	2.776 (0.019)	0.160	0.157	95.6	1.638 (0.011)	0.109	0.112	95.1	0.761 (0.005)	0.068	0.069	95.1

Abbreviations: Adj, adjusted for sex and age; CP, coverage probability; Ma, matched on sex and age; NCC, nested case-control; RMSE, root mean square error; SEE, average standard error estimator.

la Mutuelle Générale de l'Éducation Nationale) (Fournier et al., 2014). The E3N cohort received ethical approval from the French National Commission for Computed Data and Individual Freedom (*Commission Nationale de l'Informatique et des Libertés*, CNIL) and all participants in the study provided informed consent.

Our study population was composed of 38,091 postmenopausal women who were free of any cancer when they completed a detailed questionnaire on their past use of any MHT in 1992. The participants were actively followed-up until 2008 through self-administered questionnaires every 2–3 years, which included updated information on recent MHT use. Among them, 17,194 (45.1%) had ever used MHT at baseline while 7805 (20.5%) started using MHT during follow-up. A total of 2261 (5.9%) invasive breast cancers were diagnosed during 532,925 person-years of follow-up (incidence of 424 cases per 10^5 person-years).

In the full cohort, the associations of each of the two MHT exposure metrics: (i) fixed (assessed at baseline: any prior use before cohort entry) and (ii) time-varying (any previous MHT use before a given time during follow-up) with breast cancer incidence were estimated using the univariate Cox proportional hazards regression model with Efron's approximation for ties. Although these two exposure metrics resemble those in simulations, it is important to note the following differences. The first metric used fixed MHT exposure based on baseline status, thus ignoring possible exposure changes during follow-up, whereas exposure remained fixed throughout follow-up in the simulations. Regarding the second metric, a sizeable

TABLE 4 Results of the E3N cohort analyses with day as the time unit and 100 nested case-control analyses repeating the random sampling of controls

	Time-invariant ever use of MHT					Time-varying ever use of MHT				
Study design	HR† (95%CI)	Min HR	Max HR	RD of log-HR	RW of 95%CI	HR† (95%CI)	Min HR	Max HR	RD of log-HR	RW of 95%CI
Full cohort	1.229 (1.131–1.335)	–	–	Ref.	Ref.	1.494 (1.364 – 1.637)	–	–	Ref.	Ref.
NCC (1:1) B	1.204 (1.077–1.346)	1.109	1.327	−10.12%	1.315	1.439 (1.276–1.623)	1.264	1.598	−9.61%	1.270
NCC (1:1) Ef	1.217 (1.088–1.361)	1.113	1.344	−5.07%	1.333	1.470 (1.303–1.658)	1.282	1.636	−4.36%	1.300
NCC (1:1) Ex	1.232 (1.095–1.387)	1.124	1.375	1.06%	1.428	1.498 (1.320–1.700)	1.296	1.686	0.45%	1.391
NCC (1:1)*	1.227 (1.091–1.381)	1.079	1.353	−0.96%	1.418	1.499 (1.321–1.702)	1.340	1.669	0.64%	1.396
NCC (5:1) B	1.222 (1.117–1.337)	1.170	1.292	−2.83%	1.078	1.488 (1.349–1.642)	1.421	1.562	−1.06%	1.072
NCC (5:1) Ef	1.225 (1.120–1.341)	1.173	1.297	−1.39%	1.081	1.497 (1.356–1.651)	1.429	1.572	0.38%	1.078
NCC (5:1) Ex	1.228 (1.121–1.335)	1.175	1.300	−0.42%	1.096	1.501 (1.359–1.658)	1.433	1.578	1.18%	1.092
NCC (5:1)*	1.231 (1.124–1.348)	1.171	1.304	0.87%	1.098	1.503 (1.361–1.660)	1.435	1.575	1.54%	1.094

Abbreviations: B, Breslow; Ef, Efron; Ex, exact; HR (95%CI), hazard ratio (with 95% confidence interval); HR†, mean HR for NCC analysis; NCC, nested case-control; RD, relative difference; RW, relative width.
*Modified ccwc approach.

proportion of women were already exposed at baseline in the E3N data whereas all subjects were considered unexposed at the beginning of their follow-up in the simulations.

