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SEMIPARAMETRIC TRANSFORMATION MODELS WITH MULTILEVEL RANDOM EFFECTS FOR CORRELATED DISEASE ONSET IN FAMILIES

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Abstract: Large cohort studies are often used to investigate the impact of genetic variants or other risk factors on the age at onset (AAO) of a chronic disorder. These studies collect family history data, including the AAO of a disease in family members, in order to provide additional information and to improve the efficiency of estimating associations. Statistical analyses of these data are challenging owing to missing genotypes in family members and the heterogeneous dependence attributed to both their shared genetic background and shared environmental factors (e.g., lifestyle). Therefore, we propose a class of semiparametric transformation models with multilevel random effects to address these challenges. The proposed models include both the proportional-hazards model and the proportional-odds model as special cases. The multilevel random effects contain individual-specific random effects, including the kinship correlation structure dependent on the family pedigree, and a shared random effect to account for any unobserved exposure to the environment. We use a nonparametric maximum-likelihood approach for our

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inferences and propose an expectation-maximization algorithm for the computation in the presence of missing genotypes among family members. The obtained estimators are shown to be consistent, asymptotically normal, and semiparametrically efficient. Simulation studies demonstrate that the proposed method performs well with finite sample sizes. Finally, we apply the proposed method to examine genetic risks in an Alzheimer's disease study.

Key words and phrases: Family data; Multilevel random effects; Nonparametric maximum-likelihood estimation; Semiparametric efficiency; Alzheimer's disease.

1. Introduction

Long-term cohort studies are used to investigate the effects of risk factors, including genetic mutations, on the age at onset (AAO) of a disease (e.g., Alzheimer's disease (Tang et al., 2001)). These studies collect family history data, including the AAO of disease in family members, to provide additional information and to improve the efficiency of estimating associations. However, although advancements in technology have decreased the cost of genotyping, examining many family members and collecting their blood samples remains expensive. Therefore, family history data, which can be collected at relatively little cost from individuals participating in cohort studies (probands), remain a useful source of proband data and help to improve the accuracy of genetic risk assessments (Whittemore, 1995; Parmigiani et al., 1998; Whittemore and Halpern, 2003).

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There are several challenges when using a combined family history and proband data to study the impact of genetic risks on disease AAO (Gorfine et al., 2013). First, when the disease is polygenetic, the disease onset events of members of the same family are correlated, owing to their shared genetic background. Second, because family members are likely to be exposed to the same environment, such as dietary and other non-genetic risk factors, the dependence between risk factors can also be attributed to these unobserved environmental factors. Third, because genotype information on family members is usually not collected owing to resource constraints, exact genotypes are not observed in relatives. In such cases, the distributions of these genotypes need to be inferred.

A number of methods have been developed to address these challenges in analyses of proband family data. For example, Gorfine et al. (2009) analyzed a case-control family study for correlated failure times using a shared frailty proportional-hazards model. Moreover, a class of frailty models for familial risk prediction with an unknown genetic mutation status were studied in Chen et al. (2009), Graber et al. (2011), and Gorfine et al. (2013). In their proportional-hazards models, they assume that a single level of random effects are shared by a family. Garcia et al. (2017) estimated genetic risk functions from multivariate failure time data under a proportional-odds

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model. While these works adjust for shared environmental factors using random effects, they do not account for the dependence between these factors due to polygenetic effects. In an earlier work, Antoniou et al. (2008) applied a polygenic model, in which they assume that each individual has a random effect and that correlations follow the kinship correlation structure. However, they do not consider possible dependence due to family members sharing an environment or missing genotypes among family members.

In this study, we consider the general class of semiparametric transformation models of Cheng et al. (1995) and Zeng and Lin (2007), which include both the proportional-hazards model and the proportional-odds model as special cases. We include multilevel random effects in the regression model, which consist of both individual-specific random effects and random effects shared by the family. The former account for the dependence due to a shared genetic background with a kinship-structured covariance Khoury et al. (1993); the latter represent dependence due to a family's share environmental effects or lifestyle. A nonparametric maximum-likelihood approach is used to handle missing genotypes in the parameter estimation and inferences. A fast numeric integration is used to perform multi-dimensional integration. We prove the semiparametric efficiency of the proposed estimators, including establishing the invertibility of the information operator

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in a proper metric space. We also derive asymptotic variance formulae for the parameters, which avoids using a computationally intensive bootstrap procedure to compute the variances. In the simulations and in the real-data analysis, we show a substantial reduction in bias, an efficiency gain, and an improvement in the power of testing associations by properly accounting for the hierarchical correlation structure among event times. We also demonstrate an improvement in the efficiency of estimating the cumulative risk of dementia by including both proband data and data on the family history of relatives in a long-term, real-world study of aging and dementia.

The rest of the paper is organized as follows. We present the proposed model and the expectation-maximization (EM) algorithm used to estimate the parameters in Section 2. In Section 3, the derived estimators are shown to be asymptotically efficient. Extensive simulation studies are described in Section 4. Finally, we apply the proposed method to study the association between a causal mutation and the AAO of dementia based on an ongoing, large cohort study that uses structured family history data. All theoretical proofs are provided in the Supplementary Material S1.

2. Method

2.1. Model and likelihood function

Assume there are n i.i.d. families. For the jth member of the ith

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family of size n_i, let T_{ij} denote the event time of the AAO, C_{ij} be the potential right-censoring time, and X_{ij} denote the baseline covariates, including genetic polymorphisms and other risk factors. Furthermore, we denote $G_{i\cdot} = (G_{i1}, ..., G_{in_i})$ as the genotype vector for all family members, including the proband, and let Σ_i be the kinship matrix defined in accordance with family i's pedigree structure.

To study the impact of genetic risk on the AAO, we assume the following transformation model: given a family-specific random effect b_i and individual-specific random effects r_{ij}, the cumulative hazard function for T_{ij} follows

$$\Lambda_{ij}(t|G_{ij}, X_{ij}, b_i, r_{ij}) = H\{\Lambda(t)\exp(\beta G_{ij} + \gamma^T X_{ij} + b_i + r_{ij})\}, \qquad (2.1)$$

where $H(\cdot)$ is a given transformation function, and both $\Lambda(t)$ and (β, γ) are unknown. Here, β is the genetic association parameter of interest, and γ is a vector of parameters for other baseline covariates, including confounders. Moreover, b_i is the family-specific random effect representing a family's shared environment, and is assumed to follow $N(0, \sigma_b^2)$. In addition, $(r_{i1}, ..., r_{in_i})^T$ denotes the individual random effects for the shared polygenic effects (genetic background) and follows a multivariate normal distribution $MVN(0, \sigma_r^2\Sigma_i)$. In model (2.1), transformation function $H(\cdot)$ is chosen

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from the class

$$\begin{cases} \alpha^{-1}\log(1+\alpha x), & \alpha > 0, \\ x, & \alpha = 0. \end{cases}$$

Thus, $\alpha = 0$ yields the proportional-hazards model and $\alpha = 1$ yields the proportional-odds model. Additionally, we assume that Mendelian transmission holds for G_{ij}.

In cohort studies involving family history data, $G_{i\cdot}$ are often not available except for the probands who are the original participants. Instead, we observe a set $\mathcal{G}_i$ containing all possible genotypes (including the proband's genotype) that are consistent with the ith family's pedigree structure and the proband's genotype. Thus, the observed data from n families consist of $O_i = \{(Y_{ij}, \Delta_{ij}, X_{ij}, \mathcal{G}_i), j = 1, ..., n_i\}$, $i = 1, ..., n$, where $\Delta_{ij} = I(T_{ij} \leq C_{ij})$ is the censoring indicator and $Y_{ij} = \min(T_{ij}, C_{ij})$ is the observed event.

