Case-control survival analysis with a general semiparametric shared frailty model - a pseudo full likelihood approach

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Summary

In this work we deal with correlated failure time (age at onset) data arising from population-based case-control studies, where case and control probands are selected by population-based sampling and an array of risk factor measures is collected for both cases and controls and their relatives. Parameters of interest are effects of risk factors on the hazard function of failure times and within-family dependencies of failure times after adjusting for the risk factors. Due to the retrospective nature of sampling, a large sample theory for existing methods has not been established. We develop a novel estimation techniques for estimating these parameters under a general semiparametric shared frailty model. We also present a simple, easily computed, and non-iterative nonparametric estimator for the cumulative baseline hazard function. A rigorous large sample theory for the proposed estimators of these parameters is given along with simulations and a real data example illustrate the utility of the proposed method.

Keywords

Case-control study; Correlated failure times; Family study; Frailty model; Multivariate survival model
1 Introduction

Clustered failure times arise often in medical and epidemiologic studies. Examples include disease onset times of twins (in terms of age), multiple recurrences times of infections on an individual, or time to blindness for both eyes within an individual. A typical case-control family study includes a random sample of independent diseased individuals (cases) and non-diseased individuals (controls), along with their family members. An array of genetic and environmental risk factor measures is collected on these individuals. Integration of genetic and environmental data is a central problem of modern observational epidemiology (Hopper et al., 1994; Zhao et al., 1997; Malone et al., 1998; Malone et al. 2000; Becher et al., 2003). Case-control family studies are powerful because they provide an efficient way to assess the effect of risk factors on the occurrence of a rare disease, and furthermore allow researchers to dissect genetic and environmental contributions to the disease based on the familial aggregation pattern of disease clusters. Hopper (2003), in a commentary article, suggested that such study designs may be the future of epidemiology, not just genetic epidemiology. Hence the need for statistical methods that can fully utilize such data is acute.

In this work we focus on population-based case-control family studies, where a number of case and control probands are randomly sampled from a well-defined population. The probands are the index subjects because of whom the families are ascertained. Here we use the term proband in a broad sense to refer to both cases and controls, in contrast with the traditional usage in which proband refers only to cases.

Relative to classical case-control methods, analysis of such studies is complicated in several ways: (1) Comparisons are no longer solely between subjects with and without the disease under study, but rather between collections of the case probands and their relatives and the control probands and their relatives, each collection typically including many subjects both with and without the studied disease. (2) Data are clustered within families,
and hence reflect intra-familial correlation due to unmeasured genetic and environmental factors.

Our work is motivated by a recent breast cancer study conducted at the Fred Hutchinson Cancer Research Center (Malone et al., 1998; Malone et al., 2000). In this study, the cases were incident breast cancer cases ascertained from the Surveillance, Epidemiology, and End Results (SEER) registry, which is a set of geographically defined, population-based cancer registries in the United States. The controls were selected by random digit dialing, and were matched with cases based on age at diagnosis and county of residence. Female relatives of case and control probands were identified, and the risk factor and outcome information was subsequently collected on these relatives. The primary goals of the study are (a) to determine the degree of the strength of the dependency of ages at diagnosis of breast cancer between probands and their relatives; (b) assess the effects of covariates on breast cancer risk.

Two modeling approaches, marginal and conditional, are typically used for accounting for the correlation within a cluster. In the conditional model, the correlation is explicitly induced by a cluster-specific random effect, with the outcomes of the cluster members being conditionally independent given the random effect. The random effects model for failure time outcome is generally known as frailty model, in that the random effect or frailty is assumed to act multiplicatively on the baseline hazard rate of failure. Many frailty models have been considered, including gamma (Gill, 1985, 1989; Nielsen et al., 1992; Klein 1992, among others), positive stable (Hougaard, 1986; Fine et al., 2003), inverse Gaussian, compound Poisson (Aalen, 1992) and log-normal (McGilchrist, 1993; Ripatti and Palmgren, 2000; Vaida and Xu, 2000, among others). Hougaard (2000) presented a comprehensive review of the properties of various frailty distributions. Under a frailty model, the regression coefficients are cluster-specific log-hazard ratios. By contrast, in the marginal model the correlation is modelled through a multivariate distribution, such
as a copula function (Genest and MacKay, 1986; Marshall and Olkin, 1988; Shih and Louis, 1995) with a specified model for the marginal hazard functions. The regression coefficients in the marginal model represent the log-hazard ratios at the population level regardless of which cluster an individual comes from. The effect therefore is “population-averaged.” Zeger et al. (1988) provided a comprehensive comparison of the conditional and marginal modelling approaches.

Methods have been developed for the age at disease onset data from case-control family studies under both modelling approaches. Shih and Chatterjee (2002) proposed a semi-parametric quasi-partial-likelihood approach for estimating the regression coefficients in a bivariate copula model. Their cumulative hazard estimator requires an iterative solution, and thus the properties of their estimators could only be investigated so far by a simulation study. Moreover, in the presence of multiple relatives for each proband, the relatives were treated as if they were independent of each other, which may lead to loss of efficiency in the baseline hazard function estimator. In contrast, Hsu et al. (2004) presented a quasi-EM algorithm method for the popular gamma frailty model. In the random effects model of Hsu et al., the regression coefficients express the effect on a subject’s disease risk due to being exposed relative to the same subject’s level of risk when unexposed. The baseline hazard function estimator naturally accommodates multiple relatives in a family (Hsu and Gorfine, 2006). However, the properties of the proposed estimators were also studied only by simulation. The method of Shih and Chatterjee (2002) can be adapted to the family-specific frailty setting (Oakes, 1989), but with the same limitation as for the marginal model: the lack of large sample theory.

In this work, we develop a new estimation technique for the general semiparametric shared frailty model, where the parameters of interest are the regression coefficients and the frailty parameters. Our general family-specific frailty model is for any frailty distribution that has finite moments. The estimation procedure for the baseline hazard function
leads to an estimator whose asymptotic properties can be derived and expressed in a tractable manner.

Section 2 presents our model, and Section 3 describes our estimation procedure. Section 4 gives the consistency and asymptotic normality results for the estimators. In Section 5, we describe an extension of our method for the case where the proband observation times are subject to a certain restriction that can arise in some studies. Section 6 presents simulation results. In Section 7 we illustrate our method with a case-control family study of early onset breast cancer. Section 8 provides a short discussion. The Appendix provides the details of the asymptotic theory.

2 Notation and model formulation

We consider a matched case-control family study where one case proband is age-matched with one control proband, and an array of risk factors is measured on the case and control probands and their relatives. Each matched set contains one case family and one control family, and there are \( n \) i.i.d. matched sets. Let \( T^0_{ij} \) and \( C_{ij} \) denote the age of disease onset and age at censoring, respectively, for individual \( j \) of family \( i \), \( i = 1, \ldots, 2n \), \( j = 0, 1, \ldots, m_i \), where \( j = 0 \) corresponds to the proband. Following Parner (1998, p. 187), we regard \( m_i \) as a random variable over \( \{1, \ldots, m\} \) for some \( m \), and build up the remainder of the model conditional on \( m_i \). Define \( \delta_{ij} = I(T^0_{ij} \leq C_{ij}) \) to be the failure indicator and \( T_{ij} = \min(T^0_{ij}, C_{ij}) \) to be the observed follow-up time for individual \( ij \). We assume that a \( p \)-vector of covariates is observed on all subjects, and let \( Z_{ij} \) denote the value of the (time-independent) covariate vector for individual \( ij \). In addition, we associate with family \( i \) an unobservable family-level covariate \( \omega_i \), the “frailty”, which induces dependence among family members. The conditional hazard function for proband \( i \), given the family frailty
\( \omega_i \), is assumed to take the form
\[
\lambda_{i0}(t|Z_{i0}, \omega_i) = \omega_i \lambda_0(t) \exp(\beta^T Z_{i0}) \quad i = 1, \ldots, 2n. \tag{1}
\]
The conditional hazard function for relative \( ij, j = 1, \ldots, m_i \), given the family frailty \( \omega_i \) and proband \( i \)'s data, is assumed to take the form
\[
\lambda_{ij}(t|T_{i0}, \delta_{i0}, Z_{i0}, Z_{ij}, \omega_i) = \omega_i \lambda_0(t) \exp(\beta^T Z_{ij}) \quad i = 1, \ldots, 2n; \quad j = 1, \ldots, m_i. \tag{2}
\]
Here \( \beta \) is a \( p \)-vector of unknown regression coefficients, and \( \lambda_0 \) is a conditional baseline hazard of unspecified form. The above model implies that the proband and the relatives have a common conditional baseline hazard function \( \lambda_0 \), and that all the dependence between the proband and the relatives in a given family is due to the frailty factor \( \omega_i \).

The random variable \( \omega_i \) is assumed to have a density \( f(\omega) \equiv f(w; \theta) \), where \( \theta \) is an unknown parameter. For simplicity, we assume that \( \theta \) is a scalar, though the vector case could be developed in a similar manner.

We put \( \gamma = (\beta^T, \theta)^T \), and let \( \gamma^\circ = (\beta^\circ^T, \theta^\circ)^T \) denote the true value of \( \gamma \). The objective is to estimate \( \gamma \) and \( \Lambda_0(t) = \int_0^t \lambda_0(u)du \). Let \( \Lambda_0^\circ(t) \) denote the true value of \( \Lambda_0 \). Further, let \( \delta_{iR} = (\delta_{i1}, \ldots, \delta_{im_i}) \), \( T_{iR} = (T_{i1}, \ldots, T_{im_i}) \), and \( Z_{iR} = (Z_{i1}, \ldots, Z_{im_i}) \).

We make the following basic assumptions.

1. \( Z_{ij} \) is bounded.

2. The parameter \( \gamma \) lies in a compact subset \( \mathcal{G} \) of \( \mathbb{R}^{p+1} \) containing an open neighborhood of \( \gamma^\circ \).

3. Conditional on \( \{Z_{ij}\}_{j=1}^{m_i} \) and \( \omega_i \), the censoring times are independent and noninformative for \( \omega_i \) and \( (\beta, \Lambda_0) \). In addition, the frailty \( \omega_i \) is independent of \( \{Z_{ij}\}_{j=1}^{m_i} \).

4. The effect of the covariates on age at onset is subject-specific, i.e.
\[
\Pr(T_{ij}, \delta_{ij}|Z_{i0}, Z_{iR}, \omega_i) = \Pr(T_{ij}, \delta_{ij}|Z_{ij}, \omega_i). \quad \text{This implies } \Pr(T_{ij}, \delta_{ij}|Z_{i0}, Z_{iR}) = \Pr(T_{ij}, \delta_{ij}|Z_{ij}).
\]
The first two of these assumptions imply that there exists a positive constant \( \nu \) such that
\[
\nu^{-1} \leq \exp(\mathbf{\beta}^T \mathbf{Z}_{ij}) \leq \nu. \tag{3}
\]
A number of additional technical assumptions are listed in the appendix.

The likelihood function for the data can be written as
\[
L = \prod_{i=1}^{2n} f(T_{iR}, \delta_{iR}, \mathbf{Z}_{iR}, \mathbf{Z}_{i0}|T_{i0}, \delta_{i0})
= \prod_{i=1}^{2n} f(T_{iR}, \delta_{iR}|\mathbf{Z}_{iR}, \mathbf{Z}_{i0}, T_{i0}, \delta_{i0}) \times f(\mathbf{Z}_{iR}|\mathbf{Z}_{i0}) \times f(\mathbf{Z}_{i0}|T_{i0}, \delta_{i0}). \tag{4}
\]
Since \( f(\mathbf{Z}_{iR}|\mathbf{Z}_{i0}) \) does not depend on the parameters of interest \((\mathbf{\beta}, \Lambda_0, \theta)\), this term will be ignored. In the following subsections we consider the other two terms in (4).

