Alternative Models for the Heterogeneity of Mortality Risks Among the Aged

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To develop a model to estimate the degree of unobserved heterogeneity in morality risks in a population, it is necessary to specify two types of functions, one describing the age-specific rate of increase of mortality risks for individuals and the other describing the distribution of mortality risks across individuals. There has been considerable interest in the question of how sensitive the estimates of heterogeneity are to the choices of these functions. To explore this question, high-quality data were obtained from published Medicare mortality rates for the period 1968–1978 for analysis of total mortality among the aged. In addition, national vital statistics data for the period 1950–1977 were used to analyze adult lung cancer mortality. For these data, the estimates of structural parameters were less sensitive to reasonable choices of the heterogeneity distribution (gamma vs. inverse Gaussian) than to reasonable choices of the hazard rate function (Gompertz vs. Weibull).

KEY WORDS: Cohort mortality; Gompertz function; Weibull function; Gamma distribution; Inverse Gaussian distribution; Natural exponential family distributions; Medicare mortality rates; Lung cancer mortality; Survival analysis.

1. INTRODUCTION

The importance of representing the effects of unobserved population heterogeneity on estimates of transition probabilities in stochastic process models is well known. For example, the implications of heterogeneity for estimating transition rates in fertility processes were analyzed by Sheps and Menken (1973). Shepard and Zeckhauser (1977) showed that neglecting heterogeneity produces overestimates of the effects on life expectancy of a given medical improvement. Keyfitz and Littman (1979) illustrated the potential bias due to heterogeneity, using a life table model in which the heterogeneous population is represented as a discrete mixture of homogeneous subgroups. They showed that ignoring heterogeneity leads to an incorrect calculation of the expectation of life from known death rates except in the special case of fixed mortality patterns in a stationary population. A similar conclusion was reached by Vaupel, Manton, and Stallard (1979) using an infinite mixture model in which an unobserved nonnegative random variable termed *frailty* represents all individual differences in endowment for longevity.

Population heterogeneity implies a mixture problem that can be formulated as follows. Let $\{(X_i, Z_i), i = 1, 2, \ldots, n\}$ be a sequence of n iid bivariate random vectors with (X, Z) having the cdf $F(z)$ on Z and, conditionally on $Z = z$, $F(x \mid z)$ on X. Assume that $F(x \mid z)$ is absolutely continuous on $[0, \infty)$ and let $f(x \mid z)$ denote the corresponding conditional density. In our analysis of mortality, $X_i = x_i$ is the observed lifetime of the ith individual and Z_i is an unobserved random variable that is related to his or her longevity. Thus the marginal density $f(x)$ of X depends on $f(x \mid z)$ and $F(z)$ and is obtained as

$$f(x) = \int f(x \mid z)\, dF(z), \qquad x \geq 0. \tag{1.1}$$

Given that one can estimate $f(x)$ from the observed sequence $x_1, \ldots, x_n$, it is then relevant to ask whether one can also obtain unique estimates of $F(z)$ and $f(x \mid z)$ using (1.1).

Following Vaupel et al. (1979), we assume that Z is a nonnegative frailty variable that operates multiplicatively on the conditional hazard $f(x \mid Z = 1)/[1 - F(x \mid Z = 1)]$ and that $F(z)$ is absolutely continuous on $[0, \infty)$. Thus we need to consider the identifiability of the proportional hazard model (Cox 1972) in the context of an unobserved covariate. (Later we will modify the proportional hazard assumption to allow for an additive constant, but this need not concern us now.)

To apply this formulation one must impose identifying constraints on $f(x \mid z)$ and $F(z)$ (Elbers and Ridder 1982; Heckman and Singer 1984). The form of these constraints depends on the nature of the data being analyzed. Our data on total mortality are annual mortality counts for 20 cohorts in the 11-year period 1968–1978. Hence we have no covariates, the data are both left and right censored, and the individual lifetimes (x_i's) are known to lie only within a specified 2-year interval (i.e., because cohorts are defined on a 1-year age basis).

Heckman and Singer (1984) showed that identifiability of proportional hazard models with X continuous and uncensored, and with no observed covariates, requires (a) that $f(x \mid z)$ is a member of a known finite parameter family of distributions and (b) that certain restrictions are imposed on the moments of admissible distributions of Z. For example, the restriction that the mean of Z be finite is sufficient to resolve a nonidentifiability aspect of mixtures of Weibull densities described by Jewell (1982). In our case, with each x_i known only to be in a given interval, we specify both $f(x \mid z)$ and $F(z)$ to be known finite parameter families; we further restrict $F(z)$, however, to be

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a natural exponential family with all positive moments finite.

Assuming that finite parameter families for both $f(x \mid z)$ and $F(z)$ had three additional advantages in our application, we note the following. (a) With only 11 observations per cohort, it follows from Lindsay (1983) that a fitted discrete mixture model for $F(z)$ could have at most only a few support points because of the degrees of freedom consumed by the parameters of $f(x \mid z)$. Thus for our data a flexible parametric functional form for $F(z)$ is likely to represent a continuous gradation of frailty values better than a discrete mixing distribution with only a small number of support points can. (b) If we restrict our choice of $F(z)$ to parametric families for which (1.1) can be integrated analytically, the estimation problem (for uncensored data) reduces to the usual maximum likelihood problem and the potential for implementing the model is increased. (c) Whereas we can deal with right censoring in our data by conditioning the number of deaths in each calendar year on the number of persons alive in the cohort at the start of that year, dealing with left censoring presents a more difficult problem. If we restrict our choice of $F(z)$ to parametric families that are closed under mortality selection and if it can be assumed that all left censoring is due to mortality, then the conditional distribution of Z in the cohort subgroup alive at the start of each year will be of known parametric form. Furthermore, this strategy permits the multiple cohorts to be analyzed simultaneously with cross-cohort constraints imposed on selected parameters.

