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LETTER TO THE EDITOR

Letter to the editor on "New weighting methods when cases are only a subset of events in a nested case-control study" by Qian M. Zhou, Xuan Wang, Yingye Zheng, and Tianxi Cai

To the editor,

We have read with interest the article by Zhou and colleagues on the proposal of new weighting methods for nested case-control (NCC) studies in which only a subset of events is sampled (Zhou et al., 2022). We highly appreciate their work comparing novel proposed weighting methods (Edelmann et al., 2020), including one presented in our paper (Graziano et al., 2021).

Our paper aimed to compare different sampling strategies to evaluate the prognostic value of a new biomarker on a time-to-event end-point. In order to compare different designs fixing the subcohort size, we faced the issue of planning an NCC design in which a subset of events was sampled (i.e., "untypical" NCC). In agreement with our two-phase approach, we used the Cox model weighted by the inverse of the sampling probabilities. Sampling probabilities for controls ($\hat{p}_{0j}$) were derived as reported by Zhou and colleagues in their Equation (4), while, for the cases, the proportion of events selected as cases was used (π_1 following the notation of Zhou and colleagues). We were surprised to see the amount of bias of our weighting in some simulation scenarios hypothesized by Zhou et al. (2022). Although our aim was not to propose a new weight for the "untypical" NCC, our weight follows a Horvitz–Thompson approach. By looking closely at their simulation code (available at https://onlinelibrary.wiley.com/doi/10.1002/bimj.202100194#support-information-section), we found an error in the code in *SimuI.fun.R* (used to produce their Tables 2, 3 and Supplementary Tables), although our weight was correctly reported in their paper as

$$\kappa_{2,j} = \delta_j \frac{\left[V_{1j} + \left(1 - V_{1j}\right) V_{0j}\right]}{\pi_1} + \frac{\left(1 - \delta_j\right) V_{0j}}{\hat{p}_{0j}}, \tag{1}$$

where δ_j denotes the indicator of an event for subject j and V_{1j} and V_{0j} the subcohort sampling indicators denoting if subject j is selected as case or control, respectively. The weight $\kappa_{2,j}$ in Equation (1) reduces to $\frac{1}{\pi_1}$ for both events cases ($\delta_j = 1$ and $V_{1j} = 1$) and events controls ($\delta_j = 1$ and $V_{0j} = 0$), but their code (*SimuI.fun.R*) attributed a weight of 1 to events selected as cases, even if not all events were sampled (for details, see the Supporting Information), resulting in the following weight:

$$\kappa_{2,j}{}^{error} = \delta_j \left[V_{1j} + \frac{\left(1 - V_{1j}\right) V_{0j}}{\pi_1}\right] + \frac{\left(1 - \delta_j\right) V_{0j}}{\hat{p}_{0j}}. \tag{2}$$

Interestingly, this error is not present in their code *NCCIPW_DataSimulation.Rmd*, used to reproduce their Figure 3 and 4, where our weight in Equation (1) has a similar performance to their prosed Horvitz–Thompson weight w_{HT}, the details of which can be found in Zhou et al. (2022). In support of this, we corrected and modified the *SimuI.fun.R* code as reported in the Supporting Information and in the R code reproducing the results presented in Table 2 of section 4.1 of Zhou et al. (2022). Reproduced results in Table 1 indicate that, in all scenarios, the bias and the empirical standard deviation, SD, of our weight ($\kappa_{2,j}$ with corrected code) had a much lower value compared to the results presented by Zhou et at. ($\kappa_{2,j}$ with the error in code resulting in the estimator of Equation 2), and thus we suggest a correction of the latter, also motivated by the letter of Edelmann et al. (2023). Moreover, its performance is similar, if not better, than the performance of w_{HT}.

By the way, we must apologize that the sampling weight that we used for events was not completely clear in our original manuscript and we recently corrected it in Graziano et al. (2022). As sampling weight of the events (again without distinction if selected as cases or controls), we actually used the posterior sampling weight (i.e., final number of events

TABLE 1 Simulation results: estimation of β_Z (clinical marker coefficient measured on the full cohort) and β_B (biomarker coefficient measured on the subcohort) under the proportional hazard model. For each parameter, the results include the bias and empirical SD (in the parentheses) relative to the true parameter value in 100%. The NCC subcohort is constructed with matching. For details on $\beta_{Z,}$ $\beta_{B,}$ $\tilde{w}$,$\hat{w}$, w_{HT} refer to Zhou et al. (2022).