2.1 The likelihood for the proband data

For the likelihood function of the proband data, \( \prod_{i}^{2n} f(\mathbf{Z}_{i0}|T_{i0}, \delta_{i0}) \), we use a retrospective likelihood for the standard case-control study (Prentice and Breslow, 1978). We express this likelihood in terms of the marginal survival function \( S_{i0}(t) = \text{Pr}(T_{i0} > t|\mathbf{Z}_{i0}) = \int \text{Pr}(T_{i0} > t|\mathbf{Z}_{i0}, \omega) f(\omega)d\omega \). In our setting we have \( n \) one-to-one matched sets. Based on the marginal survivor function, the marginal hazard function can be written as
\[
\lambda_{i0}(t) = \lambda_0(t) \exp(\mathbf{\beta}^T \mathbf{Z}_{i0}) \frac{\mu_{1i}(t; \gamma, \Lambda_0)}{\mu_{0i}(t; \gamma, \Lambda_0)},
\]
where
\[
\mu_{ki}(t; \gamma, \Lambda_0) = \int \omega^k \exp\{-\omega H_{i0}(t)\} f(\omega)d\omega \quad k = 0, 1, 2
\]
and \( H_{i0}(t) = \Lambda_0(t) \exp(\mathbf{\beta}^T \mathbf{Z}_{i0}) \). We arrange the notation so that the first \( n \) families are the case families and the \( r \)th case family, \( r = 1, \ldots, n \), is matched with the \( (n+r) \)th control family. The likelihood for the proband data is then replaced by the following conditional
Under the gamma frailty model, we have

\[ L(1) = \prod_{r=1}^{n} \frac{\exp(\beta^T Z_{r0})\xi_{10r}(T_{r0}; \gamma, \Lambda_0)}{\exp(\beta^T Z_{r0})\xi_{10r}(T_{r0}; \gamma, \Lambda_0) + \exp(\beta^T Z_{(n+r)0})\xi_{10(n+r)}(T_{(n+r)0}; \gamma, \Lambda_0)}, \]  

where

\[ \xi_{kk'}(t; \gamma, \Lambda_0) = \frac{\mu_{ki}(t; \gamma, \Lambda_0)}{\mu_{k'i}(t; \gamma, \Lambda_0)}, \quad k, k' = 0, 1, 2. \]

Let

\[ \xi^{\beta_l}_{10r}(t; \gamma, \Lambda_0) = \frac{\partial}{\partial \beta_l} \xi_{10r}(t; \gamma, \Lambda_0) = H_{i0}(t)Z_{0i} \{ \xi^2_{10i}(t; \gamma, \Lambda_0) - \xi_{20i}(t; \gamma, \Lambda_0) \}, \]

\[ \mu^\theta_{ki}(t; \gamma, \Lambda_0) = \frac{\partial}{\partial \theta} \mu_{ki}(t; \gamma, \Lambda_0) = \int \omega^k \exp \{-\omega H_{i0}(t)\} \frac{\partial}{\partial \theta} f(\omega) d\omega, \]

and

\[ \xi^\theta_{kk'}(t; \gamma, \Lambda_0) = \frac{\partial}{\partial \theta} \xi_{kk'}(t; \gamma, \Lambda_0) = \frac{\mu_{k'i}(t; \gamma, \Lambda_0)\mu_{ki}(t; \gamma, \Lambda_0) - \mu^\theta_{k'i}(t; \gamma, \Lambda_0)\mu_{ki}(t; \gamma, \Lambda_0)}{\mu^\theta_{k'i}(t; \gamma, \Lambda_0)}, \]

for \( k, k' = 0, 1, 2 \) and \( l = 1, \ldots, p \). Then the score function for \( \beta_l \), \( l = 1, \ldots, p \), is given by

\[ U^{(1)}_l(\gamma, \Lambda_0) = \sum_{r=1}^{n} \left\{ Z_{r0} + \frac{\xi^{\beta_l}_{10r}(T_{r0}; \gamma, \Lambda_0)}{\xi_{10r}(T_{r0}; \gamma, \Lambda_0)} \right. \]

\[ \left. - \frac{\exp(\beta^T Z_{r0})[Z_{r0}\xi_{10r}(T_{r0}; \gamma, \Lambda_0) + \xi^{\beta_l}_{10r}(T_{r0}; \gamma, \Lambda_0)]}{\exp(\beta^T Z_{r0})\xi_{10r}(T_{r0}; \gamma, \Lambda_0) + \exp(\beta^T Z_{(n+r)0})\xi_{10(n+r)}(T_{(n+r)0}; \gamma, \Lambda_0)} \right], \]

and the score function for \( \theta \) is given by

\[ U^{(1)}_{p+1}(\gamma, \Lambda_0) = \sum_{r=1}^{n} \left\{ \frac{\xi^\theta_{10r}(T_{r0}; \gamma, \Lambda_0)}{\xi_{10r}(T_{r0}; \gamma, \Lambda_0)} \right. \]

\[ \left. - \frac{\exp(\beta^T Z_{r0})\xi^\theta_{10r}(T_{r0}; \gamma, \Lambda_0) + \exp(\beta^T Z_{(n+r)0})\xi^\theta_{10(n+r)}(T_{(n+r)0}; \gamma, \Lambda_0)}{\exp(\beta^T Z_{r0})\xi_{10r}(T_{r0}; \gamma, \Lambda_0) + \exp(\beta^T Z_{(n+r)0})\xi_{10(n+r)}(T_{(n+r)0}; \gamma, \Lambda_0)} \right]. \]

Under the gamma frailty model, we have

\[ \frac{\mu_{1i}(t; \gamma, \Lambda_0)}{\mu_{0i}(t; \gamma, \Lambda_0)} = \{\theta H_{i0}(t) + 1\}^{-1}, \]  

9
and so the likelihood function \([3]\) corresponds to that presented in Hsu et al. (2004) in the case of one-to-one matching. Extension to matching of multiple cases or multiple controls are straightforward, see e.g. Breslow and Day (1980).

2.2 The likelihood for the data from the relatives

Let \(N_{ij}(t) = \delta_{ij} I(T_{ij} \leq t)\), \(j = 1, \ldots, m_i\), \(N_i(t) = \sum_{j=1}^{m_i} N_{ij}(t)\), \(H_i(t) = \Lambda_0(T_{ij} \land t)\) \(\exp(\beta^T Z_{ij})\), \(j = 1, \ldots, m_i\), and \(H_i(t) = \sum_{j=1}^{m_i} H_{ij}(t)\), and let \(\tau\) be the maximum follow-up time. The likelihood of the data from the relatives then can be written as

\[
L^{(2)} = \prod_{i=1}^{2n} \int \prod_{j=1}^{m_i} \{\lambda_{ij}(T_{ij}|T_{i0}, \delta_{i0}, Z_{i0}, \omega)\}^{\delta_{ij}} S_{ij}(T_{ij}|T_{i0}, \delta_{i0}, Z_{i0}, \omega) f(w|T_{i0}, \delta_{i0}, Z_{i0}) dw
\]

\[
= \prod_{i=1}^{2n} \prod_{j=1}^{m_i} \{\lambda_0(T_{ij}) \exp(\beta^T Z_{ij})\}^{\delta_{ij}} \prod_{i=1}^{2n} \int \omega^{N_i(\tau)} \exp\{-\omega H_i(\tau)\} f(\omega|T_{i0}, \delta_{i0}, Z_{i0}) d\omega.
\]

Here, by a Bayes theorem argument,

\[
f(\omega|T_{i0}, \delta_{i0}, Z_{i0}) = \frac{\omega^{\delta_{i0}} \exp(-\omega \Lambda_0(T_{i0}) e^{\beta^T Z_{i0}}) f(\omega)}{\int \omega^{\delta_{i0}} \exp(-\omega \Lambda_0(T_{i0}) e^{\beta^T Z_{i0}}) f(\omega) d\omega}.
\]

(6)

The log-likelihood is given by

\[
\ell^{(2)} = \sum_{i=1}^{2n} \sum_{j=1}^{m_i} \delta_{ij} \log\{\lambda_0(T_{ij}) \exp(\beta^T Z_{ij})\} + \sum_{i=1}^{2n} \log \left\{ \int \omega^{N_i(\tau)} \exp\{-\omega H_i(\tau)\} f(\omega|T_{i0}, \delta_{i0}, Z_{i0}) d\omega \right\}.
\]

The scores for \((\beta_1, \ldots, \beta_p)\) are given by

\[
U^{(2)}_l(\gamma, \Lambda_0) = \sum_{i=1}^{2n} \sum_{j=1}^{m_i} \delta_{ij} Z_{ijl} + \sum_{i=1}^{2n} \frac{\int \omega^{N_i(\tau)} \exp\{-\omega H_i(\tau)\} \frac{\partial}{\partial \beta_j} f(\omega|T_{i0}, \delta_{i0}, Z_{i0}) d\omega}{\int \omega^{N_i(\tau)} \exp\{-\omega H_i(\tau)\} f(\omega|T_{i0}, \delta_{i0}, Z_{i0}) d\omega}
\]

\[- \sum_{i=1}^{2n} \frac{\int \omega^{N_i(\tau)+1} \exp\{-\omega H_i(\tau)\} f(\omega|T_{i0}, \delta_{i0}, Z_{i0}) d\omega}{\int \omega^{N_i(\tau)} \exp\{-\omega H_i(\tau)\} f(\omega|T_{i0}, \delta_{i0}, Z_{i0}) d\omega} \sum_{j=1}^{m_i} H_{ij}(\tau) Z_{ijl}
\]

for \(l = 1, \ldots, p\). The score for \(\theta\) is given by

\[
U^{(2)}_{p+1}(\gamma, \Lambda_0) = \sum_{i=1}^{2n} \frac{\int \omega^{N_i(\tau)} \exp\{-\omega H_i(\tau)\} \frac{\partial}{\partial \theta} f(\omega|T_{i0}, \delta_{i0}, Z_{i0}) d\omega}{\int \omega^{N_i(\tau)} \exp\{-\omega H_i(\tau)\} f(\omega|T_{i0}, \delta_{i0}, Z_{i0}) d\omega}.
\]
The proposed approach

We focus first on estimating the baseline cumulative hazard function \( \Lambda_0(t) \). Let \( Y_{ij}(t) = I(T_{ij} \geq t) \), and let \( \mathcal{F}_t \) denote the \( \sigma \)-algebra generated by \((T_{i0}, \delta_{i0}, Z_{i0})\) plus the entire observed history of the relatives up to time \( t \):

\[
\mathcal{F}_t = \sigma(T_{i0}, \delta_{i0}, Z_{i0}, N_{ij}(u), Y_{ij}(u), Z_{ij}; i = 1, \ldots, 2n; j = 1, \ldots, m_i; 0 \leq u \leq t).
\]

Then, as discussed by Gill (1992) and Parner (1998), the stochastic intensity process for \( N_{ij}(t), i = 1, \ldots, 2n, j = 1, \ldots, m_i \), with respect to \( \mathcal{F}_t \) is given by

\[
\lambda_0(t) \exp(\beta^T Z_{ij}) Y_{ij}(t) \psi_i(t, \gamma, \Lambda_0),
\]

where, using (6),

\[
\psi_i(t, \gamma, \Lambda_0) = E[\psi_i|\mathcal{F}_t] = \frac{\int \omega^{N_i(t)+1} \exp(-\omega H_i(t)) f(\omega|T_{i0}, \delta_{i0}, Z_{i0}) d\omega}{\int \omega^{N_i(t)} \exp(-\omega H_i(t)) f(\omega|T_{i0}, \delta_{i0}, Z_{i0}) d\omega}
\]

\[
= \frac{\int \omega^{N_i(t)+1+\delta_{i0}} \exp(-\omega \{H_i(t) + H_{i0}(T_{i0})\}) f(\omega) d\omega}{\int \omega^{N_i(t)+\delta_{i0}} \exp(-\omega \{H_i(t) + H_{i0}(T_{i0})\}) f(\omega) d\omega}.
\]

Define (for \( 0 \leq r \leq m \) and \( h \geq 0 \))

\[
\psi^*(r, h) = \frac{\int w^{r+1} e^{-hw} f(w) dw}{\int w^r e^{-hw} f(w) dw}.
\]

Some salient properties of \( \psi^*(r, h) \) are noted in Sec. 9.2. With this definition, we have \( \psi_i(t, \gamma, \Lambda_0) = \psi^*(N_i(t), H_i(t)) \).

The key to obtaining parameter estimators for a semiparametric survival model is an estimator of the nonparametric baseline hazard function. For our model, a Breslow-type estimator with a jump at each observed failure time among the relatives can be formulated in a natural way (Shih and Chatterjee, 2002). However, the hazard function for the relatives at time \( t \) depends on their respective proband’s observation time \( T_{i0} \). For example, under the gamma frailty model with expectation 1 and variance \( \theta \), \( \psi_i(t, \gamma, \Lambda_0) = \).
\( \{ \theta^{-1} + N_i(t) + \delta_{i0} \} \{ \theta^{-1} + H_i(t) + H_{i0}(T_{i0}) \}^{-1} \). Often the relevant proband’s observation time is greater than \( t \), so that the standard Breslow formula for the baseline hazard estimator at time \( t \) involves values of \( \Lambda_0 \) for times beyond time \( t \). An iterative procedure is thus required to obtain the estimator. In addition, because of this estimator’s complicated structure, its asymptotic properties have not been established.

We propose to estimate the baseline hazard function using a non-iterative two-stage procedure. The first-stage estimator is a weighted Breslow-type estimator, where the weight at time \( t \) for family \( i \) is equal to 1 if the observation time \( T_{i0} \) of the family \( i \) proband is less that \( t \), and equal to 0 otherwise. The second-stage estimator is the standard Breslow-type estimator that uses all the relatives’ failure times, plugging in the first-stage estimator where necessary.

More specifically, the estimators are defined as follows. Let \( \tau_g, g = 1, \ldots, G \), denote the observed failure times of the relatives and assume that \( d_g \) failures were observed at time \( \tau_g \). In theory, since we are dealing with continuous survival distributions, \( d_g = 1 \) for all \( g \), but we write the formula for the estimator in a form that allows for a modest level of ties in the survival times. Let \( \Lambda_{max} \) be some known (possibly large) upper bound for \( \Lambda_0^\circ(t) \).