Using this strategy, we investigated the sensitivity of the parameters of $f(x \mid z)$ to various choices of parametric families of distributions for $F(z)$ and the sensitivity of the parameters of $F(z)$ to various choices of parametric families of distributions for $f(x \mid z)$. Parametric families of distributions for $f(x \mid z)$ and $F(z)$ were selected from the demographic and actuarial literature on mortality in adult populations and were chosen to be consistent with biological insights into human mortality processes. In the following sections of the article we describe the population and mortality data used in the analyses (Sec. 2), define the concept of frailty (Sec. 3), list the parametric families of distributions fit to the data in paired combinations (Sec. 4), describe our maximum likelihood estimation procedure (Sec. 5), present results (Sec. 6), compare the results on the sensitivity of parameter estimates in the mortality analyses with the results of other analyses (Sec. 7), and present conclusions (Sec. 8).

2. DATA

2.1 Medicare Data

The first set of data consists of population and mortality counts derived from published Medicare data on cohort mortality rates for 20 male and female birth cohorts, born from 1883 to 1902, who were followed for 11 years, from 1968 to 1978 (Wilkin 1982). These cohorts included 8 million males and 10 million females at the initial observation in 1968, when they ranged in age from 65 to 84 years. Of these, 60% of the males and nearly 50% of the females died during the 11-year follow-up period.

These data represent a substantial improvement over the usual mortality and population data available from the National Center for Health Statistics (NCHS) and the Bureau of the Census. In the Medicare data, misstatement of age is minimized because of requirements of verification of age to gain entitlement, underregistration of deaths is small because of payment of lump-sum death benefits, and the problem of underenumeration in census data does not apply because the at-risk group is defined by Medicare program records. Difficulties with census and NCHS data involve incompleteness of coverage and age misreporting (Rosenwaike 1981).

2.2 Lung Cancer Data

The second set of data consists of midyear population and lung cancer mortality counts in the U.S. white population for nine male and nine female birth cohorts, born each fifth year in the period from 1880 to 1920, who were followed for 28 years, from 1950 to 1977 (Manton and Stallard 1982). The lung cancer mortality counts were obtained from tabulations of computer tapes from NCHS. The population data were obtained by linear interpolation of race- and age-specific counts from the censuses of 1950, 1960, and 1970, and intercensal estimates for 1971–1977; these data were adjusted for underenumeration, race misclassification, and age misreporting errors (Coale and Zelnik 1963; Passel, Siegel, and Robinson 1982; Siegel 1974).

3. FRAILTY

3.1 Total Mortality

To model the effects of unobserved individual differences in longevity characteristics we defined z as a measure of frailty and assumed that z operated multiplicatively on either the total mortality hazard rate or, more generally, on a component of the total mortality hazard rate. Specification of the effects of z in terms of the hazard rate is consistent with biological theories of the mortality process (Sacher and Trucco 1962); the multiplicative form of this specification is well known because of its use in the Cox regression model (Cox 1972; Kalbfleisch and Prentice 1980), where it is used to assess the effects of observed physiological factors on survival. The conditional hazard rate $\mu(x \mid z)$ is modeled as

$$\mu(x \mid z) = z\lambda(x) + \theta, \qquad z \geq 0,\ \lambda(x) \geq 0,\ \theta \geq 0, \quad (3.1)$$

where $\lambda(x)$ is a function of age x, which is independent of z, and θ represents a constant component of the mortality hazard, which is independent of age x and frailty z. Setting $\theta = 0$ in (3.1) yields the multiplicative hazard rate model. We refer to $\lambda(x)$ as the "standard" force of mortality, that is, the force of mortality obtained when $z = 1$ and $\theta = 0$. In the Cox model $\lambda(x)$ need not be specified because it cancels out of the partial likelihood function. In our model $\lambda(x)$ will be specified in (4.7)–(4.8) as one of two parametric functions of age based on biological theory.

Other possibilities for modeling frailty include the ac-

celerated failure time model with frailty operating multiplicatively on the failure time, for example,

$$\mu(x \mid z) = z\lambda(x \cdot z), \qquad z \geq 0, x \geq 0. \tag{3.2}$$

Interestingly, the two-parameter Weibull model for $\lambda(x)$ is closed under multiplication of both the hazard rate function $\lambda(x)$ and the failure time x by an arbitrary constant such as z; this property is unique to the Weibull family of distributions (Kalbfleisch and Prentice 1980). Additional levels of generality might be introduced by permitting z to vary over time or age. Models of this type are discussed in Woodbury and Manton (1977), in Manton and Stallard (1984), and in Yashin, Manton, and Vaupel (1985).

3.2 Cause-Specific Mortality

The frailty concept extends to the analysis of several causes of death, using competing risk theory (Gail 1975). Let $\mathbf{z}_i^T = (z_{il}, \ldots, z_{im})$ denote m frailty values for the ith individual and let $\mathbf{x}_i^T = (x_{il}, \ldots, x_{im})$ denote m failure times such that the observed lifetime $x_i = \min(x_{il}, \ldots, x_{im})$. Assumptions concerning the dependence between various causes of death may be introduced through the joint distribution of the elements of $(\mathbf{x}_i, \mathbf{z}_i)$ (Hougaard 1984; Manton and Stallard 1980, 1984; Vaupel and Yashin 1983). Alternatively, independent competing risk models may be formulated by assuming statistical independence of the bivariate component vectors (x_{ij}, z_{ij}), $j = 1, \ldots, m$. In either case, if each cause-specific frailty z_{ij} operates multiplicatively on an associated cause-specific standard hazard rate $\lambda_j(x)$, which is defined assuming the presence of the other failure types, then the conditional hazard rate for all causes of death is

$$\mu(x \mid \mathbf{z}_i) = z_{i1}\lambda_1(x) + \cdots + z_{im}\lambda_m(x). \tag{3.3}$$

A model of the form (3.1) with θ replaced by $\theta(x)$ is obtained by integrating all but one of the z_{ij}'s out of (3.3), assuming that the particular z_{ij} is independent of the other z_{ij}'s.

