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THE USE OF SURVIVAL TIME MODELS WITH NONPROPORTIONAL HAZARD FUNCTIONS TO INVESTIGATE AGE OF ONSET IN FAMILY STUDIES

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Abstract—The use of survival time models with non-proportional hazard functions is introduced as a method of studying age of onset effects in family studies. Statistical methods for investigating non-proportionality of the hazard function are described, and the application of these methods is illustrated using data from a family study of depression to investigate transmission of age of onset between probands and their first degree relatives. The method is broadly applicable and useful for many chronic diseases where transmission of a disorder in families varies by age of onset of the disorder. It may also be used to investigate the effect of other proband factors such as sex on the age of onset of disease in relatives.

1. INTRODUCTION

THE AGE of onset of disease is considered to be an important factor in prognosis, transmission, and severity of several disorders, e.g. diabetes, cancer and depression. Indeed, onset of illness at a characteristic age is considered to be indicative of involvement of genetic factors in the etiology of an illness [1]. Survival analysis techniques such as the proportional hazards model introduced by Cox [2] can be used to study age of onset of disease by treating this factor as a survival time, where the "scale" for measuring time is age. The proportional hazards model assumes that the underlying hazard function for any two levels of some covariate are proportional over the period of follow-up time, i.e. the relative risks for the various levels of the covariate are constant over time. If one suspects that these relative risks vary with time, then the assumption of proportional hazards may not be justified, and we need to use methods that do not assume proportionality to investigate the effects of this covariate on survival time, i.e. age of onset. The aim of this paper is to first describe some useful approaches for studying age of disease onset when the hazards may not be proportional, and to illustrate their application by presenting the analysis of a set of data using these methods, which resulted in important clinical ramifications.

These approaches were found to be useful in the analysis of family studies, when one wished to investigate the effect of a proband factor, i.e. index case factor, on the age of onset of disease in their relatives. Family studies are useful paradigms with which to investigate the role of age of onset in the pathogenesis of a disease. Familial transmission

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of age of onset can provide clues regarding genetic and environmental risk factors and validate subgroups of a disease. A recent study investigated the effect of age of onset of cancer in relatives of children with central nervous system neoplasms [3]. Data from family studies have also been used to investigate age of onset effects in diabetes [4, 5] and the major psychiatric disorders [6–8].

Previous studies have not recognized that survival time models with non-proportional hazard functions provide a convenient framework for investigating the effect of proband factors on age of onset in family studies. Recent data from our family-genetic study of depression provided evidence for a relationship between high familial loading for depression and early age of onset, with suggestion of specificity of transmission of age of onset as well [9]. In the sections that follow, we will describe some of the methods available to investigate the non-proportionality of the hazard function and illustrate how such methods can be used to study the age of onset factor, by applying them to data from a family study of depression.

2. METHODS

Several different methods exist for dealing with non-proportional hazard functions. In this section, we will describe in detail two of these methods, which we have selected from the many available. These methods were chosen by us for the following reasons: (i) their link with the familiar Cox's proportional hazards model and the well known log-linear models for discrete data analysis [10]; (ii) the cost efficiency of the second method with respect to large data sets; and (iii) their ease in implementation (computer programs for using these methods are readily available). Other survival time models which allow for time dependent relative risks, but will not be discussed here, are the time-dependent proportional hazards model [2], the proportional odds model [11], the Accelerated Failure Time model [2] and a variety of parametric models such as the models assuming the log-normal, gamma and log-logistic distributions of survival time [12].

2.1. Graphical method of investigating non-proportionality of the hazard function (Kalbfleisch and Prentice [12])

Let t_i denote the survival or follow-up time for person i, and let δ_i denote an indicator function taking value 1 if person i is dead at time t_i, or taking value 0 if the person is alive at t_i. The vector $\mathbf{z}' = (z_1, \ldots, z_p)$ denotes a set of p regression variables or covariates. Assuming that n independent persons are studied, the basic set of data for the entire group is $\{(t_i, \delta_i, \mathbf{z}_i') : i = 1, 2, \ldots, n\}$. Denote the "hazard" for an individual at time t with covariate value $\mathbf{z}$ as $\lambda(t; \mathbf{z})$. The proportional hazard model requires that, for any two covariate sets $\mathbf{z}_1$ and $\mathbf{z}_2$, the hazard functions are related by

$$\lambda(t; \mathbf{z}_1) \propto \lambda(t; \mathbf{z}_2) \quad 0 < t < \infty. \tag{1}$$

When this requirement does not hold for some factor, to accommodate such factors a simple extension of the model is available.