Define \( \bar{\psi}(r, h) = \psi^*(r, h \land h_{max}) \), with \( h_{max} = m \nu \Lambda_{max} \), where \( \nu \) is as in [3]. Further, define \( \tilde{\psi}_i(t, \gamma, \Lambda) = \bar{\psi}(N_i(t), H_i(t, \gamma, \Lambda)) \). The first-stage estimator is then defined as a step function whose \( g \)-th jump is given by

\[
\Delta \tilde{\Lambda}_0(\tau_g) = \frac{\sum_{i=1}^{2n} I(T_{i0} < \tau_g) \sum_{j=1}^{m_i} dN_{ij}(\tau_g)}{\sum_{i=1}^{2n} I(T_{i0} < \tau_g) \bar{\psi}_i(\tau_{g-1}, \gamma, \Lambda_0) \sum_{j=1}^{m_i} Y_{ij}(\tau_g) \exp(\beta^T Z_{ij})}.
\] (9)

In a similar way, the second-stage estimator is defined as a step function whose \( g \)-th jump is given by

\[
\Delta \hat{\Lambda}_0(\tau_g) = \frac{d_g}{\sum_{i=1}^{2n} \tilde{\psi}_i(\tau_{g-1}, \gamma) \sum_{j=1}^{m_i} Y_{ij}(\tau_g) \exp(\beta^T Z_{ij})},
\] (10)

where \( \tilde{\psi}_i(t, \gamma) \) is defined analogously to \( \bar{\psi}_i(t, \gamma, \Lambda_0) \), with \( \Lambda_0(T_{i0}) \) replaced by \( \tilde{\Lambda}_0(T_{i0}) \) if \( T_{i0} \geq t \) and by \( \hat{\Lambda}_0(T_{i0}) \) otherwise. It is clear that no iterative optimization process is
required here and the large-sample properties of \( \hat{\Lambda}_0(t) \) will be determined by those of \( \tilde{\Lambda}_0(t) \).

We note that there is no guarantee that \( \tilde{\Lambda}_0(t, \gamma) \) as defined above will be bounded by \( \Lambda_{\text{max}} \), but this does not matter: if desired, we can replace the estimator by \( \min\{\tilde{\Lambda}_0(t, \gamma), \Lambda_{\text{max}}\} \) without affecting the asymptotics.

For estimating \((\beta, \theta)\) we use a pseudo-likelihood approach: in the score functions based on \( L^{(1)} \) and \( L^{(2)} \), we replace the unknown \( \Lambda_0 \) by \( \hat{\Lambda}_0 \). Thus, the score function corresponding to \( \beta_l \) (for \( l = 1, \ldots, p \)) is given by \( U_l(\gamma, \hat{\Lambda}_0) = n^{-1} \left\{ U_{l}^{(1)}(\gamma, \hat{\Lambda}_0) + U_{l}^{(2)}(\gamma, \hat{\Lambda}_0) \right\} \), and the estimating function for \( \theta \) is given by \( U_{p+1}(\gamma, \hat{\Lambda}_0) = n^{-1} \left\{ U_{p+1}^{(1)}(\gamma, \hat{\Lambda}_0) + U_{p+1}^{(2)}(\gamma, \hat{\Lambda}_0) \right\} \). To summarize, our proposed estimation procedure is as follows:

1. Provide an initial value for \( \gamma \).
2. For the given values of \( \gamma \), estimate \( \Lambda_0 \) using (9) and (10).
3. For the given value of \( \Lambda_0 \), estimate \( \gamma \).
4. Repeat Steps 2 and 3 until convergence is reached with respect to \( \hat{\Lambda}_0 \) and \( \hat{\gamma} \).

## 4 Asymptotic properties

We show that \( \hat{\gamma} \) is a consistent estimator of \( \gamma^* \) and that \( \sqrt{n}(\hat{\gamma} - \gamma^*) \) is asymptotically mean-zero multivariate normal. In this section, we present a broad outline sketch of the argument. The Appendix provides the details of the proofs, including a detailed list of the technical conditions assumed. The arguments are patterned after those of Gorfine et al. (2006) and Zucker et al. (2006), but with considerable expansion.

Consistency is shown through the following steps.

**Claim A1.** \( \tilde{\Lambda}_0(t, \gamma) \) converges in probability to some function \( \Lambda^*_0(t, \gamma) \) uniformly in \( t \) and \( \gamma \). The function \( \Lambda^*_0(t, \gamma) \) satisfies \( \Lambda^*_0(t, \gamma^*) = \Lambda^*_0(t) \).
Claim A2. \( \hat{\Lambda}_0(t, \gamma) \) converges in probability to some function \( \Lambda_0(t, \gamma) \) uniformly in \( t \) and \( \gamma \). The function \( \Lambda_0(t, \gamma) \) satisfies \( \Lambda_0(t, \gamma^o) = \Lambda^o_0(t) \).

Claim B. \( U(\gamma, \hat{\Lambda}_0(\cdot, \gamma)) \) converges in probability uniformly in \( t \) and \( \gamma \) to a limit \( u(\gamma, \Lambda_0(\cdot, \gamma)) \).

Claim C. There exists a unique consistent (in pr.) root to \( U(\hat{\gamma}, \hat{\Lambda}_0(\cdot, \hat{\gamma})) = 0 \).

The proofs of Claims A1, A2, and B involve empirical process and function-space compactness arguments, while Claim C is shown using Foutz’s (1977) theorem on consistency of maximum likelihood type estimators.

The proof of asymptotic normality is based on the following decomposition:

$$
0 = U(\hat{\gamma}, \hat{\Lambda}_0(\cdot, \hat{\gamma})) \\
= U(\gamma^o, \Lambda^o_0) + [U(\gamma^o, \hat{\Lambda}_0(\cdot, \gamma^o)) - U(\gamma^o, \Lambda^o_0)] \\
+ [U(\hat{\gamma}, \hat{\Lambda}_0(\cdot, \hat{\gamma})) - U(\gamma^o, \hat{\Lambda}_0(\cdot, \gamma^o))].
$$

In the Appendix we analyze each of the above three terms and prove that \( \sqrt{n}(\hat{\gamma} - \gamma^o) \) has an asymptotic mean-zero multivariate normal distribution. Although it is possible to develop a consistent closed-form sandwich estimator for the asymptotic covariance matrix of this distribution, we do not present this estimator because it is too complicated to be practically useful. Instead, as discussed in Section 6, we recommend bootstrap standard-error estimates.

5 Extension to restricted sampling of probands

A key assumption in our procedure for estimating \( \Lambda_0 \) is that the support of the proband observation times and that of relatives’ observation times have the same lower limit, which is designated (without loss of generality) as time zero. In some applications, however, the probands’ observed times are restricted to some range \([s_0, s_1]\) with \( s_0 > 0 \). For example,
Malone et al. (2006) present a multi-center case-control breast cancer study where ages of cases and controls are restricted between ages 35-64. In a design of this form, where the probands’ observed times are left-restricted by \( s_0 \) and the relatives’ failure times are unrestricted, \( \Lambda_0 \) will be underestimated by our two-stage procedure. But this bias can be easily corrected by first estimating \( \Lambda_0(s_0) \).

We present here the resulting three-stage estimator for the left-restricted design. Let \( \Delta \tilde{\Lambda}_0\{\tau_g, \Lambda_0(s_0)\} \) and \( \Delta \hat{\Lambda}_0\{\tau_g, \Lambda_0(s_0)\} \) be defined analogously to \( \Delta \tilde{\Lambda}_0(\tau_g) \) and \( \Delta \hat{\Lambda}_0(\tau_g) \) with \( \Lambda_0(T_{i0}) = \Lambda_0(s_0) + \sum_{\tau_g \in [s_0, T_{i0}]} \Delta_0(\tau_g) \). The estimator \( \hat{\Lambda}_0(s_0) \) is defined to be the root of

\[
\sum_{\tau_g \in [0, s_0]} \Delta \hat{\Lambda}_0\{\tau_g, \Lambda_0(s_0)\} - \Lambda_0(s_0) = 0. \tag{11}
\]

The root can be found by simple univariate Newton-Raphson iteration. This completes the first stage. The second stage involves calculating \( \Delta \tilde{\Lambda}_0\{\tau_g, \hat{\Lambda}_0(s_0)\} \), \( g = 1, \ldots, G \), using the formula (9). In the third stage, we use the results of the second stage and the formula (10) to calculate the the final estimate \( \Delta \hat{\Lambda}_0(\tau_g) \), \( g = 1, \ldots, G \). In applying (10), we replace \( \Lambda_0(T_{i0}) \) by \( \tilde{\Lambda}_0\{T_{i0}, \hat{\Lambda}_0(s_0)\} \) if \( T_{i0} \geq \tau_g \) and by \( \hat{\Lambda}_0(T_{i0}) \) otherwise.

In Section 6 below, we present simulation results for this estimator. In theory, the asymptotic properties of the three-stage procedure could be worked out via an extension of the arguments for the two-stage procedure, but the algebra becomes very complicated. We hope to develop asymptotic theory for the left-restricted design in future work.

6 Simulation results - gamma frailty

We have performed a simulation study to evaluate the finite sample performance of the proposed method and compare it with existing methods. One of the most extensively used frailty models is the model with gamma-distributed frailty. Under this model, \( \theta \) quantifies the heterogeneity of risk among families. The larger the value of \( \theta \) is, the stronger the
dependence among family members. In addition, the gamma frailty model can be re-expressed in terms of the Clayton-Oakes copula-type model (Clayton, 1978; Oakes, 1989) and the cross-ratio, introduced by Oakes (1989) as a local measure of association between survival times, is constant on the support of failure time region and equals $1 + \theta$. The gamma frailty model is also convenient mathematically, because it admits a closed-form representation of the marginal survival distributions. These features make the gamma frailty model very popular. Hence we conducted our simulation study under the gamma frailty model, using, as is customary, the gamma distribution with expectation 1 and variance $\theta$.

Simulation results are based on 500 control probands matched to 500 case probands, with one relative sampled for each proband. We considered a single $U[0,1]$ distributed covariate with $\beta = \ln(2)$, $\Lambda_0(t) = t$, $\theta = 2$, and a $U[0,1]$ censoring variable, yielding a censoring rate among the relatives of approximately 60%. In Table 1 we compare the following three estimates: the proposed estimate with the two-stage procedure for $\Lambda_0$, the estimate of Hsu et al. (2004), and a modified version of Shih and Chatterjee’s (2002) estimate, with their method adapted to the gamma frailty model. Results are based on 500 simulated data sets. The efficiency difference between our two-stage estimator and that of Shih and Chatterjee is very small.

For our estimators, in addition to the above-mentioned simulation setting, we also considered $\beta = 0$, $\theta = 3$ and a censoring distribution of $U[0,4]$ with a $U[0,4]$ distributed covariate, or a censoring distribution of $U[0,0.1]$ with $U[0,1]$ distributed covariate, yielding censoring rates of approximately 30% or 90%, respectively. To construct confidence intervals, we use a bootstrap approach. In the setting of censored survival data, the usual nonparametric bootstrap is problematic because it leads to a substantial proportion of tied survival times. Hence we used the weighted bootstrap approach of Kosorok et al. (2004) instead. For the weighted bootstrap, a sample of $2n$ independent and iden-
tically distributed weights from the unit exponential distribution was generated for each bootstrap sample. Let $\xi_1, \ldots, \xi_{2n}$ be the standardized weights after dividing each weight by the average weight. Then, in the estimating functions, for any given function $h$ the empirical mean $n^{-1} \sum_{i=1}^{2n} h(T_i, \delta_i, Z_i)$ is replaced by its corresponding weighted empirical mean $n^{-1} \sum_{i=1}^{2n} \xi_i h(T_i, \delta_i, Z_i)$. Kosorok et al. (2004) proved that this weighted bootstrap procedure gives valid inference for all parameters under right-censored univariate failure times.

Results based on the two-stage procedure for $\Lambda_0$ are presented in Tables 2-4 for various levels of censoring. We present the mean, the empirical standard error, and the coverage rate of the 95% weighted bootstrap confidence interval. The results are based on 50 bootstrap samples for each of the 2000 simulated data sets of each configuration. Our estimates perform well in terms of bias and coverage probability.

For studying the case of left-restricted data, we considered a similar configuration as of Table 1, but now the probands observation times are restricted to be $> 0.1$. In Table 5 the results of our three-stage estimator are presented along with the estimators of Hsu et al. (2004) and of Shih and Chatterjee (2002). It is seen that estimating $\Lambda_0(s_0)$ yields small efficiency loss in $\hat{\Lambda}_0$, in compare to the other two methods.

