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Relative mortality for correlated lifetime data

James X. Song[a,*], James T. Wassell[b], Asha Kapadia[c]

[a] *Department of Biometry, Bayer Pharmaceuticals Corporation, 400 Morgan Lane, West Haven, CT 06516, USA*

[b] *Division of Safety Research, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, 1095 Willowdale, Morgantown, WV 26505, USA*

[c] *UT-Houston School of Public Health, 1200 Herman Pressler, Houston, TX 77030, USA*

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Abstract

Comparing correlated lifetimes for a group of individuals to a standard reference population may require variance adjustment of marginal model estimates or the use of conditional random effects models with shared frailty. We present the cumulative relative mortality, the marginal model robust variance estimator and the frailty models in estimating relative mortality for individuals who have correlated lifetimes due to group clustering. The positive stable and gamma frailty distributions are considered in the frailty models. The performances of both marginal and frailty models are compared using simulation. Applying these methods, we show siblings for centenarians had longer life spans than their US cohort reference population.
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Keywords: Correlated survival data; Cumulative relative mortality; Marginal survival model; Frailty model; Robust variance estimator; Taylor linearization

1. Introduction

In clinical and epidemiological research, investigators often want to compare the survival experience of a specific group of individuals who may have certain survival advantages (e.g. siblings of long-lived individuals) or risks (e.g. in a state of chronic disease remission) with the survival of a standard or reference population. In this setting, the hazard rate for the ith individual can be written as $h_i(t) = h_{0i}(t)b(t)$, where

* Corresponding author. Tel.: +1-203-812-3478; fax: +1-203-812-2953.
E-mail address: james.song.b@bayer.com (J.X. Song).

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$h_{0i}(t)$ is the reference hazard. The relative mortality is $b(t)$, which describes the relationship of the study group to the reference population. $b(t)=1$ indicates that individuals in the study group experience death at the same rate as the reference population, and $b(t)>1$ [$b(t)<1$] indicates a higher (or lower) mortality rate than the reference population. The cumulative relative mortality, $B(t)=\int_0^t b(t)$, described by Klein and Moeschberger (1997), provides a graphic evaluation of the survival of the exposed group compared to the known standard survival curve.

To fit multiple risk factors or a risk factor with different exposure levels, $\log[b(t)]$ is expressed as a linear combination in a multiplicative model (Breslow et al., 1983) which takes the familiar form of Cox proportional hazard model with a time-dependent covariate (Cox, 1972).

$$h_i(t)=h_{0i}(t)\exp[\beta X_i(t)], \tag{1}$$

where $X_i(t)$ is the covariate vector of ith individual at follow-up time, t, and β is the vector of regression coefficients. Departures from the standard or actuarial estimates of the hazard, $h_{0i}(t)$, which may be age, race and sex-specific (consistent with the ith individual characteristics), are described by the multiplicative factor $\exp[\beta X_i(t)]$ which can be interpreted as relative mortality. Note, when $X_i(t)=1$, (1) can be further reduced to $h_i(t)=h_{0i}(t)b$, where b is a constant relative mortality over time. In this special case, b is equivalent to the standardized mortality ratio that is a widely used measure of risk in epidemiological studies (Breslow and Day, 1985). In the remaining discussion, the general form, $\exp[\beta X_i(t)]$, is retained to include the option for covariates in certain applications. For example, a covariate might be used to test if relative mortality differs between groups of subjects with different occupational exposures. Note that in contrast to using $h_{0i}(t)$ to represent the reference population hazard, Andersen et al. (1999) introduce the log hazard of the standard or reference population as a time-dependent offset term in a Cox proportional hazard model.

The multiplicative models of relative mortality have been studied previously. Muirhead and Darby (1987) investigated radiation-induced cancers; Andersen and Vaeth (1989) considered both multiplicative and additive hazard models to evaluate post-surgery survival for malignant melanoma patients; Keiding et al. (1990) investigated excess mortality of the unemployed Danish males using Poisson regression. Andersen et al. (1999) investigated relative mortality for bone marrow transplant patients. Their model allows for different relative mortality rates depending on the risk factors the patient may have. However, estimation of relative mortality for correlated lifetimes (possibly the result of shared genetic or environmental factors) requires additional considerations.

This study investigated the mortality experience of the 184 siblings of 42 centenarians in the United States to determine if they experienced longevity in excess of vital statistics hazard estimates from the US 1900 birth cohort. In this application, we assume the lifetimes of the siblings are correlated as the result of shared genetic and environmental factors and estimate relative mortality. Andersen et al. (1993) investigated the heritability of life length and the association between the lifetimes of adoptees and their parents using the Danish adoption registry data through frailty models, but did not estimate relative mortality.