Suppose there is a nominal factor with q levels for which equation (1) may be violated. Define the hazard function for an individual in the jth stratum of this factor as

$$\lambda_j(t; \mathbf{z}) = \lambda_{0j}(t) \exp(\mathbf{z}'\boldsymbol{\beta})$$

for $j = 1, 2, \ldots, q$ where $\mathbf{z}'$ is the vector of covariates and $\boldsymbol{\beta}$ is the vector of regression coefficients. The baseline hazard function $\lambda_{01}(\cdot), \ldots, \lambda_{0q}(\cdot)$ for the q strata are allowed to be arbitrary and may be completely unrelated.

Using the approach given by Kalbfleisch and Prentice [12], estimates of $\boldsymbol{\beta}$ can be found by maximizing the marginal likelihood function

$$L(\boldsymbol{\beta}) = \prod_{j=1}^{q} L_j(\boldsymbol{\beta})$$

where $L_j(\boldsymbol{\beta})$ is the marginal likelihood of $\boldsymbol{\beta}$ arising from the jth stratum alone. Estimates

of $\boldsymbol{\beta}$ that maximize $L(\boldsymbol{\beta})$ are obtained by the iterative solution of a system of equations, which may be easily accomplished on a computer.

Once an estimate of $\boldsymbol{\beta}$ is obtained, estimates of the survivor functions in each of q strata can be obtained separately. The survivor function for each of the q strata is defined as:

$$F_{0j}(t;\mathbf{z}) = [\exp(-\int_0^t \lambda_{0j}(u)\mathrm{d}u)]^{\exp(\mathbf{z}'\boldsymbol{\beta})}, j = 1, \ldots, q.$$

It follows that $\log(-\log F_{0j}(t;\mathbf{z})) = \log \int_0^t \lambda_{0j}(u)\mathrm{d}u + \mathbf{z}'\boldsymbol{\beta}$.

Let k_j be a set of constants for $j = 1, \ldots, q$.

If

$$\lambda_{oj}(u) = k_j\lambda_0(u) \quad 0 < u < t, \quad j = 1, \ldots, q \tag{2}$$

then

$$\log(-\log F_{0j}(t;\mathbf{z})) = \log \int_0^t \lambda_0(u)\mathrm{d}u + \log k_j + \mathbf{z}'\boldsymbol{\beta}. \tag{3}$$

Equation (2) implies that the proportional hazard assumption holds for factor j; if equation (3) holds, the plots of $\log[-\log F_{0j}(t)]$ for any two levels of j should be separated by a constant factor. One can check whether the factor used in defining the q strata can be modeled in the proportional hazards way by plotting $\log[-\log \hat{F}_{0j}(t)], j = 1, \ldots, q$ vs t, where $\hat{F}_{0j}(t)$ is an estimate of the survivor function. If the assumption of proportionality is justified, it follows from equations (2) and (3) that such plots for any two values of j should exhibit approximately constant differences over time.

2.2. Analytic method of investigating the non-proportionality of the hazard function (Holford [13, 14])

The proportional hazards model introduced by Holford [13, 14] for life-table analysis provides a convenient analytic method of investigating the non-proportionality of the hazard function. This model assumes that the period of follow-up can be partitioned into I mutually exclusive, exhaustive intervals, $\Omega_1, \ldots, \Omega_I$ such that the underlying hazard function is constant within each interval. Letting λ_i denote the constant underlying hazard function in $\Omega_i, i = 1, \ldots, I$, we have

$$\lambda(t;\mathbf{z}) = \lambda_i \exp(\mathbf{z}'\boldsymbol{\beta}) \quad \text{for} \quad t \in \Omega_i \tag{4}$$

where $\mathbf{z}'$ denotes a set of p covariates, and $\boldsymbol{\beta}$ denotes the vector of regression coefficients. This assumption implies that survival times within an interval are exponentially distributed.

