

SEMIPARAMETRIC TIME TO EVENT MODELS IN THE PRESENCE OF ERROR-PRONE, SELF-REPORTED OUTCOMES—WITH APPLICATION TO THE WOMEN’S HEALTH INITIATIVE¹

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The onset of several silent, chronic diseases such as diabetes can be detected only through diagnostic tests. Due to cost considerations, self-reported outcomes are routinely collected in lieu of expensive diagnostic tests in large-scale prospective investigations such as the Women’s Health Initiative. However, self-reported outcomes are subject to imperfect sensitivity and specificity. Using a semiparametric likelihood-based approach, we present time to event models to estimate the association of one or more covariates with a error-prone, self-reported outcome. We present simulation studies to assess the effect of error in self-reported outcomes with regard to bias in the estimation of the regression parameter of interest. We apply the proposed methods to prospective data from 152,830 women enrolled in the Women’s Health Initiative to evaluate the effect of statin use with the risk of incident diabetes mellitus among postmenopausal women. The current analysis is based on follow-up through 2010, with a median duration of follow-up of 12.1 years. The methods proposed in this paper are readily implemented using our freely available R software package *icensmis*, which is available at the Comprehensive R Archive Network (CRAN) website.

1. Introduction. The onset of several chronic diseases such as diabetes are asymptomatic and can be detected only through diagnostic tests. For example, diabetes can be detected by measuring levels of fasting blood glucose or glycosylated hemoglobin levels (HbA1c). However, the costs of such gold standard diagnostic tests can be prohibitive in large-scale epidemiological studies such as the Women’s Health Initiative (WHI) that enroll and follow over a hundred thousand subjects. Disease prevalence and incidence in large observational cohorts are often ascertained through error-prone, self-reported questionnaires. In this paper, we propose

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a semiparametric model to assess the association of specific covariates of interest with a silent time to event outcome that is assessed through periodic, error-prone self-reports.

Using data from postmenopausal women enrolled in the WHI, the motivating application in this paper is the evaluation of the hypothesis that the use of cholesterol lowering medications (statins) can result in an increased risk of diabetes. The WHI recruited women ($N = 161,808$) aged 50–79 at 40 clinical centers across the U.S. from 1993–1998 with ongoing follow-up [Anderson et al. (1998)]. Prevalent and incident diabetes during the course of follow-up was ascertained by self-report obtained at each annual visit. In a recent paper, Culver et al. (2012) presented an analysis of the effects of statin use on the risk of incident diabetes in the WHI using Cox proportional hazards models. The analyses were conducted based on the assumption that self-reported outcomes of prevalent and incident diabetes are error-free. The validity of self-reports of incident and prevalent diabetes have been evaluated using data from a substudy nested within the WHI—when compared to fasting glucose levels (treated as the gold standard), diabetes self-reports had a positive predictive value of 74% and negative predictive value of 97% [Jackson et al. (2014), Margolis et al. (2008)]. Other studies such as the Nurses' Health Study, Physicians' Health Study and the Finnish Public Sector Study also commonly use self-reported outcomes [He et al. (2010), Hu et al. (2001), Oksanen et al. (2010)].

When a perfect diagnostic test is given sequentially at different points in time to the same individual, the time until the event of interest can be determined to lie in the interval between the last negative test and the first positive test—that is, the time until the event is interval censored. In this context, methods for estimating the survival distribution and assessing the effect of covariates have been developed [Finkelstein (1986), Turnbull (1976)]. However, when error-prone diagnostic procedures such as self-reports are used, standard methods for interval censored outcomes are rendered invalid. Previous work in this area includes methods for error-prone outcomes with application to data collected from laboratory-based diagnostic tests in studies in HIV, HPV and STD [Balasubramanian and Lagakos (2001, 2003), McKeown and Jewell (2010), Meier, Richardson and Hughes (2003)]. Balasubramanian and Lagakos (2003) developed a formal likelihood framework to estimate the distribution of the time to mother to child transmission of HIV. The proposed methods were applied to data from imperfect DNA PCR diagnostic tests to detect the presence of HIV in infants who were born to HIV-positive pregnant women. Meier, Richardson and Hughes (2003) extended the discrete proportional hazard model to incorporate outcomes and covariates. In related work, several papers proposed generalized Cox models in settings involving time to event outcomes with incomplete event adjudication [Cook (2000), Cook and Kosorok (2004), Snapinn (1998)]. Other related work includes that proposed by McKeown and Jewell (2010) in the context of HPV studies, where the

authors accommodate misclassification by incorporating ideas of binary generalized linear models with outcomes subject to misclassification [Neuhaus (1999)]. The problem of error-prone time to event outcomes can also be handled through the Hidden Markov Model (HMM) framework. Previous applications of HMM-based methods include the areas of breast cancer [Chen, Duffy and Tabar (1996)], HIV [Guihenneuc-Jouyaux, Richardson and Longini (2000), Satten and Longini (1996)], lung transplantation [Jackson and Sharples (2002)] and cervical smear tests [Kirby and Spiegelhalter (1994)]. Jackson et al. (2003) present a general framework for staged Markov models to handle misclassification due to error-prone screening tests. Other recent methodological advances within the general area of outcomes measured with error include the papers by García-Zattera et al. (2012) and Lyles et al. (2011), as well as works on covariate measurement error with application to the WHI and the Nurses Health Study [Shaw and Prentice (2012), Spiegelman, Rosner and Logan (2000)]. However, none of the previous literature specifically considers error-prone, self-reported time to event outcomes.