First, we describe an adjusted variance estimator of the cumulative relative mortality, $B(t)$, using Taylor linearization to account for the correlation among the siblings. Next, we consider the marginal model approach (Wei et al., 1989; Liang and Zeger, 1993; Cai and Prentice, 1995) in which the unadjusted regression coefficients remain consistent under the correlation and have the population average interpretation. A robust variance estimator is needed to replace the standard variance estimator in the independence model. The frailty model approach (Clayton, 1978; Vaupel et al., 1979; Oakes, 1989) provides for correlation among the life times of siblings as the result of a shared common random effect or frailty. The frailty model estimates relative mortality and within-cluster correlation simultaneously and the interpretation of the regression coefficients is conditional on the frailty. The two most often used frailty distributions, the unit gamma (Klein, 1992; Nielsen et al., 1992) and the positive stable (Hougaard, 1986a, b) are used to estimate the relative mortality. Finally, a simulation study is performed to compare the bias and standard error of estimates obtained from the models discussed.

2. Relative mortality estimation

2.1. Cumulative relative mortality

Let M denote the number of groups (or families) and let N_m denote the number of individuals in the mth group for which possibly censored event times (age at death or oldest surviving age) are observed. Let $t_1 < t_2 < \cdots < t_G$ be the ordered event times where G is the number of distinct event times. Define variables $c_{mk}(t_i)$ as one if individual k from group m has an event at time t_i, zero otherwise; $u_{mk}(t_i)$ is one if individual k from group m is at risk at time t_i, zero otherwise. Then, at time t_i, the number of events $d_i = \sum_{m=1}^{M} \sum_{k=1}^{N_m} c_{mk}(t_i)$; and the number of individuals at risk $n_i = \sum_{m=1}^{M} \sum_{k=1}^{N_m} u_{mk}(t_i)$. The estimator of cumulative relative mortality is

$$\hat{B}(t_j) = \sum_{i=1}^{j} \frac{d_i}{n_i h_{0i}} = \sum_{i=1}^{j} \frac{1}{h_{0i}} q_i$$

and its variance estimate is

$$\mathrm{Var}[\hat{B}(t_j)] = \sum_{i=1}^{j} \frac{d_i}{(n_i h_{0i})^2},$$

where $q_i = d_i/n_i$. The variance estimator underestimates the variance of $\hat{B}(t_j)$ when the event times within group are positively correlated. Using Taylor series approximation to obtain the unbiased variance estimator of $\hat{B}(t_j)$, Woodruff (1971) proposed a simple method that does not require estimation of the variance–covariance matrix. He demonstrated, through Taylor series, that for a given function $\hat{\theta} = F(X, Y)$, where $X = \sum_{i=1}^{n} x_i$ and $Y = \sum_{i=1}^{n} y_i$, the variance of $\hat{\theta}$ is equivalent to the variance of $Z = (\partial F_x)X + (\partial F_y)Y$. Since Z is obtained from Taylor series linearization, it is called the linearized value. We apply this formulation to the cumulative relative mortality function, $\hat{B}(t_j)$. First, the

linearized value for q_i is derived as $Z_{mk}(q_i)=(c_{mk}(t_i)-q_i u_{mk}(t_i))/n_i$, then the linearized value for $\hat{B}(t_j)$ is

$$Z_{mk}[\hat{B}(t_j)] = -\sum_{i=1}^{j} \frac{1}{h_{0i}} Z_{mk}(q_i)$$

$$= -\sum_{i=1}^{j} \frac{1}{h_{0i}} \left[\frac{c_{mk}(t_i) - q_i u_{mk}(t_i)}{n_i}\right]. \tag{2}$$

Following the practice of Donner and Hauck (1988) and Bieler and Williams (1995) in cluster data analysis, the between-group variance estimator is applied to the linearized values to estimate the variance of $\hat{B}(t_j)$

$$\mathrm{var}_{\mathrm{adj}}[\hat{B}(t_j)] = M \sum_{m=1}^{M} \{Z_m[\hat{B}(t_j)] - \bar{Z}[\hat{B}(t_j)]\}^2/(M-1), \tag{3}$$

where $Z_m[\hat{B}(t_j)]=\sum_{k=1}^{N_m} Z_{mk}[\hat{B}(t_j)]$ and $\bar{Z}[\hat{B}(t_j)]=\sum_{m=1}^{M} Z_m[\hat{B}(t_j)]/M$. Since the groups are independent sampling units in this case, the between-group variance estimator is unbiased even though the within-group correlation exists.

The statistic $\hat{B}(t_j)$ has a large sample normal distribution so that confidence intervals for the cumulative relative mortality can be constructed. Using $\hat{B}(t_j)$ and $\mathrm{var}_{\mathrm{adj}}[\hat{B}(t_j)]$, we can test the null hypothesis that the mortality rate for the study population is the same as in the standard population over the interval $[0, t_j]$. Under the null hypothesis, the test statistic is $T(t_j) = [\hat{B}(t_j) - t_j]/\sqrt{(\mathrm{var}_{\mathrm{adj}}[\hat{B}(t_j)])}$, which has a large sample standard normal distribution. When $Z_{1-\alpha/2} > T(t_j) > Z_{\alpha/2}$ we accept the null hypothesis that the mortality rates are equal over the interval $[0, t_j]$.