A log-linear hazard model follows directly from equation (4)

$$\log \lambda(t;\mathbf{z}) = \log \lambda_i + \mathbf{z}'\boldsymbol{\beta} \quad t \in \Omega_i. \tag{5}$$

Let $\log \lambda_i = \mu + \alpha_i$ and $\log \lambda_i(\mathbf{z}) = \log \lambda(t;\mathbf{z})$ for $t \in \Omega_i$ and $i = 1, \ldots, I$. Equation (5) can be rewritten as

$$\log \lambda_i(\mathbf{z}) = \mu + \alpha_i + \mathbf{z}'\boldsymbol{\beta} \tag{6}$$

where α_i can be interpreted as the effect of the ith time interval on the logarithm of the hazard function. Equation (6) can be reparameterized as:

$$\log \lambda_i(\mathbf{z}) = \mu + \mathbf{z}_0'\boldsymbol{\beta}_0 + \mathbf{z}'\boldsymbol{\beta} \tag{7}$$

where $\mathbf{z}_0' = (z_{01}, \ldots, z_{0(I-1)})$ is the set of $I-1$ dummy variables which represent the I categories of time in the regression equation, and $\boldsymbol{\beta}_0$ is the corresponding set of $I-1$ regression coefficients. For convenience of notation define $\boldsymbol{\beta}^{*\prime} = (\boldsymbol{\beta}_0', \boldsymbol{\beta}')$.

Maximum likelihood estimates of $\boldsymbol{\beta}^*$ can be easily computed by noting the following facts. Define $d_i(\mathbf{z})$ as the number of observed failures during the ith interval of follow-up time among individuals with covariate levels $(z_1, \ldots, z_p)$. Define $T_i(\mathbf{z})$ to be the sum of the

follow-up time in the ith interval for each individual in this same group. If it is assumed that $d_i(\mathbf{z})$ has a Poisson distribution conditional on $T_i(\mathbf{z})$ with mean $\lambda_i(\mathbf{z})T_i(\mathbf{z})$ where $\lambda_i(\mathbf{z})$ is as defined in equation (7), Holford [14] has shown that the maximum likelihood estimator of $\boldsymbol{\beta}^*$ under this assumption is identical to the maximum likelihood estimator of $\boldsymbol{\beta}^*$ given that $t \in \Omega_i$ has an exponential distribution with parameter $\lambda_i(\mathbf{z})$. Note that the assumption that $d_i(\mathbf{z})$ is Poisson need not be true; it is merely used as a convenient device for computing the maximum likelihood estimates of $\boldsymbol{\beta}^*$ when t_i is exponentially distributed, by using readily available computer programs [15], written for log-linear models of Poisson count data.

The model represented by equation (7) can be extended to deal with non-proportional hazard functions by including in the model interaction terms, between the variables representing the time intervals and the covariate of interest. The covariate of interest will, of course, be the factor under investigation for the appropriateness of the proportional hazards assumption. When these interaction terms are included, the ratio of the hazards for any two levels of the covariates are allowed to vary over the different time intervals, even though the covariate parameters are fixed. If the regression coefficients corresponding to the interaction terms are statistically significant, we conclude that the hazards are not proportional.

When the covariates specified by $\mathbf{z}'$ in equation (7) are all categorical, Holford's model reduces survival analysis to a special case of the log-linear model for contingency tables. The maximum likelihood estimates of $\boldsymbol{\beta}^*$ from the exponential model can also be found by using algorithms based on assuming that the $d_i(\mathbf{z})$ defined previously, instead of being Poisson, is multinomial with expectation $\lambda_i(\mathbf{z})T_i(\mathbf{z})$ for known $T_i(\mathbf{z})$ [14]. Thus, the well known computer programs for log-linear models for contingency tables [16] can be used to obtain estimates of $\boldsymbol{\beta}^*$ by taking T_i as the initial values for the estimate of the cell frequencies and then applying the programs in the usual manner.

