Received: 7 December 2017 | Accepted: 28 November 2018
DOI: 10.1111/biom.13012

ORIGINAL ARTICLE

WILEY Biometrics

A modified partial likelihood score method for Cox regression with covariate error under the internal validation design

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Abstract
We develop a new method for covariate error correction in the Cox survival regression model, given a modest sample of internal validation data. Unlike most previous methods for this setting, our method can handle covariate error of arbitrary form. Asymptotic properties of the estimator are derived. In a simulation study, the method was found to perform very well in terms of bias reduction and confidence interval coverage. The method is applied to data from the Health Professionals Follow-Up Study (HPFS) on the effect of diet on incidence of Type II diabetes.

KEYWORDS
Cox model; measurement error; modified score

1 | INTRODUCTION

In the Cox (1972) regression model for survival data, the hazard function $\lambda(t|\mathbf{x})$ for an individual with covariate vector $\mathbf{x} \in \mathbb{R}^p$ is modeled semiparametrically as

$$\lambda(t|\mathbf{x}) = \lambda_0(t)\exp(\boldsymbol{\beta}^T\mathbf{x}), \tag{1}$$

where $\boldsymbol{\beta} \in \mathbb{R}^p$ is a vector of regression coefficients and $\lambda_0(t)$ is an unspecified baseline hazard function $\lambda_0(t)$. Cox proposed drawing inference on $\boldsymbol{\beta}$ based on the notion of partial likelihood, which was subsequently justified rigorously by Tsiatis (1981), who used classical limit theory, and by Andersen and Gill (1982), who used a martingale theory approach.

In many applications, however, the covariate $\mathbf{X}$ is not measured exactly, but is subject to measurement error of some degree, often substantial. Thus, instead of observing $\mathbf{X}$, we observe a surrogate measure $\mathbf{W}$. Starting from Prentice (1982), a considerable literature has been developed on inference for the Cox regression model with covariate error in various contexts; see Zucker (2005) for a brief review.

The existing methods generally involve some model assumptions on the joint distribution of the true covariate and the surrogate. Many of the methods make use of specific parametric forms for this joint distribution. Other methods, such as those of Huang and Wang (2000) and Kong and Gu (1999), avoid use of a specific parametric form but still rely on an assumption that the covariate error is of independent additive structure. Some papers, such as Zhou and Pepe (1995), Zhou and Wang (2000), and Chen (2002), present methods without this additive error assumption for the internal validation design in which there is a subsample of individuals with a measurement on both the true covariate and the surrogate. These methods, however, have challenges as well. The approach taken by Zhou and Pepe (1995) and by Zhou and Wang (2000) involves stratification or smoothing in the covariate space; when the number of covariates is moderate to large, this approach breaks down due to the "curse of dimensionality." Chen (2002) assumes that it is possible to form a satisfactory initial estimate of the regression coefficient vector based on the validation sample alone. This is not the case, however, for studies where the event rate is low to moderate, the main study sample size is in the thousands to hundreds of thousands, and the validation study sample size is, as in all applications we know of, only a few hundred. Under these circumstances, the number of events in the validation study is very small, so that a satisfactory initial estimate of the regression coefficient vector based on the validation sample alone cannot be obtained. Thus, in such situations, which often arise in practice, Chen's approach is problematic.

This paper presents a new method for the Cox model with covariate error, which overcomes the limitations of previously proposed methods. The method involves a modified version of the classical Cox partial likelihood score function, with the internal validation data incorporated in a suitable way. Our approach is very simple in concept. It is in the spirit of Lin and Ying's (1993) work on Cox regression with incomplete covariate data. There is also some resemblance to Huang and Wang's (2000) method for Cox regression with covariate error, and to work of Kulich and Lin (2000, 2004). The method requires no assumptions on the form of the covariate error. It is especially designed for the internal validation design with a relatively small validation sample and a moderate to large number of covariates, which, as indicated above, is a challenging situation that often arises in epidemiological studies. The method is easy to implement, and its practical utility is backed by large-sample theory and small-sample simulations.

The outline of the remainder of the paper is as follows. Section 2 presents the proposed method and its asymptotic properties, Section 3 a simulation study, Section 4 an application to data from the Health Professionals Follow-Up Study (HPFS), and Section 5 a brief summary. The Web Appendix provides theoretical details.

2 | THE PROPOSED METHOD AND ITS ASYMPTOTIC PROPERTIES

2.1 | The Proposed Method

We assume a classical survival data setup. We have i.i.d. observations on n individuals. Associated with each individual i is a set of random variables $(T_i^\circ, C_i, \mathbf{X}_i, \mathbf{W}_i)$, with T_i° representing the time to event, C_i representing the time to censoring, $\mathbf{X}_i$ representing a p-vector of true covariate values, and $\mathbf{W}_i$ representing a p-vector of surrogate covariate values. We assume that the covariates are arranged so that the first p_1 covariates are the error-prone covariates and the remaining $p_2 = p - p_1$ covariates are error-free. For the error-free covariates, the relevant component of $\mathbf{W}_i$ is identical to the corresponding component of $\mathbf{X}_i$. We denote the maximum follow-up time by τ. The available data on all individuals consist of $(T_i, \delta_i, \mathbf{W}_i)$, where $T_i = \min(T_i^\circ, C_i)$ is the follow-up time and $\delta_i = I(T_i^\circ \le C_i)$, with $I(\cdot)$ being the indicator function, is the event indicator. In addition, within the main study we have a random internal validation sample of size m of individuals with both $\mathbf{X}_i$ and $\mathbf{W}_i$ observed. We take $m = ceil(\pi n)$, where π is a specified number in (0, 1) and $ceil(u)$ denotes the smallest integer greater than or equal to u. We define ω_i to be equal to 1 if individual i is in the internal validation sample and 0 otherwise. Thus, the random vector $(\omega_1, \dots, \omega_n)$ has a uniform distribution over the finite set $\mathcal{O}(n, m)$ of vectors with m ones and $n - m$ zeros (i.e., $\mathcal{O}(n, m)$ expresses the various ways of selecting m elements from a set of n elements). We write $\hat{\pi} = m/n$. Note that $\hat{\pi}$ is not an estimate, but rather is fixed by design. Also, as usual, we define $Y_i(t) = I(T_i \ge t)$ and $N_i(t) = \delta_i I(T_i \le t)$. Left truncation is handled by setting

$Y_i(t)$ to zero until the time at which individual i comes under observation.

We assume, as usual, that T_i° and C_i are conditionally independent given $\mathbf{X}_i$. We assume further that the measurement error is noninformative in the sense that $\mathbf{W}_i$ is conditionally independent of (T_i°, C_i) given $\mathbf{X}_i$. We make no assumptions about the form of the measurement error. Finally, we assume that the survival time T_i° follows the Cox model (1). We denote the true value of $\boldsymbol{\beta}$ by $\boldsymbol{\beta}^*$. We present our development for the case of the classical Cox relative risk function $e^{\boldsymbol{\beta}^T\mathbf{X}_i}$, but it is straightforward to extend the development to more general relative risk functions, as in Thomas (1981) and in Breslow and Day, 1993, Sec. 5.1(c).

We construct our procedure as follows. Let $\hat{E}$ denote empirical expectation, so that, for example,

$$\hat{E}\{Y(t)\exp(\boldsymbol{\beta}^T\mathbf{X})\} = \frac{1}{n}\sum_{j=1}^{n} Y_j(t)\exp(\boldsymbol{\beta}^T\mathbf{X}_j),$$

$$\hat{E}\{Y(t)\mathbf{X}\exp(\boldsymbol{\beta}^T\mathbf{X})\} = \frac{1}{n}\sum_{j=1}^{n} Y_j(t)\mathbf{X}_j\exp(\boldsymbol{\beta}^T\mathbf{X}_j).$$

In the absence of measurement error, the Cox partial likelihood score function is given by

$$\mathbf{U}_{COX}(\boldsymbol{\beta}) = \frac{1}{n}\sum_{i=1}^{n}\delta_i\left(\mathbf{X}_i - \left[\frac{\hat{E}\{Y(t)\mathbf{X}\exp(\boldsymbol{\beta}^T\mathbf{X})\}}{\hat{E}\{Y(t)\exp(\boldsymbol{\beta}^T\mathbf{X})\}}\right]_{t=T_i}\right). \tag{2}$$

When $\mathbf{X}$ is measured only for a sample of the individuals and only $\mathbf{W}$ is available for the others, a naive Cox analysis involves simply substituting $\mathbf{W}$ in place of $\mathbf{X}$ for the individuals without a measurement of $\mathbf{X}$. In other words, defining $\mathbf{W}_i^\circ = \omega_i\mathbf{X}_i + (1-\omega_i)\mathbf{W}_i$, the naive Cox analysis is based on the score function

$$\mathbf{U}_{NAI}(\boldsymbol{\beta}) = \frac{1}{n}\sum_{i=1}^{n}\delta_i\left(\mathbf{W}_i^\circ - \left[\frac{\hat{E}\{Y(t)\mathbf{W}^\circ\exp(\boldsymbol{\beta}^T\mathbf{W}^\circ)\}}{\hat{E}\{Y(t)\exp(\boldsymbol{\beta}^T\mathbf{W}^\circ)\}}\right]_{t=T_i}\right), \tag{3}$$

with

$$\hat{E}\{Y(t)\exp(\boldsymbol{\beta}^T\mathbf{W}^\circ)\} = S_0^\circ(t,\boldsymbol{\beta}) = \frac{1}{n}\sum_{j=1}^{n} Y_j(t)\exp(\boldsymbol{\beta}^T\mathbf{W}_j^\circ),$$

$$\hat{E}\{Y(t)\mathbf{W}^\circ\exp(\boldsymbol{\beta}^T\mathbf{W}^\circ)\} = \mathbf{S}_1^\circ(t,\boldsymbol{\beta}) = \frac{1}{n}\sum_{j=1}^{n} Y_j(t)\mathbf{W}_j^\circ\exp(\boldsymbol{\beta}^T\mathbf{W}_j^\circ).$$

We denote the corresponding estimator by $\hat{\boldsymbol{\beta}}_{NAI}$. The terms in $\mathbf{U}_{NAI}(\boldsymbol{\beta})$ are of "observed − expected" form, but the "expected" term is incorrect. Consequently, the naive score function does not have zero asymptotic expectation under $\boldsymbol{\beta}^*$, and therefore $\hat{\boldsymbol{\beta}}_{NAI}$ is biased.