Assume that the censoring times $(C_{i1}, ..., C_{in_i})^T$ are independent of $(T_{i1}, ..., T_{in_i})^T$ and $(b_i, r_{i1}, ..., r_{in_i})^T$, conditional on $(X_{i1}, ..., X_{in_i})^T$. Then, the observed likelihood function of the parameters in (2.1) takes the form

$$\prod_{i=1}^{n} \int \sum_{g_{i\cdot} \in \mathcal{G}_i} \Big\{ p_i(g_{i\cdot}) \prod_{j=1}^{n_i} \big[\lambda(Y_{ij}) \exp(\beta g_{ij} + \gamma^T X_{ij} + b_i + r_{ij}) \times H'\{\Lambda(Y_{ij}) \exp(\beta g_{ij} + \gamma^T X_{ij} + b_i + r_{ij})\} \big]^{\Delta_{ij}} \times \exp\left[-H\{\Lambda(Y_{ij}) \exp(\beta g_{ij} + \gamma^T X_{ij} + b_i + r_{ij})\} \right] \Big\}$$

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$$\times(2\pi\sigma_b^2)^{-1/2}\exp(-\frac{b_i^2}{2\sigma_b^2})(2\pi\sigma_r^2)^{-n_i/2}|\Sigma_i|^{-1/2}\exp(-\frac{r_{i\cdot}^T\Sigma_i^{-1}r_{i\cdot}}{2\sigma_r^2})\,db_i\,dr_{i\cdot},$$

where $\lambda(t) = d\Lambda(t)/dt$ and $H'(\cdot)$ denotes the derivative of $H(\cdot)$. Here, $p_i(g_{i\cdot})$ is the conditional probability of $G_{i\cdot} = g_{i\cdot}$, given the proband's genotype. Note that $p_i(g_{i\cdot})$, for $i = 1, ..., n$, can be computed under the Mendelian transmission and the family pedigree. Thus, in the remainder of this paper, we assume they are known.

2.2. Nonparametric maximum-likelihood estimation (NPMLE)

We use the NPMLE approach to estimate the parameters of $\Lambda(t)$. Specifically, we estimate $\Lambda(t)$ as a step function with jumps only at the observed failure times, and then replace $\lambda(t)$ by the corresponding jump size of Λ at t in the likelihood function. We then maximize the following function over $\theta = (\beta, \gamma^T, \sigma_b^2, \sigma_r^2)^T$ and all jump sizes of $\Lambda(\cdot)$:

$$\begin{aligned}\prod_{i=1}^{n}\int\sum_{g_{i\cdot}\in\mathcal{G}_i}\Big\{p_i(g_{i\cdot})\prod_{j=1}^{n_i}\big[\Lambda\{Y_{ij}\}\exp(\beta g_{ij}+\gamma^T X_{ij}+b_i+r_{ij})\\ \times H'\{\Lambda(Y_{ij})\exp(\beta g_{ij}+\gamma^T X_{ij}+b_i+r_{ij})\}\big]^{\Delta_{ij}}\\ \times\exp\big[-H\{\Lambda(Y_{ij})\exp(\beta g_{ij}+\gamma^T X_{ij}+b_i+r_{ij})\}\big]\Big\}\\ \times(2\pi\sigma_b^2)^{-1/2}\exp(-\frac{b_i^2}{2\sigma_b^2})(2\pi\sigma_r^2)^{-n_i/2}|\Sigma_i|^{-1/2}\exp(-\frac{r_{i\cdot}^T\Sigma_i^{-1}r_{i\cdot}}{2\sigma_r^2})\,db_i\,dr_{i\cdot},\end{aligned} \tag{2.2}$$

where $\Lambda\{Y_{ij}\}$ is the jump size of Λ at Y_{ij}.

Computationally, the above maximization can be carried out using an

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EM algorithm. First, note that the transformation $H(x)$ satisfies

$$\exp\{-H(x)\} = \int_0^\infty \exp(-tx)\psi(t)dt,$$

where $\psi(t)$ is a gamma density with shape $1/\alpha$ and scale α. Therefore, if we introduce another random variable $\xi_{ij} \sim Gamma(1/\alpha, \alpha)$, then the proposed model (2.1) is equivalent to assuming that the conditional hazard rate of T_{ij}, given ξ_{ij}, b_i, $r_{i\cdot}$, X_{ij}, and G_{ij}, is given as

$$\xi_{ij}\lambda(t)\exp(\beta G_{ij} + \gamma^T X_{ij} + b_i + r_{ij}). \tag{2.3}$$

Treating ξ_{ij}, b_i, $r_{i\cdot}$, and $G_{i\cdot}$ as missing data, the observed likelihood function in (2.2) is equivalent to the likelihood arising from the complete data consisting of $\xi_{i\cdot} = (\xi_{i1}, ..., \xi_{in_i})^T$ and $O_i^* = (G_{i\cdot}, b_i, r_{i\cdot}, O_i)$ for $i = 1, ..., n$, the joint density of which is

$$\begin{aligned} f(\xi_{i\cdot}, O_i^*) = \prod_{j=1}^{n_i} \Big[&\big\{\xi_{ij}\Lambda\{Y_{ij}\}\exp(\beta G_{ij} + \gamma^T X_{ij} + b_i + r_{ij})\big\}^{\Delta_{ij}} \\ &\times \exp\{-\xi_{ij}\Lambda(Y_{ij})\exp(\beta G_{ij} + \gamma^T X_{ij} + b_i + r_{ij})\}\frac{\alpha^{-1/\alpha}}{\Gamma(1/\alpha)}\xi_{ij}^{1/\alpha-1}\exp(-\xi_{ij}/\alpha)\Big] \\ &\times |\Sigma_i|^{-1/2}(2\pi\sigma_b^2)^{-1/2}(2\pi\sigma_r^2)^{-n_i/2}\exp\left(-\frac{b_i^2}{2\sigma_b^2} - \frac{r_{i\cdot}^T\Sigma_i^{-1}r_{i\cdot}}{2\sigma_r^2}\right)p_i(G_{i\cdot}). \end{aligned}$$

Each iteration in the EM algorithm consists of the following E- and M-steps. In the E-step, we calculate the conditional expectation of some integral function $Q(\xi_{i\cdot}, O_i^*)$, given O_i, denoted by $\widehat{E}(Q(\xi_{i\cdot}, O_i^*)|O_i)$, using

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the following equation:

$$\widehat{E}\{Q(\xi_{i\cdot}, O_i^*)|O_i\} = \frac{\sum_{g_{i\cdot}\in\mathcal{G}_i}\int_{\xi_{i\cdot},b_i,r_{i\cdot}} Q(\xi_{i\cdot}, O_i^*) f(\xi_{i\cdot}, O_i^*) I(G_{i\cdot} = g_{i\cdot}) d\xi_{i\cdot} db_i dr_{i\cdot}}{\sum_{g_{i\cdot}\in\mathcal{G}_i}\int_{\xi_{i\cdot},b_i,r_{i\cdot}} f(\xi_{i\cdot}, O_i^*) I(G_{i\cdot} = g_{i\cdot}) d\xi_{i\cdot} db_i dr_{i\cdot}}.$$

The multi-dimensional integration used to compute the above conditional expectation can be challenging owing to multiple levels of random effects (i.e., the family level and the individual level), especially when the family size is large. We propose using a numeric approximation with a multi-dimension adaptive Gaussian quadrature approach (Abramowitz and Stegum, 1972; Liu and Pierce, 1994; Evants and Swartz, 2000) to evaluate the above integral. Here, we apply the sparse grid technique (Heiss and Winschel, 2008) to generate nodes for quadratures with more than four dimensions.

