

Full Length Research Paper

Analyzing long-term mortality among female alcoholics and matched controls: Accounting for age and follow-up time

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Studies focusing on mortality data use a wide variation of strategies for data analyses, making comparison between studies difficult. The research problems focus upon different statistical analyses of mortality among patients and matched controls regarding clustered data and relations over different levels of age and follow-up time. Four hundred and twenty (420) treated female alcoholics were compared to 2,036 matched controls and public register data for a follow-up period of 27 years were used. The statistical analyses are multilevel, structural equation modeling (SEM) level-and-difference analyses, multilevel Cox regression analysis, interaction Cox models, time-dependent Cox survival models, proportional and non-proportional latent discrete-time survival models. The multilevel analyses confirm the success of the matching procedure. The interaction model adds more information to the main effect model and shows the mortality estimate to be dependent on age. Continuous time-dependent Cox regression models and latent discrete-time survival analyses show the mortality estimates to differ with time and age. Different results depend on statistical models. This illustrates how mortality as a construct not only represents hard and unequivocal evidence given by the samples studied, but also includes factors related to the statistical model used. Such methodological factors need to be incorporated in the scientific discussion of mortality studies generally.

Key words: Continuous and discrete time survival analysis, interaction models, matched data, mortality.

INTRODUCTION

Mortality statistics are one of the most important methods of reporting the health of general populations and the seriousness of a disorder. In addition, mortality is widely used in medicine to report the efficacy and risks of treatment procedures. The construct "mortality" seemingly represents hard evidence, making comparison between studies simple and unequivocal. Thus, a discussion of the applied outcome measurement may be seen as superfluous or unnecessary. However, methods of sampling and

analyses vary and the comparison of results between studies may be problematic or even misleading. Some studies report frequency of death without including time to death in the analyses. Information about this is important to take into consideration in order to explain why a group difference is found or not (Singer and Willett, 2003). Another topic is confounding variables, which more or less are taken into consideration in different studies. Regression models accounting for relevant variables,

both as main and interaction terms, may be used to control factors which themselves also may be related to mortality. A third factor is about sampling. Mortality risks are estimated in relation to a control sample. Control subjects may be randomly sampled from the general population (Gerdner and Berglund, 1997), or from a matched control population in order to control mortality related variables (Rosenbaum and Rubin, 1985).

Matching increases the efficiency of the estimation of difference between cases and controls and creates equivalence in the samples regarding relevant covariates (Smith, 1997). Increasing the numbers of matched subjects increases the accuracy of population estimates, while confounding effects may be controlled by increasing the number of matching variables. However, several matched controls for each study subject makes clustered data. In this study, up to five controls were matched for each study subject. Within cluster, women were almost identical, regarding age, civil status, socio-economic status and level of education and data may therefore be almost perfectly correlated within clusters on the matched variables and somewhat less perfectly correlated regarding other related variables. Thus, observations are not independent and statistical tests not accounting for data clustering may give biased results (Norušis, 2005; Brown and Prescott, 2006; Breslow, 1996). Multilevel analysis is a method that gives unbiased estimates and tests the success of the matching procedure (Drukker et al., 2008).

Matching variables may themselves be related to mortality (Rogers et al., 2010; Saarni et al., 2008). In addition to making cases and controls equal by matching, less unbiased estimates is achieved if such confounding matching variables also are included in the statistical model (Card et al., 2003; Jackson et al., 2007). For example, one study showed how a group difference changed from lower to higher mortality rates after accounting for age, race, gender, and major comorbidities (Yuan et al., 2001). In the present study, group difference is analyzed with statistical control for age and educational level. However, assuming mortality difference between patients and controls to be equal over all levels of age represents an oversimplification for the statistical model, especially in samples with large variation in age. The interaction term between group and age should also be considered for the model. Interaction terms are often not considered for inclusion in regression models (Cohen et al., 2003; Pedhazur and Schmelkin, 1991), nor in Cox regression models.