In this paper we present a likelihood-based approach to incorporate time-varying covariate effects specific to the setting in which the prevalence and incidence (time to event) of a chronic condition such as diabetes is ascertained through error-prone self-reports. We incorporate the situation where an unknown proportion of subjects who have already experienced the event of interest at baseline are mistakenly included into the study, due to the use of error-prone self-reports at study entry. We also provide a freely available R software package and illustrate its use [Gu and Balasubramanian (2013)]. In Section 2 we present notation, form of the likelihood function, address issues related to estimation and extensions to incorporate misclassification of subjects at study entry. In Section 3 we perform simulation studies to evaluate the effects of various degrees of error in self-reports. We investigate the effects of erroneous inclusion of subjects who have already experienced the event of interest due to imperfect negative predictive values associated with self-reports. In Section 4 we evaluate the association between statin use with the risk of incident diabetes in a subset of 152,830 women enrolled in the WHI. Last, in Section 5 we discuss the findings of this study and highlight future directions.

2. Methods. In this section we present notation, form of the likelihood and extensions to incorporate the possibility of misclassification at study entry.

2.1. Notation, likelihood, estimation. Let X refer to the random variable denoting the unobserved time to event for an individual, with associated survival, density and hazard functions denoted by $S(x)$, $f(x)$ and $\lambda(x)$, for $x \geq 0$, respectively. The time origin is set to 0, corresponding to the baseline visit at which all subjects enrolled in the study are event-free. In other words, $\Pr(X > 0) = 1$. Without loss of generality, we set $X = \infty$ when the event of interest does not occur. Let N denote the number of subjects and n_i denote the number of visits for the i th

subject. At each visit, we assume that each subject would self-report their disease status. For example, in the WHI, information on incident diabetes was collected at periodically scheduled visits using self-reported questionnaires. For the i th subject, we let \mathbf{R}_i and \mathbf{t}_i denote the $1 \times n_i$ vectors of self-reported, binary outcomes and corresponding visit times, respectively. In particular, R_{ij} is equal to 1 if the j th self-report for the i th subject is positive (indicating occurrence of the event of interest such as diabetes) and 0 otherwise. We assume that self-reports are collected at prescheduled visits up to the time of the first positive self-report, thus, the vectors of test results (\mathbf{R}_i), visit times (\mathbf{t}_i) and the number of self-reports collected per subject (n_i) are random. Let τ_1, \dots, τ_J denote the distinct, ordered visit times in the data set among N subjects, where $0 = \tau_0 < \tau_1 < \dots < \tau_J < \tau_{J+1} = \infty$, thus, the time axis can be divided into $J + 1$ disjoint intervals, $[0, \tau_1), [\tau_1, \tau_2), \dots, [\tau_J, \infty)$.

The joint probability of the observed data for the i th subject can be expressed as

$$g(\mathbf{R}_i, \mathbf{t}_i, n_i) = \sum_{j=1}^{J+1} \Pr(\tau_{j-1} < X_i \leq \tau_j) \Pr(\mathbf{R}_i, \mathbf{t}_i, n_i | \tau_{j-1} < X_i \leq \tau_j) \\ = \sum_{j=1}^{J+1} \theta_j \Pr(\mathbf{R}_i, \mathbf{t}_i, n_i | \tau_{j-1} < X_i \leq \tau_j),$$

where $\theta_j = \Pr(\tau_{j-1} < X \leq \tau_j)$, $\tau_0 = 0$ and $\tau_{J+1} = \infty$.

To simplify the form of the expression above, we make the assumption that given the true time of event X_i , an individual's n_i self-reports are independent. That is,

$$\Pr(\mathbf{R}_i | X_i, \mathbf{t}_i) = \prod_{k=1}^{n_i} \Pr(r_{ik} | X_i, t_{ik}).$$

This assumption implies that the observed values of other self-reported outcomes do not provide additional information about the distribution of a particular self-reported outcome from that provided by the actual time of the event.

Based on the derivation in Balasubramanian and Lagakos (2003), it can be shown that the joint probability of the observed data for the i th subject can be simplified as

$$(2.1) \quad g(\mathbf{R}_i, \mathbf{t}_i, n_i) = \sum_{j=1}^{J+1} \theta_j \left[\prod_{k=1}^{n_i} \Pr(r_{ik} | \tau_{j-1} < X_i \leq \tau_j, t_k) \right] \\ = \sum_{j=1}^{J+1} \theta_j C_{ij},$$

where $C_{ij} = [\prod_{k=1}^{n_i} \Pr(r_{ik} | \tau_{j-1} < X_i \leq \tau_j, t_k)]$. We assume that the probability of a positive self-report at the k th visit ($r_{ik} = 1$) conditional on the interval containing

the true event time and visit time can be expressed as

$$\Pr(r_{ik} = 1 | \tau_{j-1} < X_i \leq \tau_j, t_k) = \begin{cases} \varphi_1, & t_k \geq \tau_j, \\ 1 - \varphi_0, & t_k \leq \tau_{j-1}. \end{cases}$$

Here, φ_1 and φ_0 denote the sensitivity and specificity of self-reports, respectively. Thus, the terms C_{ij} , for $j = 1, \dots, J + 1$, in equation (2.1) can be expressed as a product involving the constants φ_1 and φ_0 . Thus, in the absence of covariates, the log likelihood for a random sample of N subjects can be expressed as

$$(2.2) \quad l(\boldsymbol{\theta}) = \log(L(\boldsymbol{\theta})) = \sum_{i=1}^N \log \left(\sum_{j=1}^{J+1} C_{ij} \theta_j \right).$$

For the special case where self-reports are perfect ($\varphi_1 = \varphi_0 = 1$), equation (2.2) reduces to the nonparametric likelihood for interval censored observations given in [Turnbull \(1976\)](#).