In the M-step, we maximize the conditional expectation of the complete data log-likelihood function, which is given by

$$\begin{aligned}
&\sum_{i=1}^{n}\sum_{j=1}^{n_i}\big\{\Delta_{ij}(\log\Lambda\{Y_{ij}\} + \log\xi_{ij} + \beta G_{ij} + \gamma^T X_{ij} + b_i + r_{ij}) \\
&\qquad - \xi_{ij}\Lambda(Y_{ij})\exp(\beta G_{ij} + \gamma^T X_{ij} + b_i + r_{ij})\big\} + \sum_{i=1}^{n}\log\{p_i(G_{i\cdot})\} \\
&-\frac{1}{2}\sum_{i=1}^{n}\left\{\log(2\pi\sigma_b^2) + \frac{b_i^2}{\sigma_b^2} + n_i\log(2\pi\sigma_r^2) + \log|\Sigma_i| + \frac{1}{\sigma_r^2} r_{i\cdot}^T\Sigma_i^{-1} r_{i\cdot}\right\},
\end{aligned}$$

given the observed data and the current parameter values. By simple algebra, we update σ_b^2 and σ_r^2 as follows:

$$\sigma_b^2 = \frac{1}{n}\sum_{i=1}^{n}\widehat{E}(b_i^2|O_i),\ \ \sigma_r^2 = \frac{1}{\sum_{i=1}^{n} n_i}\sum_{i=1}^{n}\widehat{E}(r_{i\cdot}^T\Sigma_i^{-1} r_{i\cdot}|O_i).$$

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We then update β and γ by solving

$$0 = \sum_{i=1}^{n}\sum_{j=1}^{n_i}\Delta_{ij}\Bigg\{\left(\widehat{E}(G_{ij}|O_i), X_{ij}^T\right)^T - \frac{\sum_{k=1}^{n}\sum_{l=1}^{n_i} I(Y_{kl}\geq Y_{ij})\widehat{E}\{(G_{kl}, X_{kl}^T)^T\xi_{kl}\exp(\beta G_{kl}+\gamma^T X_{kl}+b_k+r_{kl})|O_i\}}{\sum_{k=1}^{n}\sum_{l=1}^{n_i} I(Y_{kl}\geq Y_{ij})\widehat{E}\{\xi_{kl}\exp(\beta G_{kl}+\gamma^T X_{kl}+b_k+r_{kl})|O_i\}}\Bigg\}$$

using the one-step Newton–Raphson method. Based on the updated values of β and γ, we calculate the jump size of Λ at Y_{kl} as

$$\frac{\sum_{i=1}^{n}\sum_{j=1}^{n_i}\Delta_{ij}I(Y_{ij}=Y_{kl})}{\sum_{i=1}^{n}\sum_{j=1}^{n_i} I(Y_{ij}\geq Y_{kl})\widehat{E}\{\xi_{ij}\exp(\beta G_{ij}+\gamma^T X_{ij}+b_i+r_{ij})|O_i\}}. \tag{2.4}$$

Lastly, we iterate between the E- and M-steps until convergence, and denote the final estimators for θ and Λ as $\widehat{\theta}$ and $\widehat{\Lambda}$, respectively.

3. Asymptotic Properties

To establish the asymptotic distribution of the nonparametric maximum-likelihood estimator $(\widehat{\theta}, \widehat{\Lambda})$, we assume that the family size n_i is a bounded random variable. We further assume that, conditional on n_i, the pedigree structure of the family, denoted by $\mathcal{K}_i$, has a discrete distribution with finite choices, and thus Σ_i, the kinship matrix, is also random. Denote the true values of θ and $\Lambda(t)$ as θ_0 and $\Lambda_0(t)$, respectively. Then, we need the following assumptions.

(A.1) The true value θ_0 lies in a known compact set Θ in the interior of the domain of θ. Moreover, the true function Λ_0 is continuously differen-

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tiable, with $\Lambda_0'(t) > 0$ in $[0, \tau]$, where τ is the duration of the study, and is assumed to be finite.

(A.2) With probability one, X is bounded, and there exists a positive constant δ such that $P\{\sum_{j=1}^{n_i} I(Y_{ij} \geq \tau) \geq 1 | X_{ij}, j = 1, ..., n_i, n_i\} \geq \delta$.

(A.3) There exists a constant n_0 such that the family size n_i satisfies $P(1 \leq n_i \leq n_0) = 1$ and $P(n_i \geq 2) > 0$.

(A.4) Conditional on n_i, let $e_{ij} = (1, 0, ..., 0, 1, 0, ..., 0)^T$ be an $(n_i + 1) \times 1$ vector, with only the first and the jth elements equal to one for $j = 1, ..., n_i$. If $(\beta, \gamma, c_1, c_2)$ is a constant vector and $\nu(t)$ is a deterministic function satisfying

$$\nu(t) + \beta g_{ij} + \gamma^T X_{ij} + e_{ij}^T \begin{pmatrix} c_1 & 0 \\ 0 & c_2 \Sigma_i \end{pmatrix} e_{ij} = 0, \quad e_{ij}^T \begin{pmatrix} c_1 & 0 \\ 0 & c_2 \Sigma_i \end{pmatrix} e_{ij'} = 0,$$

for $j \neq j', j, j' = 1, ..., n_i$, g_{ij}, and $t \in [0, \tau]$ with probability one (note that both X_{ij} and Σ_i corresponding to the pedigree $\mathcal{K}_i$ are random), then $\beta = 0$, $\gamma = 0$, $\nu(t) = 0$ for $t \in [0, \tau]$, and $c_1 = c_2 = 0$.

(A.5) Conditional on n_i, if $\sum_{(g_1, ..., g_{n_i})} q(g_1, ..., g_{n_i}) p_i(g_1, ..., g_{n_i}) I((g_1, ..., g_{n_i}) \sim \mathcal{K}_i) = 0$ with probability one for some function $q(\cdot)$, where the summation is over all genotype vectors $(g_1, ..., g_{n_i})$, and $(g_1, ..., g_{n_i}) \sim \mathcal{K}_i$ means that $(g_1, ..., g_{n_i})$ is compatible with the pedigree $\mathcal{K}_i$, then

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$q(g_1, ..., g_{n_i}) = 0.$

Conditions (A.1)–(A.2) are standard assumptions for clustered survival data. Condition (A.3) assumes that the family size is bounded and that there exist at least some families with at least two members. Both conditions (A.4) and (A.5) are used to obtain parameter identifiability in the presence of multilevel random effects. In particular, (A.4) holds if $(1, X_{ij}, g_{ij})$ has a full rank with positive probability and if Σ_i has non-zero off-diagonal elements with a positive probability. In (A.5), we require that for a fixed family size, the matrix derived from the joint probabilities of $\{p_i(g_{i\cdot})\}$ across all possible pedigree structures is a full-rank matrix. Under the above assumptions, we obtain the following asymptotic results.