2.2. Marginal model robust variance estimation

The marginal model methods developed by Wei et al. (1989) for the Cox proportional hazards model are useful in estimation of the relative mortality based on the multiplicative model (1), whose log likelihood function is as follows:

$$L(\beta) = \sum_{i=1}^{N} \left[d_i \beta X_i(t_i) - \int_0^{t_i} \exp\{\beta X_i(t_i)\} h_{0i}(t)\, \mathrm{d}t\right]. \tag{4}$$

Huber (1967) showed that for a maximum likelihood estimate based on any distribution f, if the data in fact follow distribution g, then, under appropriate conditions, $\hat{\beta}$ is asymptotically normal with mean β and covariance $V = ABA'$, where $A = (\partial EU(\beta)/\partial\beta)^{-1}$ and B is the covariance matrix of U (U is the matrix of score residuals, $U = \sum u_i(\beta) = \sum \partial f/\partial\beta$). If the observations are independent, B can be estimated as

$$\hat{B}_I = \sum_{i=1}^{N} u_i'(\hat{\beta}) u_i(\hat{\beta}) = U'U, \tag{5}$$

where $u_i(\hat{\beta})$ is the ith row of U. For the current multiplicative model, $u_i(\beta)$ is obtained by taking the first derivative of log likelihood (4) and A is estimated by the inverse of the observed information matrix of (4). If the data are clustered, B is based on group collapsed value: $u_m(\beta)$, where $u_m(\beta) = \sum_{i \subset m} u_i(\beta)$ is the sum of rows in $u(\beta)$ for individuals in the mth group

$$\hat{B}_C = \sum_{m=1}^{M} u'_m(\beta) u_m(\beta) = \tilde{U}' \tilde{U}. \tag{6}$$

Therefore, a robust variance estimate of β in the multiplicative model for correlated event times is obtained as AB_cA'. For a generalized linear model, AB_cA' is the working independence estimate of variance proposed by Liang and Zeger (1986) for generalized estimating equation (GEE) models. Similar to the GEE models, the asymptotic results for the robust variance estimator require that the number of groups tends to infinity. As an alternative, the group jackknife (Lipsitz and Parzen, 1996) could be adapted for relative mortality variance estimation.

2.3. Frailty models

Consider that we have data on N individuals in M groups with N_m individuals in the mth group. Individuals within the mth group have dependent survival times due to some unobserved covariate information summarized in a frailty, W_m. It is assumed that, conditional on the frailty W_m, the event times are mutually independent and their conditional distributions have hazard functions $h(t_{mk})$ which satisfy the following relationship:

$$h(t_{mk}|X_{mk}, W_m) = W_m h_0(t_{mk}) \exp(\beta X_{mk}), \tag{7}$$

where X_{mk} is a vector of observed covariates associated with the kth individual in the mth group; and β is a vector of unknown regression coefficients describing the effect of X_{mk} (or, under the simplification described earlier, $b = \exp(\beta X_{mk})$, to estimate the relative mortality). $h_0(t_{mk})$ denotes the baseline hazard rate, which is known from the reference population. Note that, when $W_m = 1$ for all m, the frailty model reduces to the usual multiplicative model (1) for independent data. Distributional assumptions of W_m are made to further develop the model.

2.3.1. Positive stable frailty model

As in Hougaard (1986a, b), the random effects W_m's are assumed independent and identically distributed positive stable variates with parameter ρ (Qiou et al., 1999). Small ρ reflects greater heterogeneity between groups and thus a stronger association among individuals within a group. The strength of association between two individuals, measured by Kendall's τ, is $(1 - \rho)$, with $\rho = 1$ corresponding to $W_m = 1$, that is independence within groups. The marginal distribution of T_{mk} in (7) is given by

$$P(T_{mk} > t) = E[P(T_{mk} > t|W)] = \exp\{-[H_0(t_{mk}) \exp(\beta X_{mk})]^{\rho}\}, \tag{8}$$

where $H_0(t_{mk}) = [\Lambda_0(t_{mk})]^{1/\rho}$ is the conditional cumulative baseline hazard of individual k in the mth group and $\Lambda_0(t_{mk})$ is the marginal cumulative baseline hazard

in the reference population. The conditional baseline hazard is obtained as $h_0(t_{mk}) = H_0(t_{mk}+1) - H_0(t_{mk})$. The log likelihood is obtained using these derived values (see Appendix A).