An improved estimator can be obtained using regression calibration, which is an established technique for measurement error problems; see, for example, Carroll et al. (2006, Chapter 4). In regression calibration, we redefine $\mathbf{W}_i^\circ$ to be $\mathbf{W}_i^\circ = \omega_i\mathbf{X}_i + (1-\omega_i)\hat{\mathbf{X}}_i$, with $\hat{X}_{ir}$ $(r = 1, \ldots, p_1)$ defined as

$$\hat{X}_{ir} = \hat{\alpha}_{r0} + \sum_{s=1}^{p}\hat{\alpha}_{rs}W_{is} \tag{4}$$

where $\hat{\alpha}_{r0}, \ldots, \hat{\alpha}_{rp}$ are the ordinary least squares estimates of the regression of X_{ir} on $\mathbf{W}_i$ based on the internal validation sample. Having redefined $\mathbf{W}_i^\circ$, we redefine $S_0^\circ(t,\boldsymbol{\beta})$ and $\mathbf{S}_1^\circ(t,\boldsymbol{\beta})$ correspondingly. We denote the resulting estimator by $\hat{\boldsymbol{\beta}}_{RC}$. In (4), for the sake of generality, we have included all of the components of $\mathbf{W}_i$ in the regression, but in typical applications of regression calibration the regression model for X_{ir} includes only W_{ir} and perhaps one or two additional components of $\mathbf{W}_i$. Substantial improvement is often achieved with the regression calibration approach, but the "expected" term is still not exactly correct, and therefore the resulting estimator is not exactly consistent. The regression calibration approximation is good when the degree of measurement error is small or the regression coefficients of the error-prone covariates are small, but otherwise the approximation can be unsatisfactory (Spiegelman, Rosner, and Logan, 2000).

We present an estimator that builds on the regression calibration estimator but is exactly consistent. As in regression calibration, we use the regression model (4). However, we use this model only as a working model, and it is not necessary for the model to be correct for our estimator to be consistent. As with standard regression calibration, it is possible in principle, as written in (4), to include all of the components of $\mathbf{W}_i$ in the model, but in practice we recommend using only W_{ir} and perhaps one or two additional components.

The idea of our approach is to replace the incorrect "expected" term with a correct one. Let $\boldsymbol{\alpha}^{(r)}$ be the column vector with components $\alpha_{r0}, \alpha_{r1}, \ldots, \alpha_{rp}$, let $\boldsymbol{\alpha}$ denote the vector formed by stacking the vectors $\boldsymbol{\alpha}^{(r)}$ one on top of the other, and let $\boldsymbol{\alpha}^*$ denote the true value of $\boldsymbol{\alpha}$. To emphasize the dependence of $\hat{X}_{ir}$ on $\boldsymbol{\alpha}$, we denote the vector of X_{ir}'s by $\hat{\mathbf{X}}_i(\boldsymbol{\alpha})$.

Define

$$S_{0a}(t,\boldsymbol{\beta}) = \frac{1}{n}\sum_{j=1}^{n}\omega_j Y_j(t)\exp(\boldsymbol{\beta}^T\mathbf{X}_j), \tag{5}$$

$$S_{0b}(t,\boldsymbol{\beta},\boldsymbol{\alpha}) = \frac{1}{n}\sum_{j=1}^{n}(1-\omega_j)Y_j(t)\exp\{\boldsymbol{\beta}^T\hat{\mathbf{X}}_j(\boldsymbol{\alpha})\}, \tag{6}$$

$$S_{0c}(t,\boldsymbol{\beta},\boldsymbol{\alpha}) = \frac{1}{n}\sum_{j=1}^{n}\omega_j Y_j(t)\exp\{\boldsymbol{\beta}^T\hat{\mathbf{X}}_j(\boldsymbol{\alpha})\}, \tag{7}$$

$$\mathbf{S}_{1a}(t,\boldsymbol{\beta}) = \frac{1}{n}\sum_{j=1}^{n}\omega_j Y_j(t)\mathbf{X}_j \exp(\boldsymbol{\beta}^T\mathbf{X}_j), \tag{8}$$

$$\mathbf{S}_{1b}(t,\boldsymbol{\beta},\boldsymbol{\alpha}) = \frac{1}{n}\sum_{j=1}^{n}(1-\omega_j)Y_j(t)\widehat{\mathbf{X}}_j(\boldsymbol{\alpha})\exp\{\boldsymbol{\beta}^T\widehat{\mathbf{X}}_j(\boldsymbol{\alpha})\}, \tag{9}$$

$$\mathbf{S}_{1c}(t,\boldsymbol{\beta},\boldsymbol{\alpha}) = \frac{1}{n}\sum_{j=1}^{n}\omega_j Y_j(t)\widehat{\mathbf{X}}_j(\boldsymbol{\alpha})\exp\{\boldsymbol{\beta}^T\widehat{\mathbf{X}}_j(\boldsymbol{\alpha})\}, \tag{10}$$

$$\widetilde{\mathbf{S}}_{1a}(t,\boldsymbol{\beta},\boldsymbol{\alpha}) = \frac{1}{n}\sum_{j=1}^{n}\omega_j Y_j(t)\widehat{\mathbf{X}}_j(\boldsymbol{\alpha})\exp(\boldsymbol{\beta}^T\mathbf{X}_j), \tag{11}$$

$$S_0(t,\boldsymbol{\beta},\boldsymbol{\alpha}) = S_{0a}(t,\boldsymbol{\beta}) + \left\{\frac{S_{0a}(t,\boldsymbol{\beta})}{S_{0c}(t,\boldsymbol{\beta},\boldsymbol{\alpha})}\right\} S_{0b}(t,\boldsymbol{\beta},\boldsymbol{\alpha}), \tag{12}$$

$$\widetilde{\phi}(t,\boldsymbol{\beta},\boldsymbol{\alpha}) = S_{0b}(t,\boldsymbol{\beta},\boldsymbol{\alpha})/S_{0c}(t,\boldsymbol{\beta},\boldsymbol{\alpha}), \tag{13}$$

$$\begin{aligned}\mathbf{S}_1(t,\boldsymbol{\beta},\boldsymbol{\alpha}) &= \mathbf{S}_{1a}(t,\boldsymbol{\beta}) + \mathbf{S}_{1b}(t,\boldsymbol{\beta},\boldsymbol{\alpha}) \\ &\quad + \widetilde{\phi}(t,\boldsymbol{\beta},\boldsymbol{\alpha})\left\{\widetilde{\mathbf{S}}_{1a}(t,\boldsymbol{\beta},\boldsymbol{\alpha}) - \mathbf{S}_{1c}(t,\boldsymbol{\beta},\boldsymbol{\alpha})\right\}. \end{aligned} \tag{14}$$

We then take the score function to be

$$\mathbf{U}_{MS}(\boldsymbol{\beta},\boldsymbol{\alpha}) = \frac{1}{n}\sum_{i=1}^{n}\delta_i\left\{\mathbf{W}_i^\circ - \frac{\mathbf{S}_1(T_i,\boldsymbol{\beta},\boldsymbol{\alpha})}{S_0(T_i,\boldsymbol{\beta},\boldsymbol{\alpha})}\right\}. \tag{15}$$

The estimator $\widehat{\boldsymbol{\beta}}_{MS}$ is defined to be the solution to the score equation $\mathbf{U}_{MS}(\boldsymbol{\beta},\widehat{\boldsymbol{\alpha}}) = \mathbf{0}$. We could have used $\widehat{\phi} = (1-\widehat{\pi})/\widehat{\pi} = (n-m)/m$ in place of $\widetilde{\phi}(t,\boldsymbol{\beta},\boldsymbol{\alpha})$, but we found that better finite-sample performance is achieved with $\widetilde{\phi}(t,\boldsymbol{\beta},\boldsymbol{\alpha})$.

The motivation behind $\mathbf{U}_{MS}(\boldsymbol{\beta},\boldsymbol{\alpha})$ is as follows. The regression calibration function $\mathbf{U}_{RC}(\boldsymbol{\beta})$ can be written in counting process notation as

$$\mathbf{U}_{RC}(\boldsymbol{\beta},\boldsymbol{\alpha}) = \frac{1}{n}\sum_{i=1}^{n}\int_0^{\tau}\left\{\mathbf{W}_i^\circ - E(t,\boldsymbol{\beta},\boldsymbol{\alpha})\right\}dN_i(t)$$

with

$$E(t,\boldsymbol{\beta},\boldsymbol{\alpha}) = \frac{\mathbf{S}_1^\circ(t,\boldsymbol{\beta},\boldsymbol{\alpha})}{S_0^\circ(t,\boldsymbol{\beta},\boldsymbol{\alpha})}.$$