4. ASSUMPTIONS ABOUT $F(z)$ AND $f(x \mid z)$

4.1 Frailty Distribution

We selected the following three models of the frailty distribution $F(z)$ for evaluation.

1. Gamma

$$dF(z) = \frac{(z/\zeta\gamma^2)^{1/\gamma^2} \exp(-z/\zeta\gamma^2)}{z\Gamma(1/\gamma^2)}\, dz, \qquad z \geq 0, \zeta > 0, \gamma > 0. \tag{4.1}$$

2. Inverse Gaussian

$$dF(z) = \left(\frac{\zeta}{2\pi\gamma^2 z^3}\right)^{1/2} \exp\left[\frac{-(z-\zeta)^2}{2\zeta\gamma^2 z}\right] dz, \qquad z > 0, \zeta > 0, \gamma > 0. \tag{4.2}$$

3. Degenerate

$$F(z) = 1, \qquad z \geq \zeta, \zeta > 0 \tag{4.3a}$$

$$= 0, \qquad z < \zeta. \tag{4.3b}$$

The mean frailty is ζ and the coefficient of variation is γ. The degenerate distribution is obtained from (4.1) or (4.2) as the limiting form as $\gamma \downarrow 0$.

The gamma model of frailty is well known and was studied in a range of applications by Beard (1963), Shepard and Zeckhauser (1977), Vaupel et al. (1979), Manton and Stallard (1979, 1980, 1981, 1984), and Vaupel and Yashin (1983). General characteristics of the gamma distribution are discussed in Morris (1982, 1983). The inverse Gaussian distribution was introduced as a model of frailty by Hougaard (1984) as an alternative to the gamma model. General characteristics of the inverse Gaussian distribution are discussed in Tweedie (1957). The parameterization given in (4.2) excludes a subset of inverse Gaussian distributions with infinite moments of any finite order (Hougaard 1984). Hence mixtures of Weibull and Gompertz densities based on (4.2) will satisfy the identifiability conditions of Heckman and Singer (1984). The same comment applies to mixtures based on (4.1).

In biological applications, the fact of heterogeneity has been argued to be virtually self-evident (e.g., Matis and Wehrly 1979). Furthermore, there are numerous epidemiological studies of total and cause-specific morbidity and mortality that demonstrate (a) the wide range of risk levels in human populations and (b) that these risk levels are associated with gradients in continuously distributed covariates. The gamma and inverse Gaussian models represent rich families of distributions to describe this continuous variability in biological risks. The gamma model is also argued (Beard 1963) to be a reasonable model for the distribution of longevity potential where that potential is determined by a small number of genetic factors (Strehler 1977, pp. 367–368).

The gamma and inverse Gaussian models share an important closure property that facilitates analysis of left-censored cohort data. If the initial frailty distribution is of the form (4.1) or (4.2), then the expected frailty distribution among survivors will have the same form. More specifically, replace ζ and γ in (4.1) and (4.2) with $\zeta(x_0)$ and $\gamma(x_0)$ to represent the frailty distribution at age x_0. Then the parameters of the expected frailty distribution at any later age x are

$$\zeta(x) = \zeta(x_0)/[1 + l\zeta(x_0)\gamma^2(x_0) \int_{x_0}^{x} \lambda(t)dt]^{1/l}, \qquad x \geq x_0 \tag{4.4}$$

$$\gamma^2(x) = \gamma^2(x_0)[\zeta(x)/\zeta(x_0)]^{l-1}, \qquad x \geq x_0, \tag{4.5}$$

where l is a constant set at $l = 1$ for the gamma model and $l = 2$ for the inverse Gaussian model. The mean frailty, $\zeta(x)$, declines monotonically with age under both models. The coefficient of variation $\gamma(x)$ declines monotonically with age for the inverse Gaussian model but is constant for the gamma model [see Hougaard (1984) for further comparisons]. As pointed out by a referee, it follows from Morris (1982) that the gamma family is the unique natural exponential family for which the coefficient of variation is constant under such a mortality process.

The marginal force of mortality $\mu(x)$ is obtained from (3.1) as

$$\mu(x) = \zeta(x)\,\lambda(x) + \theta. \tag{4.6}$$

Thus the parametric form selected for $\lambda(x)$ affects $\mu(x)$ directly through the first term in (4.6) and indirectly through the effect on the denominator of the expression for $\zeta(x)$ in (4.4).

4.2 Standard Force of Mortality

Two general models of the conditional hazard rate $\mu(x \mid z)$ were selected for evaluation. These differ according to the functional form selected for $\lambda(x)$ in (3.1).

1. Makeham

$$\lambda(x) = \alpha \exp\{\beta x\}, \qquad \alpha > 0. \tag{4.7}$$

2. Extended Weibull

$$\lambda(x) = \alpha x^{\beta-1}, \qquad \alpha > 0, \beta > 0. \tag{4.8}$$

These expressions can be substituted for $\lambda(x)$ in (3.1) to obtain the associated conditional hazard rates. When $\theta = 0$, the Makeham model reduces to the well-known Gompertz form and the extended Weibull model reduces to the Weibull form.

The Gompertz function has been used by actuaries since 1825, whereas the Makeham modification ($\theta > 0$) has been in use since 1860. A number of biological theories of aging have been developed that imply a Gompertz form of the conditional hazard rates. Several of these theories are reviewed in Strehler (1977, chap. 5) and in Economos (1982).

Although the Weibull function was introduced in engineering and reliability analysis, it has been used in mortality analysis by Rosenberg, Kemeny, Smith, Skurnick, and Bandurski (1973) and by Burch, Jackson, Fairpo, and Murray (1973). It is the hazard function implied by various "hit" or genetic error models of human aging and mortality (e.g., Failla 1958). The Weibull function has also been widely accepted in studies of human carcinogenesis (Armitage and Doll 1954, 1961; Cook, Doll, and Fellingham 1969). The usual biological interpretation given to the Weibull model involves the accumulation of "hits" or the passage through various discrete stages of a process. Watson (1977) showed that the Weibull hazard model was appropriate even if certain discrete changes could be reversed.