2.3.2. Gamma frailty model

Consider now the random effect W_m's having a gamma distribution with mean of one and variance of θ. Large values of θ reflect greater heterogeneity between groups and stronger association among individuals within a group. The association between individuals in a group, measured by Kendall's τ, is $\theta/(\theta+2)$. When $\theta = 0$, the W_m's are equal to one, leading to independence among individual event times within groups. The marginal survival function for the kth individual in the mth group is

$$P(T_{mk} > t) = [1 + \theta H_0(t_{mk}) \exp(\beta X_{mk})]^{-1/\theta}, \tag{9}$$

where $H_0(t_{mk}) = \{\exp[\Lambda_0(t_{mk})\theta] - 1\}/\theta$. The log likelihood function of θ and β is shown in Appendix B.

In both positive stable and gamma frailty models, as $h_0(t_{mk})$ and $H_0(t_{mk})$ can be calculated from the known marginal hazard and cumulative hazard, maximum likelihood estimates of the parameters are available by directly maximizing the log likelihood functions in the Appendix. Estimates of the variance of the parameter estimates are obtained by inverting the information matrix. As a simple alternative, the group jackknife resampling technique can be implemented to calculate the empirical variability of the parameter estimates.

3. An example

We apply these methods to determine if the life span of individuals with long-living siblings exceeds that of their contemporaries. The data include 184 siblings (alive or dead) of 42 centenarians who were born around 1900. The average number of siblings for the centenarians is 4.4, ranging from 1 to 11 per family. Only ages of siblings are included in the current study since other reliable demographic informations were not obtained for all 184 siblings. Siblings of centenarians may have longer life spans, compared to their contemporaries, because of shared genes and a common early environment. We also hypothesize that there is a significant positive within-family correlation. Standard US mortality data which have been published every 10 years since 1900 (Faber and Wade, 1983) were used to compile an annual 1900 birth cohort life table as the reference to estimate the baseline hazard.

3.1. Cumulative relative mortality

The 95% confidence intervals of the cumulative relative mortality estimate, $\hat{B}(t)$, based on adjusted and unadjusted standard errors are shown in Fig. 1. It appears that the confidence bands generally are wider after adjustment for correlation when t is approximately above 50. When t is below 50 the unadjusted errors are generally greater than the adjusted errors indicating no positive correlation among siblings

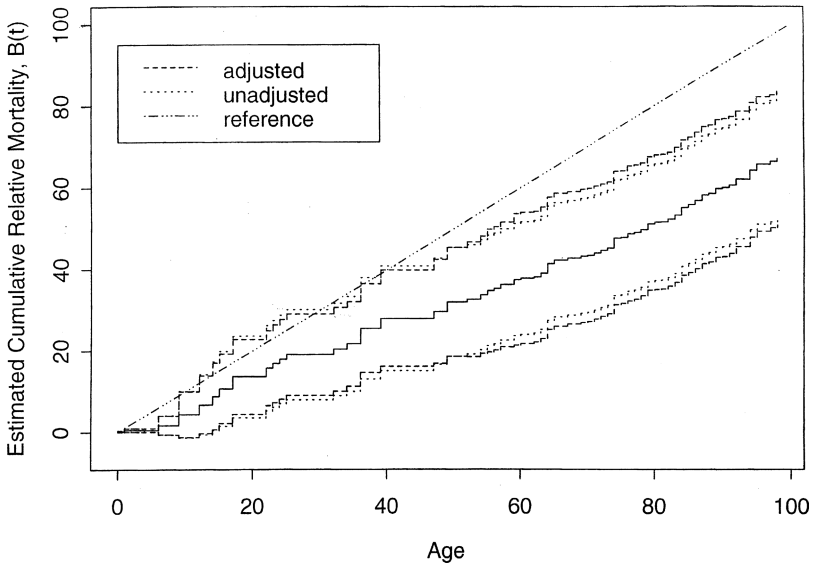

Fig. 1.

exists. A Wilcoxon signed rank test was used to test for any differences of the adjusted and unadjusted variance estimates at 58 different ages where a death of the siblings was observed. The null hypothesis of equivalence between the adjusted and unadjusted variance estimates cannot be rejected ($p=0.78$), indicating the within-family correlation is small, if it exists. The upper confidence intervals from both the adjusted and unadjusted methods are below the reference line $[b(t) = 1]$ for most of the ages. The slope of $\hat{B}(t)$ in Fig. 1, is a crude estimator of the relative risk function $b(t)$, and implies the hazard of the siblings is about 0.667 of the baseline standard hazard illustrating that siblings of centenarians lived longer than their contemporary counterparts. As $\hat{B}(t)$ generally follows a straight line in Fig. 1, the constant relative mortality assumption seems reasonable. Alternatively, parallel plots of the log–log survival can verify the constant relative mortality assumption for siblings and the baseline reference (not shown). Since the oldest sibling died at age 98, following the discussion in Section 2.1, we test the null hypothesis that the mortality rates of the siblings are equal to the baseline standard hazards over the interval [0, 98]. From Fig. 1, we observe $\hat{B}(t=98)=65.4$ with standard error of 7.8. As suggested in Section 2.1, we can calculate $T(98)=(65.4-98)/7.8=-4.18<-1.96$. Therefore, we reject the null hypothesis and conclude that the siblings had a lower cumulative mortality rate as compared to their contemporary counterparts.