In most settings, including the WHI, it is of interest to evaluate the association of a vector of covariates with respect to the time to event of interest. Let \mathbf{Z} denote the $P \times 1$ vector of explanatory variables with the corresponding $P \times 1$ vector of regression coefficients denoted by $\boldsymbol{\beta}$. To incorporate the effect of covariates, we assume the proportional hazards model, $\lambda(t|\mathbf{Z} = \mathbf{z}) = \lambda_0(t)e^{\mathbf{z}'\boldsymbol{\beta}}$, or, equivalently, $S(t|\mathbf{Z} = \mathbf{z}) = S_0(t)e^{-\mathbf{z}'\boldsymbol{\beta}}$.

To derive the form of the log-likelihood based on the assumption of the proportional hazards model, we first reparameterize the log likelihood in (2.2) in terms of the survival function, $\mathbf{S} = (1 = S_1, S_2, \dots, S_{J+1})^T$, where $S_j = \Pr(X > \tau_{j-1})$. Since $S_j = \sum_{l=j}^{J+1} \theta_l$, the vector of interval probabilities can be expressed as $\boldsymbol{\theta} = T_r \mathbf{S}$, where T_r is the $(J + 1) \times (J + 1)$ transformation matrix. Let $C = [C_{ij}]$ denote the $N \times (J + 1)$ matrix of the coefficients, C_{ij} , and let the $N \times (J + 1)$ matrix D be defined as $D_{N \times (J+1)} = C \times T_r$. Then, the log-likelihood function for the one-sample setting in (2.2) can be expressed as

$$(2.3) \quad l(\mathbf{S}) = \sum_{i=1}^N \log \left(\sum_{j=1}^{J+1} D_{ij} S_j \right),$$

where $S_1 = 1$ and S_2, S_3, \dots, S_{J+1} are the unknown parameters of interest.

Let $1 = S_1 > S_2 > \dots > S_{J+1}$ denote the baseline survival functions (i.e., corresponding to $\mathbf{Z} = \mathbf{0}$), evaluated at the left boundaries of the intervals $[0, \tau_1), [\tau_1, \tau_2), \dots, [\tau_J, \infty)$. Then, for subject i , with corresponding covariate vector \mathbf{z}_i , $S_j^{(i)} = (S_j)^{e^{\mathbf{z}_i' \boldsymbol{\beta}}}$. Thus, the log-likelihood function for a random sample of N subjects can be expressed as

$$(2.4) \quad l(\mathbf{S}, \boldsymbol{\beta}) = \sum_{i=1}^N \log \left(\sum_{j=1}^{J+1} D_{ij} (S_j)^{e^{\mathbf{z}_i' \boldsymbol{\beta}}} \right).$$

The elements of the D matrix are functions of the observed data including the visit times and corresponding self-reported results, as well as the constants φ_0, φ_1 . Assuming that φ_0, φ_1 are known constants, the maximum likelihood estimates of the unknown parameters $\beta_1, \dots, \beta_P, S_2, \dots, S_{J+1}$ can be obtained by numerical maximization of the log-likelihood function, subject to the constraints that $1 > S_2 > S_3 > \dots > S_{J+1} > 0$. Statistical inference regarding the parameters of interest ($\beta_1, \dots, \beta_P, S_2, \dots, S_{J+1}$) can be made by using asymptotic properties of the maximum likelihood estimators [Cox and Hinkley (1979)]. The estimated covariance matrix of the maximum likelihood estimates can be obtained by inverting the Hessian matrix. Hypothesis tests regarding the unknown parameters can be carried out using the likelihood ratio or Wald test.

2.2. *Misclassification at study entry.* In this section we incorporate the setting in which a self-report of being event(disease)-free at baseline or study entry is used as the inclusion criterion. The evaluation of the association between statin use and risk of incident diabetes in the WHI was based on all women who self-reported to be diabetes-free at baseline [Culver et al. (2012)]. However, diabetes self-reports at study entry in the WHI have been found to be less than perfect—the study by Margolis et al. (2008) found that the negative predictive value of prevalent diabetes at baseline was approximately 97%, that is, 3% of women who self-reported as being diabetes-free were, in fact, diabetic. In this situation, the assumption that $S(0) = 1$ is invalid.