Theorem 1. *Under (A.1)–(A.5), we have* $\left|\widehat{\theta}_n - \theta_0\right| \to 0$ *and* $\|\widehat{\Lambda}_n - \Lambda_0\|_\infty \to 0$ *almost surely, where* $|\cdot|$ *is the Euclidean norm and* $\|\cdot\|_\infty$ *is the supremum norm in the interval* $[0, \tau]$.

The proof of Theorem 1 is given in the Supplementary Material S1. The key idea of the proof is to first show that $\widehat{\Lambda}$ is bounded, and thus is weakly compact. Then, we show that any convergence sequence of $(\widehat{\theta}, \widehat{\Lambda})$ should converge to the true parameters. The latter makes use of the Glivenko–Cantelli theorem for empirical processes and the identifiability results under conditions (A.4) and (A.5) to be established in the proof.

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To establish the asymptotic distribution, let $\mathcal{L} = \{h(t) : h(t) \in BV[0,\tau], \|h\|_{BV} \leq 1\}$, where $\|h\|_{BV}$ denotes the total variation of h. Then, by defining $\widehat{\Lambda}_n(h) = \int_0^\tau h(s)d\widehat{\Lambda}_n(s)$ for $h \in \mathcal{L}$, $\widehat{\Lambda}_n(t)$ is considered to be a bounded linear function in $l^\infty(\mathcal{L})$. Hence, $(\widehat{\theta}_n - \theta_0, \widehat{\Lambda}_n - \Lambda_0)$ is viewed as a random element in the metric space $\mathbb{R}^d \times l^\infty(\mathcal{L})$, where d is the dimension of θ_0. Then, the asymptotic distribution of the estimators is given as follows.

Theorem 2. *Under (A.1)–(A.5), it holds that* $\sqrt{n}(\widehat{\theta}_n - \theta_0, \widehat{\Lambda}_n - \Lambda_0)$ *converges weakly to a mean zero Gaussian process in the metric space* $\mathbb{R}^d \times l^\infty(\mathcal{L})$. *In addition, the asymptotic covariance matrix of* $\sqrt{n}(\widehat{\theta}_n - \theta_0)$ *attains the semiparametric efficiency bound.*

Theorem 2 concludes that $\widehat{\theta}_n$ is an efficient estimator for θ_0. The proof of Theorem 2 mostly follows the standard arguments for the semiparametric transformation models in Zeng and Lin (2007). A key challenge in the proof is to establish the invertibility of the information operator under the proposed multilevel random-effect models. Furthermore, following the result of Theorem 4 in Zeng and Lin (2007), the asymptotic covariance of $\widehat{\theta}$ can be estimated as the inverse of the observed information matrix. The latter can be calculated using the Louis formula method (Louis, 1982). Thus, using the estimated covariance matrix, we can construct the asymptotic confidence intervals for β_0 and conduct a score test for the null hypothesis

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$\beta_0 = 0$.

4. Simulation Studies

Extensive simulation studies are conducted to assess the performance of the proposed method in finite samples. In the simulations, we consider the transformation $H(x) = x$ and $\log(1 + x)$, corresponding to the proportional-hazards model and the proportional-odds model, respectively. We generate one binary covariate X_{ij} from Bernoulli(0.5) and the random effect $b_i \sim N(0, \sigma_b^2)$, with $\sigma_b = 0.5$. To generate the random effects $r_{i\cdot}$ and $G_{i\cdot}$, we consider two types of family pedigree structures, as shown in Figure 1, namely Case I and Case II. In particular, Case I is a two-generation pedigree that includes four members: Father (F), Mother (M), Sibling (S) and Proband (P). Case II is a three-generation pedigree with five members: Father (F), Mother (M), Sibling (S), Child (C), and Proband (P). Corresponding to each case, the kingship matrices are respectively given as

$$\Sigma_1 = \begin{array}{c} \begin{array}{cccc} \text{F} & \text{M} & \text{S} & \text{P} \end{array} \\ \begin{pmatrix} 1.00 & 0.00 & 0.50 & 0.50 \\ 0.00 & 1.00 & 0.50 & 0.50 \\ 0.50 & 0.50 & 1.00 & 0.50 \\ 0.50 & 0.50 & 0.50 & 1.00 \end{pmatrix} \end{array}, \Sigma_2 = \begin{array}{c} \begin{array}{ccccc} \text{F} & \text{M} & \text{S} & \text{C} & \text{P} \end{array} \\ \begin{pmatrix} 1.00 & 0.00 & 0.50 & 0.25 & 0.50 \\ 0.00 & 1.00 & 0.50 & 0.25 & 0.50 \\ 0.50 & 0.50 & 1.00 & 0.50 & 0.50 \\ 0.25 & 0.25 & 0.50 & 1.00 & 0.50 \\ 0.50 & 0.50 & 0.50 & 0.50 & 1.00 \end{pmatrix} \end{array}.$$

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Using the kinship matrices, we generate $r_{i\cdot}$ from a multivariate normal distribution with mean zero and covariance matrix $\sigma_r^2\Sigma_k$ for $k = 1, 2$, with $\sigma_r^2 = 0.5$ or 1.0. The proband's alleles are obtained with equal probabilities. Next, we use the Monte Carlo method to obtain $p_i(\cdot)$s for the ith family under its given pedigree structure: assuming the minor allele frequency is 0.02, and using the Mendelian principles of inheritance, we use the pedigree structure to simulate all genotypes for the whole family, including the proband, by starting from the top level of the pedigree. We repeat this simulation 30,000 times and retain those relatives' genotypes that match the proband's genotype. Then, $p_i(\cdot)$ is calculated as the proportion of the relatives' genotypes in the retained samples. Finally, the disease onset time, T_{ij}, is generated from model (2.1), with $\beta = 0.4$, $\gamma = -0.5$, and $\lambda(t) = 1/2$. The censoring time is simulated from the uniform distribution in $[0, 6]$, yielding around 30–35% censoring rates. In the simulations, we consider sample sizes of $n = 300$ and 500 and conduct simulations using 1,000 replicates.

For each simulated data value, we use the proposed EM algorithm with a multi-dimension adaptive Gaussian quadrature to calculate the NPMLEs. In the EM algorithm, the initial values of β and γ are set to zero, the initial values of σ_b^2 and σ_r^2 are set to one, and the initial values of the jump sizes of $\Lambda(t)$ are set to $1/m$, where m is the total number of disease events. We use

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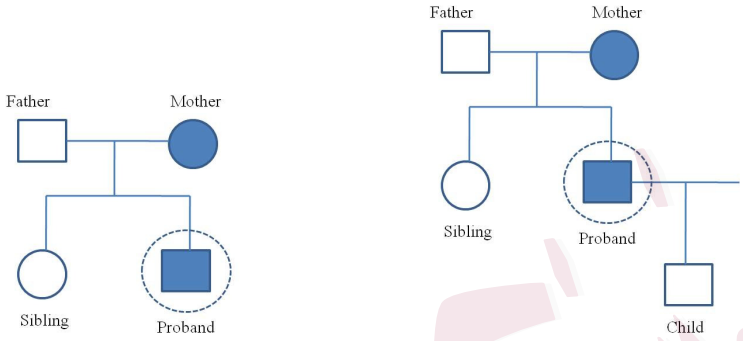

Case I Case II

Figure 1: The pedigree structures used to simulate the genotype data: black solid icons indicate mutation gene carriers for one particular mutation example.

the inverse of the observed information matrix computed using the Louis formula to estimate the covariances, and use the Satterthwaite approximation (e.g., Satterthwaite, 1946; Burdick and Graybill, 1992) to construct the 95% confidence interval for σ_b^2 and σ_r^2: $(\upsilon\hat{\sigma}^2/\chi^2_{\upsilon,.975}, \upsilon\hat{\sigma}^2/\chi^2_{\upsilon,.025})$, where $\upsilon = 2\{\hat{\sigma}^2/\widehat{\text{SE}}(\hat{\sigma}^2)\}^2$, $\widehat{\text{SE}}(\hat{\sigma}^2)$ is the estimated standard error of $\hat{\sigma}^2$, $\chi^2_{\upsilon,q}$ is the q-quantile of the chi-squared distribution with υ degrees of freedom, and $\hat{\sigma}^2 = \hat{\sigma}_b^2$ or $\hat{\sigma}_r^2$. Additionally, we compare analyses under the proposed model with those under a misspecified model similar to (2.1), except that no r_{ij} is included. Thus, in the misspecified model, only the family's shared random effect is used to account for the dependence within the family.