N	π_1	$1:m$	$\tilde{w}$	$\hat{w}$	w_{HT}	κ_2^{error}	$\kappa_2^{correct}$	κ_2^*
				$\beta_Z = 0.5$				
5000	0.2	1:1	9.8 (99.4)	0.5 (41.4)	0.5 (41.4)	21.7 (55.9)	−0.1 (40.1)	1.5 (40.9)
5000	0.2	1:3	6.8 (66.9)	0.6 (32.4)	1.4 (31.6)	21.2 (40.0)	−0.6 (29.0)	3.7 (30.6)
5000	0.5	1:1	3.6 (53.7)	2.0 (27.4)	2.1 (27.2)	11.4 (30.4)	1.8 (26.7)	2.7 (27.0)
5000	0.5	1:3	2.4 (38.9)	1.1 (19.8)	1.3 (19.4)	10.1 (21.1)	0.4 (18.6)	2.8 (19.2)
5000	0.8	1:1	2.5 (33.1)	2.1 (21.1)	2.1 (21.0)	5.2 (21.8)	2.0 (20.9)	2.3 (21.0)
5000	0.8	1:3	1.3 (22.7)	1.2 (16.5)	1.2 (16.3)	4.1 (16.6)	1.0 (16.0)	1.8 (16.2)
10,000	0.2	1:1	8.2 (80.3)	0.0 (29.1)	0.6 (29.0)	22.6 (39.4)	−0.1 (28.0)	1.4 (28.6)
10,000	0.2	1:3	2.5 (54.0)	−0.5 (21.8)	0.1 (20.7)	19.7 (26.8)	−1.9 (19.2)	2.4 (20.1)
10,000	0.5	1:1	−0.9 (47.1)	−0.6 (18.5)	−0.6 (18.3)	8.4 (20.4)	−0.8 (17.9)	0.1 (18.2)
10,000	0.5	1:3	2.4 (31.4)	0.0 (14.7)	0.2 (14.3)	9.1 (15.3)	−0.6 (13.7)	1.7 (14.1)
10000	0.8	1:1	1.5 (24.1)	0.4 (14.7)	0.5 (14.6)	3.5 (15.1)	0.4 (14.5)	0.7 (14.5)
10,000	0.8	1:3	−0.7 (18.8)	0.2 (11.8)	0.2 (11.6)	3.1 (11.9)	0.0 (11.5)	0.8 (11.6)
				$\beta_B = 0.5$				
5000	0.2	1:1	11.8 (76.3)	2.7 (29.6)	2.7 (29.5)	27.3 (41.8)	2.6 (28.5)	4.3 (29.2)
5000	0.2	1:3	6.4 (49.9)	1.4 (22.3)	1.4 (21.8)	24.0 (28.0)	0.7 (20.2)	5.2 (21.1)
5000	0.5	1:1	6.3 (39.6)	1.2 (18.7)	1.3 (18.7)	11.5 (21.0)	1.4 (18.3)	2.3 (18.5)
5000	0.5	1:3	1.5 (29.2)	0.5 (14.6)	0.6 (14.4)	11.0 (15.7)	0.6 (13.8)	3.0 (14.2)
5000	0.8	1:1	1.0 (24.7)	0.0 (14.9)	0.0 (14.9)	3.2 (15.5)	0.1 (14.8)	0.4 (14.8)
5000	0.8	1:3	1.2 (16.7)	0.1 (11.9)	0.2 (11.8)	3.5 (12.1)	0.3 (11.6)	1.1 (11.8)
10,000	0.2	1:1	6.1 (58.7)	0.7 (20.8)	0.6 (20.6)	23.3 (28.1)	0.8 (19.9)	2.3 (20.4)
10,000	0.2	1:3	4.9 (38.2)	0.1 (15.4)	0.5 (14.9)	23.8 (19.0)	0.2 (13.9)	4.5 (14.5)
10,000	0.5	1:1	5.1 (34.2)	1.6 (12.9)	1.6 (12.8)	11.5 (14.4)	1.8 (12.6)	2.7 (12.8)
10,000	0.5	1:3	0.3 (24.6)	0.4 (10.8)	0.5 (10.5)	10.9 (11.2)	0.7 (10.1)	3.0 (10.4)
10,000	0.8	1:1	2.0 (17.8)	0.8 (10.5)	0.8 (10.5)	4.0 (10.9)	0.9 (10.4)	1.2 (10.5)
10,000	0.8	1:3	1.0 (13.3)	0.5 (8.3)	0.6 (8.1)	3.9 (8.3)	0.7 (8.0)	1.5 (8.1)

sampled in the subcohort, as cases or controls, divided by the number of all events in the cohort):

$$\pi_1^* = \frac{\sum_{j=1}^{N} \delta_j \left[V_{1j} + \left(1 - V_{1j}\right) V_{0j}\right]}{\sum_{j=1}^{N} \delta_j},$$

where N denotes the size of the full cohort. Thus, the weight becomes

$$k_{2,j}^* = \delta_j \frac{\left[V_{1j} + \left(1 - V_{1j}\right) V_{0j}\right]}{\pi_1 *} + \frac{\left(1 - \delta_j\right) V_{0j}}{\hat{p}_{0j}}. \tag{3}$$

Also, simulation results using $\kappa_{2*,j}$ confirmed a better performance than the one shown by Zhou et al. (2022). A similar performance of estimators in Equations (1) and (3) was also shown in other scenarios. Implementation of $\kappa_{2*,j}$ was also provided in the Supporting Information.

We would like to take this opportunity to mention that we applied $k_{2,j}^*$ also to "untypical" countermatching designs in which a subset of all events was sampled. Future works exploring the performance of the weights proposed by Zhou and colleagues in this sampling design would be interesting.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data used in the article are available in the Supporting Information.

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

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