For the i th subject, let G_i denote the baseline binary self-report, where $G_i = 1$ denotes a self-report indicating that the event of interest has already occurred and $G_i = 0$ denotes otherwise. Similarly, let B_i denote the true event status at baseline. In other words, $B_i = 1 \stackrel{\text{def}}{=} X_i \leq 0$ and $B_i = 0 \stackrel{\text{def}}{=} X_i > 0$. Consider a subject who has a negative self-report at baseline (i.e., $G_i = 0$) and is thus included in the data set. As before, let the vector of observed self-reports for the i th subject be denoted by \mathbf{R}_i . Let the negative predictive value of self-reports at baseline be denoted by η , that is, $\Pr(B_i = 0 | G_i = 0) = \eta$. Then the likelihood function for the i th subject can be expressed as

$$\begin{aligned}
 L_i &= \Pr(\mathbf{R}_i, \mathbf{t}_i, n_i | G_i = 0) \\
 (2.5) \quad &= \eta \Pr(\mathbf{R}_i, \mathbf{t}_i, n_i | B_i = 0, G_i = 0) \\
 &\quad + (1 - \eta) \Pr(\mathbf{R}_i, \mathbf{t}_i, n_i | B_i = 1, G_i = 0).
 \end{aligned}$$

We assume that subjects who self-report negative ($G_i = 0$) and are truly negative for event at baseline ($B_i = 0$) are a random sample from all subjects who are true negative at baseline. Then we have $\Pr(\mathbf{R}_i, \mathbf{t}_i, n_i | B_i = 0, G_i = 0) = \Pr(\mathbf{R}_i, \mathbf{t}_i, n_i | B_i = 0)$, which corresponds to the likelihood function derived in Section 2.1. Thus, $\Pr(\mathbf{R}_i, \mathbf{t}_i, n_i | B_i = 0, G_i = 0) = \sum_{j=1}^{J+1} D_{ij}(S_j) e^{z_i \beta}$. Moreover, $\Pr(\mathbf{R}_i, \mathbf{t}_i, n_i | B_i = 1, G_i = 0) = D_{i1}(S_1) e^{z_i \beta}$.

The likelihood function for the i th subject has the form

$$\begin{aligned}
 L_i(\boldsymbol{\beta}, \mathbf{S}) &= \eta \sum_{j=1}^{J+1} D_{ij}(S_j) e^{\mathbf{z}'_i \boldsymbol{\beta}} + (1 - \eta) D_{i1}(S_1) e^{\mathbf{z}'_i \boldsymbol{\beta}} \\
 (2.6) \qquad \qquad &= \sum_{j=1}^{J+1} D'_{ij}(S_j) e^{\mathbf{z}'_i \boldsymbol{\beta}},
 \end{aligned}$$

where $D'_{i1} = D_{i1}$ and $D'_{ij} = \eta D_{ij}$ for $j > 1$. Thus, the likelihood function incorporating baseline misclassification has the same general form as in equation (2.4). The likelihood function in equation (2.4) can be obtained as a special case when $\eta = 1$ in equation (2.6).

2.3. Time-varying covariates. We consider the situation where covariate values can change with time and are collected at each visit. Let \mathbf{z}_{ij} denote the $p \times 1$ vector of covariate values for subject i at time τ_j . In extending the likelihood function [equation (2.4)] to handle time-varying covariates, we make the additional assumption that the values of the covariates \mathbf{z}_{ij} remain constant during the interval $[\tau_j, \tau_{j+1})$. Let Λ_j denote the cumulative hazard function during the period of $[\tau_j, \tau_{j+1})$ for the subjects in the reference group (i.e., $\mathbf{Z} = 0$). Under the model $\lambda_{\mathbf{z}_i}(t) = \lambda_0(t) e^{\boldsymbol{\beta}' \mathbf{z}_i}$, the corresponding cumulative hazard function during the period $[\tau_j, \tau_{j+1})$ for subject i is equal to $\Lambda_j \exp(\mathbf{z}'_{ij} \boldsymbol{\beta})$. The survival function at τ_{j-1} can then be expressed as

$$S_j^{(i)} = \exp\left(-\sum_{j'=0}^{j-2} \Lambda_{j'} \exp(\mathbf{z}'_{ij'} \boldsymbol{\beta})\right),$$

where $j = 2, \dots, J + 1$, where $S_1^{(i)} = 1$. The log-likelihood function can be expressed as a function of the derived $S_j^{(i)}$,

$$l(\mathbf{S}, \boldsymbol{\beta}) = \sum_{i=1}^N \log\left(\sum_{j=1}^{J+1} D_{ij} S_j^{(i)}\right).$$

The log-likelihood function can be optimized with respect to the parameters $\Lambda_0, \dots, \Lambda_{J-1}$ and β_1, \dots, β_p subject to constraints $\Lambda_j \geq 0$. In practice, if a subject has missing visits or missing covariate values at some visits, one can carry forward the last observation as one approach to impute missing covariate values. However, unless the proportion of missing is very small, these ad hoc approaches toward handling missing data may result in biased estimates of parameters and their associated standard errors.

2.4. *Unknown sensitivity and specificity.* Identifiability of the sensitivity and specificity parameters is closely tied to the study design and the paradigm used for determining number and timing of visits (tests). For example, in several epidemiological cohorts in which self-reported outcomes of chronic diseases such as diabetes are collected, data collection on the incidence of the condition ceases following the first positive self-report. In such study designs, it is implicitly assumed that self-reports following the first positive self-report will be positive with probability 1, thus, subsequent self-reports are noninformative. In settings that incorporate an adaptive testing paradigm, the form of the likelihood is shown in equation (2.4)—while this is a function of the constants φ_1, φ_0 that characterize the sensitivity and specificity of self-reports, these parameters cannot be estimated jointly with the parameters of interest, namely, $\beta_1, \dots, \beta_p, S_2, \dots, S_{J+1}$. If the sensitivity and specificity parameters are unknown, an augmented study design in which a subset of subjects are given a perfect diagnostic test in addition to self-reported questionnaires could be considered. In these studies, the parameters φ_1, φ_0 can be jointly estimated with the unknown parameters of interest. A similar approach was proposed by Lyles et al. (2011) for mismeasured outcomes in logistic regression models.