Tables 1 and 2 display the simulation results for Cases I and II with sample sizes of $n = 300$ and 500 and $\sigma_r^2 = 0.5$ and 1.0. As seen in these

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tables, the estimates of $(\beta_0, \gamma_0, \sigma_{b0}^2, \sigma_{r0}^2)$ and $\Lambda_0(\cdot)$ are virtually unbiased for larger sample sizes. Because the parameter σ_{r0}^2 is non-negative, the empirical distribution of $\hat{\sigma}_r^2$ is not symmetric, in practice. The estimated standard errors (SE) of σ_{r0}^2 are slightly larger than the standard deviations (SD) for small sample sizes. However, as the sample size increases, the performance improves significantly. Overall, the estimated standard errors accurately reflect the true variability. Furthermore, in comparison with the misspecified model, which ignores the dependence due to the shared genetic background, the estimates from our multilevel method are more accurate and reliable, especially when estimating the genetic association parameter β. The coverage probabilities obtained under the misspecified model are much lower than the nominal level. Table 3 shows the root mean of the integrated squared error used to estimate the cumulative hazard functions under both the proposed model and the misspecified model. Clearly, the misspecified model can lead to estimates with large bias and variability. This conclusion is also reflected in Figure 2, where the relative bias of the estimated Euclidean parameter θ is defined as $|(\widehat{\theta}_n - \theta_0)/\theta_0|$, and the relative efficiency improvement of the proposed model over the misspecified model in terms of the root mean integrated squared errors (abbreviated as MSE) is defined as $\left|\left(\mathrm{MSE}(\widehat{\Lambda}_n) - \mathrm{MSE}_{missp}(\widehat{\Lambda}_n)\right)/\mathrm{MSE}(\widehat{\Lambda}_n)\right|$. For example, the

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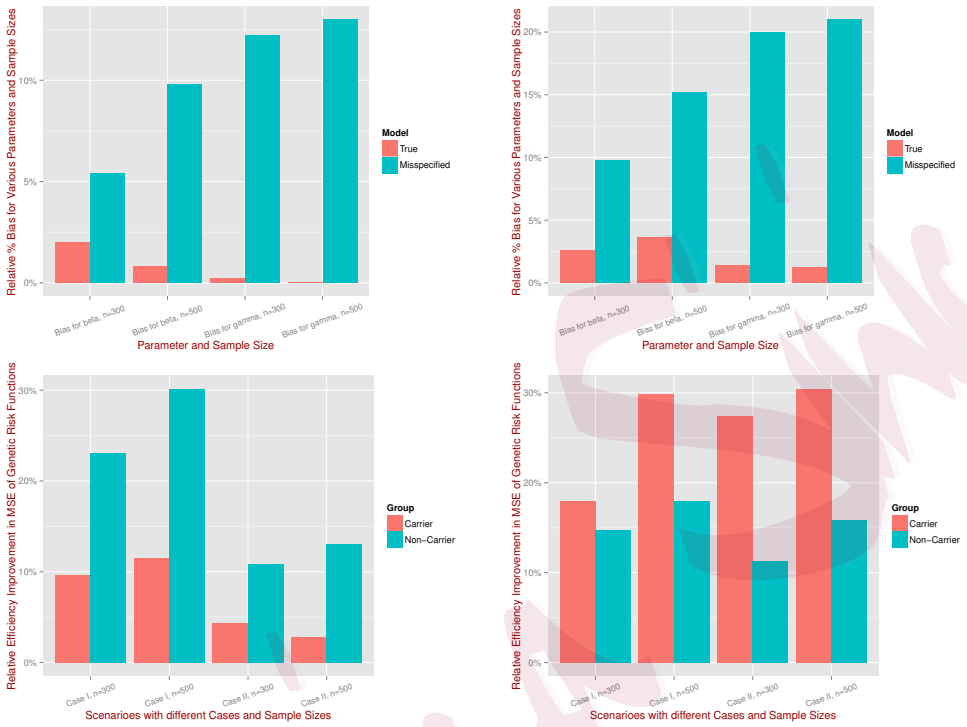

Figure 2: The first row presents bar plots of the relative biases of the estimated β and γ under Case I (left) and Case II (right). The second row shows bar plots of the relative efficiency improvement in terms of the root mean integrated squared errors when estimating Λ, where the left panel and right panel correspond to $\alpha = 0$ and $\alpha = 1$, respectively.

relative bias under the misspecified single-level model can be as high as 20%, and the relative efficiency gain of the multilevel model can be as high as 30%.

Finally, we compare the type-I errors of the score test for the true model and the misspecified model, where $\beta = 0$ and the other parameters remain the same. Our simulation results show that for both the

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Table 1: Simulation results under Case I