7 Example

We apply our method to the breast cancer study mentioned in the introduction. Various risk factors were measured on probands and their relatives. For illustrative purposes we consider age at first full-term pregnancy with the relatives of the probands being the mothers. The following analysis is based on 437 breast cancer case probands matched with 437 control probands and a total of 874 mothers. The number of mothers who had breast cancer was 70 among the case families and 35 among the control families.
The number of women whose first live birth occurred before age 20 was 142 among the probands and 181 among the mothers. In the following analysis, the gamma frailty model is used with expectation 1 and variance $\theta$. Three estimation procedures are considered: our proposed method, the Hsu et al. (2004) method, and the modified Shih-Chatterjee (2002) method. For our proposed method, the two-stage procedure for $\Lambda_0$ is used since the age range of the mothers with breast cancer was 20-76 and of the age range of the probands was 22-44. Table 6 presents the regression coefficient parameter estimate $\hat{\beta}$, the dependency parameter estimate, $\hat{\theta}$, and $\hat{\Lambda}_0$ at ages 40, 50, 60 and 70 years old, along with their respective bootstrap standard errors. The proposed approach and that of Shih and Chatterjee yielded similar dependency estimates with the proposed approach being moderately more efficient. Hsu et al.’s approach gave a slightly lower dependence estimate. The regression coefficient estimates of Hsu et al. and that of Shih and Chatterjee are similar, with the latter being slightly more efficient. The proposed approach yielded a slightly lower covariate effect. The cumulative baseline hazard estimates are similar under the three estimation techniques. The results, based on the three methods, imply that women who had their first full-term pregnancy before age 20 have a reduced risk of developing breast cancer, supporting the observation of breast cancer risk reduced by early first full-term pregnancy (e.g. Coditz et al., 1996; among others). The estimates of the dependency parameter imply that after adjusting for the first full-term pregnancy, there remains a significant dependency between the ages of onset for mothers and daughters with cross ratio $(1 + \theta)$ close to 2.

8 Discussion

In this work we have presented a new estimator for case-control family study survival data under a frailty model, allowing an arbitrary frailty distribution with finite moments.
Rigorous large sample theory has been provided. Simulation results under the popular gamma frailty model indicate that the proposed procedure provides estimates with minimal bias and confidence intervals with the appropriate coverage rate. Moreover, our estimators were seen to be essentially identical in efficiency to estimators based on the more complex approach of Shih and Chatterjee (2002).

Rigorous large sample theory has been provided for unrestricted sampling of probands. For restricted sampling, the asymptotic theory could be worked out largely following the arguments for the two-stage estimator but the algebra becomes very complicated. It is beyond the scope of the current paper and will be presented in a future communication.

9 Appendix: Asymptotic theory

This appendix presents the technical conditions we assume for the asymptotic results and the proofs of these results. The development is patterned after Zucker (2005) and Zucker et al. (2006), but considerable extension of the arguments is required. In the presentation below, we focus on the added arguments needed for the present setting, and refer back to Zucker (2005) and Zucker et al. (2006) for the other segments of the development.

9.1 Assumptions and background

In deriving the asymptotic properties of $\hat{\gamma}$, we make a number of assumptions. Several of these assumptions have already been presented in the main text. Below we list the additional assumptions.

1. There is a finite maximum follow-up time $\tau > 0$, with $E[\sum_{j=1}^{m_i} Y_{ij}(\tau)] = y^* > 0$ for all $i$.

2. The frailty random variable $\omega_i$ has finite moments up to order $(m + 2)$. 
3. There exist $b > 0$ and $C > 0$ such that

$$\lim_{w \to 0} w^{-(b-1)} f(w) = C.$$ 

4. The baseline hazard function $\lambda_0^\circ(t)$ is bounded over $[0, \tau]$ by some fixed (but not necessarily known) constant $\lambda_{\text{max}}$.

5. The function $f'(w; \theta) = (d/d\theta) f(w; \theta)$ is absolutely integrable.

6. For any given family, there is a positive probability of at least two failures.

7. Defining $\pi(s) = E[I(T_{i0} < s) \sum_{j=1}^{m_i} Y_{ij}(s)]$, we have

$$\xi_r(u) \equiv \int_0^u \frac{\lambda_0^\circ(t)}{\pi(s)^r} ds < \infty \quad \text{for all } u \in [0, \tau] \text{ and } r = 1, 2, 3.$$  \hspace{1cm} (12)

This assumption is needed in the analysis of the first-stage estimator. For $r = 1$, it parallels Assumption (5.4) of Keiding and Gill (1990),

8. The matrix $[(\partial / \partial \gamma) U(\gamma, \hat{\Lambda}_0(\cdot, \gamma))]_{\gamma = \gamma^o}$ is invertible with probability going to 1 as $n \to \infty$.

### 9.2 Technical Preliminaries

With $\psi^*(r, h)$ as in (8), we define $\psi^*_{\text{min}}(h) = \min_{0 \leq r \leq m} \psi^*(r, h)$ and $\psi^*_{\text{max}}(h) = \max_{0 \leq r \leq m} \psi^*(r, h)$. In (8), the numerator and denominator are bounded above since $\omega_i$ is assumed to have finite $(m + 2)$-th moment. Also, since $\omega_i$ is nondegenerate, the numerator and denominator are strictly positive. Thus $\psi^*_{\text{max}}(h)$ is finite and $\psi^*_{\text{min}}(h)$ is strictly positive. We present below two lemmas. The first lemma, which can be proved by elementary calculus, is taken from Zucker et al. (2006). The second lemma parallels Lemma 3 of Zucker et al. (2006).

**Lemma 1:** The function $\psi^*(r, h)$ is decreasing in $h$. Hence for all $\gamma \in \mathcal{G}$ and all $t$,
\[ \psi_i(\gamma, \Lambda, t) \leq \psi_{i \text{max}}(0) \text{ and } \psi_i(\gamma, \Lambda, t) \geq \psi_{i \text{min}}(mvA(t)). \] In addition, there exist \( B > 0 \) and \( \bar{h} > 0 \) such that, for all \( h \geq \bar{h}, \psi_{i \text{min}}(h) \geq Bh^{-1}. \)

**Lemma 2:** For any \( \epsilon > 0 \), we have \( \sup_{s \in [\epsilon, \tau]} |\tilde{\Lambda}_0(s, \gamma^0) - \tilde{\Lambda}_0(s, \gamma^0)| \to 0 \) as \( n \to \infty. \)

### 9.3 Consistency

As indicated in Sec. 4, the consistency proof proceeds in several stages.

**Claim A1:** \( \tilde{\Lambda}_0(t, \gamma) \) converges in probability to some function \( \Lambda_0^*(t, \gamma) \) uniformly in \( t \) and \( \gamma \). The function \( \Lambda_0^*(t, \gamma) \) satisfies \( \Lambda_0^*(t, \gamma^0) = \Lambda_0^*(t, \psi). \)

**Remark:** We give here an in pr. consistency result, rather than an a.s. result as in Zucker et al. (2006). The reason will be explained in the course of the proof.

**Proof:** We can write \( \tilde{\Lambda}_0(t, \gamma) \) as

\[
\tilde{\Lambda}_0(t, \gamma) = \int_0^t \frac{n^{-1} \sum_{i=1}^n I(T_{i0} < s) \sum_{j=1}^{m_i} dN_{ij}(s)}{n^{-1} \sum_{i=1}^n I(T_{i0} < s) \psi_i(s-, \gamma, \Lambda) \sum_{j=1}^{m_i} Y_{ij}(s) \exp(\beta^T Z_{ij})}. \tag{13}
\]

The proof here builds here on that of the corresponding Claim A in Zucker et al. The main point needing attention here is the fact that, because of the indicators \( I(T_{i0} < s) \), the denominator of (13) tends to 0 as \( s \to 0 \). Special arguments are needed to deal with this “vanishing denominator” problem.

Define, in parallel with Zucker et al. (2006),

\[
\Xi_n(t, \gamma, \Lambda) = \int_0^t \frac{n^{-1} \sum_{i=1}^n I(T_{i0} < s) \sum_{j=1}^{m_i} dN_{ij}(s)}{n^{-1} \sum_{i=1}^n I(T_{i0} < s) \psi_i(s-, \gamma, \Lambda) \sum_{j=1}^{m_i} Y_{ij}(s) \exp(\beta^T Z_{ij})}.
\]

and

\[
\Xi(t, \gamma, \Lambda) = \int_0^t \frac{E[I(T_{i0} < s) \psi_i(s-, \gamma, \Lambda^0) \sum_{j=1}^{m_i} Y_{ij}(s) \exp(\beta^{T} Z_{ij})]}{E[I(T_{i0} < s) \psi_i(s-, \gamma, \Lambda) \sum_{j=1}^{m_i} Y_{ij}(s) \exp(\beta^{T} Z_{ij})]} \lambda_0^*(s) ds.
\]

By definition, \( \tilde{\Lambda}_0(t, \gamma) \) satisfies the equation \( \tilde{\Lambda}_0(t, \gamma) = \Xi_n(t, \gamma, \Lambda_0(, \gamma)). \)

**Remark:** In Zucker et al. (2006), we had a result to the effect that \( \Xi_n(t, \gamma, \Lambda) \to \Xi(t, \gamma, \Lambda) \) a.s. as \( n \to \infty \), uniformly over \( t \in [0, \tau] \), \( \gamma \in \mathcal{G} \), and \( \Lambda \) in a certain set. We
we find that the equation \( \Lambda(t^*) < \epsilon \) in Zucker et al. Similarly, as in Zucker et al., the function \( q \) could not obtain the corresponding result here; the argument of Aalen (1976) fails in the neighborhood of zero because of the vanishing denominator problem. This is why we give only an in pr. consistency result rather than an a.s. result.

Again in parallel with Zucker et al. (2006), define

\[
q_\gamma(s, \Lambda) = \frac{\mathbb{E}[I(T_{i0} < s) \tilde{\psi}_i(s-, \gamma, \Lambda_0) \sum_{j=1}^{m_i} Y_{ij}(s) \exp(\beta^T Z_{ij})]}{\mathbb{E}[I(T_{i0} < s) \tilde{\psi}_i(s-, \gamma, \Lambda) \sum_{j=1}^{m_i} Y_{ij}(s) \exp(\beta^T Z_{ij})]} \lambda_0^\gamma(s).
\]

This function \( q_\gamma(s, \Lambda) \) has the same properties as noted for the corresponding function in Zucker et al. These properties are not interfered with by the insertion of the indicator function \( I(T_{i0} < s) \). In particular, from Lemma 1 we have

\[
\frac{\tilde{\psi}_i(s-, \gamma, \Lambda_0)}{\tilde{\psi}_i(s-, \gamma, \Lambda)} \leq \frac{\psi_{\max}^*(0)}{\psi_{\min}(h_{\max})},
\]

Pulling this bound outside of the expectation, we get the a bound on \( q_\gamma(s, \Lambda) \) analogous to that in Zucker et al. Similarly, as in Zucker et al., the function \( q_\gamma(s, \Lambda) \) has the following Lipschitz-like property: \( |q_\gamma(s, \Lambda_1) - q_\gamma(s, \Lambda_2)| \leq K \sup_{0 \leq u \leq s} |\Lambda_1(u) - \Lambda_2(u)| \). Accordingly, we find that the equation \( \Lambda(t) = \Xi(t, \gamma, \Lambda) \) has a unique solution, which we denote by \( \Lambda_0(t, \gamma) \). The claim then is that \( \Lambda_0(t, \gamma) \) converges in pr. (uniformly in \( t \) and \( \gamma \)) to \( \Lambda_0^\gamma(t, \gamma) \).

We now define, for any \( \epsilon > 0 \), the quantities

\[
\Xi_n(t, \gamma, \Lambda, \epsilon) = \int_0^t \frac{n^{-1} \sum_{i=1}^n I(T_{i0} < s) \sum_{j=1}^{m_i} dN_{ij}(s)}{n^{-1} \sum_{i=1}^n I(T_{i0} < s) \tilde{\psi}_i(s-, \gamma, \Lambda) \sum_{j=1}^{m_i} Y_{ij}(s) \exp(\beta^T Z_{ij})}
\]

and

\[
\Xi(t, \gamma, \Lambda, \epsilon) = \int_0^t \frac{\mathbb{E}[I(T_{i0} < s) \tilde{\psi}_i(s-, \gamma, \Lambda_0) \sum_{j=1}^{m_i} Y_{ij}(s) \exp(\beta^T Z_{ij})]}{\mathbb{E}[I(T_{i0} < s) \tilde{\psi}_i(s-, \gamma, \Lambda) \sum_{j=1}^{m_i} Y_{ij}(s) \exp(\beta^T Z_{ij})]} \lambda_0^\gamma(s) ds.
\]

We next define \( \Lambda_0(t, \gamma, \epsilon) \) to be the solution of the equation \( \Lambda_0(t, \gamma, \epsilon) = \Xi_n(t, \gamma, \Lambda_0(\cdot, \gamma), \epsilon) \), starting from \( \Lambda_0(\epsilon, \gamma, \epsilon) = 0 \). We extend the definition of \( \Lambda_0(t, \gamma, \epsilon) \) by setting it equal to 0 for \( t < \epsilon \). Similarly, we define \( \Lambda_0^\gamma(t, \gamma, \epsilon) \) to be the solution of the equation \( \Lambda_0(t, \gamma, \epsilon) = \Xi(t, \gamma, \Lambda_0(\cdot, \gamma), \epsilon) \), starting from \( \Lambda_0(\epsilon, \gamma, \epsilon) = 0 \), and extend the definition by setting \( \Lambda_0^\gamma(t, \gamma, \epsilon) \) equal to 0 for \( t < \epsilon \).
For $t \in [\epsilon, \tau]$, the difference between $\Lambda^*_0(t, \gamma)$ and $\Lambda^*_0(t, \gamma, \epsilon)$ is as follows: $\Lambda^*_0(t, \gamma)$ is the solution to $\Lambda_0(t, \gamma, \epsilon) = \Xi(t, \gamma, \Lambda_0(\cdot, \gamma), \epsilon)$, starting from $\Lambda_0(\epsilon, \gamma, \epsilon) = \Lambda_0(\epsilon, \gamma)$, whereas $\Lambda^*_0(t, \gamma, \epsilon)$ is the solution to $\Lambda_0(t, \gamma, \epsilon) = \Xi(t, \gamma, \Lambda_0(\cdot, \gamma), \epsilon)$, starting from $\Lambda_0(\epsilon, \gamma, \epsilon) = 0$.