In other clinical settings, the mismeasured outcome arises from laboratory-based diagnostic tests characterized by imperfect sensitivity and specificity. When the testing paradigm involves giving the diagnostic test according to a predetermined testing schedule, the form of the likelihood can be shown to be identical to that in equation (2.4) [Balasubramanian and Lagakos (2003)]. In this case, it is possible to observe seemingly inconsistent patterns of test results where one or more negative test results follow a positive result. Examples include data collected from DNA PCR assays to detect HIV infection in infants in pediatric HIV clinical trials. Studies in which subjects are tested according to a predetermined testing schedule, the sensitivity, specificity parameters (φ_1, φ_0) can be jointly estimated with the unknown parameters of interest [Meier, Richardson and Hughes (2003)].

3. Simulation. In this section we present results from simulation studies to illustrate the effects of (1) error-prone self-reported outcomes; and (2) misclassification at study entry. We present the effects of these factors with regard to the bias associated with the estimated regression parameter of interest.

3.1. *Effects of error-prone self-reported outcomes.* We present average results from 1000 simulated data sets in which 1000 subjects were randomly assigned to two exposure groups with equal proportion, assuming all subjects were event-free at baseline (i.e., $X_i > 0$ for all i). We assumed that there is a single binary covariate of interest Z_i , corresponding to the exposure status of the i th subject. The associated regression parameter in the likelihood [equation (2.4)] was set to $\beta = 1$. For each subject, self-reported questionnaires were collected at 8 scheduled visits over a duration of 8 years, each with a random missing probability of 30%.

TABLE 1

Comparing estimates of the regression parameter β from an “adjusted” analysis that accounts for the error in self-reported outcomes to an “unadjusted” analysis that incorrectly assumes that self-reports are perfect

| φ_1 | φ_0 | S_{J+1} | Analysis type | Bias (%) | Std Err | RMSE | Coverage (%) |
|-------------|-------------|-----------|---------------|----------|---------|------|--------------|
| 0.75 | 1.00 | 0.90 | Adjusted | 0.3 | 0.17 | 0.17 | 96.8 |
| 0.75 | 1.00 | 0.90 | Unadjusted | 0.1 | 0.17 | 0.17 | 97.0 |
| 1.00 | 0.75 | 0.90 | Adjusted | -6.7 | 0.82 | 0.82 | 93.8 |
| 1.00 | 0.75 | 0.90 | Unadjusted | -90.2 | 0.07 | 0.90 | 0.0 |
| 0.61 | 0.995 | 0.90 | Adjusted | 1.4 | 0.21 | 0.22 | 94.9 |
| 0.61 | 0.995 | 0.90 | Unadjusted | -16.4 | 0.17 | 0.23 | 82.9 |
| 0.75 | 1.00 | 0.50 | Adjusted | 0.1 | 0.09 | 0.09 | 95.1 |
| 0.75 | 1.00 | 0.50 | Unadjusted | -1.9 | 0.09 | 0.09 | 93.5 |
| 1.00 | 0.75 | 0.50 | Adjusted | 0.2 | 0.19 | 0.19 | 94.4 |
| 1.00 | 0.75 | 0.50 | Unadjusted | -59.2 | 0.07 | 0.60 | 0.0 |
| 0.61 | 0.995 | 0.50 | Adjusted | 0.5 | 0.09 | 0.09 | 94.2 |
| 0.61 | 0.995 | 0.50 | Unadjusted | -6.9 | 0.08 | 0.11 | 86.7 |

All self-reports following the first positive report were assumed to be positive with probability 1. The simulation mechanism assumed that the time to the event of interest X followed an exponential distribution. The hazard rate λ governing the time to the event of interest in the reference group ($Z_i = 0$) was set to equal 0.0132 or 0.0866, corresponding to a cumulative incidence by study end ($1 - S_{J+1}$) of 0.10 or 0.50, respectively. As shown in Table 1, we compare results across several sets of values for the parameters (φ_1, φ_0) , corresponding to the sensitivity and specificity of self-reports.

In Table 1, for each parameter setting, we present estimates of bias, associated standard error, root mean square error (RMSE) and coverage probability associated with the estimation of β . Coverage probability was calculated as the proportion of data sets in which the 95% confidence interval for β contains its true value. We compare results from two sets of analyses for estimating β : (a) maximizing the likelihood presented in equation (2.4), assuming that the true values of φ_1, φ_0 are known; and (b) maximizing the likelihood presented in equation (2.4), assuming that self-reports are perfect (i.e., $\varphi_1 = \varphi_0 = 1$). In general, when the true values of φ_0, φ_1 are incorporated into the analysis, the estimates of β are nearly unbiased. Similarly, the true coverage probability corresponding to a 95% confidence interval is close to its nominal value. On the other hand, when self-reports are incorrectly assumed to be perfect, the estimates of β may be significantly biased, especially in settings where φ_0 is low. When $\varphi_0 \ll 1$, early false positive self-reports result in significant loss of information due to premature cessation of data collection. In this case, coverage probabilities deviated significantly from 95%. Last, incorporat-

ing the uncertainty in error-prone self-reports increases the standard error of the maximum likelihood estimates of β .