Let us now define $dM_i(t) = dN_i(t) - Y_i(t)e^{\boldsymbol{\beta}^{*T}\mathbf{X}_i}\lambda_0(t)dt$. We can then write

$$\begin{aligned}\mathbf{U}_{RC}(\boldsymbol{\beta},\boldsymbol{\alpha}) &= \frac{1}{n}\sum_{i=1}^{n}\int_0^{\tau}\left\{\mathbf{W}_i^\circ - E(t,\boldsymbol{\beta},\boldsymbol{\alpha})\right\}Y_i(t)e^{\boldsymbol{\beta}^{*T}\mathbf{X}_i}\lambda_0(t)dt \\ &\quad + \frac{1}{n}\sum_{i=1}^{n}\int_0^{\tau}\left\{\mathbf{W}_i^\circ - E(t,\boldsymbol{\beta},\boldsymbol{\alpha})\right\}dM_i(t) \\ &= \int_0^{\tau}\left\{\mathbf{S}_1^{\circ\circ}(t,\boldsymbol{\beta}^*,\boldsymbol{\alpha}) - E(t,\boldsymbol{\beta},\boldsymbol{\alpha})S_{0d}(t,\boldsymbol{\beta}^*)\right\}\lambda_0(t)dt \\ &\quad + \frac{1}{n}\sum_{i=1}^{n}\int_0^{\tau}\left\{\mathbf{W}_i^\circ - E(t,\boldsymbol{\beta},\boldsymbol{\alpha})\right\}dM_i(t), \end{aligned} \tag{16}$$

where

$$S_{0d}(t,\boldsymbol{\beta}) = \frac{1}{n}\sum_{j=1}^{n}Y_j(t)e^{\boldsymbol{\beta}^T\mathbf{X}_j},$$

$$\begin{aligned}\mathbf{S}_1^{\circ\circ}(t,\boldsymbol{\beta},\boldsymbol{\alpha}) &= \frac{1}{n}\sum_{j=1}^{n}Y_j(t)\mathbf{W}_j^\circ e^{\boldsymbol{\beta}^T\mathbf{X}_j} = \mathbf{S}_{1a}(\boldsymbol{\beta},\boldsymbol{\alpha}) \\ &\quad + \frac{1}{n}\sum_{j=1}^{n}(1-\omega_j)Y_j(t)\widehat{\mathbf{X}}_j(\boldsymbol{\alpha})e^{\boldsymbol{\beta}^T\mathbf{X}_j}.\end{aligned}$$

Using counting process theory (Gill, 1984), it can be seen that the second term of (16) has expectation zero. In the absence of measurement error, the value at $\boldsymbol{\beta}^*$ of the quantity in brackets in the first term of (16) is zero, so that the score function is unbiased. In the presence of measurement error, the value at $\boldsymbol{\beta}^*$ of this quantity is in general nonzero. We need to redefine $E(t,\boldsymbol{\beta},\boldsymbol{\alpha})$ so that the limiting value of this quantity at $\boldsymbol{\beta}^*, \boldsymbol{\alpha}^*$ is zero. Define

$$\begin{aligned}\mathcal{E}_X(t,\boldsymbol{\beta}) &= E\{Y(t)\exp(\boldsymbol{\beta}^T\mathbf{X})\}, \\ \boldsymbol{\mathcal{E}}_{XX}(t,\boldsymbol{\beta}) &= E\{Y(t)\mathbf{X}\exp(\boldsymbol{\beta}^T\mathbf{X})\}, \\ \boldsymbol{\mathcal{E}}_{WX}(t,\boldsymbol{\beta},\boldsymbol{\alpha}) &= E\{Y(t)\widehat{\mathbf{X}}(\boldsymbol{\alpha})\exp(\boldsymbol{\beta}^T\mathbf{X})\}.\end{aligned}$$

The limiting value of $S_{0d}(t,\boldsymbol{\beta})$ is then $\mathcal{E}_X(t,\boldsymbol{\beta},\boldsymbol{\alpha})$ and the limiting value of $\mathbf{S}_1^{\circ\circ}(t,\boldsymbol{\beta},\boldsymbol{\alpha})$ is $\mathbf{s}_1(t,\boldsymbol{\beta},\boldsymbol{\alpha}) = \pi\boldsymbol{\mathcal{E}}_{XX}(t,\boldsymbol{\beta},\boldsymbol{\alpha}) + (1-\pi)\boldsymbol{\mathcal{E}}_{WX}(t,\boldsymbol{\beta},\boldsymbol{\alpha})$. We thus have to redefine $E(t,\boldsymbol{\beta},\boldsymbol{\alpha})$ so that its limiting value is equal to $\mathbf{s}_1(t,\boldsymbol{\beta},\boldsymbol{\alpha})/\mathcal{E}_X(t,\boldsymbol{\beta},\boldsymbol{\alpha})$. Taking $E(t,\boldsymbol{\beta},\boldsymbol{\alpha}) = \mathbf{S}_1(t,\boldsymbol{\beta},\boldsymbol{\alpha})/S_0(t,\boldsymbol{\beta},\boldsymbol{\alpha})$ achieves this objective. At the same time, our estimator reduces to the usual Cox estimator under zero measurement error. We regard this reducibility property to be important for measurement error correction methods.

We reiterate that our method makes no assumptions about the form of the covariate error, and that the model (4) is only a working model, with our estimator still being consistent even if the working model is misspecified. In addition, our method requires only estimation of unconditional means involving Y, $\mathbf{W}$, and $\mathbf{X}$, and therefore does not require use of smoothing methods. For this reason, a modestly-sized internal validation sample is sufficient. By contrast, the approaches taken by Zhou and Pepe (1995) and by Zhou and Wang (2000) require consistent estimates of conditional means, which involve stratification or smoothing in the covariate space, and thus require a larger validation sample. In addition, since our method is based on separate empirical averages for each risk set, a rare disease approximation is not needed.

We have worked in the setting of time-independent covariates, but it is possible to consider extension to the case of time-dependent covariates. When the covariate processes are measured on an approximately continuous basis ($\mathbf{W}(t)$ for the full cohort and $\mathbf{X}(t)$ for the internal validation sample), the method and its asymptotic theory carry over with notational changes only. Since the method is based on separate empirical averages for each risk set, changes over time in the measurement error distribution are handled automatically. The method and the asymptotic theory also carry over to the case where the covariate processes are measured only intermittently, as commonly occurs in practice, but the processes vary slowly, so that carrying forward the last observed covariate value is a reasonable approximation. In the case where the the covariate processes are measured only intermittently and vary more rapidly, the extension to the case of time-dependent covariates is more complex and is beyond the scope of this paper.

2.2 | Asymptotic Properties

The asymptotic properties of the estimator are presented in the following theorem.

Theorem 1. *Under the regularity conditions stated in the Web Appendix, $\hat{\boldsymbol{\beta}}_{MS}$ converges almost surely to $\boldsymbol{\beta}^*$, and $\sqrt{n}(\hat{\boldsymbol{\beta}}_{MS} - \boldsymbol{\beta}^*)$ is asymptotically mean-zero multivariate normal with covariance matrix that can be estimated consistently by the sandwich-type estimator described below.*

We present here a sketch of the proof of this result. The details are presented in the Web Appendix.

The consistency proof hinges on the fact that, as explained above, $\mathbf{U}_{MS}(\boldsymbol{\beta}, \boldsymbol{\alpha})$ is constructed so that it converges to a limit $\mathbf{u}(\boldsymbol{\beta}, \boldsymbol{\alpha})$ for which $\mathbf{u}(\boldsymbol{\beta}^*, \boldsymbol{\alpha}^*) = \mathbf{0}$. We can then appeal to arguments of Foutz (1977) to obtain the consistency result.

The asymptotic normality proof is based on estimating equations theory, and uses an argument along the lines of Lin and Wei (1989). Setting $\boldsymbol{\theta} = (\boldsymbol{\beta}, \boldsymbol{\alpha})$, we can define the estimator $\hat{\boldsymbol{\theta}}$ of $\boldsymbol{\theta}$ to be the solution $\hat{\boldsymbol{\theta}}$ to $\boldsymbol{\mathcal{U}}(\boldsymbol{\theta}) = \mathbf{0}$ with $\boldsymbol{\mathcal{U}}(\boldsymbol{\theta}) = (\mathbf{U}^{(1)}, \mathbf{U}^{(2)})$, where $\mathbf{U}^{(1)}(\boldsymbol{\theta})$ is the $\mathbf{U}_{MS}(\boldsymbol{\beta}, \boldsymbol{\alpha})$ defined in (15) and $\mathbf{U}^{(2)}(\boldsymbol{\theta})$ is given by stacking the vectors

$$\mathbf{U}_r^{(2)}(\boldsymbol{\alpha}) = \frac{1}{n} \sum_{i=1}^{n} \omega_i \left(X_{ir} - \alpha_{r0} - \sum_{s=1}^{p} \alpha_{rs} W_{is} \right) \begin{bmatrix} 1 \\ \mathbf{W}_i \end{bmatrix}$$

where we include $\mathbf{U}_r^{(2)}$ only for covariates that are subject to measurement error. We can write

$$\mathbf{U}^{(2)}(\boldsymbol{\theta}) = \frac{1}{n} \sum_{i=1}^{n} \omega_i \mathbf{Z}_i^{(12)}(\boldsymbol{\theta})$$

with

$$\mathbf{Z}_i^{(12)}(\boldsymbol{\theta}) = (\mathbf{x}_i \otimes \overline{\mathbf{w}}_i) - \{\mathbf{I}_{p_1} \otimes (\overline{\mathbf{w}}_i \overline{\mathbf{w}}_i^T)\}\boldsymbol{\alpha}$$

where $\mathbf{x}_i$ consists of $X_{i1}, \ldots, X_{ip_1}$, $\overline{\mathbf{w}}_i$ consists of a 1 followed by the components of $\mathbf{W}_i$, $\otimes$ denotes the Kronecker product, and $\mathbf{I}_b$ denotes the $b \times b$ identity matrix. The vector $\mathbf{U}^{(2)}(\boldsymbol{\theta})$ is of length $(p+1)p_1$. When the model for a given X_{ir} includes only some of the W_{is}'s, we delete the superfluous elements of $\boldsymbol{\alpha}$ and $\mathbf{Z}_i^{(12)}(\boldsymbol{\theta})$.