Both the Gompertz and the Weibull hazard rate functions correspond to extreme value distributions (Mann, Schafer, and Singpurwalla 1974, pp. 106–108). In this framework, if the failure of a complex organ system occurs at the time of failure of the first of many components, then the approximate mortality hazard rate can be Gompertz or Weibull in form, even though the hazard rate functions for the failure of the individual components are not Weibull or Gompertz in form.

Traditionally, the Gompertz function has been used for modeling total mortality and the Weibull function has been used for cause-specific mortality, such as that due to lung cancer. Because biologically plausible arguments have been made, however, for using the Weibull function for total mortality (Burch et al. 1973; Rosenberg et al. 1973) and the Gompertz function for lung cancer mortality (Dix, Cohen, and Flannery 1980), we will use both functions in both contexts.

5. ESTIMATION

Maximum likelihood estimation procedures were used to fit 12 models (4 hazard rate models paired with 3 mixing distributions) to the Medicare data and a subset of 6 models to the lung cancer data. The Medicare data were in the form of annual numbers of deaths paired with estimates of the initial exposed population at the start of the year. Thus the likelihood is binomial in form,

$$\mathfrak{L} = \prod_j \prod_k e^{-M_{jk}(N_{jk}-D_{jk})}(1 - e^{-M_{jk}})^{D_{jk}}, \tag{5.1}$$

where j denotes cohort and k denotes the observation within cohort, D_{jk} and N_{jk} denote the counts of deaths and the exposed population size for the kth observation on cohort j, and M_{jk} denotes the integral of the marginal hazard rate over the 1-year interval. Parameters were introduced into (5.1) using the approximation $M_{jk} = \mu(x_{jk} + \frac{1}{2})$, where x_{jk} is the midpoint of the 1-year age interval spanned by the cohort at the start of the year and

$$\mu(x) = \frac{\lambda(x)}{\left[1 + l\gamma^2(0)\int_0^x \lambda(t)dt\right]^{1/l}} + \theta, \tag{5.2}$$

which is the same as (4.6) except that $\zeta(0) = 1$ and $x_0 = 0$.

The lung cancer data were in the form of annual numbers of deaths due to lung cancer paired with estimates of the midyear population counts, which were assumed to be equal to the person-years of exposure. Under the assumption that lung cancer frailty is independent of all other cause-specific frailties and using the approximation $M_{jk} = \mu(x_{jk} + \frac{1}{2})$, the likelihood is Poisson in form,

$$\mathfrak{L} = \prod_j \prod_k (M_{jk}\,P_{jk})^{D_{jk}} \exp(-M_{jk}\,P_{jk})/D_{jk}!, \tag{5.3}$$

where D_{jk} denotes the number of deaths due to lung cancer and P_{jk} is the person-years of exposure. Using (4.7) or (4.8) to parameterize $\lambda(x)$ in (5.2), we see that the parameters to be estimated are α, β, $\gamma^2(0)$, and θ. For the degenerate mixture model, $\gamma^2(0)$ is set to zero and the right side of (5.2) reduces to $\lambda(x) + \theta$. As noted previously, $l = 1$ for the gamma mixture model and $l = 2$ for the inverse Gaussian mixture model. For the Gompertz and Weibull hazard rate models, θ was fixed at $\theta = 0$; for the Makeham and extended Weibull hazard rate models, θ was restricted to be nonnegative on the basis of biological arguments (Horiuchi and Coale 1983).

Certain subsets of the models are nested. Statistical testing of nested models was conducted using standard likelihood ratio tests (Kendall and Stuart 1973). In addition, (5.1) achieves a maximum $\mathfrak{L}^*$ at $\hat{M}_{jk} = -\ln(1 - D_{jk}/N_{jk})$ and (5.3) achieves a maximum $\mathfrak{L}^*$ at $\hat{M}_{jk} = D_{jk}/P_{jk}$. An approximate goodness-of-fit test can be performed using

$\chi^2 \simeq -2 \ln(\mathcal{L}/\mathcal{L}^*)$. Furthermore, estimates of standard errors can be obtained from the observed information matrix (Efron and Hinkley 1978).

6. RESULTS

6.1 Medicare Data

As described, we fit 12 alternative models to population and mortality count data for 20 male and female cohorts. The various models evaluated are named according to the distribution and hazard rate assumptions employed. The likelihood ratio chi-squared test statistics for the various models are presented in Table 1. These χ^2 values refer to the fit of each model vis-à-vis the completely saturated model. Alternative tests can be constructed in the case of nested hierarchical models. For example, one may compare the gamma/Gompertz χ^2 of 1,020.63 for males with the degenerate/Gompertz χ^2 of 1,216.74 to obtain a chi-squared value of 196.11 with 1 df—a highly significant value.

All models indicated in Table 1 were estimated with 20 cohort-specific values for the parameters α and β. These parameters consumed 40 df in each analysis, leaving a residual of 180 df. For the models with 178 or 179 df, parameter estimates for $\gamma^2(0)$ and θ (in Makeham and extended Weibull hazard rate models) were constrained equally across cohorts and hence consumed 1 df each. The models with 160 df were estimated with 20 cohort-specific values for $\gamma^2(0)$ and with $\theta = 0$.