We note that while the true event times were simulated based on the exponential distribution, the proposed methods make no distribution assumptions. Thus, the performance of the proposed methods does not depend on the underlying distributions of the event times. When event times were simulated based on a Weibull distribution, similar results were observed (results available upon request).

3.2. *Effects of misclassification at study entry.* In this simulation we incorporate the setting in which an error-prone, self-report of being event(disease)-free at study entry is used as the inclusion criterion. As before, let η denote the negative predictive value of the baseline self-report. That is, each subject included in the study has a probability of $1 - \eta$ of having already experienced the event of interest prior to study entry. Each simulated data set included 1000 subjects, of whom $1000 \times (1 - \eta)$ had already experienced the event of interest prior to entry into the study (i.e., $X < 0$). The data were simulated as described in Section 3.1, where $\varphi_1 = 0.61$ and $\varphi_0 = 0.995$. We compare results for various settings by varying the cumulative incidence of the event of interest ($1 - S_{J+1}$) to equal 0.10 or 0.50, and by varying the value of η to equal 0.99, 0.96 or 0.93.

Table 2 presents the simulation results, averaged over 1000 data sets. We present results from an “adjusted” model that properly accounts for misclassification at baseline based on the likelihood presented in equation (2.6) compared to the model

TABLE 2
 Comparing estimates of the regression parameter β from an “adjusted” analysis that incorporates the possibility of misclassification at baseline to an “unadjusted” analysis that incorrectly assumes that all subjects are event-free at study entry or that $\eta = 1$. We assume that $\varphi_1 = 0.61$ and $\varphi_0 = 0.995$

| S_{J+1} | η | Analysis type | Bias (%) | Std Err | RMSE | Coverage (%) |
|-----------|--------|---------------|----------|---------|------|--------------|
| 0.90 | 0.99 | Adjusted | 2.6 | 0.22 | 0.23 | 95.0 |
| 0.90 | 0.99 | Unadjusted | -4.5 | 0.20 | 0.21 | 94.1 |
| 0.90 | 0.96 | Adjusted | 1.2 | 0.24 | 0.24 | 95.8 |
| 0.90 | 0.96 | Unadjusted | -22.9 | 0.17 | 0.29 | 72.7 |
| 0.90 | 0.93 | Adjusted | 0.1 | 0.25 | 0.25 | 95.2 |
| 0.90 | 0.93 | Unadjusted | -36.4 | 0.15 | 0.40 | 36.3 |
| 0.50 | 0.99 | Adjusted | 0.0 | 0.09 | 0.09 | 95.2 |
| 0.50 | 0.99 | Unadjusted | -1.5 | 0.09 | 0.09 | 94.1 |
| 0.50 | 0.96 | Adjusted | 0.1 | 0.10 | 0.10 | 94.2 |
| 0.50 | 0.96 | Unadjusted | -5.7 | 0.09 | 0.11 | 89.2 |
| 0.50 | 0.93 | Adjusted | 0.6 | 0.10 | 0.10 | 94.1 |
| 0.50 | 0.93 | Unadjusted | -9.4 | 0.09 | 0.13 | 80.9 |

in equation (2.4) that incorrectly assumes that $\eta = 1$ (denoted “unadjusted”). In both models, the true values of the sensitivity and specificity are assumed. As expected, the adjusted model is nearly unbiased and has uniformly lower bias when compared to the unadjusted model. The bias of the unadjusted model increases with decreasing values of negative predictive value (η), and it is more pronounced when the cumulative incidence is low ($1 - S_{J+1} = 0.10$). In general, the inclusion of subjects who have already experienced the event of interest at study entry results in the exposure groups becoming less distinguishable. Thus, ignoring this issue in data analysis results in estimates of exposure effects (β) that are biased toward the null. In contrast, incorporating the effect of baseline misclassification increases the standard error of $\hat{\beta}$. The effects on the bias and the standard error of $\hat{\beta}$ are reflected in the RMSE values—the adjusted model has smaller RMSE than the unadjusted model in all settings except when $S_{J+1} = 0.9$ and $\eta = 0.99$. The coverage probability of the adjusted model is approximately 95% in all settings considered in this study. However, the coverage probability of the unadjusted model decreases with decreasing negative predictive value (η) due to increased bias.

4. Application: Risk of diabetes mellitus with statin use in the Women’s Health Initiative.

Background. We analyze data collected on 152,830 women from the Women’s Health Initiative (WHI) to evaluate the effects of statin use on the risk of incident diabetes mellitus (DM). Culver et al. (2012) reported an increased risk of incident DM with baseline statin use (multivariate-adjusted HR, 1.48; 95% CI, 1.38–1.59). These results were based on Cox proportional hazards models where the time to event variable was calculated as the interval between enrollment date and the earliest of the following: (1) date of annual medical history update when new diabetes is self-reported (positive outcome); (2) date of last annual medical update during which diabetes status can be ascertained (censorship); or (3) date of death (censorship). The methods used in Culver et al. (2012) were based on the assumptions that: (1) all subjects who self-reported as being diabetes-free at baseline were truly not diabetic (i.e., $\eta = 1$); and (2) the self-reports of incident diabetes at each follow-up visit were error-free (i.e., $\varphi_1 = \varphi_0 = 1$). We compare the results from Culver et al. (2012) to results based on application of the likelihood-based methods described in this paper.