Hence, by an induction argument similar to that in the proof of Hartman (1973, Thm. 1.1), we find that

$$|\Lambda^*_0(t, \gamma, \epsilon) - \Lambda^*_0(t, \gamma)| \leq e^K \Lambda_0(\epsilon, \gamma),$$

where $K$ is the Lipschitz constant for $q_\gamma(s, \Lambda)$. We thus have

$$\sup_{\gamma \in \mathcal{G}, t \in [0, \tau]} |\Lambda^*_0(t, \gamma, \epsilon) - \Lambda^*_0(t, \gamma)| \to 0 \quad \text{as } \epsilon \to 0. \quad (14)$$

Now, for any given $\epsilon > 0$, there is no vanishing denominator problem on the interval $[\epsilon, \tau]$. Hence, the argument in Zucker et al. (2006) goes through as is, and we get the following result: for any $\epsilon > 0$,

$$\sup_{\gamma \in \mathcal{G}, t \in [\epsilon, \tau]} |\tilde{\Lambda}_0(t, \gamma, \epsilon) - \Lambda^*_0(t, \gamma, \epsilon)| \to 0 \quad \text{a.s. as } n \to \infty. \quad (15)$$

In fact, in the supremum above, we can replace $[\epsilon, \tau]$ by $[0, \tau]$, since by definition $\tilde{\Lambda}_0(t, \gamma, \epsilon) = \Lambda_0(t, \gamma, \epsilon) = 0$ for $t < \epsilon$.

The above a.s. result immediately yields the corresponding in pr. result:

$$\sup_{\gamma \in \mathcal{G}, t \in [0, \tau]} |\tilde{\Lambda}_0(t, \gamma, \epsilon) - \Lambda^*_0(t, \gamma, \epsilon)| \to 0 \quad \text{in pr. as } n \to \infty. \quad (16)$$

Our aim now is to show that

$$\sup_{\gamma \in \mathcal{G}, t \in [0, \tau]} |\tilde{\Lambda}_0(t, \gamma) - \Lambda^*_0(t, \gamma)| \to 0 \quad \text{in pr. as } n \to \infty. \quad (17)$$

That is, we want to show the following: for any $\rho, \delta > 0$, there exists $n^*(\rho, \delta)$ large enough such that

$$\Pr(\sup_{\gamma \in \mathcal{G}, t \in [0, \tau]} |\tilde{\Lambda}_0(t, \gamma) - \Lambda^*_0(t, \gamma)| > \rho) \leq \delta$$

for all $n \geq n^*(\rho, \delta)$. 

23
Let \( \rho \) and \( \delta \) be given. By (14), we can find \( \epsilon > 0 \) small enough such that
\[
\sup_{\gamma \in \mathcal{G}, t \in [0, \tau]} |\Lambda_0(t, \gamma, \epsilon) - \Lambda_0^*(t, \gamma)| \leq \frac{\rho}{3}.
\]
Further, for this fixed \( \epsilon \), the result (16) implies that there exists \( \tilde{n} \) such that
\[
\Pr \left( \sup_{\gamma \in \mathcal{G}, t \in [0, \tau]} |\tilde{\Lambda}_0(t, \gamma, \epsilon) - \Lambda_0^*(t, \gamma, \epsilon)| > \frac{\rho}{3} \right) \leq \frac{\delta}{2}
\]
for all \( n \geq \tilde{n} \).

Now
\[
|\tilde{\Lambda}_0(t, \gamma) - \Lambda_0^*(t, \gamma)|
\leq |\tilde{\Lambda}_0(t, \gamma) - \tilde{\Lambda}_0(t, \gamma, \epsilon)| + |\tilde{\Lambda}_0(t, \gamma, \epsilon) - \Lambda_0^*(t, \gamma, \epsilon)| + |\Lambda_0^*(t, \gamma, \epsilon) - \Lambda_0^*(t, \gamma)|
\]
(18)
The developments just above imply that, for \( n \geq \tilde{n} \), the supremum over \( \gamma \in \mathcal{G} \) and \( t \in [0, \tau] \) of the sum of the last two terms is bounded by \( \frac{2}{3}\rho \) with probability at least \( 1 - \frac{1}{2}\delta \). It remains to deal with the first term.

Define
\[
C_1(s) = \frac{1}{n} \sum_{i=1}^{n} I(T_{i0} < s)\tilde{\psi}_i(s-, \gamma, \tilde{\Lambda}(\cdot, \gamma)) \sum_{j=1}^{m_i} Y_{ij}(s) \exp(\beta^T Z_{ij}),
\]
\[
C_2(s) = \frac{1}{n} \sum_{i=1}^{n} I(T_{i0} < s)\tilde{\psi}_i(s-, \gamma, \tilde{\Lambda}(\cdot, \gamma, \epsilon)) \sum_{j=1}^{m_i} Y_{ij}(s) \exp(\beta^T Z_{ij}).
\]
We can then write
\[
\tilde{\Lambda}_0(t, \gamma) - \Lambda_0(t, \gamma, \epsilon) = \tilde{\Lambda}_0(t \wedge \epsilon, \gamma) + A(t, \epsilon),
\]
(19)
where
\[
A(t, \epsilon) = \int_{t \wedge \epsilon}^{t} \left[ C_1(s)^{-1} - C_2(s)^{-1} \right] \left[ \frac{1}{n} \sum_{i=1}^{n} I(T_{i0} < s) \sum_{j=1}^{m_i} dN_{ij}(s) \right].
\]
We deal with the two terms on the right side of (19) in turn. In what follows, we let \( R \) denote a "generic" constant which may vary from one appearance to another, but does not depend on the unknown parameters or \( \epsilon \).
Denote
\[ \Pi(s) = \frac{1}{n} \sum_{i=1}^{n} I(T_{i0} < s) \sum_{j=1}^{m_i} Y_{ij}(s) \]
and recall the definition \( \pi(s) = E[I(T_{i0} < s) \sum_{j=1}^{m_i} Y_{ij}(s)] \). Also recall
\[ \tilde{\Lambda}(t, \gamma) = \int_0^t \frac{1}{n} \sum_{i=1}^{n} I(T_{i0} < s) \sum_{j=1}^{m_i} dN_{ij}(s) \exp(\beta^T Z_{ij}) \]
It is clear that \( \tilde{\Lambda}(t, \gamma) \leq R \tilde{Y}(t, \gamma) \), where
\[ \tilde{Y}(t, \gamma) = \int_0^t \frac{1}{n} \sum_{i=1}^{n} I(T_{i0} < s) \sum_{j=1}^{m_i} Y_{ij}(s) \exp(\beta^T Z_{ij}) \Pi(s) \frac{dN_{ij}(s)}{\Pi(s)} \]
We can write
\[ \tilde{Y}(t, \gamma) = \int_0^t \Pi(s)^{-1} \left[ \frac{1}{n} \sum_{i=1}^{n} I(T_{i0} < s) \sum_{j=1}^{m_i} Y_{ij}(s) \exp(\beta^T Z_{ij}) \right] \lambda_0(s) ds \]
\[ + \int_0^t \Pi(s)^{-1} \left[ \frac{1}{n} \sum_{i=1}^{n} I(T_{i0} < s) \sum_{j=1}^{m_i} dM_{ij}(s) \right] \]
where \( M_{ij} \) is the martingale process corresponding to \( N_{ij} \):
\[ M_{ij}(t) = N_{ij}(t) - \int_0^t \lambda_0(u) \exp(\beta^T Z_{ij}) Y_{ij}(u) \psi_i(\gamma, \Lambda_0, u-) du. \quad (20) \]
The first term is clearly bounded by \( R \Lambda_0^2(t) \). Thus, denoting the second term by \( M^*(t) \), we have
\[ \tilde{\Lambda}(t, \gamma) \leq R[\Lambda_0^2(t) + \sup_{u \in [0, t]} |M^*(u)|] \quad (21) \]
We next examine \( A(t, \epsilon) \). We can restrict to \( t \geq \epsilon \), since \( A(t, \epsilon) = 0 \) for \( t < \epsilon \). Denote
\( \Delta(t) = \tilde{\Lambda}_0(t, \gamma) - \tilde{\Lambda}_0(t, \gamma, \epsilon) \). Bearing in mind the Lipschitz property of \( \tilde{\psi} \), we find that
\[ |A(t, \epsilon)| \leq R \int_{\epsilon}^t |\Delta(s-)| d\tilde{Y}(s). \]
Note that, for \( t \geq \epsilon \), \( dA(t, \epsilon) = d\Delta(t) \). Thus, a simple induction and some additional simple manipulations lead to the following, where we employ the symbol \( \mathcal{P} \) to denote product integral and use the fact that \( \Delta(\epsilon) = \tilde{\Lambda}(\epsilon, \gamma) \):
\[ |A(t, \epsilon)| \leq |\Delta(\epsilon)| \mathcal{P}_\epsilon^{t}(1 + R \tilde{Y}(s)) \leq |\Delta(\epsilon)| \exp(R[\tilde{Y}(t) - \tilde{Y}(\epsilon)]) \leq |\tilde{\Lambda}(\epsilon, \gamma)| \exp(R\tilde{Y}(\tau)) \]
In view of the analysis above of $\Upsilon(t)$, we get

$$|A(t, \epsilon)| \leq |\bar{\Lambda}(\epsilon, \gamma)| \exp(R[\Lambda_0^0(\tau) + \sup_{u \in [0, \tau]} |M^*(u)|]). \quad (22)$$

Putting (19), (21), and (22) together, we get

$$|\bar{\Lambda}_0(t, \gamma) - \bar{\Lambda}_0(t, \gamma, \epsilon)| \leq R_1[\Lambda_0^0(\epsilon) + \sup_{u \in [0, \tau]} |M^*(u)|](1 + \exp(R_2[1 + \sup_{u \in [0, \tau]} |M^*(u)|]). \quad (23)$$

for suitable absolute constants $R_1$ and $R_2$.

The last main step is to analyze the martingale process

$$M^*(u) = \int_0^u \Pi(s)^{-1} \left[ \frac{1}{n} \sum_{i=1}^n I(T_{i0} < s) \sum_{j=1}^{m_i} Y_{ij}(s) \exp(\beta^T Z_{ij}) \right] \lambda_0^0(s) ds.$$

Our argument is patterned after the argument given by Keiding and Gill (1990, p. 595).

By Lenglart’s and Markov’s inequalities, we have, for any positive $\kappa$ and $\eta$ and any $c \in [0, \tau]$,

$$\Pr(\sqrt{n} \sup_{u \in [0, c]} |M^*(t)| > \kappa) \leq \eta + \Pr(n\langle M^* \rangle(c) > \eta/\kappa^2) \leq \eta + \frac{\kappa^2}{\eta} E[n\langle M^* \rangle(c)].$$

Define $J(s) = I(\Pi(s) > 0)$. Then

$$n\langle M^* \rangle(c) = \int_0^c \Pi(s)^{-2} \left[ \frac{1}{n} \sum_{i=1}^n I(T_{i0} < s) \sum_{j=1}^{m_i} Y_{ij}(s) \exp(\beta^T Z_{ij}) \right] \lambda_0^0(s) ds$$

$$\leq R \int_0^c \frac{nJ(s)}{n\Pi(s)} \lambda_0^0(s) ds \leq R \int_0^c \frac{n+1}{n\Pi(s) + 1} \lambda_0^0(s) ds.$$

As in Keiding and Gill,

$$E\left[ \frac{n+1}{n\Pi(s) + 1} \right] \leq \frac{1}{\pi(s)}.$$

Hence $E[n\langle M^* \rangle(c)] \leq R\xi_1(c)$, where $\xi_1$ is as in Assumption 7. We thus get

$$\Pr(\sup_{u \in [0, c]} |M^*(u)| > \kappa n^{-1/2}) \leq \eta + R\kappa^2 \eta^{-1} \xi_1(c). \quad (24)$$
Now, the main quantities in the bound in (23) are $\Lambda_0^0(\varepsilon)$ and $\sup_{u \in [0, \tau]} |M^*(u)|$. By decreasing $\varepsilon$ if necessary, we can make $\Lambda_0^0(\varepsilon)$ as small as we need. The behavior of $\sup_{u \in [0, \tau]} |M^*(u)|$ is characterized by (24). We see that by decreasing $\varepsilon$ if necessary and choosing $\eta$ appropriately, we can guarantee that the probability that the right side of (23) is less than $\frac{1}{3} \rho$ will be at least $1 - \frac{1}{2} \delta$ for all $n$ sufficiently large. With this, we have taken care of the first term of (18). The desired convergence has thus been established. It is easy to see that $\Lambda_0^0(t, \gamma^\circ) = \Lambda_0^0(t, \gamma^\circ)$.  