In the Web Appendix we show that $\mathbf{U}^{(1)}(\boldsymbol{\theta}^*)$ is asymptotically equivalent to the quantity

$$\mathbf{U}^{(1)*}(\boldsymbol{\theta}^*) = \hat{\pi} \left\{ \frac{1}{m} \sum_{i=1}^{n} \omega_i \mathbf{Z}_i^{(11)}(\boldsymbol{\theta}^*) \right\} + (1 - \hat{\pi}) \left\{ \frac{1}{n-m} \sum_{i=1}^{n} (1 - \omega_i) \mathbf{Z}_i^{(21)}(\boldsymbol{\theta}^*) \right\}$$

where $\{\mathbf{Z}_i^{(11)}(\boldsymbol{\theta}) : \omega_i = 1\}$ and $\{\mathbf{Z}_i^{(21)}(\boldsymbol{\theta}) : \omega_i = 0\}$ are each sets of i.i.d. vectors with mean zero under $\boldsymbol{\theta} = \boldsymbol{\theta}^*$, the expressions for which are presented in the Web Appendix. Thus, the solution to $\boldsymbol{\mathcal{U}}(\boldsymbol{\theta}^*) = \mathbf{0}$ is asymptotically equivalent to the solution to $\boldsymbol{\mathcal{U}}^*(\boldsymbol{\theta}^*) = \mathbf{0}$, with $\boldsymbol{\mathcal{U}}^* = (\mathbf{U}^{(1)*}, \mathbf{U}^{(2)})$. Let $\mathbf{Z}_i^{(1)}$ denote the stacked vector formed by $\mathbf{Z}_i^{(11)}$ and $\mathbf{Z}_i^{(12)}$ and let $\mathbf{Z}_i^{(2)}$ denote the stacked vector formed by $\mathbf{Z}_i^{(21)}$ and the zero vector of length $(p+1)p_1$. We can then write

$$\boldsymbol{\mathcal{U}}^*(\boldsymbol{\theta}) = \hat{\pi} \left\{ \frac{1}{m} \sum_{i=1}^{n} \omega_i \mathbf{Z}_i^{(1)}(\boldsymbol{\theta}^*) \right\} + (1 - \hat{\pi}) \left\{ \frac{1}{n-m} \sum_{i=1}^{n} (1 - \omega_i) \mathbf{Z}_i^{(2)}(\boldsymbol{\theta}^*) \right\}.$$

Define $\mathbf{C}_1 = \mathrm{Cov}(\mathbf{Z}_i^{(1)})$, $\mathbf{C}_2 = \mathrm{Cov}(\mathbf{Z}_i^{(2)})$, and $\mathbf{C} = \hat{\pi}\mathbf{C}_1 + (1 - \hat{\pi})\mathbf{C}_2$. We see that the asymptotic distribution of $\sqrt{n}\,\boldsymbol{\mathcal{U}}^*(\boldsymbol{\theta}^*)$ is mean-zero normal with covariance matrix $\mathbf{C}$. Consequently $\sqrt{n}(\hat{\boldsymbol{\beta}}_{MS} - \boldsymbol{\beta}^*)$ is asymptotically mean-zero normal with covariance matrix $\mathbf{V} = \boldsymbol{\mathcal{R}}\mathbf{C}\boldsymbol{\mathcal{R}}^T$, where $\boldsymbol{\mathcal{R}}$ is the matrix consisting of the first p rows of $\mathbf{d}(\boldsymbol{\theta})^{-1}$, where $\mathbf{d}(\boldsymbol{\theta})$ is the limiting value of the matrix $\mathbf{D}(\boldsymbol{\theta})$ given by -1 times the Jacobian of $\boldsymbol{\mathcal{U}}(\boldsymbol{\theta})$. In principle, we can estimate $\mathbf{V}$ by $\hat{\mathbf{V}} = \hat{\boldsymbol{\mathcal{R}}}\hat{\mathbf{C}}\hat{\boldsymbol{\mathcal{R}}}$, where $\hat{\boldsymbol{\mathcal{R}}}$ consists of the first p rows of $\mathbf{D}(\hat{\boldsymbol{\theta}})^{-1}$ and $\hat{\mathbf{C}} = \hat{\pi}\hat{\mathbf{C}}_1 + (1 - \hat{\pi})\hat{\mathbf{C}}_2$, where $\hat{\mathbf{C}}_s$ is the sample covariance of $\mathbf{Z}_i^{(s)}(\boldsymbol{\theta})$, i.e.

$$\hat{\mathbf{C}}_s = \frac{1}{n} \sum_{i=1}^{n} \mathbf{Z}_i^{(s)}(\boldsymbol{\theta}) \mathbf{Z}_i^{(s)}(\boldsymbol{\theta})^T. \tag{17}$$

In actuality, the terms of $\mathbf{U}^{(1)*}$ involve additional unknown quantities, so we compute $\hat{\mathbf{C}}_s$ using the sample covariance of the vectors $\hat{\mathbf{Z}}_i^{(s)}(\hat{\boldsymbol{\theta}})$ defined by replacing these quantities with consistent estimates. The detailed derivations of the expressions for $\mathbf{Z}_i^{(11)}(\boldsymbol{\theta})$, $\mathbf{Z}_i^{(21)}(\boldsymbol{\theta})$, and $\mathbf{D}(\boldsymbol{\theta})$ are presented in the Web Appendix.

3 | SIMULATION STUDY

We examined the performance of the proposed method in a simulation study. We constructed the simulation setup so as to be representative of a typical epidemiological cohort study. We considered a setup where the time metameter is age, with age at entry to the study being uniformly distributed over the interval 30 to 50 years. The study horizon was 12 years. We took the censoring distribution to be exponential with a rate of 1% per year. We took the baseline survival function to be Weibull with shape parameter 5, as in Zucker and Spiegelman (2004, 2008). In terms of the sample size and the event rate (determined by the Weibull scale parameter), we considered two scenarios: a rare event scenario with $n = 10,000$ and a cumulative event rate of about 5% (so that the number of events is about 500), and a common event scenario with $n = 500$ and a cumulative event rate of about 25% (so that the number of events is about 125). The internal validation sample size was 200. Thus, in the rare event case, the internal validation sample size included a mere handful of events, which may hamper the use of Chen's (2002) approach.

We carried out two sets of simulations. In the first set, we worked with a single covariate X, generated from a standard normal distribution. We considered two measurement error models, as follows:

Independent Measurement Error Model: $W = X + \epsilon$ with $\epsilon \sim N(0, a)$ independently of X

Dependent Measurement Error Model: $W = X + \epsilon$ with $\epsilon | X \sim N(0, a(1 + |X|))$

We chose a range of a values corresponding to the following range of values for the correlation between X and W: 0.9, 0.7, 0.5. Finally, we took $e^{\beta} = 1.5, 2.5$, or 4. We compared our proposed estimator (MS) against Chen's (2002) estimator (CH), the regression calibration estimator obtained by replacing X by $\widehat{X}$ in the Cox score function (RC), the "complete case" (CC) estimator based only on the data with a measurement of X, and the naive estimator ignoring the measurement error (NA). In the second set of simulations, we worked with five covariates $X_1, \dots, X_5$, with X_1 error-prone and the other covariates error-free. We took the five covariates to be $N(0, 1)$ random variables, either independent or equally-correlated with a correlation of 0.2. We took the hazard function to be $\lambda(t) = \lambda_0(t) \exp(\beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_4 x_4 + \beta_5 x_5)$ with $\beta_2 = \beta_3 = \beta_4 = \beta_5 = \log(1.5)$, where, as before, we took $\lambda_0(t)$ to be Weibull with shape parameter 5 and $e^{\beta} = 1.5, 2.5$, or 4. The other settings were as in the the first set of simulations. The simulation results were based on 10,000 replications. If the zero-finding procedure with our method failed to converge, we used the RC estimate. In the univariate simulations this usually occurred in less than 1% of the replications, and in the worst instance it occurred in 6% of the replications. In the multivariate simulations, convergence failure usually occurred in less than 5% of the replications, and in the worst instance it occurred in 10% of the replications. In both the univariate and multivariate simulation, the worst instance was with the highest value of β_1 and the highest degree of measurement error. The results for the rare event scenario are presented in Tables 1-6. The corresponding results for the common event scenario are presented in the Supplementary Web Materials in Tables S1-S6.

The naive estimator was seriously biased in all cases studied, often dramatically. In the single covariate setup, the MS method exhibited low bias across the board, while the RC method often exhibited appreciable bias, especially under the dependent error model, with the bias increasing as the true β increases and as the degree of measurement error increases. In the rare disease case, as expected, the CC method had very high variance, while the variance of the MS method was usually considerably lower. In the common disease case, the MS method had lower variance than the CC method in most configurations, although there are some configurations in which the CC method had lower variance. As expected, Chen's method performed very well in the common disease setup, where the MS method and Chen's method are comparable in terms of bias, variance and coverage probability. In the rare disease setup, Chen's estimator had low bias in some cases and considerable bias in other cases. In addition, the standard deviation of Chen's estimator was substantially greater than that of the MS estimator, in some cases around 3 times greater. Also, the estimate of the standard deviation tended to underestimate, leading to considerably lower than nominal confidence interval coverage rates.

In the multiple-covariate setup, the MS method exhibited noticeable bias in some configurations, but the bias with the MS method was typically lower than with the RC method, often considerably so. The patterns were similar across the disease incidence levels (common/rare) and the measurement error models (independent/dependent). The performance of the MS method with dependent covariates was similar to that with independent covariates, and no systematic trends emerged between the dependent covariate case and the independent covariate case in the relative performance of the MS method as compared with the other methods. Chen's method had a noticeably lower standard deviation than the MS method in the multivariate common disease setting with for large β and moderate correlation between the surrogate and the true exposure (Tables S3-S6 in the Web Appendix, bottom panel). To explore the relative performance of the two methods further, we conducted additional simulations with $e^{\beta} = 4$ under an "intermediate event rate" scenario with $n = 500$, validation sample size of 200, and a cumulative event rate of about 15% (Table S7 in the Web Appendix). In these simulations, Chen's method again had a noticeably lower standard deviation than the MS method; at the same time, Chen's estimate of the standard deviation of the estimate was noticeably lower than the empirical standard deviation. As a rough practical guide, we suggest that the MS estimator is to be preferred when the number of events in the validation study is very low, while Chen's estimator is to be preferred when the number of events in the

TABLE 1 Simulation results for the single-covariate rare disease case with independent measurement error. β^* is the true value of β. Bias(%) is the relative bias, *i.e.* Bias(%)=$100 \times (\hat{\beta} - \beta^*)/\beta^*$. IQR is 0.74 times the interquartile range of the $\hat{\beta}$ values. SE is the mean of the estimated standard error of $\hat{\beta}$. SD is the empirical standard deviation of the $\hat{\beta}$ values. CR is the empirical coverage rate of the asymptotic 95% confidence interval. Methods considered: MS = modified score, CH = Chen, RC = regression calibration, CC = complete case, NA = naive.