3.2. Robust variance estimator

The first and second derivatives of log likelihood in Eq. (4) were computed. The resulting β and its robust variance estimator are $\hat{\beta} = -0.4056$, $\mathrm{Var}_R(\hat{\beta}) = 0.0039$ and

Table 1
Relative mortality analysis under the positive stable and the gamma frailty models

Effect	Positive stable			Gamma		
	Value	SE	p-value	Value	SE	p-value
Frailty distribution	0.7513	0.0771[a]	0[a]	0.3047	0.1393[a]	0.029[a]
Parameter		0.0357[b]	0[b]		0.1003[b]	0.002[b]
Relative mortality	−0.4139	0.0898[a]	0[a]	−0.6159	0.1413[a]	0.00001[a]
Parameter (β)		0.1322[b]	0.002[b]		0.1493[b]	0.00004[b]
Kendall's τ	0.2487			0.1322		
Full log likelihood	−788.41			−791.50		
LRT[c] ($\tau = 0$)	$\chi^2(1) = 13.64^{***}$			$\chi^2(1) = 7.46^{**}$		
LRT[d] ($b = 1$)	$\chi^2(1) = 15.88^{***}$			$\chi^2(1) = 23.35^{***}$		

[a]Standard error using jackknife method.
[b]Standard error using information matrix.
[c]Log likelihood ratio test of no correlation when log likelihood under the independent model is −795.23.
[d]Log likelihood ratio test of no group effect when log likelihood for the model of $\beta = 0$ is −796.35 under the positive stable frailty and −803.18 under the gamma frailty.
** $p < 0.01$.
*** $p < 0.001$.

Wald's statistic is $\chi^2(1) = 41.80$, $p < 0.0001$. Assuming independent observations, the variance estimate of β is $\mathrm{Var}_I(\hat{\beta}) = 0.0033$ and Wald's statistic is $\chi^2(1) = 49.57$, $p < 0.0001$. When positive correlation exists, the variance estimates under the independent model underestimate the true variance. Nevertheless, significant group effects are found in both models.

3.3. Frailty model

Maximization of log likelihood was carried out using a S-PLUS (1997) optimization function *nlminb*, which follows a quasi-Newton method to approximate curvature. The standard errors were computed using the jackknife method and the inverse of the information matrix. Both Wald's tests and log likelihood ratio tests indicate that β and ρ (or θ) are significant in the positive stable and the gamma frailty models (Table 1).

The coefficient estimates ($\hat{\beta}$) in Table 1 represent the log relative risk of siblings of centenarians compared to individuals in the reference population with identical frailties. Relative mortality of the siblings is better explained in terms of the marginal hazard. For the positive stable frailty model, the relative mortality estimate is $\exp[\rho\beta X_i(t)] = 0.73$ (73% of the baseline reference cohort hazard, i.e. significantly lower mortality than the reference population). For the gamma frailty model, the relative mortality risk for the siblings of long-lived individuals can be evaluated from the marginal hazards:

$$R(t) = \exp(\beta)\exp[\Lambda_0(t)\theta]/\{1 + \exp(\beta)\{\exp[\Lambda_0(t)\theta] - 1\}\}. \quad (10)$$

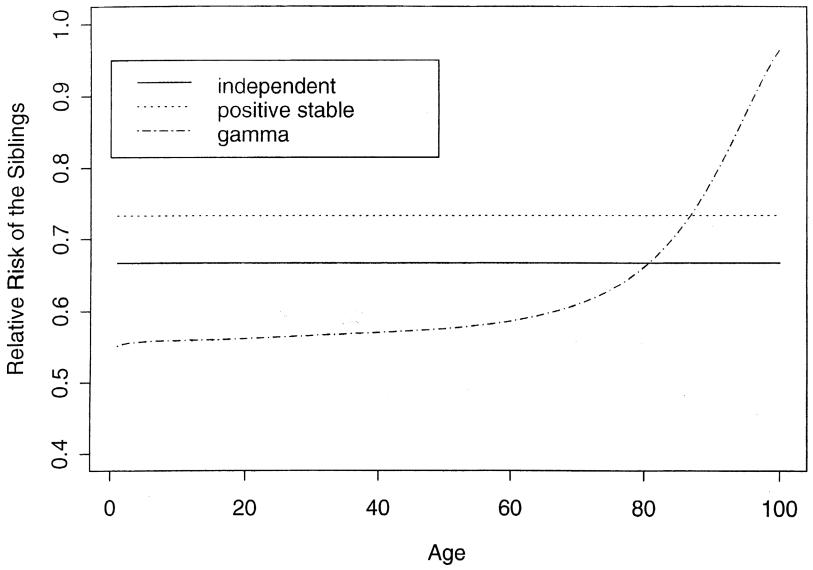

Fig. 2.