Diabetes self-reports. Prevalent diabetes at baseline and incident diabetes were assessed through self-reported questionnaires in the WHI. At baseline and at each annual visit, participants were asked whether she has ever received a physician diagnosis of and/or treatment for diabetes when not pregnant since the time of the last self-report (visit). Using data from a WHI substudy, estimates of sensitivity, specificity and baseline negative predictive value of self-reported diabetes outcomes were obtained by comparing self-reported outcomes to fasting glucose

levels and medication data [Margolis et al. (2008)]. A woman was considered to be truly diabetic if she had either taken anti-diabetic medication and/or had a fasting glucose level ≥ 126 mg/dl. From a representative subset of 5485 women, with information at baseline on self-reported diabetes, fasting glucose levels and medication inventory, we estimated that self-reports have a sensitivity of 0.61, the specificity of 0.995, and a negative predictive value of 0.96 at baseline. These estimated parameter values are used in our analysis. We used the following definitions: (1) sensitivity: proportion of diabetics with a positive self-report; (2) specificity: proportion of nondiabetics with a negative self-report; and (3) negative predictive value: proportion of subjects who were diabetes-free among those with a negative self-report. In practice, estimating measurement error parameters from validation studies should proceed with caution as validation studies may differ from their study populations.

Methods. The analysis data set included 152,830 women out of a total of 161,808 women enrolled in the WHI. Women who self-reported diabetes at baseline or those who ever took Cerivastatin were excluded. In addition, women with missing data at baseline on diabetes status or medication inventory were excluded [Culver et al. (2012)]. The results presented here are based on follow-up until 2010. The median duration of follow-up was 12.1 years, including 1,688,967 person-years of total follow-up. During the course of follow-up, 10.4% of women self-reported being diagnosed with diabetes. Information on statin use was obtained from medical inventory information, which was available for selected follow-up years. Information on statin use was available for 152,830, 59,505, 128,507, 55,043 and 12,039 subjects at baseline, years 1, 3, 6 and 9, respectively. Models included either baseline statin use or statin use as a time-varying covariate—in the latter case, the most recent medication inventory data available was carried forward for time points at which current medication use was not collected. In multivariable models, other covariates included race, smoking status, alcohol intake, age, education, WHI study, BMI, recreational physical activity, dietary energy intake, family history of diabetes and hormone therapy use [Culver et al. (2012)]. We assumed that self-reports following the first report of incident diabetes are noninformative. Annual visit times were rounded to the nearest year in order to limit the number of parameters estimated to describe the baseline survival function (S_2, \dots, S_{J+1}) .

Results. Table 3 presents the estimated hazard ratio (95% confidence interval) for statin use by modeling statin use at baseline or as a time-varying covariate. For each, we present results from univariable models as well as multivariable models incorporating potential confounders. In each setting, the results from the methods proposed in this paper are compared to results from Cox models. In all models, by incorporating the imperfect sensitivity and specificity of self-reports and the potential misclassification at study entry, the hazard ratio of statin use is consistently increased when comparing to the corresponding Cox models. Using the proposed

TABLE 3
Analysis of the effects of statin use on incident diabetes mellitus risk in the WHI

| Statin variable type | Type of analysis | Univariable/ multivariable* | N | Hazard ratio (95% CI) |
|----------------------|------------------|--------------------------------|---------|--------------------------|
| Baseline statin | Proposed model | Univariable | 152,830 | 2.33 (2.12, 2.56) |
| Baseline statin | Proposed model | Multivariable | 138,338 | 1.81 (1.65, 1.99) |
| Baseline statin | Cox model | Univariable | 152,830 | 1.69 (1.60, 1.78) |
| Baseline statin | Cox model | Multivariable | 138,338 | 1.54 (1.46, 1.63) |
| Time-varying statin | Proposed model | Univariable | 152,830 | 2.49 (2.31, 2.68) |
| Time-varying statin | Proposed model | Multivariable | 138,338 | 1.88 (1.75, 2.02) |
| Time-varying statin | Cox model | Univariable | 152,830 | 1.65 (1.59, 1.72) |
| Time-varying statin | Cox model | Multivariable | 138,338 | 1.48 (1.42, 1.54) |

*Covariates adjusted include race, smoking status, alcohol intake, age, education, WHI study, BMI, recreational physical activity, dietary energy intake, family history of diabetes and hormone therapy use.

methods in equation (2.6), the hazard ratio for baseline statin use from univariate analysis was 2.33 (95% CI: 2.12–2.56). In the multivariable model, the hazard ratio of baseline statin use was 1.81 (95% CI: 1.65–1.99), suggesting a relatively strong confounding effect. When statin use was modeled as a time-varying covariate, the hazard ratios of statin use from univariate and multivariate models were 2.49 (95% CI: 2.31–2.68) and 1.88 (95% CI: 1.75–2.02), respectively.

The goodness of fit of the multivariable model incorporating statin use as a time-varying covariate was assessed in an augmented model that included 2 additional terms corresponding to the interactions of time periods (in years) (3, 6] and (6, 16] with statin use. This model allows the effect of statin use to vary between the time periods (0, 3], (3, 6] and (6, 16] years. The Wald test p values corresponding to the interactions of statin use with the time periods (3, 6] and (6, 16] were 0.89 and 0.11, respectively; these results indicate that the augmented model provided no improvement in fit when compared to the model without the additional interaction terms.