The NCC analyses with the conditional logistic regression model were repeated 100 times for each of one and five controls per case, using four different approaches to handle ties: the exact method, Breslow's and Efron's approximations, as well as the modified *ccwc* approach. In secondary analyses, to increase the number of ties, the time unit of analysis was changed from day to month. We compared the estimates obtained from each approach using unadjusted HR with empirical 95% CI, relative difference of log-HR (difference between mean log-HR of NCC and log-HR of cohort design over the latter), and relative width of 95% CI (ratio of the width of the 95% CI from each of NCC analyses over the width of 95% CI from full cohort design).

3.2 | Results

With daily time units, there were 1984 distinct times at which at least one event occurred. Among them, tied events occurred at 253 event times but the number of ties was relatively low with at most four cases occurring at the same time (see Table A.6 in Supporting Information Appendix 5). Table 4 compares the estimates obtained with full cohort (top row) versus the mean of 100 NCC-based estimates, observed using different NCC analytical strategies. All full cohort and NCC analyses indicated that both time-invariant and time-varying MHT exposures were associated with a statistically significant albeit moderate increase in breast cancer risk (Table 4). The estimated HR for full cohort was 1.23 (95% CI, 1.13–1.34) and 1.49 (95% CI, 1.36–1.64) for, respectively, time-invariant and TVE. Mean NCC estimates for one control per case using the exact method or the modified *ccwc* approach were closer to those obtained from the full cohort analysis than mean NCC estimates obtained using Breslow's or Efron's approximation (relative difference in log-HR of about 1% versus 5–10%, and <1% versus >4% for, respectively, time-invariant and time-varying ever use of MHT, Table 4). As in simulations (Sections 2.2), the Breslow and Efron methods suggested somewhat weaker associations than the full cohort analyses. Consistently with simulation results, differences were much smaller for all NCC approaches with five controls.

When the time unit of analysis was changed to months, the number of ties increased markedly. There were 363 distinct times at which at least one event occurred. Among them, tied events occurred at 309 event times and the number of ties was high, with up to 20 cases occurring at the same event time (Table A.7 in Supporting Information Appendix 5). NCC estimates with Breslow's and Efron's approximations differed considerably from those obtained from the full cohort analysis (relative difference in log-HR up to, respectively, 45% and 23% for one control per case and time-invariant ever use of MHT; Table 5). Consistently with the simulation results, using the Breslow and Efron methods for handling ties resulted in substantial biases toward the null, relative to the estimates yielded by full cohort analyses (Table 5). The use of the exact method or modified *ccwc* approach for NCC analyses greatly reduced this difference (relative difference in log-HR fell to 2% and 4% for one control per case and time-invariant ever use of MHT; Table 5). Overall, although exposure features were

TABLE 5 Results of the E3N cohort analyses with month as the time unit and 100 nested case-control analyses repeating the random sampling of controls