Claim A2: $\hat{\Lambda}_0(t, \gamma)$ converges in probability to some function $\Lambda_0(t, \gamma)$ uniformly in $t$ and $\gamma$. The function $\Lambda_0(t, \gamma)$ satisfies $\Lambda_0(t, \gamma^\circ) = \Lambda_0(t, \gamma^\circ)$.  

Proof: We can write $\hat{\Lambda}_0(t, \gamma)$ as  

$$\hat{\Lambda}_0(t, \gamma) = \int_0^t \frac{n^{-1} \sum_{i=1}^n \sum_{j=1}^{m_j} dN_{ij}(s)}{n^{-1} \sum_{i=1}^n \bar{\psi}_i(s, \gamma) \sum_{j=1}^{m_i} Y_{ij}(s) \exp(\beta^T Z_{ij})}. $$

In view of Claim A1 above, up to a uniform error of $o_P(1)$ we can replace all instances of $\tilde{\Lambda}_0(u, \gamma)$ in the definition of $\tilde{\psi}_i(s, \gamma)$ by $\Lambda_0^0(u, \gamma)$. The desired result then can be obtained using the argument used to prove Claim A of Zucker et al. (2006).

Claim A3: We have  

$$\sup_{s \in [0, \tau], \gamma \in G} |\tilde{\Lambda}_0(s, \gamma^\circ) - \tilde{\Lambda}_0(s^-, \gamma^\circ)| \xrightarrow{P} 0 \text{ as } n \to \infty, $$

$$\sup_{s \in [0, \tau], \gamma \in G} |\hat{\Lambda}_0(s, \gamma^\circ) - \hat{\Lambda}_0(s^-, \gamma^\circ)| \xrightarrow{P} 0 \text{ as } n \to \infty. $$

Proof: These results follow from Claims A1 and A2 and the fact that $\Lambda_0^0(t, \gamma)$ and $\Lambda_0^0(t, \gamma)$ are continuous.

Claim B: $U(\gamma, \hat{\Lambda}_0(\cdot, \gamma))$ converges in probability uniformly in $t$ and $\gamma$ to a limit $u(\gamma, \Lambda_0(\cdot, \gamma))$.  

Proof: As in Claim B of Zucker et al. (2006).

Claim C: There exists a unique consistent (in pr.) root to $U(\hat{\gamma}, \hat{\Lambda}_0(\cdot, \gamma)) = 0$.  

Proof: By appeal to Foutz’s (1977) theorem, as in Claim C of Zucker et al. (2006).
9.4 A workable representation of $\hat{\Lambda}_0(t) - \Lambda_0^\circ(t)$

In order to develop our asymptotic normality result, we need a workable representation of $\hat{\Lambda}_0(t) - \Lambda_0^\circ(t)$. The first step is to develop a suitable representation of $\tilde{\Lambda}_0(t) - \Lambda_0^\circ(t)$. Then, building on this, we develop our representation of $\hat{\Lambda}_0(t) - \Lambda_0^\circ(t)$.

9.4.1 Representation of $\tilde{\Lambda}_0(t) - \Lambda_0^\circ(t)$

Our starting point is the following simple lemma.

**Lemma:** Let $R_n(t)$ and $S_n(t)$ be stochastic processes, and let $A_n(t, \epsilon)$ and $B_n(t, \epsilon)$ be quantities that are bounded in probability uniformly in $t$ and $\epsilon$. Define

\[
R_n(t, \epsilon) = R_n(t) - A_n(t, \epsilon) R_n(\epsilon),
\]

\[
S_n(t, \epsilon) = B_n(t, \epsilon) [S_n(t) - S_n(\epsilon)].
\]

Suppose that:

1. $\sup_{t \in [\epsilon, \tau]} \sqrt{n} |R_n(t, \epsilon) - S_n(t, \epsilon)| \xrightarrow{P} 0$ as $n \to \infty$ for any fixed $\epsilon > 0$.

2. $\lim_{\epsilon \downarrow 0} \limsup_{n \to \infty} \Pr(\sup_{t \in [0, \epsilon]} \sqrt{n} |R_n(t)| > \delta) = 0$ for all $\delta > 0$.

3. $\lim_{\epsilon \downarrow 0} \limsup_{n \to \infty} \Pr(\sup_{t \in [0, \epsilon]} \sqrt{n} |S_n(t)| > \delta) = 0$ for all $\delta > 0$.

4. $B_n(t, \epsilon) \to B_n(t, 0)$ uniformly in $t$ as $\epsilon \to 0$ with probability converging to one as $n \to \infty$.

Then $\sup_{t \in [0, \tau]} \sqrt{n} |R_n(t) - B_n(t, 0) S_n(t, 0)| \xrightarrow{P} 0$.

We apply this lemma with $R_n(t) = \sqrt{n} [\tilde{\Lambda}_0(t) - \Lambda_0^\circ(t)]$. We have to check the four conditions enumerated in the lemma.

Condition 1
Arguments along the lines of Zucker et al. (2006) yield the result of Condition 1, with

\[ S_n(t) = \int_0^t \tilde{p}(s, \epsilon) \left[ \frac{1}{n} \sum_{i=1}^{2n} \sum_{j=1}^{m_i} I(T_{i0} < s) dM_{ij}(s) \right], \]

\[ A_n(t, \epsilon) = B_n(t, \epsilon) = \tilde{p}(t, \epsilon)^{-1}, \]

where

\[ \tilde{p}(t, \epsilon) = \prod_{s \in [t, t]} \left[ 1 + \frac{1}{n} \sum_{i=1}^{2n} \sum_{j=0}^{m_i} \Omega_{ij}(s, t) d\tilde{N}_{ij}(s) + \frac{1}{n} \Omega^*(s) I(T_{i0} < s) \delta_{ij} \right]. \]

Here

\[ \tilde{Y}(s, \Lambda) = \frac{1}{n} \sum_{i=1}^{2n} I(T_{i0} < s) \psi_i(\gamma, \Lambda, s) R_i(s) \]

with

\[ R_i(s) = \sum_{j=1}^{m_i} Y_{ij}(s) \exp(\beta^T Z_{ij}), \]

\[ \Omega^*(s) = \frac{1}{n} \sum_{k=1}^{2n} \frac{R_k(s) \eta_{k1}(s) I(T_{k0} < s)}{\{\tilde{Y}(s, \Lambda_0)\}^2} \sum_{l=1}^{m_k} I(T_{kl} > s) \exp(\beta^T Z_{kl}), \]

\[ \Omega_{i0}(s, t) = \frac{1}{n} \int_s^t \frac{R_i(u) \eta_{i1}(u) \exp(\beta^T Z_{ij})}{\{\tilde{Y}(u, \Lambda_0)\}^2} \sum_{k=1}^{m_k} \sum_{l=1}^{m_k} dN_{kl}(u), \]

and for \( j \geq 1 \)

\[ \Omega_{ij}(s, t) = \frac{1}{n} \int_s^t \frac{I(T_{i0} < u) R_i(u) \eta_{i1}(u) \exp(\beta^T Z_{ij})}{\{\tilde{Y}(u, \Lambda_0)\}^2} \sum_{k=1}^{m_k} \sum_{l=1}^{m_k} I(T_{k0} < u) dN_{kl}(u). \]

In the above, \( \eta_{i1}(s) \) is defined as

\[ \eta_{i1}(s) = \frac{\phi_{3i}(\gamma, \Lambda_0, s)}{\phi_{1i}(\gamma, \Lambda_0, s)} - \left\{ \frac{\phi_{2i}(\gamma, \Lambda_0, s)}{\phi_{1i}(\gamma, \Lambda_0, s)} \right\}^2. \]

In Sec. 9.3.2 below, we present in detail a similar argument for \( \hat{\Lambda}_0(t) - \Lambda_0(t) \).

Appealing to Assumption 7 and using arguments similar to those used in the consistency proof, we find that the \( \Omega \) quantities defined above converge in probability uniformly in \( s \) and \( t \), so that \( \tilde{p}(t, \epsilon) \) converges in probability to a deterministic limit uniformly in \( t \) and \( \epsilon \).

**Condition 2, 3, and 4**
In regard to Condition 2, we have

\[ \tilde{\Lambda}_0(t, \gamma) - \Lambda_0^o(t) = \Delta_1(t) + \Delta_2(t), \]

where

\[ \Delta_1(t) = \int_0^t [\Gamma(s, \gamma) - 1] \lambda_0^o(s) ds, \]
\[ \Delta_2(t) = \int_0^t \frac{n^{-1} \sum_{i=1}^n I(T_{i0} < s) \sum_{j=1}^{m_i} dM_{ij}(s)}{n^{-1} \sum_{i=1}^n I(T_{i0} < s) \psi_i(s-) \sum_{j=1}^{m_i} Y_{ij}(s) \exp(\beta^T Z_{ij})}, \]

where

\[ \Gamma(s, \gamma) = \frac{n^{-1} \sum_{i=1}^n I(T_{i0} < s) \psi_i(s-) \sum_{j=1}^{m_i} Y_{ij}(s) \exp(\beta^T Z_{ij})}{n^{-1} \sum_{i=1}^n I(T_{i0} < s) \psi_i(s-) \sum_{j=1}^{m_i} Y_{ij}(s) \exp(\beta^T Z_{ij})} \]

and \( M_{ij}(t) \) is defined as in [20]. We will deal with \( \Delta_1(t) \) and \( \Delta_2(t) \) in turn, starting with \( \Delta_2(t) \). In the development below, \( R \) denotes a “generic” absolute constant.

The quadratic variation process of \( \Delta_2(t) \) is given by

\[ \langle \Delta_2 \rangle(t) = \int_0^t \left[ \frac{n^{-1} \sum_{i=1}^n I(T_{i0} < s) \psi_i(s-) \sum_{j=1}^{m_i} Y_{ij}(s) \exp(\beta^T Z_{ij})}{n^{-1} \sum_{i=1}^n I(T_{i0} < s) \psi_i(s-) \sum_{j=1}^{m_i} Y_{ij}(s) \exp(\beta^T Z_{ij})} \right] \lambda_0^o(s) ds. \]

By arguments similar to those used in connection with \( M^*(t) \) in the proof of Claim A1, we find that \( \text{E}[n\langle \Delta_2 \rangle(t)] \leq R\xi_1(t) \). An application of Lenglart’s inequality then gives

\[ \Pr(\sqrt{n} \sup_{t \in [0, \varepsilon]} |\Delta_2(t)| > \kappa) \leq \eta + R\kappa^2 \eta^{-1} \xi_1(\varepsilon) \quad \forall \eta > 0. \]

Assumption 7 implies that \( \xi_1(\varepsilon) \downarrow 0 \) as \( \varepsilon \downarrow 0 \), and this takes care of \( \Delta_2(t) \).

We now turn to \( \Delta_1(t) \). As before, denote \( J(s) = I(\Pi(s) > 0) \). We can write

\[ \Delta_1(t) = \Delta_{1a}(t) + \Delta_{1b}(t) \]

with

\[ \Delta_{1a}(t) = \int_0^t [\Gamma(s, \gamma) - 1] J(s) \lambda_0^o(s) ds \]

and

\[ \Delta_{1b}(t) = \int_0^t [J(s) - 1] \lambda_0^o(s) ds. \]
The term $\Delta_{1b}(t)$ can be shown to be uniformly $O_p(n^{-1/2})$ by the argument in the middle of page 595 in Keiding and Gill (1990). As for $\Delta_{1a}(t)$, we have

$$\Delta_{1a}(t) \leq Rt|\tilde{\Lambda}_0(t, \gamma) - \Lambda_0^\circ(t)| \leq Rt|\Delta_1(t)| + Rt|\Delta_2(t)| \leq Rt|\Delta_{1a}(t)| + Rt|\Delta_{1b}(t)| + Rt|\Delta_2(t)|.$$ 

Thus, for $t$ small,

$$|\Delta_{1a}(t)| \leq \frac{Rt}{1 - Rt} [\Delta_{1b}(t) + \Delta_2(t)],$$

and the terms on the right hand side have already been taken care of.

The proof of Condition 3 is similar to that given above for $\Delta_2(t)$. Condition 4 follows easily from the uniform convergence of the $\Omega$ quantities.