Fig. 2 shows the relative risks under the positive stable and the gamma frailty models. In contrast to the constant relative risk under the positive stable model, the relative risk under the gamma model is dependent on the age of sibling, increasing towards one as age increases.

Table 1 displays the log likelihood of both positive stable and gamma frailty models. Akaike's information for the positive stable frailty model (1572.82) is smaller than the gamma frailty model (1579.00), indicating a better fit of the data. The standard deviations for the parameters are also smaller in the positive stable frailty model. In theory, since siblings share their early environment, a positive stable frailty model that implies higher early dependence seems more appropriate.

The results from all the above models indicate that the siblings of centenarians lived longer than their contemporary counterparts. The fixed effect estimates are consistent between marginal model with robust variance estimates and positive stable frailty model. However, the fixed effect estimate, $\hat{\beta}$, in the gamma frailty model is smaller indicating greater group effect and its standard deviation is larger than those in the marginal models and positive stable frailty model. The difference might be caused by the lack of robustness of the gamma frailty model to the underlying true frailty distribution. Not specifically designed to test within family correlation, neither Fig. 1 of the cumulative relative mortality estimate nor the marginal models indicate the existence of a consistent positive correlation among siblings. On contrary, the random estimate is significant in both frailty models. In general, the correlation in the lifetimes of the siblings is small. The effect of adjusting for correlation is also small in the example.

4. Simulations

A simulation was carried out using a range of parameter values consistent with our application of frailty models. The hazards of the 1900 US cohort was chosen as the baseline marginal hazard to simulate data from the conditional hazard, $h_0(t)$. The clustered survival times were generated by the inverse method $t_{mk} = S^{-1}(U)$ for $U \sim \text{Uniform}(0,1)$ and $S(t) = \exp\{-\int_0^{t_{mk}} W_m h_0(u) e^{\beta}\, du\}$. The random variable W_m follows a positive stable distribution with parameter ρ and was generated following the method described in Chambers et al. (1976) (Table 3). Alternatively, W_m was generated from a gamma distribution with mean one and variance θ (Table 4). The censored times, generated from a uniform distribution, resulted in 10% censored observation. One thousand datasets were generated for each parameter combination. Each dataset includes 100 clusters with a cluster size of 4. The values of random parameter were chosen so that Kendall's τ is $(0, 0.1, 0.33)$, reflecting independence, small and medium group correlation. The values of the parameter β were fixed at $(0, -0.2, -0.5)$, reflecting that hazards of the simulated survival time are approximately equal to the hazards of 1900 US cohort, 10% reduction, or 39% reduction, respectively, of the 1900 US hazards.

Table 2 summarizes the results of fitting both frailty and marginal models to the 1000 datasets. The fixed parameter estimates in all models are close to the target values and the coverage of the 95% confidence interval is very reasonable, suggesting that inferences based on these models are consistent. The marginal models tend to

Table 2
Observed bias, standard deviation and 95% coverage proportions of $\hat{\rho}$ (or $\hat{\theta}$) and $\hat{\beta}$ under the positive stable and gamma frailty models, marginal models with independent and robust variance estimators using simulation for specified values of β when data are independent ($\tau = 0$)

	β	$\hat{\rho}$			$\hat{\beta}$		
		Bias	STD	CP	Bias	STD	CP
Positive stable	0	−0.002	0.005	95	−0.027	0.031	92
	−0.2	−0.003	0.005	94	−0.032	0.027	94
	−0.5	−0.003	0.005	95	−0.008	0.018	97
Gamma	0	0.006	0.005	94	−0.025	0.034	92
	−0.2	0.009	0.009	91	−0.035	0.027	91
	−0.5	0.015	0.015	90	−0.033	0.023	92
Independent model	0				−0.001	0.003	94
	−0.2				−0.002	0.003	93
	−0.5				−0.002	0.002	93
Robust variance model	0				−0.001	0.004	95
	−0.2				−0.002	0.003	93
	−0.5				−0.002	0.003	93

Table 3
Observed bias, standard deviations and 95% coverage proportions of $\hat{\rho}$ (or $\hat{\theta}$) and $\hat{\beta}$ under the positive stable and gamma frailty models and marginal models with independent and robust variance estimators using simulation for specified values of τ and β when the frailty is generated by a positive stable distribution