Examination of Table 1 indicates that certain models are to be preferred. For example, in all Makeham models the unrestricted maximum likelihood estimator $\hat{\theta}$ is negative and is biologically unacceptable; hence $\hat{\theta}$ is constrained to zero. For the extended Weibull models mixed with either the gamma or inverse Gaussian distributions, $\hat{\theta}$ is positive but not statistically significant. To test the hypothesis of homogeneity of frailty in the cohort, one can compare each degenerate model with one of the two other models on the same line in Table 1; 16 tests can be specified and all are highly significant. Thus under all choices of either the heterogeneity distribution or the hazard rate function within these families the hypothesis of homogeneity is rejected. The smallest χ^2 value is 48.08 for the comparison for males of the degenerate/Weibull model with the inverse Gaussian/Weibull model. Thus our attention is focused on the four models involving the combination of the gamma and inverse Gaussian distributions with the Gompertz and Weibull hazard rates.

Having rejected the degenerate distribution models, we also tested the adequacy of the pooled estimate of $\gamma^2(0)$ in each of the four models. This was a 19-df test involving comparison of the 160-df χ^2 with the corresponding 179-df χ^2 in Table 1. The gamma/Gompertz model yielded a marginally significant χ^2 value for females ($\chi^2 = 34.81$; $p \simeq .015$); the other seven tests were not significant. As a consequence we preferred the four 179-df models on the basis of parsimony.

To evaluate the relative performance of these four models, we compared the χ^2 goodness-of-fit statistics obtained in Table 1. This is an informal evaluation because the models are not nested hierarchically; methods of constructing formal tests are discussed in Loh (1985). For males, the best fit is obtained for the gamma/Weibull model ($\chi^2 = 1{,}015$) and the worst fit is obtained for the inverse Gaussian/Gompertz model ($\Delta\chi^2 = 38.22$). The inverse Gaussian/Weibull model is a close second ($\Delta\chi^2 = 4.00$), with the gamma/Gompertz model ranking third ($\Delta\chi^2 = 5.45$). Thus the gamma model performs better as a distribution of frailty, and using the gamma the Weibull model fits better than the Gompertz model. Figure 1 illustrates the fit of the gamma/Weibull model to the observed data for males born in 1885, 1890, 1895, and 1900.

For females the best fit is obtained for the gamma/Weibull model ($\chi^2 = 1{,}196$). The worst fit is produced by the inverse Gaussian/Gompertz model ($\Delta\chi^2 = 54.98$). The inverse Gaussian/Weibull ($\Delta\chi^2 = 5.16$) and gamma/Gompertz ($\Delta\chi^2 = 19.18$) models rank second and third. Thus the results for females support a choice of the gamma/Weibull as the preferred distribution/hazard rate model.

Because our sample size was very large (8 million males; 10 million females), we expected to find that the χ^2 goodness-of-fit values produced in the analysis would be large even if the fit of the model was good in terms of percentage error (e.g., as in Fig. 1). Nonetheless, the values in Table

Table 1. Likelihood Ratio Goodness-of-Fit χ^2 Values for Alternative Models

Conditional hazard	Gamma	Inverse Gaussian	Degenerate
	Males		
Makeham	1020.63 (178)	1053.40 (178)	1216.74 (179)
Gompertz	1020.63 (179)	1053.40 (179)	1216.74 (180)
	996.62 (160)	1042.72 (160)	
Extended Weibull	1014.82 (178)	1018.70 (178)	1067.26 (179)
Weibull	1015.18 (179)	1019.18 (179)	1067.26 (180)
	997.92 (160)	1001.95 (160)	
	Females		
Makeham	1215.34 (178)	1251.14 (178)	1542.41 (179)
Gompertz	1215.34 (179)	1251.14 (179)	1542.41 (180)
	1180.53 (160)	1229.05 (160)	
Extended Weibull	1196.13 (178)	1200.30 (178)	1301.65 (179)
Weibull	1196.16 (179)	1201.32 (179)	1301.65 (180)
	1178.36 (160)	1183.11 (160)	

NOTE: Degrees of freedom are given in parentheses.

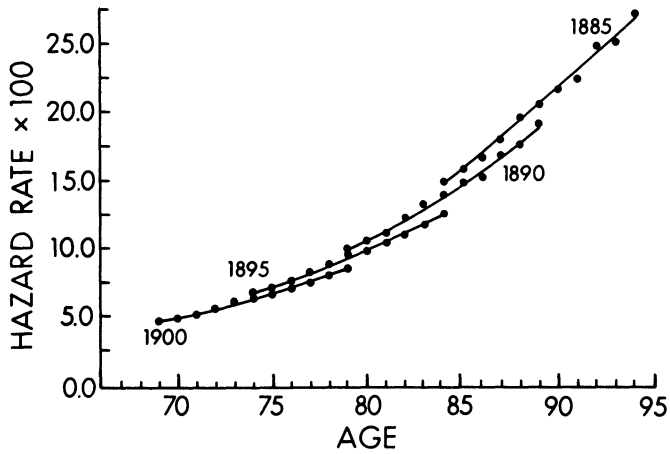

Figure 1. Fit of the Gamma/Weibull Model to Medicare Mortality Data for Four Male Cohorts Born in 1885, 1890, 1895, and 1900. The four smooth lines show the age trajectory of the marginal hazard rate function within the age range of observation for each of the four cohorts. These marginal hazard rates were computed as indicated in Equation (5.2) with parameter estimates obtained from the 179-df gamma/Weibull model with cohort specific estimates of α and β and pooled estimates of $\gamma^2(0)$. The scatter is the set of observed cumulative hazard rates for the 1-year interval of observation, plotted at the midpoint $x_{jk} + \frac{1}{2}$ of the age interval $(x_{jk}, x_{jk} + 1)$.

1 were large enough to warrant examination of the pattern of residuals. We defined a chi-variate as $\chi = \sqrt{\chi^2}$ with the sign set the same as the sign of the residual and computed these values for our four models. We found that the number of sign runs within cohort was near expectation, but across cohort there were several years for which all residuals had the same sign. This suggested that there were "period effects" operating on our data that tended to raise or lower the death rates in a given year for all cohorts. We attempted to determine if the lack of fit of the gamma/Weibull model could be explained by period effects, represented by linear trends in the χ values for each year. Fitting these period effects produced an absolute fit for males (i.e., a residual χ^2 of 176.9 with at least 157 df; $p \simeq .13$) and given the population size, a near fit for females ($\chi^2 = 205.6$ with at least 157 df; $p \simeq .006$).