					Proposed Model				Misspecified Model			
$H(x)$	σ_r^2	n	Par	True	Bias	SD	SE	CP%	Bias	SD	SE	CP%
$\alpha=0$	0.5	300	σ_b^2	0.25	0.001	0.121	0.129	92.0	0.080	0.099	0.097	77.0
			σ_r^2	0.50	0.001	0.328	0.341	93.4	——	——	——	——
			β	0.50	−0.028	0.335	0.332	95.0	−0.033	0.328	0.305	93.6
			γ	−0.50	−0.005	0.119	0.113	94.2	0.056	0.098	0.095	89.0
			$\Lambda(\tau/4)$	1.25	0.044	0.216	0.208	93.6	0.020	0.207	0.186	91.0
			$\Lambda(\tau/2)$	1.50	0.089	0.437	0.425	93.6	−0.099	0.365	0.327	86.4
		500	σ_b^2	0.25	−0.007	0.091	0.101	94.2	0.072	0.071	0.074	72.6
			σ_r^2	0.50	−0.011	0.265	0.272	95.2	——	——	——	——
			β	0.50	−0.009	0.258	0.256	95.6	−0.010	0.254	0.236	93.6
			γ	−0.50	−0.001	0.085	0.087	95.6	0.056	0.073	0.073	87.0
			$\Lambda(\tau/4)$	0.75	0.017	0.156	0.156	94.2	−0.006	0.149	0.139	91.6
			$\Lambda(\tau/2)$	1.50	0.031	0.315	0.314	95.2	−0.146	0.257	0.242	81.8
	1.0	300	σ_b^2	0.25	0.017	0.146	0.154	89.9	0.136	0.110	0.106	56.8
			σ_r^2	1.00	−0.076	0.468	0.492	97.0	——	——	——	——
			β	0.50	−0.022	0.387	0.378	94.1	−0.023	0.379	0.335	91.4
			γ	−0.50	0.001	0.128	0.124	94.7	0.093	0.098	0.097	83.2
			$\Lambda(\tau/4)$	0.75	0.047	0.249	0.237	93.5	0.003	0.234	0.199	88.0
			$\Lambda(\tau/2)$	1.50	0.073	0.503	0.481	93.4	−0.211	0.393	0.331	75.2
		500	σ_b^2	0.25	0.003	0.110	0.123	92.8	0.129	0.079	0.081	45.0
			σ_r^2	1.00	−0.068	0.433	0.392	94.9	——	——	——	——
			β	0.50	−0.014	0.293	0.292	94.9	−0.007	0.293	0.258	92.6
			γ	−0.50	0.006	0.094	0.096	95.2	0.096	0.074	0.074	74.8
			$\Lambda(\tau/4)$	0.75	0.021	0.178	0.177	94.2	−0.025	0.167	0.148	89.6
			$\Lambda(\tau/2)$	1.50	0.032	0.369	0.360	94.9	−0.251	0.274	0.245	67.8
$\alpha=1$	0.5	300	σ_b^2	0.25	0.003	0.171	0.211	91.9	0.117	0.163	0.163	75.3
			σ_r^2	0.50	0.017	0.386	0.527	96.2	——	——	——	——
			β	0.50	−0.007	0.439	0.438	94.7	−0.008	0.436	0.422	94.5
			γ	−0.50	−0.012	0.155	0.148	94.7	0.020	0.140	0.135	93.6
			$\Lambda(\tau/4)$	0.75	0.040	0.280	0.276	93.6	0.045	0.276	0.264	92.6
			$\Lambda(\tau/2)$	1.50	0.087	0.569	0.554	93.2	0.015	0.527	0.498	90.9
		500	σ_b^2	0.25	−0.013	0.130	0.167	94.3	0.110	0.122	0.127	73.0
			σ_r^2	0.50	0.033	0.334	0.417	94.2	——	——	——	——
			β	0.50	−0.002	0.334	0.339	95.2	−0.003	0.333	0.327	95.3
			γ	−0.50	−0.005	0.112	0.114	95.4	0.026	0.104	0.105	94.3
			$\Lambda(\tau/4)$	0.75	0.022	0.204	0.207	94.3	0.019	0.202	0.199	93.6
			$\Lambda(\tau/2)$	1.50	0.049	0.406	0.415	94.5	−0.030	0.376	0.374	90.6
	1.0	300	σ_b^2	0.25	0.045	0.193	0.245	88.7	0.210	0.179	0.178	52.5
			σ_r^2	1.00	−0.095	0.563	0.734	97.2	——	——	——	——
			β	0.50	−0.007	0.474	0.471	95.1	−0.025	0.471	0.447	94.0
			γ	−0.50	−0.006	0.164	0.156	95.1	0.043	0.141	0.137	93.6
			$\Lambda(\tau/4)$	0.75	0.055	0.301	0.299	93.4	0.004	0.295	0.279	92.5
			$\Lambda(\tau/2)$	1.50	0.097	0.618	0.598	92.6	−0.109	0.549	0.511	88.5
		500	σ_b^2	0.25	0.027	0.153	0.190	89.6	0.206	0.131	0.137	42.8
			σ_r^2	1.00	−0.075	0.480	0.561	96.7	——	——	——	——
			β	0.50	0.000	0.359	0.365	95.6	0.002	0.362	0.346	94.1
			γ	−0.50	0.004	0.116	0.120	95.6	0.050	0.105	0.106	91.5
			$\Lambda(\tau/4)$	0.75	0.024	0.218	0.223	94.6	0.018	0.217	0.209	93.0
			$\Lambda(\tau/2)$	1.50	0.035	0.433	0.444	93.8	−0.083	0.390	0.381	88.6

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Table 2: Simulation results under Case II

					Proposed Model				Misspecified Model			
$H(x)$	σ_r^2	n	Par	True	Bias	SD	SE	CP%	Bias	SD	SE	CP%
$\alpha=0$	0.5	300	σ_b^2	0.25	−0.001	0.106	0.105	91.8	0.075	0.079	0.075	71.6
			σ_r^2	0.50	−0.002	0.283	0.311	94.8	——	——	——	——
			β	0.50	0.010	0.207	0.204	95.2	−0.027	0.191	0.183	94.8
			γ	−0.50	0.001	0.100	0.097	94.6	0.061	0.085	0.081	86.6
			$\Lambda(\tau/4)$	0.75	0.004	0.124	0.120	92.8	0.000	0.113	0.107	92.4
			$\Lambda(\tau/2)$	1.50	0.002	0.260	0.249	93.2	−0.141	0.198	0.187	83.6
		500	σ_b^2	0.25	−0.001	0.083	0.084	94.0	0.075	0.060	0.058	63.0
			σ_r^2	0.50	0.011	0.238	0.257	94.7	——	——	——	——
			β	0.50	−0.004	0.163	0.159	94.3	−0.049	0.149	0.142	91.8
			γ	−0.50	0.000	0.074	0.076	96.0	0.065	0.062	0.062	82.4
			$\Lambda(\tau/4)$	0.75	0.004	0.095	0.094	95.1	0.005	0.086	0.084	93.8
			$\Lambda(\tau/2)$	1.50	0.012	0.198	0.198	96.0	−0.126	0.150	0.147	82.4
	1.0	300	σ_b^2	0.25	0.011	0.127	0.128	89.8	0.129	0.086	0.081	47.2
			σ_r^2	1.00	−0.062	0.430	0.452	95.6	——	——	——	——
			β	0.50	0.013	0.227	0.229	95.8	−0.049	0.201	0.192	92.0
			γ	−0.50	0.007	0.113	0.107	93.4	0.100	0.085	0.082	73.6
			$\Lambda(\tau/4)$	0.75	0.003	0.136	0.134	93.4	−0.006	0.117	0.112	91.6
			$\Lambda(\tau/2)$	1.50	−0.015	0.294	0.280	92.0	−0.231	0.197	0.184	68.8
		500	σ_b^2	0.25	0.004	0.102	0.104	92.0	0.129	0.065	0.063	28.6
			σ_r^2	1.00	−0.017	0.357	0.369	94.4	——	——	——	——
			β	0.50	−0.020	0.181	0.178	95.2	−0.076	0.157	0.149	90.8
			γ	−0.50	0.006	0.082	0.083	95.2	0.105	0.062	0.063	62.8
			$\Lambda(\tau/4)$	0.75	0.013	0.108	0.106	95.4	0.001	0.090	0.087	94.4
			$\Lambda(\tau/2)$	1.50	0.027	0.236	0.224	94.4	−0.216	0.150	0.144	61.2
$\alpha=1$	0.5	300	σ_b^2	0.25	−0.004	0.163	0.192	89.1	0.118	0.137	0.126	68.9
			σ_r^2	0.50	0.047	0.372	0.566	93.1	——	——	——	——
			β	0.50	0.002	0.268	0.269	95.0	−0.027	0.254	0.252	94.5
			γ	−0.50	0.001	0.132	0.130	95.0	0.050	0.121	0.116	93.0
			$\Lambda(\tau/4)$	0.75	0.002	0.165	0.159	93.5	0.001	0.157	0.151	93.4
			$\Lambda(\tau/2)$	1.50	0.012	0.328	0.325	93.7	−0.140	0.294	0.286	90.9
		500	σ_b^2	0.25	−0.008	0.124	0.149	93.9	0.120	0.102	0.097	58.1
			σ_r^2	0.50	0.081	0.317	0.446	93.9	——	——	——	——
			β	0.50	−0.015	0.209	0.208	94.8	−0.035	0.198	0.195	93.5
			γ	−0.50	−0.001	0.095	0.101	96.0	0.052	0.088	0.090	92.8
			$\Lambda(\tau/4)$	0.75	0.011	0.125	0.125	94.1	0.021	0.120	0.118	94.5
			$\Lambda(\tau/2)$	1.50	0.024	0.253	0.254	94.1	−0.023	0.228	0.224	92.5
	1.0	300	σ_b^2	0.25	0.033	0.190	0.206	85.4	0.215	0.149	0.137	42.3
			σ_r^2	1.00	−0.086	0.554	0.672	95.8	——	——	——	——
			β	0.50	0.019	0.287	0.288	95.4	−0.029	0.274	0.261	94.2
			γ	−0.50	0.011	0.140	0.136	94.9	0.057	0.116	0.117	93.7
			$\Lambda(\tau/4)$	0.75	0.009	0.176	0.171	93.7	0.027	0.168	0.159	92.0
			$\Lambda(\tau/2)$	1.50	−0.007	0.347	0.342	92.4	−0.076	0.293	0.290	89.3
		500	σ_b^2	0.25	0.021	0.145	0.164	88.1	0.216	0.110	0.106	26.5
			σ_r^2	1.00	−0.028	0.468	0.533	94.3	——	——	——	——
			β	0.50	−0.021	0.225	0.222	95.3	−0.052	0.209	0.202	92.9
			γ	−0.50	0.006	0.101	0.106	95.8	0.058	0.090	0.091	91.0
			$\Lambda(\tau/4)$	0.75	0.019	0.136	0.134	94.9	0.029	0.126	0.123	94.7
			$\Lambda(\tau/2)$	1.50	0.025	0.273	0.270	94.7	−0.066	0.229	0.225	90.0