				Mean		Median					
Corr(X, W)	exp(β^*)	β^*	**Method**	$\hat{\beta}$	**Bias(%)**	$\hat{\beta}$	**Bias (%)**	**IQR**	**SE**	**SD**	**CR**
0.90	1.5	0.4055	MS	0.4050	-0.1	0.4011	-1.1	0.0577	0.0525	0.0517	0.965
			CH	0.4230	4.3	0.4313	6.4	0.1621	0.1373	0.1743	0.879
			RC	0.4036	-0.5	0.4032	-0.6	0.0562	0.0511	0.0506	0.957
			CC	0.4188	3.3	0.4163	2.7	0.3120	0.3384	0.3684	0.945
			NA	0.3287	-18.9	0.3309	-18.4	0.0404	0.0402	0.0386	0.543
0.70	1.5	0.4055	MS	0.4088	0.8	0.4040	-0.4	0.0737	0.0738	0.0753	0.945
			CH	0.4277	5.5	0.4403	8.6	0.2545	0.2126	0.2979	0.855
			RC	0.4029	-0.6	0.4032	-0.6	0.0704	0.0688	0.0690	0.965
			CC	0.4188	3.3	0.4163	2.7	0.3120	0.3384	0.3684	0.945
			NA	0.1993	-50.9	0.2011	-50.4	0.0346	0.0313	0.0306	0.000
0.50	1.5	0.4055	MS	0.4129	1.8	0.4103	1.2	0.1081	0.1099	0.1186	0.938
			CH	0.4326	6.7	0.4459	10.0	0.3006	0.2518	0.3558	0.859
			RC	0.4030	-0.6	0.4004	-1.3	0.1052	0.0976	0.1011	0.938
			CC	0.4188	3.3	0.4163	2.7	0.3120	0.3384	0.3684	0.945
			NA	0.1022	-74.8	0.1036	-74.4	0.0237	0.0224	0.0223	0.000
0.90	2.5	0.9163	MS	0.9279	1.3	0.9221	0.6	0.0750	0.0720	0.0721	0.949
			CH	0.9401	2.6	0.9289	1.4	0.1857	0.1599	0.2120	0.875
			RC	0.9098	-0.7	0.9045	-1.3	0.0619	0.0584	0.0575	0.973
			CC	0.9380	2.4	0.9259	1.0	0.3401	0.3590	0.4109	0.941
			NA	0.7412	-19.1	0.7406	-19.2	0.0393	0.0409	0.0395	0.004
0.70	2.5	0.9163	MS	0.9449	3.1	0.9376	2.3	0.1269	0.1279	0.1324	0.957
			CH	0.9545	4.2	0.9511	3.8	0.2756	0.2394	0.3477	0.867
			RC	0.8944	-2.4	0.8910	-2.8	0.0904	0.0878	0.0845	0.949
			CC	0.9380	2.4	0.9259	1.0	0.3401	0.3590	0.4109	0.941
			NA	0.4434	-51.6	0.4438	-51.6	0.0272	0.0315	0.0307	0.000
0.50	2.5	0.9163	MS	0.9620	5.0	0.9460	3.2	0.2069	0.2263	0.2401	0.957
			CH	0.9577	4.5	0.9601	4.8	0.3152	0.2761	0.4026	0.855
			RC	0.8785	-4.1	0.8766	-4.3	0.1345	0.1263	0.1258	0.914
			CC	0.9380	2.4	0.9259	1.0	0.3401	0.3590	0.4109	0.941
			NA	0.2254	-75.4	0.2270	-75.2	0.0191	0.0224	0.0223	0.000
0.90	4.0	1.3863	MS	1.4214	2.5	1.4080	1.6	0.1166	0.1162	0.1196	0.930
			CH	1.4359	3.6	1.4159	2.1	0.2352	0.2004	0.2625	0.875
			RC	1.3464	-2.9	1.3476	-2.8	0.0718	0.0687	0.0651	0.906
			CC	1.4460	4.3	1.4134	2.0	0.3881	0.4063	0.4590	0.957
			NA	1.0967	-20.9	1.0997	-20.7	0.0449	0.0426	0.0422	0.000
0.70	4.0	1.3863	MS	1.4862	7.2	1.4587	5.2	0.2271	0.2405	0.2590	0.957
			CH	1.4654	5.7	1.4196	2.4	0.3281	0.2837	0.3986	0.856
			RC	1.2863	-7.2	1.2901	-6.9	0.1112	0.1079	0.1020	0.781
			CC	1.4460	4.3	1.4134	2.0	0.3881	0.4063	0.4590	0.957
			NA	0.6384	-53.9	0.6388	-53.9	0.0337	0.0319	0.0312	0.000
0.50	4.0	1.3863	MS	1.4992	8.1	1.4446	4.2	0.3384	0.3698	0.3786	0.944
			CH	1.4752	6.4	1.4155	2.1	0.3636	0.3168	0.4497	0.863
			RC	1.2358	-10.9	1.2302	-11.3	0.1650	0.1496	0.1490	0.739
			CC	1.4460	4.3	1.4134	2.0	0.3881	0.4063	0.4590	0.957
			NA	0.3206	-76.9	0.3228	-76.7	0.0227	0.0225	0.0221	0.000

TABLE 2 Simulation results for the single-covariate rare disease case with dependent measurement error. β^* is the true value of β. Bias(%) is the relative bias, *i.e.* Bias(%)=$100 \times (\hat{\beta} - \beta^*)/\beta^*$. IQR is 0.74 times the interquartile range of the $\hat{\beta}$ values. SE is the mean of the estimated standard error of $\hat{\beta}$. SD is the empirical standard deviation of the $\hat{\beta}$ values. CR is the empirical coverage rate of the asymptotic 95% confidence interval. Methods considered: MS = modified score, CH = Chen, RC = regression calibration, CC = complete case, NA = naive.

				Mean		Median					
Corr(X, W)	**exp(β^*)**	**β^***	**Method**	$\hat{\beta}$	**Bias(%)**	$\hat{\beta}$	**Bias(%)**	**IQR**	**SE**	**SD**	**CR**
0.90	1.5	0.4055	MS	0.4043	-0.3	0.4012	-1.1	0.0558	0.0525	0.0516	0.957
			CH	0.4255	4.9	0.4314	6.4	0.1628	0.1345	0.1729	0.871
			RC	0.4005	-1.2	0.4009	-1.1	0.0517	0.0499	0.0497	0.949
			CC	0.4188	3.3	0.4163	2.7	0.3120	0.3384	0.3684	0.945
			NA	0.3299	-18.6	0.3315	-18.3	0.0392	0.0400	0.0382	0.531
0.70	1.5	0.4055	MS	0.4071	0.4	0.4055	0.0	0.0739	0.0730	0.0729	0.953
			CH	0.4272	5.4	0.4406	8.7	0.2622	0.2126	0.3012	0.867
			RC	0.3992	-1.5	0.3980	-1.8	0.0694	0.0669	0.0667	0.957
			CC	0.4188	3.3	0.4163	2.7	0.3120	0.3384	0.3684	0.945
			NA	0.1974	-51.3	0.1985	-51.0	0.0322	0.0308	0.0301	0.000
0.50	1.5	0.4055	MS	0.4156	2.5	0.4111	1.4	0.1020	0.1122	0.1175	0.953
			CH	0.4267	5.2	0.4287	5.7	0.3036	0.2509	0.3561	0.855
			RC	0.4016	-1.0	0.3995	-1.5	0.1007	0.0974	0.0995	0.949
			CC	0.4188	3.3	0.4163	2.7	0.3120	0.3384	0.3684	0.945
			NA	0.1023	-74.8	0.1042	-74.3	0.0224	0.0223	0.0224	0.000
0.90	2.5	0.9163	MS	0.9226	0.7	0.9091	-0.8	0.0763	0.0840	0.0801	0.949
			CH	0.9386	2.4	0.9283	1.3	0.1835	0.1623	0.2210	0.859
			RC	0.8798	-4.0	0.8778	-4.2	0.0579	0.0550	0.0552	0.887
			CC	0.9380	2.4	0.9259	1.0	0.3401	0.3590	0.4109	0.941
			NA	0.7247	-20.9	0.7229	-21.1	0.0354	0.0392	0.0376	0.000
0.70	2.5	0.9163	MS	0.9415	2.8	0.9221	0.6	0.1341	0.1433	0.1346	0.961
			CH	0.9492	3.6	0.9506	3.7	0.2732	0.2431	0.3613	0.867
			RC	0.8631	-5.8	0.8669	-5.4	0.0861	0.0807	0.0779	0.879
			CC	0.9380	2.4	0.9259	1.0	0.3401	0.3590	0.4109	0.941
			NA	0.4268	-53.4	0.4264	-53.5	0.0261	0.0297	0.0292	0.000
0.50	2.5	0.9163	MS	0.9616	4.9	0.9365	2.2	0.2144	0.2861	0.2327	0.953
			CH	0.9367	2.2	0.9367	2.2	0.3046	0.2777	0.3913	0.871
			RC	0.8675	-5.3	0.8698	-5.1	0.1360	0.1257	0.1246	0.902
			CC	0.9380	2.4	0.9259	1.0	0.3401	0.3590	0.4109	0.941
			NA	0.2230	-75.7	0.2246	-75.5	0.0202	0.0219	0.0226	0.000
0.90	4.0	1.3863	MS	1.4056	1.4	1.3595	-1.9	0.1087	0.2276	0.2203	0.928
			CH	1.4280	3.0	1.4047	1.3	0.2489	0.2089	0.2907	0.883
			RC	1.2652	-8.7	1.2619	-9.0	0.0659	0.0635	0.0608	0.508
			CC	1.4460	4.3	1.4134	2.0	0.3881	0.4063	0.4590	0.957
			NA	1.0416	-24.9	1.0429	-24.8	0.0417	0.0392	0.0386	0.000
0.70	4.0	1.3863	MS	1.4559	5.0	1.4036	1.2	0.2359	0.3021	0.2920	0.939
			CH	1.4517	4.7	1.4043	1.3	0.3466	0.2888	0.4162	0.859
			RC	1.2086	-12.8	1.2094	-12.8	0.0963	0.0962	0.0906	0.535
			CC	1.4460	4.3	1.4134	2.0	0.3881	0.4063	0.4590	0.957
			NA	0.5969	-56.9	0.5988	-56.8	0.0304	0.0288	0.0284	0.000
0.50	4.0	1.3863	MS	1.4663	5.8	1.4039	1.3	0.3186	0.3821	0.3793	0.934
			CH	1.4564	5.1	1.3922	0.4	0.3705	0.3192	0.4530	0.856
			RC	1.2105	-12.7	1.1978	-13.6	0.1572	0.1490	0.1478	0.696
			CC	1.4460	4.3	1.4134	2.0	0.3881	0.4063	0.4590	0.957
			NA	0.3135	-77.4	0.3149	-77.3	0.0239	0.0214	0.0221	0.000