The model described in this section by equation (4) is also similar to Cox's proportional hazards model [2]. The main difference between the two models is that while no assumption is made about the form of the baseline hazard function in the Cox model, the Holford model assumes that the baseline hazard function is associated with a piecewise exponential survival distribution. From a practical standpoint, it has been found [14, 17] that the Holford model is particularly well-suited for large data sets in terms of cost efficiency, especially when the covariates are all categorical and the sum of the number of levels of each covariate, i.e. the total number of cells, is considerably less than the total number of observations.

When interaction terms between the time intervals and the covariate of interest are included in the Holford model, it is analogous to Cox's model with time-dependent covariates [2]. It has been noted [18] that the computation time required to obtain parameter estimates for Cox's model when the covariates are time-dependent are much longer than the time required when the model only contains fixed covariates, and the user is advised to use such models with caution. Hence, for large data sets it is expected that the cost efficiency would be even greater between the Holford model and the Cox model with time-dependent covariates.

3. APPLICATION

To illustrate the application of these methods in investigating the non-proportionality of the hazard function, we consider data from a family genetic study of depression.

The family-genetic study of depression included 133 probands with major depression, 82 never previously ill controls, and 1518 of their first-degree relatives. The full details of the design, diagnostic criteria and methods have been described elsewhere [19, 20]. Initially the major effect of interest in this study was the proband group effect. Namely, did the relatives of depressed probands have higher rates of major depression than the relatives of the normal controls. This association has been investigated using log-linear models [19]. After controlling for potential confounders such as sex and age of relative and interview

status, we previously reported a twofold risk of major depression in the first degree relatives of depressed probands when compared to the relatives of normal probands.

Additionally, we were interested in the manner in which the age of onset of major depression in probands was associated with the age of onset of major depression in relatives. This analysis was restricted to the depressed probands and their first degree relatives, first step in investigating this association was to stratify the sample of relatives, by the age of onset of probands, where the age of onset of depression in probands was divided into four categories: less than 20 years, 20–29 years, 30–39 years, and 40 or more years. For each of these strata we then computed the hazard functions, i.e. age-specific incidence rates of major depression, using life table methods [21]. A plot of these hazard functions is shown in Fig. 1. As can be seen, if the age of onset of depression in a proband is less than 20 years, the most likely age of onset of depression in a relative is between 10 and 20 years. If the age of onset of depression in a proband is between 20 and 29 years, the most likely age of onset of depression in a relative is between 30 and 40 years. When the proband has an age of onset between 30 and 39 years, the most likely age of onset in a relative is also between 30 and 40 years, although having an onset of depression between 10 and 20 years is almost as likely. When the proband has an age of onset of 40 or more years, the most likely age of onset in relatives is between 20 and 30 years, although these relatives are almost as likely to have onset of depression between the ages of 40 and 50 years.

We were interested in determining if these findings held, when previously identified confounding variables, such as age of relative, sex of relative, interview status and age of proband were controlled [19]. The usual method of analyzing survival data, controlling for covariates is by using the proportional hazards regression model. However, if there is an association between age of onset of proband, and the age of onset of relative, the relative risk of developing the disease will not remain constant over time for any two levels of the age of onset of proband. Hence, we would not expect the hazard functions for the different levels of age of onset of proband to be proportional. Thus, investigation of the assumption of proportionality was critical to this analysis.