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Table 3: Results of the mean of the square root of the integrated squared error ($\times 10^{-2}$) for the estimated cumulative distribution functions of the carrier and non-carrier groups

				Proposed Model		Misspecified Model		Ratio	
Case	$H(x)$	σ_r^2	n	Carrier	Non-Carr	Carrier	Non-Carr	Carrier	Non-Carr
I	$\alpha = 0$	0.5	300	6.472	13.276	6.736	14.715	1.041	1.109
			500	5.092	10.163	5.339	11.665	1.049	1.148
		1.0	300	6.583	14.124	7.215	17.378	1.096	1.231
			500	5.142	10.619	5.734	13.822	1.115	1.301
	$\alpha = 1$	0.5	300	8.234	17.465	8.975	19.284	1.090	1.104
			500	6.587	13.126	7.495	14.561	1.138	1.109
		1.0	300	8.361	17.592	9.862	20.181	1.180	1.147
			500	6.653	13.138	8.641	15.510	1.299	1.180
II	$\alpha = 0$	0.5	300	5.426	8.713	5.548	9.204	1.022	1.056
			500	4.302	6.668	4.416	7.192	1.026	1.079
		1.0	300	5.523	8.870	5.758	9.841	1.043	1.109
			500	4.488	6.664	4.614	7.540	1.028	1.131
	$\alpha = 1$	0.5	300	6.876	10.980	7.703	11.710	1.120	1.067
			500	5.625	8.320	6.274	9.103	1.115	1.094
		1.0	300	6.856	10.985	8.736	12.220	1.274	1.113
			500	5.618	8.451	7.325	9.792	1.304	1.159

proportional-hazard model and the proportional-odds model, the type-I errors of the misspecified model are heavily inflated. Specifically, for the Cox proportional-hazard model, when the sample size is 300, the type-I error of the misspecified model is around 0.112, with $\sigma_r^2 = 1.0$, and it becomes 0.094 when the sample size increases to 500. The respective type-I error rates are 0.120 and 0.109 for the proportional-odds model. The type-I error rates from our approach are mostly around the significance level of 0.05.

5. Application

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The Washington Heights-Inwood Community Aging Project (WHICAP) is a prospective, community-based cohort study of aging, dementia, and Alzheimer's disease (AD) in Northern Manhattan, New York City (Tang et al., 2001). The ongoing, decades-long study has collected rich information on neuropsychiatric measures, environmental exposure, and genetic risk factors from thousands of participants. The incidence of dementia in proband participants is carefully monitored. The familial aggregation of dementia and AD is well established. First-degree relatives of AD patients have approximately twice the expected lifetime risk of dementia compared with persons without an affected first-degree relative (Devi et al., 2000). An increase in the relative risk of AD among first-degree relatives of patients is also observed among African Americans (ranging from 1.4 in a community-based sample to 2.6 in a clinic-based sample). These findings suggest a substantial heritable contribution to AD and dementia, as well as non-genetic pathways due to shared environmental risk factors or lifestyles.

A structured family history interview (Maestre et al., 1995) is administered to the probands. The family history interview collects pedigree structure, birth order, vital status, level of education, family history of cognitive impairment, dementia, and AAO among first-degree relatives, including the non-WHICAP parent and siblings. We include 1705 probands and 1342 rel-

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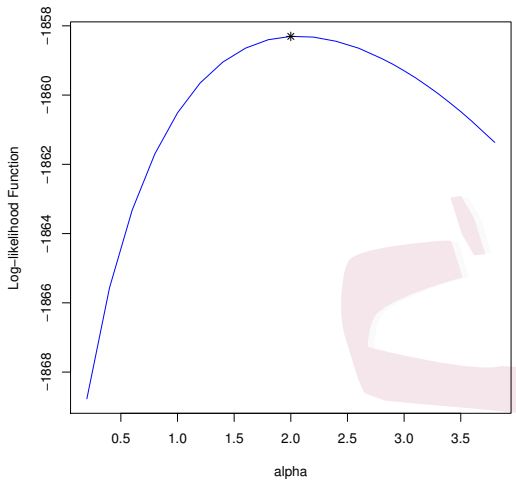

Figure 3: The log-profile-likelihood function, along with different values of α calculated from the combined data of probands and relatives.

atives from 692 families in our data analysis. The censoring rates of the probands' and relatives' observations are 89.6% and 91.99%, respectively. Apolipoprotein-E (APOE) genotypes are also obtained for each proband. Here, we wish to estimate the cumulative incidence of dementia for the APOE-ε4 mutation carrier group and the non-carrier group, adjusting for two potential confounders, namely, gender and education.

To select the best transformation, we vary α in $H(\cdot)$ from 0 to 4, and choose the optimal model that gives the largest likelihood function. The optimal value of α is 2 (see Figure 3), the variance calculated using the negative inverse of the curvature of the log-profile-likelihood function at

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Table 4: Estimated log hazard ratios and variance components from combined data on probands and relatives in the WHICAP study

Parameters	Estimate	Standard error	p-value
APOE-ε4	0.930	0.193	< 0.0001
gender	0.009	0.180	0.961
education	-0.687	0.091	< 0.0001
σ_b^2	0.132	0.152	0.383
σ_r^2	0.224	0.197	0.254

the estimated α is 0.249, and the 95% confidence interval is $[1.02, 2.98]$. The results based on the transformation model with $\alpha = 2$ are presented in Table 4. From the table, the estimated log hazard ratio for the APOE-ε4 is 0.930, with $p < 0.0001$, indicating a significantly higher risk of dementia occurring in the APOE-ε4 carrier group. Gender is not statistically significant in either analysis. The table also shows that a lower level of education significantly increases the risk of dementia.