A statistically acceptable fit to the data is not helpful if parameter estimates are not in the range considered biologically feasible for the mortality processes being evaluated (Murphy 1978). Hence we will evaluate the physical implications of our parameter estimates. First, in Table 2 we present alternative estimates of the parameter $\gamma^2(0)$ for our four models. For males, the estimates range from .091 for the gamma/Weibull model to .443 for the inverse Gaussian/Gompertz model. For females, the estimates range from .141 to .662 for the same two models. The gamma/Gompertz estimates are just over twice those of the gamma/Weibull model; the inverse Gaussian/Gompertz estimates are from 3.2 to 3.6 times those of the inverse Gaussian/Weibull model.

Though estimates of $\gamma^2(0)$ for the gamma model are smaller than for the inverse Gaussian model, the coefficient of variation in the gamma model is invariant over age, whereas it declines with age in the inverse Gaussian model. Thus at more advanced ages the relative heterogeneity will be similar under the two models. Table 3 displays the values of $\gamma^2(x)$ obtained from Equation (4.5) for the 1892 birth cohort (the 11th cohort in our set of 20 cohorts).

The change in $\gamma^2(x)$ is larger from ages 65 to 95 years than from ages 0 to 65 years. For males, the value of $\gamma^2(x)$ at age 90 years is below the corresponding value for the gamma model. For females, the value at age 90 is still larger than the value for the gamma model, though it is seen that they will eventually cross over. Within the range of the data (ages 65 to 94 years) the estimates of the coefficients of variation of the conditional frailty distribution are similar in the gamma and inverse Gaussian models.

The ratio of $\gamma^2(x)$ at age 90 years between the Gompertz and the Weibull functions is approximately 2 to 1. This occurs for both sexes and replicates the behavior of the $\gamma^2(0)$ estimates for the gamma model in Table 2. Thus one can see that the estimate of the heterogeneity of frailty at age 90 years is sensitive to the function selected to represent the conditional hazard rate but is relatively insensitive to the function selected to represent the conditional frailty distribution.

Table 4 contains alternative estimates of β for 10 alternate male cohorts for 3 Gompertz conditional hazard rate

Table 2. Alternative Estimates of Squared Coefficient of Variation, $\gamma^2(0)$, of Marginal Frailty Distribution

Conditional hazard	Gamma	Inverse Gaussian
	Males	
Gompertz	.211	.443
	(.015)	(.079)
Weibull	.091	.122
	(.013)	(.024)
	Females	
Gompertz	(.288)	.662
	(.016)	(.089)
Weibull	.141	.208
	(.014)	(.030)

NOTE: Standard errors are given in parentheses.

Table 3. Alternative Estimates of $\gamma^2(x)$, Age-Specific Squared Coefficient of Variation of Conditional Inverse Gaussian Frailty Distribution Based on α and β Parameter Estimates for the 1892 Birth Cohorts

	Males		*Females*	
Age	*Gompertz*	*Weibull*	*Gompertz*	*Weibull*
0	.443	.122	.662	.208
45	.430	.121	.653	.207
65	.375	.117	.597	.202
70	.347	.115	.561	.198
75	.313	.111	.511	.192
80	.275	.106	.449	.182
85	.236	.099	.381	.170
90	.198	.092	.312	.155
95	.163	.084	.249	.138
		Gamma model		
	.211	.091	.288	.141
	[88.2]	[90.5]	[91.8]	[94.1]

NOTE: Values in brackets indicate ages at which $\gamma^2(x)$ for the inverse Gaussian model are the same values as for the Gamma model.

Table 4. Alternative Estimates of Gompertz Rate Parameter β Under Three Marginal Distributions of Frailty, for Males

Cohort/ age range	Gamma	$\beta \times 10^2$ Inverse Gaussian	Degenerate
1902	7.34	7.96	6.26
65–75	(.10)	(.24)	(.06)
1900	7.38	8.03	6.11
67–77	(.11)	(.26)	(.06)
1898	7.73	8.40	6.26
69–79	(.12)	(.28)	(.06)
1896	7.88	8.54	6.18
71–81	(.14)	(.30)	(.06)
1894	8.20	8.84	6.22
73–83	(.15)	(.31)	(.06)
1892	8.65	9.24	6.32
75–85	(.18)	(.33)	(.06)
1890	9.14	9.67	6.44
77–87	(.21)	(.35)	(.07)
1888	9.48	9.83	6.34
79–89	(.24)	(.36)	(.07)
1886	9.81	9.90	6.17
81–91	(.28)	(.35)	(.08)
1884	10.29	10.06	6.09
83–93	(.32)	(.35)	(.09)

NOTE: Standard errors are given in parentheses.

models (i.e., the gamma/Gompertz and inverse Gaussian/Gompertz models with 179 df each and the degenerate/Gompertz model). Corresponding estimates for the Weibull models are contained in Table 5. In all cases, the estimates of β under the degenerate distribution model (i.e., for the homogeneity model) are much smaller than for the two models with heterogeneity. Thus not only is the fit of the degenerate distribution model worse than the fit of the models with heterogeneity but the trajectory of the age increase in risk implied by the β estimates is biased downward vis-à-vis both heterogeneity models. The parameter estimates obtained for both heterogeneity models are similar. This is consistent with the finding that the coefficients of variation of frailty within the range of the data are also comparable for both heterogeneity models.