TABLE 3 Simulation results for the multiple-covariate rare disease case with independent covariates and independent measurement error. β^* is the true value of β. Bias(%) is the relative bias, *i.e.* Bias(%)=$100 \times (\hat{\beta} - \beta^*)/\beta^*$. IQR is 0.74 times the interquartile range of the $\hat{\beta}$ values. SE is the mean of the estimated standard error of $\hat{\beta}$. SD is the empirical standard deviation of the $\hat{\beta}$ values. CR is the empirical coverage rate of the asymptotic 95% confidence interval. Methods considered: MS = modified score, CH = Chen, RC = regression calibration, CC = complete case, NA = naive.

				Mean		Median					
Corr(X,W)	exp(β^*)	β^*	**Metho**	$\hat{\beta}$	**Bias(%)**	$\hat{\beta}$	**Bias(%)**	**IQR**	**SE**	**SD**	**CR**
0.90	1.5	0.4055	MS	0.4118	1.6	0.4101	1.1	0.0512	0.0684	0.0573	0.949
			CH	0.4136	2.0	0.4106	1.3	0.1962	0.1352	0.2432	0.772
			RC	0.4074	0.5	0.4063	0.2	0.0486	0.0523	0.0507	0.945
			CC	0.4717	16.3	0.4533	11.8	0.3626	0.3782	0.4538	0.961
			NA	0.3321	-18.1	0.3337	-17.7	0.0420	0.0410	0.0408	0.567
0.70	1.5	0.4055	MS	0.4175	3.0	0.4067	0.3	0.0761	0.0860	0.0814	0.957
			CH	0.4292	5.8	0.4518	11.4	0.3221	0.2026	0.4050	0.749
			RC	0.4066	0.3	0.4074	0.5	0.0700	0.0709	0.0684	0.949
			CC	0.4717	16.3	0.4533	11.8	0.3626	0.3782	0.4538	0.961
			NA	0.1997	-50.8	0.2017	-50.2	0.0333	0.0319	0.0320	0.000
0.50	1.5	0.4055	MS	0.4300	6.1	0.4148	2.3	0.1105	0.1402	0.1340	0.952
			CH	0.4274	5.4	0.4542	12.0	0.3518	0.2358	0.4852	0.749
			RC	0.4081	0.6	0.4065	0.3	0.1050	0.1016	0.0986	0.957
			CC	0.4717	16.3	0.4533	11.8	0.3626	0.3782	0.4538	0.961
			NA	0.1013	-75.0	0.1021	-74.8	0.0248	0.0228	0.0228	0.000
0.90	2.5	0.9163	MS	0.9429	2.9	0.9289	1.4	0.1076	0.1272	0.1230	0.937
			CH	0.9757	6.5	0.9480	3.5	0.2110	0.1596	0.2607	0.785
			RC	0.9109	-0.6	0.9133	-0.3	0.0536	0.0595	0.0569	0.961
			CC	1.0757	17.4	1.0305	12.5	0.3716	0.4151	0.4676	0.945
			NA	0.7424	-19.0	0.7429	-18.9	0.0441	0.0415	0.0418	0.016
0.70	2.5	0.9163	MS	0.9657	5.4	0.9398	2.6	0.1901	0.2015	0.2146	0.955
			CH	1.0211	11.4	0.9778	6.7	0.3117	0.2287	0.4124	0.754
			RC	0.8962	-2.2	0.8896	-2.9	0.0883	0.0901	0.0865	0.930
			CC	1.0757	17.4	1.0305	12.5	0.3716	0.4151	0.4676	0.945
			NA	0.4408	-51.9	0.4428	-51.7	0.0311	0.0318	0.0333	0.000
0.50	2.5	0.9163	MS	1.0264	12.0	0.9356	2.1	0.3004	0.3131	0.3227	0.938
			CH	1.0330	12.7	1.0100	10.2	0.3453	0.2602	0.4751	0.762
			RC	0.8868	-3.2	0.8738	-4.6	0.1235	0.1308	0.1308	0.930
			CC	1.0757	17.4	1.0305	12.5	0.3716	0.4151	0.4676	0.945
			NA	0.2228	-75.7	0.2244	-75.5	0.0221	0.0226	0.0236	0.000
0.90	4.0	1.3863	MS	1.4395	3.8	1.4175	2.3	0.1245	0.1333	0.1490	0.943
			CH	1.5051	8.6	1.4591	5.2	0.3151	0.2087	0.4670	0.769
			RC	1.3467	-2.9	1.3496	-2.6	0.0732	0.0705	0.0683	0.902
			CC	1.6563	19.5	1.5847	14.3	0.4873	0.5055	0.5971	0.945
			NA	1.0974	-20.8	1.0969	-20.9	0.0440	0.0438	0.0453	0.000
0.70	4.0	1.3863	MS	1.5253	10.0	1.4410	3.9	0.3180	0.3329	0.3486	0.936
			CH	1.5592	12.5	1.5045	8.5	0.4789	0.2822	0.5824	0.741
			RC	1.2853	-7.3	1.2782	-7.8	0.1074	0.1110	0.1091	0.805
			CC	1.6563	19.5	1.5847	14.3	0.4873	0.5055	0.5971	0.945
			NA	0.6327	-54.4	0.6349	-54.2	0.0354	0.0326	0.0347	0.000
0.50	4.0	1.3863	MS	1.5407	11.1	1.4472	4.4	0.4363	0.4511	0.4404	0.925
			CH	1.5903	14.7	1.5255	10.0	0.5249	0.3138	0.6286	0.706
			RC	1.2423	-10.4	1.2252	-11.6	0.1481	0.1546	0.1546	0.789
			CC	1.6563	19.5	1.5847	14.3	0.4873	0.5055	0.5971	0.945
			NA	0.3156	-77.2	0.3164	-77.2	0.0238	0.0229	0.0236	0.000

TABLE 4 Simulation results for the multiple-covariate rare disease case with independent covariates and dependent measurement error. β^* is the true value of β. Bias(%) is the relative bias, *i.e.* Bias(%)=$100 \times (\hat{\beta} - \beta^*)/\beta^*$. IQR is 0.74 times the interquartile range of the $\hat{\beta}$ values. SE is the mean of the estimated standard error of $\hat{\beta}$. SD is the empirical standard deviation of the $\hat{\beta}$ values. CR is the empirical coverage rate of the asymptotic 95% confidence interval. Methods considered: MS = modified score, CH = Chen, RC = regression calibration, CC = complete case, NA = naive.