In Table 5, we report the estimated cumulative distribution functions for the carrier and non-carrier groups, with other covariates fixed at the sample mean level. Furthermore, to demonstrate the usefulness of the family history data on relatives, we also report the estimates from the best transformation using the proband data only, in which no random effects are used and the best transformation is $\alpha = 0.6$. Interestingly, for the carrier group, both analyses give similar results. However, in the non-carrier

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Table 5: Estimated cumulative risk of dementia ($\times 10^{-2}$) from combined data on probands and relatives in the WHICAP study

	Proband and relative data						Proband data only					
	Carrier			Non-Carrier			Carrier			Non-Carrier		
Age	Est.	SE	95% CI	Est.	SE	95% CI	Est.	SE	95% CI	Est.	SE	95% CI
70	0.32	0.14	(0.14, 0.75)	0.13	0.05	(0.05, 0.29)	0.22	0.13	(0.07, 0.70)	0.11	0.07	(0.04, 0.36)
75	1.47	0.37	(0.90, 2.39)	0.58	0.14	(0.36, 0.93)	1.13	0.33	(0.64, 1.98)	0.59	0.17	(0.34, 1.02)
80	6.54	1.13	(4.61, 9.24)	2.63	0.41	(1.94, 3.57)	6.86	1.11	(4.98, 9.41)	3.64	0.53	(2.72, 4.84)
85	15.93	2.37	(11.66, 21.57)	6.62	0.83	(5.15, 8.48)	16.07	2.24	(12.19, 21.03)	8.73	1.05	(6.89, 11.03)
90	32.31	4.20	(24.07, 42.48)	14.26	1.59	(11.33, 17.87)	32.57	4.12	(25.24, 41.37)	18.58	2.03	(14.96, 22.95)

group, using both proband and family data gives slightly lower estimates for the cumulative risk of dementia, with smaller variability (also see Figure 4). This analysis demonstrates the efficiency gain of including family history data on relatives.

6. Discussion

In this study, we examined a class of transformation models with multilevel random effects for the correlated disease AAO. The proposed method incorporated multilevel random effects to explain polygenic heterogeneity and a shared family environment and accounted for missing genotype information on family relatives. The NPMLE has been shown to perform well in small sample. Our application shows that using family history data can increase the accuracy of estimating the risk of disease in a non-carrier group. It can be conjectured that adding family history data leads to improved

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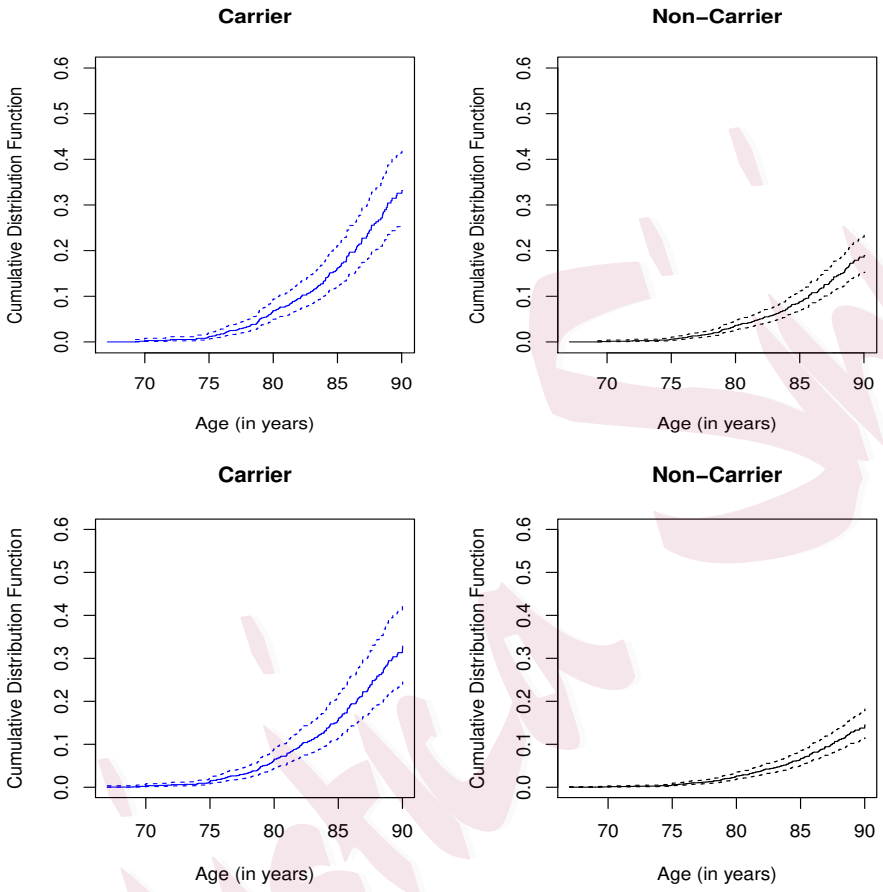

Figure 4: Estimated cumulative risk of dementia for APOE$-\varepsilon 4$ carriers and non-carriers: the top two plots are estimates from proband data only, and the bottom two use both proband and relative data.

power to detect genetic associations in genome-wide association studies.

Although the proposed model is described for time-invariant covariates, it can be easily generalized to incorporate time-varying covariates, where

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model (2.1) becomes

$$\begin{aligned}&\Lambda_{ij}(t|G_{ij}, X_{ij}(s), b_i, r_{ij}; s \le t)\\ =\ & H\left\{\int_0^t I(s \le T_{ij}) \exp(\beta G_{ij} + \gamma^T X_{ij}(s) + b_i + r_{ij})\, d\Lambda(s)\right\}. \qquad (6.1)\end{aligned}$$

The approaches dealing with time-varying covariates in (Zeng and Lin, 2007) can be adapted to make inferences for model (6.1). However, if b_i or r_{ij} is also time-varying, the estimation would become more complicated. Currently, there is a lack of efficient methods for handling such scenarios.

When the family size is large, a computational challenge is how to handle multi-dimensional integrals in the proposed method, because the dimension of the quadratures in the EM algorithm increases as the family size increases. One alternative is to sample a manageable number of family members from large families. The proposed method can then be applied to this subset of the data. This process can be repeated multiple times. Then, a proper combination of the results, after accounting for sampling weights and data overlapping, can be used to obtain the final estimates. Moreover, using data on relatives should always improve efficiency, in theory, but with a large σ_b^2, the efficiency gain may not be significant. Thus, we also recommend randomly selecting a small pedigree from each family for analysis, which greatly reduces the computation cost, without much of an efficiency loss.

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In some cases, data on disease prevalence in the non-carrier group are available on the entire population (e.g., age-specific population risk of dementia). This information can be used to further increase the efficiency and numeric stability of analyses of familial data. In future work, we will calibrate the parameter estimation and prediction using information available on the population.

Supplementary Material

Proofs of Theorem 1 and Theorem 2 and additional simulation studies mimicking the real data are presented in the supplemental file. The simulations show an adequate performance of selecting transformation parameter based on the profile likelihood method and little efficiency loss of our method as compared to the standard frailty model when true $\sigma_r^2 = 0$.

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