### 9.4.2 Representation of $\hat{\Lambda}_0(t) - \Lambda_0^\circ(t)$

Let

$$\mathcal{Y}(s, \{\tilde{\Lambda}_0, \hat{\Lambda}_0\}) = \frac{1}{n} \sum_{i=1}^{2n} \tilde{\psi}_i(\gamma^\circ, \hat{\Lambda}_0, s) R_i(s)$$

and

$$\mathcal{Y}(s, \Lambda) = \frac{1}{n} \sum_{i=1}^{2n} \psi_i(\gamma^\circ, \Lambda, s) R_i(s)$$

so that in $\tilde{\psi}_i(\gamma^\circ, \hat{\Lambda}_0, s)$ we take $\hat{\Lambda}_0(T_{i0})$ if $T_{i0} \geq s$ and $\hat{\Lambda}_0(T_{ij})$ if $T_{ij} < s$, $j \geq 0$. By Claim A3, we have that also $\sup_{s \in [0, \tau]} |\hat{\Lambda}_0(s, \gamma^\circ) - \hat{\Lambda}_0(s-, \gamma^\circ)|$ converges to zero. Thus, we obtain the following approximation, uniformly over $t \in [0, \tau]$:

$$\hat{\Lambda}_0(t, \gamma^\circ) - \Lambda_0^\circ(t) \approx \frac{1}{n} \int_0^t \{\mathcal{Y}(s, \Lambda_0^\circ)\}^{-1} \sum_{i=1}^{2n} \sum_{j=1}^{m_i} dM_{ij}(s)$$

$$+ \frac{1}{n} \int_0^t \left[\{\mathcal{Y}(s, \{\tilde{\Lambda}_0, \hat{\Lambda}_0\})\}^{-1} - \{\mathcal{Y}(s, \Lambda_0^\circ)\}^{-1}\right] \sum_{i=1}^{2n} \sum_{j=1}^{m_i} dN_{ij}(s).$$

Now let

$$\mathcal{X}(s, r) = \{\mathcal{Y}(s, \Lambda_0^\circ + r\Delta^*)\}^{-1}$$

with $\Delta^* = \hat{\Lambda}_0 - \Lambda_0^\circ$ or $\tilde{\Lambda}_0 - \Lambda_0^\circ$, according to the estimator being used. Define $\dot{\mathcal{X}}$ and $\ddot{\mathcal{X}}$ as the first and second derivative of $\mathcal{X}$ with respect to $r$, respectively. Then, by a first
The fourth term can be written, by plugging in the representation for $\Lambda_0 - \Lambda_0^o$, as

$$-n^{-2} \int_0^t \sum_{l=1}^{2n} \sum_{j=1}^{m_1} R_k(s) \eta_{1k}(s) \frac{1}{\{V(s, \Lambda_0^o)^2 \}} I(T_{kl} > s) \exp(\beta^T Z_{kl}) \{\hat{\Lambda}_0(s) - \Lambda_0^o(s)\} \sum_{i=1}^{2n} dN_{ij}(s).$$

The justification for ignoring the remainder term in the Taylor expansion is as in the parallel argument in Zucker et al. (2006).

The second, third and fifth terms of the above equation can be written, by interchanging the order of integration, as

$$-n^{-2} \int_0^t \sum_{l=1}^{2n} \sum_{j=1}^{m_1} R_k(s) \eta_{1k}(s) \frac{1}{\{V(s, \Lambda_0^o)^2 \}} I(T_{kl} > s) \exp(\beta^T Z_{kl}) \{\hat{\Lambda}_0(s) - \Lambda_0^o(s)\} \sum_{i=1}^{2n} dN_{ij}(s).$$

and for $j \geq 1$

$$\Upsilon_{ij}(s,t) = -n^{-1} \int_s^t \frac{R_i(s) \eta_{1i}(s) \exp(\beta^T Z_{ij})}{\{V(u, \Lambda_0^o)^2 \}} \sum_{k=1}^{2n} \sum_{l=1}^{m_k} dN_{kl}(u).$$

The fourth term can be written, by plugging in the representation for $\hat{\Lambda}_0 - \Lambda_0^o$, as

$$-n^{-1} \int_0^t \frac{A(s,t) \tilde{p}(s-)}{\{V(s, \Lambda_0^o)^2 \}} \sum_{i=1}^{2n} \sum_{j=1}^{m_i} I(T_{i0} < s) \exp(\beta^T Z_{kl}) \delta_{kl}. $$

The justification for ignoring the remainder term in the Taylor expansion is as in the parallel argument in Zucker et al. (2006).
To show that

\[ 9.5 \text{ Asymptotic normality} \]

and \( N_{k0}^*(t) = I(T_{k0} \leq t) \). Given all the above, we get

\[
\hat{\Lambda}_0(t, \gamma^o) - \Lambda_0^o(t) \approx n^{-1} \int_0^t \{ \mathcal{Y}(s, \Lambda_0^0) \}^{-1} \sum_{i=1}^{2n} \sum_{j=1}^{m_i} dM_{ij}(s) \\
- n^{-1} \int_0^t A(s, \gamma^o) \delta(s-) \sum_{i=1}^{2n} \sum_{j=1}^{m_i} I(T_{i0} < s) dM_{ij}(s) \\
- n^{-1} \int_0^t \{ \hat{\Lambda}_0(s) - \Lambda_0^o(s) \} \sum_{i=1}^{2n} \sum_{j=0}^{m_i} \mathcal{T}_{ij}(s, t) d\tilde{N}_{ij}(s).
\]

By solving the above approximation recursively, for the relatives’ failure times, we get

\[
\hat{\Lambda}_0(t, \gamma^o) - \Lambda_0^o(t) \approx \frac{1}{n \hat{\delta}(t)} \int_0^t \hat{\delta}(s-) \sum_{i=1}^{2n} \sum_{j=1}^{m_i} dM_{ij}(s) \\
+ \frac{1}{n \hat{\delta}(t)} \int_0^t B(s, t) \sum_{i=1}^{2n} \sum_{j=1}^{m_i} \hat{\delta}(s-) \sum_{i=1}^{2n} \sum_{j=1}^{m_i} I(T_{i0} < s) dM_{ij}(s) \\
- \frac{\hat{\delta}(t-)}{n \hat{\delta}(t)} dN(t) \sum_{i=1}^{2n} \sum_{j=1}^{m_i} A(s, t) \sum_{i=1}^{2n} \sum_{j=1}^{m_i} \hat{\delta}(s-) \sum_{i=1}^{2n} \sum_{j=1}^{m_i} I(T_{i0} < s) dM_{ij}(s)
\]

where \( N(t) = \sum_{i=1}^{2n} \sum_{j=1}^{m_i} N_{ij}(t) \),

\[
B(s, t) = n^{-1} \int_0^t A(s, u) \hat{\delta}(u-) \sum_{i=1}^{2n} \sum_{j=0}^{m_i} \mathcal{T}_{ij}(u, t-) dN_{ij}(u)
\]

and

\[
\hat{\delta}(t) = \prod_{s \leq t} \left[ 1 + \frac{1}{n} \sum_{i=1}^{2n} \sum_{j=0}^{m_i} \mathcal{T}_{ij}(s, t) d\tilde{N}_{ij}(s) \right].
\]

### 9.5 Asymptotic normality

To show that \( \hat{\gamma} \) is asymptotically normally distributed, we write

\[
0 = U(\hat{\gamma}, \hat{\Lambda}_0(\cdot, \hat{\gamma})) \\
= U(\gamma^o, \Lambda_0^o) + [U(\gamma^o, \hat{\Lambda}_0(\cdot, \gamma^o)) - U(\gamma^o, \Lambda_0^o)] \\
+ [U(\hat{\gamma}, \hat{\Lambda}_0(\cdot, \hat{\gamma})) - U(\gamma^o, \hat{\Lambda}_0(\cdot, \gamma^o))].
\]
We examine in turn each of the terms on the right-hand side of the above equation.

**Step I**

We can write

$$U(\gamma^o, \Lambda^o_0)$$

as

$$U(\gamma^o, \Lambda^o_0) = \frac{1}{n} \left( \sum_{i=1}^{n} \xi_i^{(1)} + \sum_{i=1}^{2n} \xi_i^{(2)} \right).$$

Here $$\xi_i^{(1)}$$, $$i = 1, \ldots, n$$ are iid mean-zero random $$(p + 1)$$-vectors stemming from the likelihood of the proband data, while $$\xi_i^{(2)}$$, $$i = 1, \ldots, 2n$$ are iid mean-zero random $$(p + 1)$$-vectors stemming from the likelihood of the relatives’ data. It follows immediately from the classical central limit theorem that $$n^{-1/2} U(\gamma^o, \Lambda^o_0)$$ is asymptotically mean-zero multivariate normal.

**Step II**

Let $$\hat{U}_r = U_r(\gamma^o, \hat{\Lambda}_0), r = 1, \ldots, p$$, and $$\hat{U}_{p+1} = U_{p+1}(\gamma^o, \hat{\Lambda}_0)$$ (in this segment of the proof, when we write $$(\gamma^o, \hat{\Lambda}_0)$$ the intent is to signify $$(\gamma^o, \hat{\Lambda}_0(\cdot, \gamma^o))$$. First order Taylor expansion of $$\hat{U}_r$$ about $$\Lambda^o_0$$, $$r = 1, \ldots, p + 1$$, gives

$$n^{1/2} \{ U_r(\gamma^o, \hat{\Lambda}_0) - U_r(\gamma^o, \Lambda^o_0) \}$$

$$= n^{-1/2} \sum_{i=1}^{2n} \sum_{j=0}^{2n} \sum_{i=1}^{m_i} \sum_{j=0}^{m_j} \int_0^{t_i} Q_{ijr}(\gamma^o, \Lambda^o_0, T_{ij}) \{ \hat{\Lambda}_0(T_{ij}, \gamma^o) - \Lambda^o_0(T_{ij}) \} \, dN^{\star}_{ij}(t) + o_p(1), \quad (27)$$

where

$$Q_{ijr}(\gamma^o, \Lambda^o_0, T_{ij}) = \frac{\partial U_r(\gamma^o, \Lambda^o_0)}{\partial \Lambda^o_0(T_{ij})} \quad i = 1, \ldots, 2n \quad j = 0, \ldots, m_i \quad r = 1, \ldots, p + 1.$$

Now let $$N^{\star}_{ij}(t) = I(T_{ij} \leq t) \quad i = 1, \ldots, 2n \quad j = 0, \ldots, m_i$$. Then

$$U_r(\gamma^o, \hat{\Lambda}_0) - U_r(\gamma^o, \Lambda^o_0) = \frac{1}{n} \sum_{i=1}^{2n} \sum_{j=0}^{m_i} \int_0^{t_i} Q_{ijr}(\gamma^o, \Lambda^o_0, T_{ij}) \{ \hat{\Lambda}_0(s, \gamma^o) - \Lambda^o_0(s) \} \, dN^{\star}_{ij}(s). \quad (28)$$

Define

$$A_r^{(1)}(u) = \frac{\hat{p}(u-)}{\hat{p}(u, \Lambda^o_0)} \frac{1}{n} \sum_{i=1}^{2n} \sum_{j=0}^{m_i} \int_0^{u} Q_{ijr}(\gamma^o, \Lambda^o_0, s) \, dN^{\star}_{ij}(s),$$
\[ A_r^{(2)}(u) = \frac{\bar{p}(u-)}{\mathcal{Y}(u, \Lambda_0^\circ)} \frac{1}{n} \sum_{i=1}^{2n} \sum_{j=0}^{m_i} \int_0^r Q_{ijr}(\gamma^\circ, \Lambda^\circ, s) B(u, s) \frac{\hat{p}(s)}{\hat{p}(s)} dN_{ij}^*(s), \]

and

\[ A_r^{(3)}(u) = \frac{\bar{p}(u-)}{\mathcal{Y}(u, \Lambda_0^\circ)} \frac{1}{n} \sum_{i=1}^{2n} \sum_{j=0}^{m_i} \int_0^r Q_{ijr}(\gamma^\circ, \Lambda^\circ, s) \hat{p}(s- \Lambda(u, s)) \frac{\hat{p}(s)}{\hat{p}(s)} dN_{ij}(s). \]

Also, let \( \alpha_r^{(1)}(u), \alpha_r^{(2)}(u) \) and \( \alpha_r^{(3)}(u) \) denote the corresponding limiting values of \( A_r^{(1)}(u), A_r^{(2)}(u) \) and \( A_r^{(3)}(u) \) as \( n \) goes to infinity. Then, after plugging into (28) the representation in Sec. 9.3.2 for \( \sqrt{n} [\hat{\Lambda}_0(s, \gamma^\circ) - \Lambda_0^\circ(s)] \) and replacing the \( A \)’s with their limiting values, we obtain

\[ U_r(\gamma^\circ, \hat{\Lambda}_0) - U_r(\gamma^\circ, \Lambda_0^\circ) \approx \frac{1}{n} \sum_{k=1}^{2n} \sum_{l=1}^{m_i} \int_0^r \left[ \alpha_r^{(1)}(u) + I(T_k 0 < u) \{ \alpha_r^{(2)}(u) - \alpha_r^{(3)}(u) \} \right] dM_{kl}(u). \quad (29) \]

This gives a representation of \( U_r(\gamma^\circ, \hat{\Lambda}_0) - U_r(\gamma^\circ, \Lambda_0^\circ) \) as the average of independent mean zero iid random variables. Hence, asymptotic normality follows from the classical central limit theorem.

**Step III**

First order Taylor expansion of \( U(\hat{\gamma}, \hat{\Lambda}_0, \check{\gamma}) \) about \( \gamma^\circ = (\beta^g, \theta^g)^T \) gives

\[ U(\hat{\gamma}, \hat{\Lambda}_0, \check{\gamma}) = U(\gamma^\circ, \hat{\Lambda}_0, \gamma^\circ) + D(\gamma^\circ)(\hat{\gamma} - \gamma^\circ)^T + o_p(1), \]

where

\[ D_{ls}(\gamma) = \frac{\partial U_l(\gamma, \hat{\Lambda}_0, \check{\gamma})}{\partial \gamma_s} \]

for \( l, s = 1, \ldots, p + 1 \).