To evaluate how the results depend on the choice of parameters such as sensitivity, specificity and baseline negative predictive value of self-reported diabetes, we performed a sensitivity analysis by varying each of these parameters. Table 4 presents how the estimated hazard ratio of statin use changes with different combinations of the parameters. Statin use was modeled as a time-varying covariate while simultaneously adjusting for potential confounders. We observed that the estimated hazard ratio of statin use is most sensitive to change in specificity. This is largely due to the fact that the cumulative incidence of diabetes was low (10.4%), and thus false positive self-reports due to imperfect specificity have a big influence on estimated parameters. In general, the hazard ratio of statin use decreases as

TABLE 4

Statin use versus risk of incident diabetes mellitus in the WHI—sensitivity analysis for varying sensitivity (φ_1), specificity (φ_0) and baseline negative predictive value (η) associated with diabetes self-reports. All models incorporate statin use as a time-varying covariate and adjust for potential confounders

| Sensitivity (φ_1) | Specificity (φ_0) | Negative predictive value (η) | Hazard ratio (95% CI) |
|-----------------------------|-----------------------------|--------------------------------------|-----------------------|
| 0.50 | 0.993 | 0.96 | 2.11 (1.92, 2.31) |
| 0.50 | 0.993 | 0.98 | 2.10 (1.92, 2.30) |
| 0.50 | 0.995 | 0.96 | 1.93 (1.79, 2.08) |
| 0.50 | 0.995 | 0.98 | 1.93 (1.79, 2.07) |
| 0.50 | 0.997 | 0.96 | 1.76 (1.65, 1.88) |
| 0.50 | 0.997 | 0.98 | 1.77 (1.66, 1.88) |
| 0.61 | 0.993 | 0.96 | 2.05 (1.88, 2.24) |
| 0.61 | 0.993 | 0.98 | 2.06 (1.89, 2.24) |
| 0.61 | 0.995 | 0.96 | 1.88 (1.75, 2.02) |
| 0.61 | 0.995 | 0.98 | 1.89 (1.76, 2.03) |
| 0.61 | 0.997 | 0.96 | 1.73 (1.63, 1.84) |
| 0.61 | 0.997 | 0.98 | 1.74 (1.64, 1.84) |
| 0.70 | 0.993 | 0.96 | 2.02 (1.85, 2.20) |
| 0.70 | 0.993 | 0.98 | 2.03 (1.86, 2.21) |
| 0.70 | 0.995 | 0.96 | 1.86 (1.73, 2.00) |
| 0.70 | 0.995 | 0.98 | 1.87 (1.74, 2.00) |
| 0.70 | 0.997 | 0.96 | 1.71 (1.61, 1.82) |
| 0.70 | 0.997 | 0.98 | 1.72 (1.62, 1.82) |

specificity increases. Changes in sensitivity and negative predictive value at baseline have modest effects on the resulting model fit.

The models presented here can be implemented using our freely available R software package *icensmis* [Gu and Balasubramanian (2013)] as described in the supplemental material [Gu, Ma and Balasubramanian (2015)].

5. Discussion. Due to cost considerations, the use of self-reported outcomes is common to diagnose prevalent and incident disease in large-scale epidemiologic investigations. In this paper we present a likelihood-based framework to model the association of a time-varying covariate with a time to event outcome, that is observed through periodically collected, error-prone, self-reported data. We incorporate the possibility of erroneous inclusion of subjects who have already experienced the event of interest prior to study entry as a result of the use of self-reported outcomes at baseline in determining the study population. R code for implementing the models proposed here are presented in the supplemental material [Gu, Ma and Balasubramanian (2015)].

We presented results from simulation studies to assess the impact of ignoring error in self-reported outcomes—in all cases considered, the use of statistical models that correctly accommodate the error inherent in self-reports resulted in nearly unbiased estimates of the regression parameter of interest. The largest bias as a result of ignoring error in self-reported outcomes was found in settings where the cumulative incidence was low and specificity was less than perfect. Models that correctly accommodate error in self-reports also resulted in increased variance of the estimated regression parameters. However, in most settings, the RMSE values that combine the impact of bias and variance of the estimated regression parameter favored the use of methods that appropriately account for error in self-reported outcomes.

The methods proposed in this paper were applied to prospective data from 152,830 women enrolled in the WHI to evaluate the effect of statin use and risk of incident diabetes. By accounting for the imperfect sensitivity, specificity and negative predictive value at baseline for diabetes self-reports, we observed that the hazard ratio for statin use was significantly larger than that estimated in naive analyses that ignored the error in self-reported outcomes. In particular, the hazard ratio of statin use in a multivariable model adjusted for potential confounders was 1.88 (95% CI: 1.75–2.02) as compared to the multivariable hazard ratio estimate from Cox model 1.48 (95% CI: 1.42–1.54).

In the methods developed here, we assumed that the sensitivity and specificity of self-reported outcomes are invariant with respect to time since entry and independent of covariates. In many real-world settings, this assumption may result in over-simplified models, particularly in applications in which visits are unequally spaced. In addition, the methods developed here assumed that the parameters governing the characteristics of self-reported outcomes are known. However, in many cases these are estimated values—in this context, it would be useful to extend the methods proposed here to consider study designs including validation subsets that would allow joint estimation of the sensitivity and specificity of self-reported outcomes together with the other parameters of interest.

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SUPPLEMENTARY MATERIAL

Tutorial for using the R package *icensmis* (DOI: [10.1214/15-AOAS810SUPP](https://doi.org/10.1214/15-AOAS810SUPP.pdf); .pdf). We present a short tutorial using the R package *icensmis* to perform the analysis described in this paper.

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