	Time-invariant ever use of MHT					Time-varying ever use of MHT				
Study design	HR† (95%CI)	Min HR	Max HR	RD of log-HR	RW of 95%CI	HR† (95%CI)	Min HR	Max HR	RD of log-HR	RW of 95%CI
Full cohort	1.227 (1.129–1.333)	–	–	Ref.	Ref.	1.491 (1.361–1.634)	–	–	Ref.	Ref.
NCC (1 :1) B	1.119 (1.027–1.221)	1.063	1.178	−44.93%	0.951	1.260 (1.146–1.386)	1.178	1.338	−42.28%	0.880
NCC (1 :1) Ef	1.164 (1.067–1.270)	1.088	1.243	−25.77%	0.994	1.360 (1.236–1.496)	1.242	1.466	−23.20%	0.955
NCC (1 :1) Ex	1.232 (1.095–1.386)	1.119	1.354	1.65%	1.425	1.510 (1.332–1.711)	1.341	1.677	2.87%	1.391
NCC (1 :1)*	1.217 (1.082–1.370)	1.063	1.331	−4.35%	1.409	1.500 (1.321–1.703)	1.340	1.676	1.09%	1.398
NCC (5 :1) B	1.190 (1.094–1.295)	1.126	1.241	−14.86%	0.983	1.414 (1.289–1.551)	1.365	1.472	−13.45%	0.960
NCC (5 :1) Ef	1.208 (1.111–1.315)	1.139	1.264	−7.55%	0.999	1.453 (1.324–1.594)	1.399	1.518	−6.61%	0.988
NCC (5 :1) Ex	1.226 (1.119–1.343)	1.149	1.287	−0.46%	1.095	1.493 (1.352–1.648)	1.434	1.564	0.16%	1.086
NCC (5 :1)*	1.231 (1.124–1.348)	1.170	1.284	1.40%	1.100	1.495 (1.354–1.651)	1.419	1.557	0.52%	1.089

Abbreviations: B, Breslow; Ef, Efron; Ex, exact; HR (95%CI), hazard ratio (with 95% confidence interval); HR†, mean HR for NCC analysis; NCC, nested case-control; RD, relative difference; RW, relative width.
*Modified *ccwc* approach.

not quite identical to those in simulations (see above), these results were consistent with those from simulations both for fixed exposure and TVE.

4 | DISCUSSION

In this paper, we have performed a simulation study to investigate and compare the performances of full cohort versus different NCC analyses for estimating associations between either fixed exposure or TVE and the risk of an adverse event. Our initial findings suggested that NCC estimates could be substantially biased, especially when only a single control was matched to each case. The bias of NCC estimates increased with higher proportion of events, while estimates from the full cohort analysis remained unbiased across all simulated scenarios. However, it appeared that such bias mostly resulted from tied events so that, once appropriately taken into account with the exact method or modified *ccwc* approach, or after matching on confounders, NCC estimates were almost free of bias and quite close to those from the full cohort analysis.

To the best of our knowledge, most studies comparing the relative performances of full cohort and NCC analyses have been limited to fixed exposures (Bertke et al., 2013; Essebag et al., 2005). In our simulations, the performances of cohort and NCC analyses were comparable for fixed exposure and TVE. While our study was limited to simple TVE with a single change from unexposed to exposed during the follow-up, further work should investigate more complex TVEs with multiple changes (Desquilbet & Meyer, 2005), decreasing HRs (Brickner, 2015) or with TVE representing cumulative effects of past exposures (Abrahamowicz et al., 2012; Pazzagli et al., 2018; Sylvestre & Abrahamowicz, 2009). Further work is also warranted to compare cohort and NCC design in the presence of competing events (Austin et al., 2012).

In all the scenarios we investigated, the NCC design with Breslow's (1974) or Efron's (1977) approximations for handling ties in event times resulted in greater bias and lower precision than the full cohort design. The loss of precision of NCC estimates compared to those of the full cohort analysis was expected because in the cohort design all data are used whereas in the NCC only data on cases and selected controls are used. The bias still apparent with five controls per case, however, was less expected and contradictory to the general idea that NCC analyses with a sufficient number of controls per case provide estimates close to those of full cohort analyses (Bertke et al., 2013; Breslow & Day 1987; Essebag et al., 2005; Goldstein & Langholz, 1992; Pang 1999). Moreover, counterintuitively, bias tended to increase with higher proportion of events, a similar finding to that reported by Austin et al. (2012) whereas one could expect more accurate estimation as the wealth of information increases. In our case, however, the observed biases most likely resulted from tied events and the way they were handled. Those biases were indeed markedly reduced (at the expense of slightly lower precision for lower proportion of events) when the exact method (Peto, 1972) or modified *ccwc* approach was used instead of Breslow's or Efron's approximation.