				Mean		Median					
Corr(X,W)	**exp(β^*)**	**β^***	**Method**	**$\hat{\beta}$**	**Bias(%)**	**$\hat{\beta}$**	**Bias(%)**	**IQR**	**SE**	**SD**	**CR**
0.90	1.5	0.4055	MS	0.4098	1.1	0.4057	0.1	0.0558	0.0564	0.0546	0.948
			CH	0.4157	2.5	0.4113	1.4	0.2128	0.1334	0.2410	0.760
			RC	0.4045	−0.2	0.4017	−0.9	0.0482	0.0511	0.0504	0.949
			CC	0.4717	16.3	0.4533	11.8	0.3626	0.3782	0.4538	0.961
			NA	0.3339	−17.6	0.3367	−16.9	0.0417	0.0408	0.0406	0.571
0.70	1.5	0.4055	MS	0.4141	2.1	0.4062	0.2	0.0735	0.0833	0.0800	0.957
			CH	0.4250	4.8	0.4472	10.3	0.3061	0.2026	0.4028	0.733
			RC	0.4036	−0.5	0.4043	−0.3	0.0710	0.0690	0.0678	0.953
			CC	0.4717	16.3	0.4533	11.8	0.3626	0.3782	0.4538	0.961
			NA	0.1984	−51.1	0.1994	−50.8	0.0331	0.0315	0.0320	0.000
0.50	1.5	0.4055	MS	0.4312	6.4	0.4123	1.7	0.1164	0.1460	0.1453	0.957
			CH	0.4299	6.0	0.4346	7.2	0.3686	0.2346	0.4725	0.753
			RC	0.4084	0.7	0.4070	0.4	0.1048	0.1017	0.1004	0.953
			CC	0.4717	16.3	0.4533	11.8	0.3626	0.3782	0.4538	0.961
			NA	0.1019	−74.9	0.1031	−74.6	0.0260	0.0227	0.0233	0.000
0.90	2.5	0.9163	MS	0.9414	2.7	0.9183	0.2	0.0839	0.1050	0.1148	0.956
			CH	0.9741	6.3	0.9437	3.0	0.2253	0.1617	0.2700	0.782
			RC	0.8828	−3.7	0.8821	−3.7	0.0492	0.0562	0.0548	0.891
			CC	1.0757	17.4	1.0305	12.5	0.3716	0.4151	0.4676	0.945
			NA	0.7284	−20.5	0.7276	−20.6	0.0411	0.0399	0.0400	0.004
0.70	2.5	0.9163	MS	0.9504	3.7	0.9223	0.7	0.1275	0.1366	0.1429	0.935
			CH	1.0096	10.2	0.9775	6.7	0.3164	0.2295	0.4197	0.754
			RC	0.8686	−5.2	0.8685	−5.2	0.0795	0.0833	0.0803	0.883
			CC	1.0757	17.4	1.0305	12.5	0.3716	0.4151	0.4676	0.945
			NA	0.4271	−53.4	0.4276	−53.3	0.0298	0.0302	0.0318	0.000
0.50	2.5	0.9163	MS	1.0023	9.4	0.9252	1.0	0.2244	0.2382	0.2352	0.928
			CH	1.0173	11.0	0.9848	7.5	0.3487	0.2594	0.4739	0.750
			RC	0.8800	−4.0	0.8685	−5.2	0.1307	0.1311	0.1323	0.906
			CC	1.0757	17.4	1.0305	12.5	0.3716	0.4151	0.4676	0.945
			NA	0.2219	−75.8	0.2228	-75.7	0.0235	0.0221	0.0238	0.000
0.90	4.0	1.3863	MS	1.4155	2.1	1.3822	−0.3	0.1549	0.1720	0.1881	0.942
			CH	1.4825	6.9	1.4324	3.3	0.3299	0.2126	0.4456	0.764
			RC	1.2701	−8.4	1.2703	−8.4	0.0645	0.0654	0.0639	0.571
			CC	1.6563	19.5	1.5847	14.3	0.4873	0.5055	0.5971	0.945
			NA	1.0474	−24.4	1.0466	−24.5	0.0405	0.0405	0.0424	0.000
0.70	4.0	1.3863	MS	1.4339	3.4	1.3776	−0.6	0.3308	0.3563	0.3666	0.930
			CH	1.5297	10.3	1.4711	6.1	0.4686	0.2837	0.5652	0.732
			RC	1.2156	−12.3	1.2144	−12.4	0.1054	0.0997	0.0980	0.567
			CC	1.6563	19.5	1.5847	14.3	0.4873	0.5055	0.5971	0.945
			NA	0.5969	−56.9	0.6004	−56.7	0.0320	0.0297	0.0320	0.000
0.50	4.0	1.3863	MS	1.4985	8.1	1.3904	0.3	0.4507	0.4740	0.4678	0.926
			CH	1.5673	13.1	1.5050	8.6	0.5324	0.3130	0.6322	0.710
			RC	1.2240	−11.7	1.2001	−13.4	0.1560	0.1549	0.1561	0.758
			CC	1.6563	19.5	1.5847	14.3	0.4873	0.5055	0.5971	0.945
			NA	0.3112	−77.6	0.3120	−77.5	0.0249	0.0220	0.0234	0.000

TABLE 5 Simulation results for the multiple-covariate rare disease case with dependent covariates and independent measurement error. β^* is the true value of β. Bias(%) is the relative bias, *i.e.* Bias(%)=$100\times(\hat{\beta}-\beta^*)/\beta^*$. IQR is 0.74 times the interquartile range of the $\hat{\beta}$ values. SE is the mean of the estimated standard error of $\hat{\beta}$. SD is the empirical standard deviation of the $\hat{\beta}$ values. CR is the empirical coverage rate of the asymptotic 95% confidence interval. Methods considered: MS = modified score, CH = Chen, RC = regression calibration, CC = complete case, NA = naive.

				Mean		Median					
Corr(X,W)	exp(β^*)	β^*	**Method**	$\hat{\beta}$	**Bias (%)**	$\hat{\beta}$	**Bias (%)**	**IQR**	**SE**	**SD**	**CR**
0.90	1.5	0.4055	MS	0.4095	1.0	0.4045	−0.2	0.0526	0.0570	0.0589	0.957
			CH	0.4199	3.6	0.4149	2.3	0.1793	0.1364	0.2120	0.825
			RC	0.3954	−2.5	0.3916	−3.4	0.0503	0.0482	0.0510	0.941
			CC	0.4373	7.8	0.4208	3.8	0.3744	0.3529	0.3891	0.961
			NA	0.3221	−20.6	0.3215	−20.7	0.0393	0.0378	0.0398	0.375
0.70	1.5	0.4055	MS	0.4139	2.1	0.4063	0.2	0.0787	0.0902	0.0883	0.949
			CH	0.4355	7.4	0.4363	7.6	0.2904	0.2044	0.3414	0.774
			RC	0.3768	−7.1	0.3721	−8.2	0.0596	0.0638	0.0657	0.910
			CC	0.4373	7.8	0.4208	3.8	0.3744	0.3529	0.3891	0.961
			NA	0.1861	−54.1	0.1840	−54.6	0.0304	0.0288	0.0305	0.000
0.50	1.5	0.4055	MS	0.4320	6.5	0.3959	−2.4	0.1214	0.1533	0.1429	0.941
			CH	0.4391	8.3	0.4414	8.9	0.3502	0.2381	0.3977	0.770
			RC	0.3603	−11.1	0.3601	−11.2	0.0824	0.0885	0.0870	0.906
			CC	0.4373	7.8	0.4208	3.8	0.3744	0.3529	0.3891	0.961
			NA	0.0916	−77.4	0.0905	−77.7	0.0204	0.0203	0.0212	0.000
0.90	2.5	0.9163	MS	0.9375	2.3	0.9201	0.4	0.0837	0.1190	0.1109	0.937
			CH	0.9507	3.8	0.9219	0.6	0.1921	0.1569	0.2324	0.840
			RC	0.8767	−4.3	0.8719	−4.8	0.0541	0.0543	0.0581	0.875
			CC	0.9886	7.9	0.9803	7.0	0.3273	0.3707	0.4115	0.961
			NA	0.7140	−22.1	0.7141	−22.1	0.0453	0.0373	0.0395	0.000
0.70	2.5	0.9163	MS	0.9738	6.3	0.9403	2.6	0.1825	0.2151	0.2035	0.934
			CH	0.9886	7.9	0.9670	5.5	0.2972	0.2296	0.3536	0.809
			RC	0.8191	−10.6	0.8130	−11.3	0.0862	0.0801	0.0827	0.699
			CC	0.9886	7.9	0.9803	7.0	0.3273	0.3707	0.4115	0.961
			NA	0.4042	−55.9	0.4042	−55.9	0.0306	0.0280	0.0297	0.000
0.50	2.5	0.9163	MS	1.0112	10.4	0.9172	0.1	0.2953	0.3348	0.3250	0.928
			CH	0.9965	8.8	0.9604	4.8	0.3475	0.2607	0.4162	0.805
			RC	0.7736	−15.6	0.7737	−15.6	0.1150	0.1118	0.1099	0.683
			CC	0.9886	7.9	0.9803	7.0	0.3273	0.3707	0.4115	0.961
			NA	0.1975	−78.4	0.1969	−78.5	0.0216	0.0196	0.0206	0.000
0.90	4.0	1.3863	MS	1.4361	3.6	1.3980	0.8	0.1537	0.2373	0.1928	0.938
			CH	1.4638	5.6	1.3997	1.0	0.2668	0.2105	0.3759	0.824
			RC	1.2871	−7.2	1.2805	−7.6	0.0675	0.0648	0.0665	0.606
			CC	1.6191	16.8	1.5145	9.2	0.4535	0.4886	0.7240	0.969
			NA	1.0479	−24.4	1.0419	−24.8	0.0425	0.0392	0.0421	0.000
0.70	4.0	1.3863	MS	1.5063	8.7	1.4175	2.3	0.2952	0.3454	0.3020	0.920
			CH	1.5515	11.9	1.4604	5.3	0.3985	0.2887	0.5080	0.807
			RC	1.1605	−16.3	1.1516	−16.9	0.1026	0.0986	0.0994	0.383
			CC	1.6191	16.8	1.5145	9.2	0.4535	0.4886	0.7240	0.969
			NA	0.5725	−58.7	0.5714	−58.8	0.0348	0.0285	0.0310	0.000
0.50	4.0	1.3863	MS	1.4931	7.7	1.4066	1.5	0.3796	0.4436	0.4172	0.918
			CH	1.5455	11.5	1.4421	4.0	0.4568	0.3185	0.5594	0.792
			RC	1.0735	−22.6	1.0742	−22.5	0.1330	0.1334	0.1296	0.367
			CC	1.6191	16.8	1.5145	9.2	0.4535	0.4886	0.7240	0.969
			NA	0.2753	−80.1	0.2737	−80.3	0.0256	0.0197	0.0209	0.000

TABLE 6 Simulation results for the multiple-covariate rare disease case with with dependent covariates and dependent measurement error. β^* is the true value of β. Bias(%) is the relative bias, *i.e.* Bias(%)=$100 \times (\hat{\beta} - \beta^*)/\beta^*$. IQR is 0.74 times the interquartile range of the $\hat{\beta}$ values. SE is the mean of the estimated standard error of $\hat{\beta}$. SD is the empirical standard deviation of the $\hat{\beta}$ values. CR is the empirical coverage rate of the asymptotic 95% confidence interval. Methods considered: MS = modified score, CH = Chen, RC = regression calibration, CC = complete case, NA = naive.