3.1. Application of graphical method

The model described in Section 2.1 was fitted to the data using the Biomedical Computer Program Series P Program 2L (Survival Analysis with Covariates—Cox Models) [18]. The survivor functions were computed for each of the four levels of age on onset of proband,

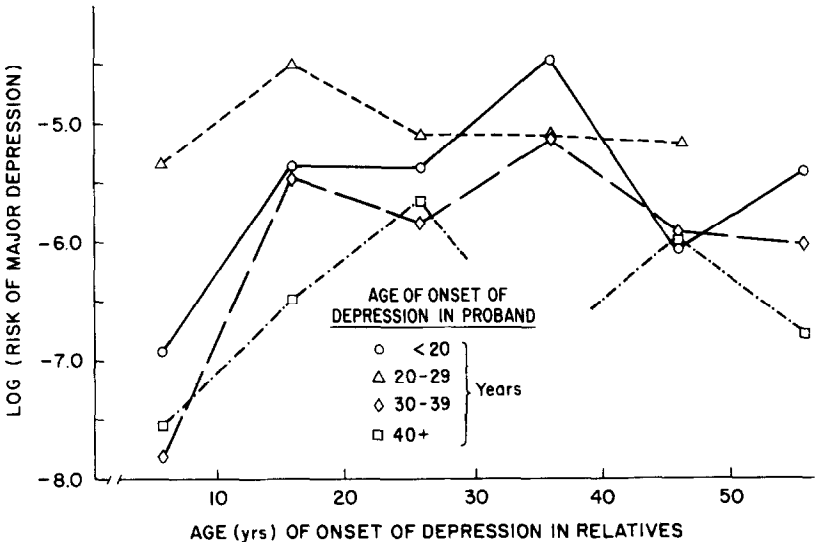

FIG. 1. Risk of major depression in relatives by age of onset of depression in relatives (stratified by age of onset in proband).

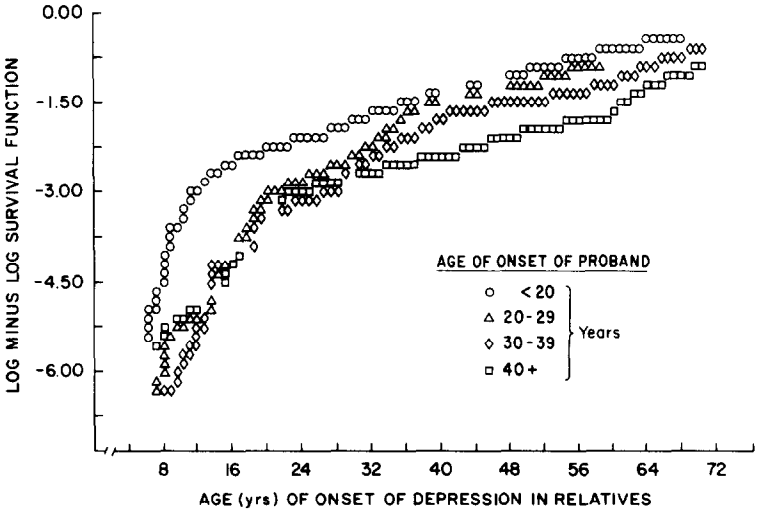

FIG. 2. Log minus log plot of survival function by age of onset of depression in relatives (stratified by age of onset in proband).

while controlling for the covariates—age, sex and interview status of relative, and age and sex of proband. Plots of $\log[-\log \hat{F}(t)]$ for the different levels of the age of onset of proband are shown in Fig. 2.

It will be noted that the separation between these plots is not constant, i.e. there is a wide separation between the plot for the age of onset of proband less than 20 years, and the other levels of the age of onset of proband, for earlier ages of relatives. This separation decreases with increasing age of relative. This implies that relatives of probands with age of onset less than 20 are at greater risk of being depressed at an earlier age, than those relatives of probands with an age of onset category greater than 20. One drawback of this method is that simple statistical tests of differences between the age of onset of proband categories cannot be made.

3.2. Application of analytic methods

The model described in Section 2.2 was fitted to the data using GLIM [22, 23]. The covariates considered were age of onset of proband grouped into four categories as before, sex of relative and interview status. The period of follow-up in the context of this analysis is the number of years from birth to current age or age at death if the relative was not affected. If the relative was affected, it is the age of onset of depression. The period of follow-up was divided into a series of 10-year intervals, i.e. less than 10 years, 10–19 years, 20–29 years, 30–39 years, 40–49 years, 50 and over.