The observed trend of increasing biases with greater proportion of events in Breslow's and Efron's approximations is consistent with the previous finding that these approximations deteriorate as the proportion of tied events increases

(Farewell & Prentice, 1980). In our simulation setting, as the proportion of events, that is, the number of cases in a fixed-size cohort of 5000 individuals, increases, so does the probability of having two or more events occurring at the same time within a limited timeframe of 730 days. Increasing the proportion of tied events had strong detrimental impact on NCC estimates, while estimates from the full cohort analysis were hardly affected and remained virtually unbiased. Indeed, in full cohort analyses, the proportion of ties within risk sets at each event time is considerably diluted among all subjects belonging to the risk set at that time whereas, in NCC analyses, the risk set is much smaller, constrained to the cases occurring at this specific event time and their matched controls. Formerly, Farewell and Prentice (1980) had shown through simulations of case-control data with 5, 20, and 50 cases (i.e., tied events) per stratum that NCC estimates with Efron's approximation, and to an even greater extent with Breslow's approximation, are affected by systematic underestimation bias. They, therefore, advised not to use these two approximation methods for case-control or cohort studies in which the number of ties per event time is large. Other authors have advocated the use of the exact method (Peto, 1972) to analyze case-control studies when the proportion of cases in each case-control stratum is not small enough (Langholz & Richardson, 2010). This problem can also be avoided in case-control studies by arranging the case-control sets in such a way as to obtain a single case per stratum and, thus, not to have tied events in the strata. This solution requires, however, that each of the cases occurring at the same event time may be allocated a sufficient number of matched controls. This motivated our modification of the *ccwc* function in R, in accordance with the sampling procedure performed in SAS macro %nCCsampling (Desai et al., 2016).

We are concerned that researchers may not be aware of the potential deterioration of NCC estimation in the presence of numerous tied events and that this problem may be insufficiently taken into account in practice. In particular, researchers should be aware of the possible limitations of the default options used in the available statistical software for implementing conditional logistic regression. In R, while the *clogit* function uses the exact method by default, it calls the *coxph* function which uses Efron's approximation by default. In SAS, conditional logistic regression can be performed using either the PHREG procedure with a STRATA statement, which employs Breslow's approximation as the default, or the LOGISTIC procedure with a STRATA statement. The latter procedure relies upon the exact method for discrete data assuming that events really occurred at exactly the same time (Allison, 2010). This procedure is called, for example, by the %nCCsampling macro which performs incidence density sampling for NCC analysis (Desai et al., 2016). In our simulated and example data, especially when a month was taken as the time unit, ties resulted from an imprecise measurement of continuous time. Consequently, the exact method assuming that there is a true but unknown ordering for the tied event times should be used. The computation of the exact likelihood, which considers all possible orderings of tied events, "can be a daunting task" (Allison, 2010) for full cohort analyses but, in our experience, resulted in a reasonable computation time for NCC analyses.

In conclusion, our simulation study showed that NCC analyses with Breslow's or Efron's approximations could lead to substantial bias when there is a large number of tied events in the data. However, once ties were taken correctly into account, NCC estimates were almost free of bias and close to those from the full cohort analysis. We strongly recommend checking datasets for ties and using appropriate strategies for handling ties (like using the exact or modified *ccwc* method) in NCC analyses when there are many tied event times.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

The E3N dataset analyzed during the current study was available from the E3N study team but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are, however, available from the E3N study team upon reasonable request and permission of the E3N principal investigator.

OPEN RESEARCH BADGES

This article has earned an Open Data badge for making publicly available the digitally-shareable data necessary to reproduce the reported results. The data is available in the Supporting Information section.

This article has earned an open data badge "**Reproducible Research**" for making publicly available the code necessary to reproduce the reported results. The results reported in this article could fully be reproduced.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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