	τ	ρ (or θ)	β	$\hat{\rho}$			$\hat{\beta}$		
				Bias	STD	CP	Bias	STD	CP
Positive stable	0.1	0.9	0	0.022	0.031	86	−0.028	0.032	93
			−0.2	0.019	0.025	90	−0.031	0.028	92
			−0.5	0.011	0.023	92	0.008	0.025	95
	0.33	0.67	0	0.028	0.032	84	−0.045	0.061	93
			−0.2	0.027	0.034	85	−0.035	0.077	96
			−0.5	0.021	0.031	85	0.014	0.072	96
Gamma	0.1	0.22	0	−0.057	0.053	80	−0.061	0.068	86
			−0.2	−0.062	0.079	78	−0.058	0.071	87
			−0.5	−0.071	0.081	83	−0.064	0.057	84
	0.33	1	0	−0.073	0.071	75	−0.112	0.104	83
			−0.2	−0.091	0.074	73	−0.129	0.113	81
			−0.5	−0.110	0.081	70	−0.131	0.107	80
Independent model	0.1		0				−0.028	0.022	86
			−0.2				−0.029	0.019	84
			−0.5				0.021	0.020	86
	0.33		0				−0.043	0.025	75
			−0.2				−0.033	0.024	78
			−0.5				0.035	0.025	75
Robust variance model	0.1		0				−0.028	0.023	90
			−0.2				−0.029	0.022	88
			−0.5				0.021	0.035	85
	0.33		0				−0.043	0.030	85
			−0.2				−0.033	0.041	86
			−0.5				0.035	0.055	84

have smaller biases and standard errors as compared to the frailty models. The random parameter estimates in the frailty models have good performances as well.

Table 3 shows the results when the frailty is generated by a positive stable distribution. The independent marginal model underestimates the standard deviation of the fixed parameter. Therefore, its coverage proportions are low. The results show the importance of adjusting for the intracluster correlation when it exists. The positive stable model generally has the best performance in terms of bias, standard deviation and coverage proportions. Its advantages over the gamma frailty model and the independent marginal model increase when the correlation is moderate ($\tau = 0.33$). The marginal model with robust variance estimator has adjusted standard deviations. Its parameter coverage proportions are reasonable. It is noted that the marginal models generally have smaller fixed parameter estimates (absolute value) and smaller standard deviations than

Table 4
Observed bias, standard deviations and 95% coverage proportions of $\hat{\rho}$ (or $\hat{\theta}$) and $\hat{\beta}$ under the positive stable and gamma frailty models and marginal models with independent and robust variance estimators using simulation for specified values of τ and β when the frailty is generated by a gamma distribution

	τ	ρ (or θ)	β	$\hat{\rho}$			$\hat{\beta}$		
				Bias	STD	CP	Bias	STD	CP
Positive stable	0.1	0.9	0	0.027	0.033	88	−0.040	0.041	90
			−0.2	0.033	0.028	84	−0.033	0.045	92
			−0.5	0.022	0.027	88	−0.025	0.053	93
	0.33	0.67	0	0.035	0.038	83	−0.046	0.051	91
			−0.2	0.037	0.036	80	−0.052	0.053	87
			−0.5	0.034	0.033	82	−0.052	0.060	89
Gamma	0.1	0.22	0	−0.031	0.035	88	−0.041	0.055	91
			−0.2	−0.035	0.032	87	−0.028	0.056	94
			−0.5	−0.027	0.029	89	−0.021	0.052	92
	0.33	1	0	−0.048	0.051	86	−0.042	0.052	94
			−0.2	−0.053	0.052	84	−0.053	0.064	91
			−0.5	−0.051	0.048	83	−0.047	0.058	90
Independent model	0.1		0				−0.039	0.037	87
			−0.2				−0.033	0.031	84
			−0.5				0.045	0.038	84
	0.33		0				−0.045	0.032	79
			−0.2				−0.049	0.028	76
			−0.5				−0.044	0.023	74
Robust variance model	0.1		0				−0.039	0.041	91
			−0.2				−0.033	0.035	89
			−0.5				0.045	0.042	89
	0.33		0				−0.045	0.047	88
			−0.2				−0.049	0.042	86
			−0.5				−0.044	0.038	85

the frailty models. Most models have negative biases in parameter estimation. The biases in the gamma model are especially large when $\tau = 0.33$.

To examine the impact of the underlying true frailty distribution on the chosen frailty model, the simulation in Table 3 is repeated by using the data generated by a gamma frailty. The results are summarized in Table 4. The gamma frailty model has better performance as compared to Table 3. The coverage proportions for both fixed and random estimators in the positive stable model are lowered slightly. In general, both positive stable and gamma frailty models give satisfactory coverage proportions. The marginal model with robust variance estimator shows smaller absolute parameter estimates and reasonable parameter coverages as has been shown in Table 3.