In order to investigate the non-proportionality of the hazard function, we included an interaction term between the follow-up time intervals and the age of onset of proband. When the data were categorized by sex of relative, interview status and age of onset of proband, the number of depressed persons in some of the later time intervals is zero, making these interaction parameters inestimable. To overcome this problem, rather than fitting an interaction term consisting of the four age-of-onset of proband categories multiplied by the six age-of-onset of relative categories, we fitted a term which only accounted for the interaction between age of onset of proband less than 20, and age-of-onset of relative less than 20. This interaction term was obtained by multiplying the dummy variable which denoted age of onset of proband less than 20 years, by the dummy variables denoting age of onset of relative less than 10 years, and 10–19 years, respectively. This enabled us to explore the hypothesis that relatives of probands with an age of onset less than 20 have a greater risk of getting depressed at an early age (<20) than relatives of probands with age of onset greater than 20.

TABLE 1. RESULTS OF FITTING MODELS

Model	df	G^2	Effect	Δdf	ΔG^2	p value
P', R', S, I	83	85.20				
P, R, S, I	85	93.49	Age of onset of proband (<20) × age of onset of relative (<20)	2	8.29	$0.01 < p < 0.025$
R, S, I	88	115.19	Age of onset (proband) P	3	21.70	$p < 0.001$
P, S, I	90	124.66	Age of onset (relative) R	5	31.17	$p < 0.001$
P, R, I	86	97.59	Sex of relative S	1	4.10	$0.025 < p < 0.05$
P, R, S	86	105.87	Interview status I	1	12.38	$p < 0.001$

The significance of the main effect of age of onset of proband indicates that when controlling for sex of relative and interview status, the age of onset of proband has a highly significant ($p < 0.001$) effect on the incidence of major depression in relatives. Table 1 shows the results of fitting these models. The letters P, R, S and I refer to age of onset of Proband, age of onset of Relative, Sex of relative and Interview status, respectively. For example, the model P, R, S, I refers to a model which contains these four main effects and the grand mean. The model P', R', I, S refers to a model with main effects P, R, I, S and including the interaction term between age of onset of proband less than 20 and age of onset of relative less than 20, as described previously. The significance of the interaction term indicates that there is an important association between early age of onset (<20) of major depression in probands and early age of onset (<20) of major depression in relatives.

It will be noted that the model P', R', I, S has a G^2 (likelihood ratio statistic) value of 85.20 with 83 df; the expected value of G^2 when it is assumed that its distribution is approximated by a χ^2 distribution with 83 df is 83, which is very close to the observed value. This seems to imply that the model gives a good fit to the data, and that there is probably no need to consider the effects of any other covariates. However, because some of the individual cell frequencies are small (even though the total number N of observations is large), the approximation of the distribution of G^2 by a χ^2 distribution becomes uncertain [24]. The χ^2 approximation to the distribution of ΔG^2 has been shown [24] to be far more reliable; consequently the tests of significance of parameters using ΔG^2 as the test statistic, have been emphasized over the tests of goodness of fit of the models, using G^2 as the test statistic.

Table 2 gives a comparison of the ratio of hazards when (a) assuming proportionality and (b) adjusting for non-proportionality. The results of fitting the model assuming proportionality show that the risk of getting depressed given that one has a first degree relative who was depressed at age <20, is 1.36 times higher than if one has a first degree relative who was depressed between ages of 20 and 29. Similarly, the risks of getting depressed given that one has a first degree relative who was depressed at age <20 is twice as high as the risk if one had a first degree relative depressed between ages 30 and 39. This model implicitly assumes that this relative risk (ratio of hazards) remains constant during the time an individual is at risk for getting depressed.