Table 5. Alternative Estimates of Weibull Exponent Parameter β Under Three Marginal Distributions of Frailty, for Males

Cohort/ age range	Gamma	β, Inverse Gaussian	Degenerate
1902	5.77	5.85	5.44
65–75	(.06)	(.09)	(.04)
1900	5.86	5.94	5.46
67–77	(.07)	(.10)	(.04)
1898	6.16	6.26	5.69
69–79	(.08)	(.11)	(.04)
1896	6.31	6.41	5.75
71–81	(.09)	(.13)	(.05)
1894	6.58	6.69	5.91
73–83	(.10)	(.14)	(.05)
1892	6.91	7.03	6.11
75–85	(.12)	(.17)	(.05)
1890	7.29	7.40	6.33
77–87	(.14)	(.19)	(.06)
1888	7.51	7.61	6.36
79–89	(.17)	(.21)	(.06)
1886	7.69	7.77	6.33
81–91	(.20)	(.24)	(.07)
1884	7.98	8.01	6.38
83–93	(.24)	(.27)	(.08)

NOTE: Standard errors are given in parentheses.

For the Gompertz model, $\beta \times 10^2$ is the annual percentage increase in the force of mortality. For the 1890 birth cohort, the gamma/Gompertz model suggests an increase of 9.1% per year; the inverse Gaussian model suggests 9.7% per year. The values for younger cohorts, though lower for both models, agree to within about .6% per year. The values for the inverse Gaussian/Gompertz model are all within the range .080–.104 cited by Spiegelman (1969, p. 132) as biologically plausible.

For the Weibull model, β is the slope of the logarithm of the cumulative hazard rate as a function of the logarithm of age. As with the Gompertz parameters, one can see in Table 5 that the estimates of the Weibull β's are similar for the gamma and inverse Gaussian models. This is consistent with the result in Table 3 that the estimated coefficients of variation at about age 90 years are also relatively insensitive to the selected form of the frailty distribution. The bias generated in estimating β by ignoring heterogeneity appears to be greater than the bias induced by selecting a reasonable model of the frailty distribution.

6.2 Lung Cancer Mortality

To model the lung cancer death rates, we used the cohort lung cancer data for nine male and nine female cohorts in the U.S. white population for the period 1950–1977 (see Sec. 2). In fitting these data, we made the assumption that lung cancer frailty is statistically independent from all other cause-specific frailties. Chi-squared goodness-of-fit statistics for the six models fit to these data are presented in Table 6. For all models, cohort specific estimates of the parameters α and β were obtained; this accounts for the 234 df in the degenerate distribution models in Table 6. The gamma and inverse Gaussian distribution models were estimated in the following two forms: (a) with pooled estimates of $\gamma^2(0)$ across cohorts (233 df) and (b) with cohort specific estimates of $\gamma^2(0)$ (225 df).

From Table 6 one can see that the only statistically acceptable fit for males is obtained with the 225-df gamma/Weibull model ($\chi^2 = 249.33$; $p \simeq .13$; $\Delta\chi^2 = 48.67$ over the next best model, the gamma/Gompertz model). The best fit for females is obtained with the 225-df gamma/Gompertz model, but this is marginally significant ($\chi^2 = 271.90$; $p \simeq .018$). For males the models with cohort-spe-

Table 6. Likelihood Ratio Goodness-of-Fit χ^2 Values for Six Alternative Models: Lung Cancer Mortality 1950–1977, U.S. White Population

Conditional hazard	Gamma	Inverse Gaussian	Degenerate
		Males	
Gompertz	580.94 (233)	1814.97 (233)	3451.85 (234)
	298.00 (225)	1573.26 (225)	
Weibull	401.11 (233)	777.02 (233)	1896.87 (234)
	249.33 (225)	744.20 (225)	
		Females	
Gompertz	303.97 (233)	300.44 (233)	426.05 (234)
	271.90 (225)	277.62 (225)	
Weibull	292.69 (233)	294.00 (233)	299.78 (234)
	282.27 (225)	281.78 (225)	

NOTE: Degrees of freedom are given in parentheses.

cific estimates of $\gamma^2(0)$ all fit significantly better than models with pooled estimates (e.g., $\Delta\chi^2 = 151.78$ with 8 df); and both forms of the heterogeneity models fit much better than the comparable degenerate models. Comparable results are obtained for females for the models with Gompertz hazard rates. For females, for the models with Weibull hazard rates, the cohort-specific estimates of $\gamma^2(0)$ do not significantly improve the fit over that achieved by models with pooled estimates.

The fit of the 225-df gamma/Weibull model for males is illustrated in Figure 2 for the 1885, 1895, 1905, and 1915 birth cohorts. It can be seen that the model does a good job in reproducing the systematic increases over age in the cohort mortality data. It is also clear that a degenerate/Weibull model will be unable to fit the almost constant hazard rate after age 85.

In Table 7 are displayed the estimates of $\gamma^2(x)$ based on Equation (4.5) for persons born in 1900, evaluated at several ages by using parameters estimated in the 225-df models. Here we see that the estimates of $\gamma^2(x)$ for a specific hazard function and sex group for the inverse Gaussian model are equal to the estimates of $\gamma^2(0)$ for the gamma model in the age range 59 to 72 years. This is within the age range 50 to 77 years at which this cohort was observed. Furthermore, we see that the estimates of $\gamma^2(x)$ for males are only moderately sensitive to the function selected to represent the conditional hazard rate (a ratio of 1.6 to 1 for the gamma model) and to the function selected to represent the conditional frailty distribution. The sensitivity to the hazard rate function is more extreme in the female data: the gamma model produced estimates of $\gamma^2(0)$ with a ratio of 3.0 to 1. In addition, from Table 7 one can see that the estimates of $\gamma^2(x)$ for the gamma and inverse Gaussian mixtures for both hazard rate models will be nearly equal in value at about age 70 for females. Thus the estimate of