The results from this simulation study emphasize the importance of adjusting for the intracluster correlation when analyzing clustered data. The results suggest that both

positive stable and gamma frailty models perform well when the correlation is small. However, when the correlation is moderate, the performances of the gamma frailty model largely depend on the true underlying frailty distribution. Overall, the positive stable frailty model is more robust than the gamma frailty model. The marginal model with robust variance estimate shows good performances. It should be considered when the correlation is not the main interest of the study.

5. Discussion

We present several methods of estimating relative mortality for correlated survival times based on marginal models and frailty models. The cumulative relative mortality provides an effective graphic evaluation and does not assume a constant relative mortality. Taylor linearization is used to derive the adjusted variance estimator for the cumulative relative mortality under correlation. A simulation study by Carr and Portier (1993) shows that the variance estimate using Taylor linearization is consistent when the number of groups is large.

While the conditional constant relative risk assumption has to be made in the robust variance estimator and frailty model, both approaches can fit other risk factors besides sibling group effect. They can be easily extended to model data under stratification given stratified external baseline hazards are provided. Due to the limited data on other risk factors in the sibling data, only constant relative mortality risk ratios are obtained in the example. The robust variance estimator approach is equivalent to the method described in Wei et al. (1989) in a Cox regression where the baseline hazards are unknown. The implementation of the method is simple and does not require distributional assumptions. It is particularly useful when the main interest is the regression coefficients rather than the correlation within cluster.

The frailty model that assumes positive stable or gamma frailty distribution is used to estimate relative risk of individuals in the exposed group. Although the estimation is not as straightforward as in the marginal model, the frailty model can estimate the within-family correlation coefficient that is of interest in our study. A simulation study shows both positive stable and gamma frailty distribution models perform reasonably well when the correlation is small. But the positive stable frailty model is shown to be more robust to the true underlying frailty distribution in the data. The gamma frailty model describes high late dependence, whereas the positive stable frailty distribution implies high early dependence (Hougaard, 2000). Since the association between the lifetimes of the siblings induced by their exposure to the same environment at early times decreases as they leave their families, a positive stable distribution seems more appropriate. Akaike's information confirms a better fit of the sibling data using the positive stable frailty model. The positive stable frailty model preserves the proportional hazards effects of the covariates in both the marginal and conditional distributions, so it is more appropriate for regression models than gamma frailty.

The methods proposed in the paper can be applied to occupational, environmental, and community health studies where multiple events or injuries for a study subject are

observed or group clustering exists. The methods assume that the underlying mortality rates in Eq. (1) were known from a standard reference population or vital statistics. It is essential to use such an external standard in evaluation of relative risks under conditions such as the homogeneity of the study population, as we have seen in the sibling example. Future study is needed to develop the asymptotic theory, as well as diagnostic techniques for checking the model assumptions and identifying outliers and high-leverage observations.

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Appendix A. The log likelihood in the PS frailty model

In Hougaard (1986b), the log likelihood in the positive stable frailty model is as follows:

$$L(\rho,\beta)=\sum_{m=1}^{M} D_m[\ln(\rho)+(\rho-1)\ln(G_m)]-G_m^{\rho}+\ln[J(D_m,G_m)]$$
$$+\sum_{k=1}^{N_m} I_{mk}[\beta X_{mk}+\ln[h_0(t_{mk})]].$$

Let I_{mk} denote the censoring indicator, with $I_{mk}=1$ if an event occurs and $I_{mk}=0$ otherwise. $G_m=\sum_{k=1}^{N_m} H_0(t_{mk})\exp(\beta X_{mk})$, and $D_m=\sum_{k=1}^{N_m} I_{mk}$ is the observed number of events in the mth group. Define $J[q,s]=\sum_{j=0}^{q-1} C_{q,j}s^{-j\rho}$, $q=0,1,\ldots$; $s>0$. $C_{q,j}$ is a polynomial of degree j given recursively by

$$C_{q,0}=1;\quad C_{q,j}=C_{q-1,j}+C_{q-1,j-1}\{(q-1)/\rho-(q-j)\};$$
$$C_{q,q-1}=\rho^{1-q}\Gamma(q-\rho)/\Gamma(1-\rho).$$

Appendix B. The log likelihood in the gamma frailty model

In Klein (1992), the log likelihood in the gamma frailty model is as follows:

$$L(\theta,\beta)=\sum_{m=1}^{M}\left[D_m\ln(\theta)-\ln\Gamma\left(\frac{1}{\theta}\right)+\ln\Gamma\left(\frac{1}{\theta}+D_m\right)-\left(\frac{1}{\theta}+D_m\right)\right.$$
$$\left.\times\ln\left(1+\theta\sum_{k=1}^{N_m} H_0(t_{mk})\exp(\beta X_{mk})\right)\right]+\sum_{m=1}^{M} I_{mk}[\beta X_{mk}+\ln(h_0(t_{mk}))].$$

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