TABLE 2. A COMPARISON OF RISKS OF MAJOR DEPRESSION IN RELATIVES USING PROPORTIONAL AND NONPROPORTIONAL HAZARD MODELS

	Age of onset of relatives			
		Non-proportional hazards		
Age of onset of proband	Proportional hazards All ages	<10	10–19	20+
<20 vs 20–29	1.36	1.90	5.25	0.84
<20 vs 30–39	2.05	2.86	7.90	1.26
<20 vs 40+	3.74	5.27	14.53	2.32

However, when proportional hazard functions are not assumed, we see that this excess risk, conferred by having a first degree relative who was depressed at age <20, when compared to the risk when one has a relative who was depressed between ages 20 and 29, is limited to the ages 0–20 years, of the person at risk. After age 20, the risk actually decreases, as shown by the fact that the ratio of hazards (0.8) is less than 1. These results show that there is a positive association between early age of onset (<20) of major depression in probands and early age of onset (<20) in relatives. Similarly, although the excess risk conferred by having a first degree relative who was depressed at age <20, when compared to the risk of having a depressed relative whose age of onset was between 30 and 39 years is positive throughout the entire period of risk, the ratio of hazards differs greatly between the different periods at risk.

4. DISCUSSION

In our analysis, we found that the graphical and analytic methods of investigating non-proportionality of the hazard function complemented each other. The data were first analyzed using the Graphical Method to investigate potential confounding variables. We found that sex of proband, and age of proband were not associated with the risk of getting depression in relatives, although it is possible that the data did not carry enough power to detect these associations; however, sex of relative, interview status and year of birth of relative were found to be associated with the risk of getting depression in relatives. As a result, when applying the Analytic Method to the data, we controlled for sex of relative and interview status. When we attempted to control for year of birth, we ran into large numbers of cells with zero values, and thus we could not control for this variable. However, it was discovered that when the sample was stratified by age of onset of proband, the distribution of year of birth in each of these four strata was, by a fortuitous circumstance, almost identical. Hence, year of birth, although related to the risk of getting depression, was not a confounder of the overall effect of age of onset of proband, on risk of depression in relatives.

As noted previously, this method of investigating non-proportionality using Holford's Method, is similar to including a time-dependent covariate in the more traditional form of Cox's proportional hazards model [2]. Because of the large sample size ($N = 1518$), analyzing the data using the model described here should be less costly in terms of computer time.

A limitation of this method is that the assumption of independence among members of a family, implicit in this model, may be unjustified. Ideally, we need a survival time model that can handle covariates with mixed effects; the effect of family can then be treated as a random effect, while the other covariates are treated as fixed effects. Logistic-linear mixed models that can handle fixed and random effects for binary responses, and which can be readily extended to categorical responses, have recently been developed [25]. Since Holford's method essentially reduces survival analysis to a special case of the log-linear model for contingency tables, when all covariates are categorical, it may be feasible to use these recently developed mixed model approaches to analyze survival time data, where the covariates are treated as having mixed effects. Alternatively, we could select one member at random from each family, and proceed with the analysis. This selection procedure would ensure that the assumption of independence is met, but would greatly reduce the sample size and hence the statistical power of the analysis.

5. CONCLUSION

The analysis of these data, using both graphical and analytic methods of investigating non-proportionality of the hazard function, indicates that the hazard function for the different levels of the age of onset of proband is not proportional over the period of follow-up time, i.e. age of onset of relative. This indicates that there is an association between the age of onset of depression in the proband and the age of onset of depression

in the relative [9]. These data suggest that similar to early onset diabetes, early onset depression may constitute a distinct subtype of depressive illness [26]. While data from a study of early onset depression were used to illustrate these methods, they are broadly applicable and useful for the investigation of familial transmission of many chronic diseases. Furthermore, this method of analysis is also applicable to investigating the effect of any other proband factor on the age of onset of disease in relatives, with the important feature of this method being the recognition that age of onset of disease can be treated as a survival time, with censoring occurring when no disease appears by the end of the follow-up period.