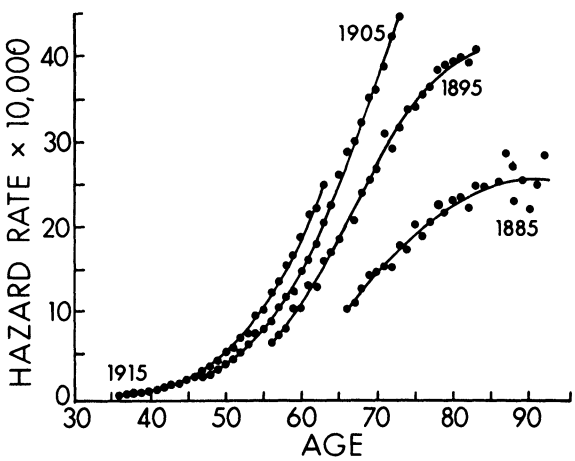

Figure 2. Fit of the Gamma/Weibull Model to Lung Cancer Mortality Data for Four White Male Cohorts Born in 1885, 1895, 1905, and 1915. The four smooth lines show the age trajectory of the marginal hazard rate function within the age range of observation for each of the four cohorts. These marginal hazard rates were computed as indicated in Equation (5.2) with parameter estimates obtained from the 225-df gamma/Weibull model with cohort specific estimates of α, β, and $\gamma^2(0)$. The scatter is the set of observed lung cancer death rates for the 1-year interval of observation, plotted at the midpoint $x_{jk} + \frac{1}{2}$ of the age interval $(x_{jk}, x_{jk} + 1)$.

Table 7. Alternative Estimates of $\gamma^2(x)$, Squared Coefficient of Variation of Conditional Inverse Gaussian Frailty Distribution for Persons Born in 1900: Lung Cancer Mortality 1950–1977, U.S. White Population

	Males		Females	
Age	Gompertz	Weibull	Gompertz	Weibull
0	37.8	39.2	146.8	31.0
	(4.5)	(6.7)	(73.8)	(22.2)
45	35.3	38.2	142.0	30.9
65	21.7	22.9	108.4	28.9
75	12.9	13.3	74.3	25.7
85	7.0	7.5	44.0	21.0
95	3.7	4.4	20.3	15.9
		Gamma model		
	27.6	16.7	86.7	28.7
	(1.3)	(1.0)	(19.1)	(16.1)
	[58.6]	[70.9]	[71.5]	[65.9]

NOTE: Standard errors are given in parentheses. Values in brackets indicate ages at which $\gamma^2(x)$ for the inverse Gaussian model are the same values as for the Gamma model.

$\gamma^2(x)$ at these ages is much less sensitive to the choice between the gamma and the inverse Gaussian mixture models than to the choice between the Gompertz and Weibull hazard rate models.

7. SELECT OBSERVATIONS AND COMPARISONS

There are several comparisons that can be made to yield greater insight into the results of our analysis.

1. Supplementary analyses were conducted on the Medicare data, which included the adjacent five older birth cohorts (i.e., 1878–1882). Pooled estimates of $\gamma^2(0)$ from these analyses were only slightly larger than the estimates presented in Table 2. The main difference occurred in the estimates of the parameter β. For both the inverse Gaussian and the degenerate mixture models (and less so for the gamma model), the β values obtained for the five older birth cohorts declined substantially over cohort age. This pattern of decline was unexpected but was consistent with the view that the Medicare age reporting at extreme ages is progressively less reliable.

2. The estimates of β in Table 4 for the gamma/Gompertz and inverse Gaussian/Gompertz models are consistent with the range cited by Spiegelman (1969, p. 132) as biologically plausible. This range was developed from analyses of mortality data in a broad range of cohort and cross-sectional data and from a range of national data sets for the adult age range, primarily ages 35 to 85. Our analysis indicated that the same range of β applied to the Medicare mortality data, if the effects of heterogeneity were adequately represented in the model. At the younger ages the effects of heterogeneity can be ignored (e.g., see Strehler and Mildvan 1960), but at the older ages the penalty is severely downward-biased estimates of β (e.g., in Table 4, the range is from .059 to .065).

3. The estimates of $\gamma^2(0)$ for the gamma/Gompertz model of the Medicare data compare well with estimates derived from an independent analysis of eight U.S. white cohorts born 1850–1885 using interpolated mortality data at 12 ages in the ranges 35 to 85 and 89 years (Manton, Stallard, and

Vaupel 1981, table 2). Using the transformation $\gamma^2(0) = 1/k$, that analysis produced an estimate of .255 for $\gamma^2(0)$ for U.S. males (approximately .211) and .352 for U.S. white females (approximately .288). These estimates are also consistent with the range obtained from Swedish cohort mortality data, in the same age range, for which a lengthy historical data series of high quality is available (Manton et al. 1981).

4. In proposing the inverse Gaussian mixture model, Hougaard (1984) suggested that it might be preferable to the gamma mixture model because it implies that the population is more homogeneous at older ages. Our analysis indicates that within the range of the data both models produce comparable estimates of $\gamma^2(x)$. Indeed, from Table 3 we see that the inverse Gaussian mixture model implies greater heterogeneity in total mortality risks at all ages up to the range 88 to 94 years.

5. For both total and lung cancer mortality data, the estimates of $\gamma^2(x)$ at the midrange of the data were generally more sensitive to the choice of Gompertz versus Weibull hazard rate models than to the choice of gamma versus inverse Gaussian mixture models. This may simply reflect the condition in elderly populations that endowment for longevity is unimodally distributed and that both mixing distributions are flexible enough to provide a reasonable approximation. A referee has noted that Ridder and Verbakel (1983) also found in a related context that their results were less sensitive to the choice of frailty distributions than to the choice of conditional failure models.

8. CONCLUSION

The conclusion to be reached from the analyses and discussions is that estimation of hazard functions in heterogeneous populations is subject to the same limitations as any other statistical analysis. That is, the firmer are the theoretical foundations and the more extensive is the data base, the greater is the detail of a model that can be estimated. A key point is that heterogeneous population models may be constructed to be generalizations of homogeneous population models. In this case, if the heterogeneity parameters prove to be significant in a hierarchical series of tests, then failure to utilize the heterogeneous population form of the model is a serious analytic error.

[*Received November 1983. Revised November 1985.*]

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