Combining the results of Steps I-III above we get that \( n^{1/2}(\hat{\gamma} - \gamma^\circ) \) is asymptotically zero-mean normally distributed with a covariance matrix that can be consistently estimated by a sandwich-type estimator.
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Table 1: Simulation results: 500 control proband matched with 500 case probands; One relative for each proband; $\beta = 0.693$, $\Lambda_0(t) = t$, $\theta = 2.0$, 500 samples.

|                  | Proposed Method | Hsu et al.      | Shih and Chatterjee |
|------------------|-----------------|-----------------|---------------------|
|                  | mean            | Empirical mean  | Empirical mean      | Empirical mean  |
|                  | Standard Error  | Standard Error  | Standard Error      | Standard Error  |
| $\beta$          | 0.706           | 0.197           | 0.697               | 0.201           | 0.698               | 0.182               |
| $\theta$         | 2.003           | 0.312           | 1.986               | 0.302           | 1.992               | 0.303               |
| $\hat{\Lambda}_0(0.2)$ | 0.201          | 0.034           | 0.204               | 0.030           | 0.202               | 0.029               |
| $\hat{\Lambda}_0(0.4)$ | 0.402          | 0.063           | 0.407               | 0.058           | 0.403               | 0.054               |
| $\hat{\Lambda}_0(0.6)$ | 0.603          | 0.095           | 0.612               | 0.090           | 0.605               | 0.084               |
| $\hat{\Lambda}_0(0.8)$ | 0.809          | 0.136           | 0.820               | 0.131           | 0.811               | 0.122               |
Table 2: Simulation results for the proposed estimators: 500 control proband matched with 500 case probands; One relative for each proband; $\Lambda_0(t) = t$; 90% censoring rate; 2000 samples.

| $\beta$ | $\theta$ | Estimator | Mean  | Standard Error | Coverage Rate |
|---------|----------|-----------|-------|----------------|---------------|
| 0.0     | 2.0      | $\hat{\beta}$ | -0.013 | 0.217          | 93.5          |
|         |          | $\hat{\theta}$ | 2.127 | 0.872          | 96.0          |
|         |          | $\hat{\Lambda}_0(0.02)$ | 0.020 | 0.006          | 94.2          |
|         |          | $\hat{\Lambda}_0(0.04)$ | 0.041 | 0.010          | 94.7          |
|         |          | $\hat{\Lambda}_0(0.06)$ | 0.061 | 0.015          | 94.8          |
|         |          | $\hat{\Lambda}_0(0.08)$ | 0.081 | 0.020          | 95.0          |
| 3.0     | 2.0      | $\hat{\beta}$ | -0.025 | 0.226          | 91.7          |
|         |          | $\hat{\theta}$ | 3.126 | 1.142          | 94.2          |
|         |          | $\hat{\Lambda}_0(0.02)$ | 0.020 | 0.005          | 95.7          |
|         |          | $\hat{\Lambda}_0(0.04)$ | 0.041 | 0.012          | 95.8          |
|         |          | $\hat{\Lambda}_0(0.06)$ | 0.062 | 0.016          | 96.1          |
|         |          | $\hat{\Lambda}_0(0.08)$ | 0.082 | 0.021          | 95.9          |
| 0.693   | 2.0      | $\hat{\beta}$ | 0.694  | 0.200          | 96.0          |
|         |          | $\hat{\theta}$ | 2.082 | 0.667          | 94.8          |
|         |          | $\hat{\Lambda}_0(0.02)$ | 0.020 | 0.005          | 95.2          |
|         |          | $\hat{\Lambda}_0(0.04)$ | 0.040 | 0.010          | 95.2          |
|         |          | $\hat{\Lambda}_0(0.06)$ | 0.060 | 0.014          | 96.1          |
|         |          | $\hat{\Lambda}_0(0.08)$ | 0.080 | 0.019          | 96.1          |
| 3.0     | 2.0      | $\hat{\beta}$ | 0.689  | 0.206          | 95.4          |
|         |          | $\hat{\theta}$ | 3.172 | 0.964          | 95.7          |
|         |          | $\hat{\Lambda}_0(0.02)$ | 0.020 | 0.005          | 94.8          |
|         |          | $\hat{\Lambda}_0(0.04)$ | 0.040 | 0.010          | 95.9          |
|         |          | $\hat{\Lambda}_0(0.06)$ | 0.060 | 0.014          | 96.5          |
|         |          | $\hat{\Lambda}_0(0.08)$ | 0.080 | 0.019          | 95.7          |
Table 3: Simulation results for the proposed estimators: 500 control proband matched with 500 case probands; One relative for each proband; \( \Lambda_0(t) = t \); 60% censoring rate; 2000 samples.

| \( \beta \) | \( \theta \) | Estimator | Mean   | Empirical Standard Error | Coverage Rate |
|------------|------------|-----------|--------|--------------------------|---------------|
| 0.0        | 2.0        | \( \hat{\beta} \) | 0.007  | 0.191                    | 96.0          |
|            |            | \( \hat{\theta} \) | 2.031  | 0.348                    | 97.5          |
|            |            | \( \hat{\Lambda}_0(0.2) \) | 0.200  | 0.035                    | 95.1          |
|            |            | \( \hat{\Lambda}_0(0.4) \) | 0.399  | 0.067                    | 95.1          |
|            |            | \( \hat{\Lambda}_0(0.6) \) | 0.598  | 0.099                    | 95.1          |
|            |            | \( \hat{\Lambda}_0(0.8) \) | 0.797  | 0.135                    | 95.1          |
| 3.0        | 2.0        | \( \hat{\beta} \) | 0.003  | 0.199                    | 95.5          |
|            |            | \( \hat{\theta} \) | 3.039  | 0.499                    | 97.0          |
|            |            | \( \hat{\Lambda}_0(0.2) \) | 0.201  | 0.042                    | 95.6          |
|            |            | \( \hat{\Lambda}_0(0.4) \) | 0.402  | 0.078                    | 95.8          |
|            |            | \( \hat{\Lambda}_0(0.6) \) | 0.602  | 0.114                    | 95.9          |
|            |            | \( \hat{\Lambda}_0(0.8) \) | 0.806  | 0.157                    | 94.6          |
| 0.693      | 2.0        | \( \hat{\beta} \) | 0.702  | 0.201                    | 96.5          |
|            |            | \( \hat{\theta} \) | 2.019  | 0.310                    | 96.4          |
|            |            | \( \hat{\Lambda}_0(0.2) \) | 0.199  | 0.036                    | 95.4          |
|            |            | \( \hat{\Lambda}_0(0.4) \) | 0.399  | 0.068                    | 96.5          |
|            |            | \( \hat{\Lambda}_0(0.6) \) | 0.598  | 0.099                    | 96.1          |
|            |            | \( \hat{\Lambda}_0(0.8) \) | 0.797  | 0.138                    | 95.5          |
| 3.0        | 2.0        | \( \hat{\beta} \) | 0.699  | 0.211                    | 96.5          |
|            |            | \( \hat{\theta} \) | 3.037  | 0.444                    | 97.3          |
|            |            | \( \hat{\Lambda}_0(0.2) \) | 0.201  | 0.042                    | 95.6          |
|            |            | \( \hat{\Lambda}_0(0.4) \) | 0.402  | 0.081                    | 96.8          |
|            |            | \( \hat{\Lambda}_0(0.6) \) | 0.600  | 0.118                    | 95.0          |
|            |            | \( \hat{\Lambda}_0(0.8) \) | 0.804  | 0.163                    | 93.7          |
Table 4: Simulation results for the proposed estimators: 500 control proband matched with 500 case probands; One relative for each proband; $\Lambda_0(t) = t$; 30% censoring rate; 2000 samples.

| $\beta$ | $\theta$ | Estimator | Mean | Standard Error | Coverage Rate |
|---------|----------|-----------|------|----------------|--------------|
| 0.0     | 2.0      | $\hat{\beta}$ | 0.007 | 0.047 | 95.5 |
|         |          | $\hat{\theta}$ | 2.013 | 0.247 | 95.3 |
|         |          | $\hat{\Lambda}_0(0.2)$ | 0.200 | 0.037 | 95.5 |
|         |          | $\hat{\Lambda}_0(0.4)$ | 0.397 | 0.073 | 95.0 |
|         |          | $\hat{\Lambda}_0(0.6)$ | 0.596 | 0.110 | 95.1 |
|         |          | $\hat{\Lambda}_0(0.8)$ | 0.794 | 0.147 | 95.5 |
| 3.0     |          | $\hat{\beta}$ | 0.006 | 0.048 | 97.3 |
|         |          | $\hat{\theta}$ | 3.009 | 0.370 | 95.3 |
|         |          | $\hat{\Lambda}_0(0.2)$ | 0.200 | 0.040 | 94.0 |
|         |          | $\hat{\Lambda}_0(0.4)$ | 0.399 | 0.078 | 94.1 |
|         |          | $\hat{\Lambda}_0(0.6)$ | 0.597 | 0.116 | 95.0 |
|         |          | $\hat{\Lambda}_0(0.8)$ | 0.796 | 0.155 | 95.6 |
| 0.693   | 2.0      | $\hat{\beta}$ | 0.703 | 0.063 | 96.5 |
|         |          | $\hat{\theta}$ | 1.993 | 0.196 | 95.5 |
|         |          | $\hat{\Lambda}_0(0.2)$ | 0.197 | 0.045 | 94.5 |
|         |          | $\hat{\Lambda}_0(0.4)$ | 0.394 | 0.085 | 94.0 |
|         |          | $\hat{\Lambda}_0(0.6)$ | 0.591 | 0.125 | 94.0 |
|         |          | $\hat{\Lambda}_0(0.8)$ | 0.788 | 0.166 | 94.1 |
| 3.0     |          | $\hat{\beta}$ | 0.703 | 0.061 | 97.2 |
|         |          | $\hat{\theta}$ | 2.999 | 0.314 | 96.0 |
|         |          | $\hat{\Lambda}_0(0.2)$ | 0.197 | 0.047 | 94.4 |
|         |          | $\hat{\Lambda}_0(0.4)$ | 0.392 | 0.091 | 94.0 |
|         |          | $\hat{\Lambda}_0(0.6)$ | 0.586 | 0.133 | 94.9 |
|         |          | $\hat{\Lambda}_0(0.8)$ | 0.792 | 0.176 | 95.0 |
Table 5: Simulation results of left-restricted data: 500 control proband matched with 500 case probands; One relative for each proband; $s_0 = 0.1$, $\beta = 0.693$, $\Lambda_0(t) = t$, $\theta = 2.0$, 500 samples.

|                  | Proposed Method | Hsu et al. | Shih and Chatterjee |
|------------------|-----------------|------------|---------------------|
|                  | Empirical mean  | Empirical mean | Empirical mean |
|                  | Standard Error  | Standard Error | Standard Error |
| $\beta$          | 0.735           | 0.698       | 0.694               |
|                  | 0.214           | 0.234       | 0.170               |
| $\theta$         | 2.040           | 2.080       | 2.080               |
|                  | 0.336           | 0.338       | 0.337               |
| $\hat{\Lambda}_0(0.2)$ | 0.195       | 0.198       | 0.198               |
|                  | 0.049           | 0.034       | 0.031               |
| $\hat{\Lambda}_0(0.4)$ | 0.392       | 0.402       | 0.401               |
|                  | 0.090           | 0.068       | 0.062               |
| $\hat{\Lambda}_0(0.6)$ | 0.589       | 0.604       | 0.603               |
|                  | 0.129           | 0.102       | 0.092               |
| $\hat{\Lambda}_0(0.8)$ | 0.786       | 0.813       | 0.810               |
|                  | 0.172           | 0.143       | 0.128               |
| $\hat{\Lambda}_0(s_0)$ | 0.098       | -           | -                   |

Table 6: Analysis of a case-control family study of breast cancer.

|                  | Proposed Method | Hsu et al. | Shih and Chatterjee |
|------------------|-----------------|------------|---------------------|
|                  | Bootstrap mean  | Bootstrap mean | Bootstrap mean |
|                  | Standard Error  | Standard Error | Standard Error |
| $\beta$          | -0.440          | -0.484      | -0.476              |
|                  | 0.158           | 0.216       | 0.168               |
| $\theta$         | 0.952           | 0.889       | 0.944               |
|                  | 0.443           | 0.443       | 0.460               |
| $\hat{\Lambda}_0(40)$ | 0.005       | 0.005       | 0.005               |
|                  | 0.002           | 0.002       | 0.002               |
| $\hat{\Lambda}_0(50)$ | 0.022       | 0.023       | 0.023               |
|                  | 0.006           | 0.006       | 0.006               |
| $\hat{\Lambda}_0(60)$ | 0.048       | 0.051       | 0.049               |
|                  | 0.010           | 0.010       | 0.010               |
| $\hat{\Lambda}_0(70)$ | 0.091       | 0.095       | 0.092               |
|                  | 0.016           | 0.016       | 0.016               |