				Mean		Median					
Corr(X, W)	$\exp(\beta^*)$	β^*	Method	$\hat{\beta}$	Bias (%)	$\hat{\beta}$	Bias (%)	IQR	SE	SD	CR
0.90	1.5	0.4055	MS	0.4132	1.9	0.4034	−0.5	0.0535	0.0638	0.0717	0.949
			CH	0.4256	5.0	0.4184	3.2	0.1716	0.1510	0.2117	0.840
			RC	0.3882	−4.3	0.3845	−5.2	0.0475	0.0467	0.0494	0.930
			CC	0.4373	7.8	0.4208	3.8	0.3744	0.3529	0.3891	0.961
			NA	0.3201	−21.1	0.3190	−21.3	0.0385	0.0373	0.0389	0.363
0.70	1.5	0.4055	MS	0.4097	1.0	0.3965	−2.2	0.0741	0.0937	0.0875	0.953
			CH	0.4247	4.7	0.3979	-1.9	0.3105	0.2402	0.3989	0.832
			RC	0.3656	−9.8	0.3627	−10.5	0.0552	0.0612	0.0621	0.875
			CC	0.4373	7.8	0.4208	3.8	0.3744	0.3529	0.3891	0.961
			NA	0.1804	−55.5	0.1782	−56.0	0.0308	0.0280	0.0294	0.000
0.50	1.5	0.4055	MS	0.4249	4.8	0.3938	−2.9	0.1226	0.1663	0.1591	0.936
			CH	0.3966	−2.2	0.3846	−5.2	0.3626	0.2814	0.4833	0.816
			RC	0.3519	−13.2	0.3498	−13.7	0.0848	0.0876	0.0842	0.890
			CC	0.4373	7.8	0.4208	3.8	0.3744	0.3529	0.3891	0.961
			NA	0.0897	−77.9	0.0885	−78.2	0.0226	0.0200	0.0209	0.000
0.90	2.5	0.9163	MS	0.9330	1.8	0.9018	−1.6	0.0899	0.1134	0.1229	0.929
			CH	0.9425	2.9	0.9136	−0.3	0.2188	0.1830	0.2600	0.871
			RC	0.8400	−8.3	0.8350	−8.9	0.0495	0.0512	0.0541	0.625
			CC	0.9886	7.9	0.9803	7.0	0.3273	0.3707	0.4115	0.961
			NA	0.6922	−24.5	0.6923	−24.4	0.0386	0.0356	0.0370	0.000
0.70	2.5	0.9163	MS	0.9499	3.7	0.9150	−0.1	0.1512	0.1800	0.1843	0.921
			CH	0.9770	6.6	0.9371	2.3	0.3183	0.2731	0.4340	0.855
			RC	0.7789	−15.0	0.7735	−15.6	0.0799	0.0733	0.0742	0.484
			CC	0.9886	7.9	0.9803	7.0	0.3273	0.3707	0.4115	0.961
			NA	0.3834	−58.2	0.3838	−58.1	0.0297	0.0262	0.0273	0.000
0.50	2.5	0.9163	MS	0.9763	6.5	0.8980	−2.0	0.2604	0.3032	0.2847	0.896
			CH	0.9659	5.4	0.9285	1.3	0.3232	0.3116	0.4971	0.863
			RC	0.7554	−17.6	0.7568	−17.4	0.1147	0.1110	0.1063	0.641
			CC	0.9886	7.9	0.9803	7.0	0.3273	0.3707	0.4115	0.961
			NA	0.1929	−79.0	0.1929	−78.9	0.0214	0.0189	0.0200	0.000
0.90	4.0	1.3863	MS	1.4213	2.5	1.3515	−2.5	0.1523	0.1813	0.1713	0.870
			CH	1.4668	5.8	1.4018	1.1	0.2839	0.2350	0.4104	0.832
			RC	1.2054	−13.1	1.1996	−13.5	0.0561	0.0602	0.0609	0.160
			CC	1.6191	16.8	1.5145	9.2	0.4535	0.4886	0.7240	0.969
			NA	0.9925	−28.4	0.9893	−28.6	0.0387	0.0362	0.0386	0.000
0.70	4.0	1.3863	MS	1.4304	3.2	1.3619	−1.8	0.2769	0.3131	0.3011	0.870
			CH	1.5199	9.6	1.4261	2.9	0.3573	0.3232	0.5417	0.848
			RC	1.0864	−21.6	1.0744	−22.5	0.0961	0.0883	0.0886	0.129
			CC	1.6191	16.8	1.5145	9.2	0.4535	0.4886	0.7240	0.969
			NA	0.5337	−61.5	0.5336	−61.5	0.0309	0.0259	0.0281	0.000
0.50	4.0	1.3863	MS	1.4489	4.5	1.3289	−4.1	0.3643	0.4592	0.4374	0.871
			CH	1.5204	9.7	1.4437	4.1	0.3662	0.3563	0.5615	0.848
			RC	1.0487	−24.4	1.0493	−24.3	0.1392	0.1332	0.1277	0.324
			CC	1.6191	16.8	1.5145	9.2	0.4535	0.4886	0.7240	0.969
			NA	0.2686	-80.6	0.2676	−80.7	0.0230	0.0188	0.0204	0.000

TABLE 7 HPFS Results. SE = standard error of estimate. SE Ratio = Ratio between the standard error of the estimate and the standard error of the modified score estimate. Methods considered: MS = modified score, CH = Chen, RC = regression calibration, CC = complete case, NA = naive.

	Diet Score Coefficient			BMI Coefficient		
Method	**Estimate**	**SE**	**SE Ratio**	**Estimate**	**SE**	**SE Ratio**
Naive	0.0216	0.0027	0.1107	0.0867	0.0019	0.2346
CC	0.0788	0.0738	3.0246	0.0913	0.1335	16.4815
RC	0.0485	0.0096	0.3934	0.0867	0.0078	0.9630
CH	0.0136	0.0383	1.5697	0.0800	0.0220	2.7160
MS	0.0712	0.0244	1.0000	0.0865	0.0081	1.0000

validation study is 30 or more, with some caution needed with Chen's estimate of the standard deviation of the estimator.

In both the single-covariate and the multiple-covariate setups, the empirical coverage rate of the asymptotic confidence interval based on the MS method is generally close to the nominal level of 95%, while for the RC method the coverage rate tended to be considerably below nominal for $e^{\beta} = 4$.

For the multiple-covariate setup, we conducted additional simulations to examine the bias of the MS method for larger sample sizes. These results are reported in the Supplementary Web Materials in Tables S8-S9. When the sample size is increased, the bias decreases, eventually to a very small level.

4 | EXAMPLE

We illustrate the method on data from the Health Professionals Follow-Up Study (HPFS), a prospective cohort study of 51,529 middle-aged (age 40-75 years at baseline) male health professionals. Participants were recruited in 1986 and were mailed questionnaires every other year to assess health status and lifestyle. Here, we analyze the relationship between onset of Type 2 diabetes (T2D) and a diet score relating to intake of carbohydrates, protein, and fat (de Koning et al., 2011). The diet score ranged from 0 to 30, with the score increasing under a decrease in carbohydrate intake or an increase in protein or fat intake. The analysis included the 41,616 study participants who were free of T2D, cardiovascular disease, or cancer at baseline, among whom there were 2,790 cases of incident T2D during follow-up. Diet was assessed with a 131-item semiquantitative food frequency questionnaire (FFQ), an instrument which is subject to substantial measurement error. In a subsample of 105 participants, another diet assessment was carried out using a more accurate diet record (DR). The analysis was stratified by age and adjusted for body mass index (BMI). We analyzed the data using the naive Cox method, the RC method, the complete case method, Chen's method, and our proposed MS method. There were only 6 events among the 105 individuals in the validation sample, which puts Chen's method and the complete case method at a very severe disadvantage. Table 7 presents the results for the various methods. For the regression coefficient for the diet score, the RC estimate was considerably larger than the naive estimate, and the MS and complete case estimates were noticeably larger than the RC estimate. The estimate with Chen's method was lower than that with the naive method. The standard error with Chen's method was a bit over 1.5 times the standard error with the MS method. For the regression coefficient for BMI, the estimates were similar across all methods, and the standard error with Chen's method was 2.7 times that of the standard error with the MS method.

5 | SUMMARY AND DISCUSSION

We have developed a new method for covariate error correction in the Cox survival regression model, given internal validation data. The method can handle covariate error of arbitrary form, not just independent additive measurement error. Only a modestly-sized internal validation sample is required. The method can handle the case where the number of covariates is moderate to large. In a simulation study, the method was found to perform very well in terms of bias reduction and confidence interval coverage.

We have worked in the setting of time-independent covariates, but it is possible to consider extension to the case of time-dependent covariates. When the covariate processes are measured on an approximately continuous basis ($\mathbf{W}(t)$ for the full cohort and $\mathbf{X}(t)$ for the internal validation sample), the method and its asymptotic theory carry over with notational changes only. The same is true in the case where the covariate processes are measured only intermittently, as commonly occurs in practice, but the processes vary slowly, so that carrying forward the last observed covariate value is a reasonable approximation.

If the association between $\mathbf{W}$ and $\mathbf{X}$ is very weak, the proposed estimate will remain consistent and asymptotically normal, but the variance will be very high. If there is no association at all between $\mathbf{W}$ and $\mathbf{X}$, then $\mathbf{W}$ is not a suitable surrogate for $\mathbf{X}$ and no correction method will help. If the relationship between $\mathbf{W}$ and $\mathbf{X}$ is highly nonlinear, the working model (4) can be modified to include nonlinear W terms. A plot of X_{ir} versus W_{ir} for the individuals in the internal validation sample can be used to examine whether nonlinear W terms are needed in the working model for X_{ir}.

ACKNOWLEDGMENTS

We thank Yi-Hau Chen for sharing with us the code for his method. In addition, we thank the editor, associate editor, and referees for helpful comments that led to substantial improvements in the paper.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.
The Web Appendix, referenced in Sections 2 and 3, is available with this paper at the Biometrics website on Wiley Online Library, as is the code we used to implement the various method.

How to cite this article: Zucker DM, Zhou X, Liao X, Li Y, Spiegelman D. A modified partial likelihood score method for Cox regression with covariate error under the internal validation design. *Biometrics.* 2019;75:414–427. https://doi.org/10.1111/biom.13012