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REFERENCES

1. Winokur G, Clayton PJ, Reich T: **Manic-depressive Illness.** St Louis: Mosby, 1969. pp. 34–43
2. Cox DR: Regression models and life tables (with discussion). **J R Stat Soc B** 34: 187–220, 1972
3. Farwell J, Flannery JT: Cancer in relatives of children with central-nervous-system neoplasms. **N Engl J Med** 311: 749–753, 1984
4. Warram JH, Krolewski AS, Gottlieb MS, Kahn CR: Differences in risk of insulin-dependent diabetes in offspring of diabetic mothers and diabetic fathers. **N Engl J Med** 311: 149–152, 1984
5. Gottlieb MS: Diabetes in Offspring and siblings of juvenile- and maturity-onset-type diabetics. **J Chron Dis** 33: 331–339, 1980
6. Gershon ES, Hamovit J, Guroff JJ, Dibble E, Leckman JF, Sceery W, Targum SD, Nurnberger JI, Goldin LR, Bunney Jr WE: A family study of schizoaffective, bipolar I, bipolar II, unipolar, and normal control probands. **Arch Gen Psychiat** 39: 1157–1167, 1982
7. Mendlewicz J, Baron M: Morbidity risks in subtypes of unipolar depressive illness: Differences between early and late onset forms. **Br J Psychiat** 139: 463–466, 1981
8. Baron M, Risch N, Mendlewicz J: Age of onset in bipolar-related major affective illness: Clinical and genetic implications. **J Psychiat Res** 17: 5–18, 1982
9. Weissman MM, Wickramaratne P, Merikangas KR, Leckman JF, Prusoff BA, Caruso KA, Kidd KK, Gammon GD: Onset of major depression in early adulthood: Increased familial loading and specificity. **Arch Gen Psychiat** 41: 1136–1143, 1984
10. Bishop YMM, Feinberg SE, Holland PW: **Discrete Multivariate Analysis: Theory and Practice.** Cambridge, Mass: MIT Press, 1975
11. Bennett S: Analysis of survival data by the proportional odds model. **Stat Med** 2: 273–278, 1983
12. Kalbfleisch JD, Prentice RL: **The Statistical Analysis of Failure Time Data.** New York: John Wiley, 1980
13. Holford TR: Life tables with concomitant information. **Biometrics** 32: 587–597, 1976
14. Holford TR: The analysis of rates and survivorship using log-linear models. **Biometrics** 36: 299–305, 1980
15. Baker RJ, Nelder JA: The GLIM System, Release 3, **Generalized Linear Interactive Modelling.** Numerical Algorithms Group, Oxford, 1978
16. Health Science Computing Facility: **BMDP 4F Two-Way and Multiway Frequency Tables—Measures of Association and the Log-Linear Model (Complete and Incomplete Tables).** Berkeley, CA: University of California, 1983
17. Laird N, Olivier D: Covariance analysis of censored survival data using log-linear analysis techniques. **J Am Stat Assoc** 76: 231–240, 1981
18. Health Science Computing Facility: **BMDP 2L Survival Analysis with Covariates—Cox Models.** Berkeley, CA: University of California, 1983
19. Weissman MM, Kidd KK, Prusoff BA: Variability in the rates of affective disorders in relatives of depressed and normal probands. **Arch Gen Psychiat** 39: 1397–1403, 1982
20. Weissman MM, Gershon ES, Kidd KK, Prusoff BA, Leckman JF, Dibble E, Hamovit J, Thompson WD, Pauls DL, Guroff JJ: Psychiatric disorders in the relatives of probands with affective disorders: The Yale-NIMH collaborative family study. **Arch Gen Psychiat** 41: 13–21, 1984
21. Cutler SJ, Ederer F: Maximum utilization of the life-table method in analyzing survival. **J Chron Dis** 8: 699–712, 1958
22. Aitkin M, Clayton D: The fitting of exponential, Weibull and extreme value distributions to complex censored survival data using GLIM. **Appl Stat** 29: 156–163, 1980
23. Whitehead J: Fitting Cox's regression model to survival data using GLIM. **Appl Stat** 29: 268–275, 1980
24. Haberman SJ: **Analysis of Qualitative Data.** Vol. I, **Introductory Topics.** New York: Academic Press, 1978. pp. 325–326
25. Stiratelli R, Laird N, Ware JH: Random effects models for serial observations with binary response. **Biometrics** 40: 961–971, 1984
26. Rotter J, Rimoin D, Samloff I: Genetic heterogeneity in diabetes mellitus and peptic ulcer: In **Genetic Epidemiology,** Morton NE, Chung CS (Eds). New York: Academic Press, 1978. pp. 381–414