Mortality difference between two groups may vary during the follow-up interval, particularly if this interval is of long duration. Follow-up interval may vary between studies from months to decades, and comparisons over studies are difficult. To divide the number of deaths on the duration of follow-up time in order to compare findings from different studies may be a problematic procedure (Timko et al., 2006), as this strategy represents an average number of deaths for each unit of time and mask potential differences between groups regarding when deaths

occur. For example, a treatment study may show the preventive effect to be stronger right after the intervention than in the long run (Cuijpers et al., 2004). This will be reflected in varying mortality rates over time, a situation that represents a threat against the proportional hazard assumption (Norušis, 2005). Time-dependent interaction effects should be considered in order to explore this research problem (Willett et al., 1998). Also, time may be treated as a continuous variable or as discrete-time interval variables (Masyn, 2003).

The present research problems focuses on statistical analyses of mortality among patients and matched controls regarding clustered data with several matched controls for each study subject, the effect of statistical models including the group mortality difference and predictor relations over different levels of age and follow-up time. The data analyzed is from an alcohol study (Haver et al., 2009). However, the discussion of alcohol related mortality is not the substantial theme here, since this topic of methodology extends to mortality studies in general and to studies of long follow-up duration in particular.

MATERIALS AND METHODS

Participants

The subjects were 420 women not previously treated for alcohol use disorders, who participated in the European Workplace and Alcohol (EWA) project at the Karolinska Hospital, Stockholm, Sweden (Haver et al., 2009). This sample consists of four sub groups (sequence strata); one pilot study sample from 1981 to 1982 (N = 100), another randomized controlled trial (RCT) study sample with two groups receiving different treatments from 1983 to 1984 (N = 200), and a comorbidity study sample from 1991 to 1993 (N = 120). In 2009, a matched general population control (MGPC) group was obtained from the Swedish Causes of Death Register (N = 2036), with up to five matched controls for each study woman. The follow-up period was up to 27 years.

Measures

Variables used for analyses are group (addicted versus MGPC women), age and time since intake to treatment, mortality status, and education level. The education variable was ordinal with 3 categories: primary school, high school and college/university. Two Helmert contrast variables were constructed, specifying the difference between the low level and the sum of the two other levels (Edu_H1 = 1, -.5, -.5) and the difference between the two last education categories (Edu_H2 = 0, 1, -1).

Analyses

Due to strata and clustering of data, bootstrapping with stratified resampling was used to estimate confidence intervals (Timmerman et al., 2009; Barber and Thompson, 2000). Bootstrapping handles deviation from normal distribution well (Hair et al., 1998; Wehrens et al., 2000), and gives more precise estimates in samples smaller in size (Haukoos and Lewis, 2005). Clustered data may be analyzed with multilevel models, giving within and between cluster estimates (Brown and Prescott, 2006; Smith, 1997; Norušis, 2005). Such models

may also control for measurement errors (Breslow, 1996). With relatively few cases within clusters, structural equation latent level-and-difference modeling may be used as an alternative (Newsom, 2002). Both statistical methods are used as an illustration of the analyses of within and between cluster levels and variations of age. In addition, the multilevel relationship between age and mortality is analyzed. Since the total sample consisted of four strata, potential strata effects are accounted for (Muthén and Satorra 1995, Stapleton 2006).

Cox regression is used to analyze survival models with continuous and categorical predictor variables (Bradburn et al., 2003). Age is analyzed as a continuous variable, since categorizing a continuous variable may give biased estimates and is encumbered with reduced statistical power (Royston et al., 2006; Cohen et al., 2003). Interaction models often introduce multicollinearity problems and resulting in instability in estimates. Different solutions exist; centering and incremental significance testing (Hair et al., 1998), or the use of the residualized interaction term (Delacroix and Ragin, 1978). Centering changes the interpretation of the main effects and has implications regarding what level of the main effect that is tested for statistical significance (Hair et al., 1998, Cohen et al., 2003). In the present study, the age variable is centered. Visualization may be a good way to present survival differences between cases and controls at low and high levels of age. These age levels are arbitrary set and entered into the Cox regression equation to give predicted scores for women being 30 and 50 years, illustrating survival at those age levels.

Allowing for group differences in mortality rates over time is done by entering variables as time dependent covariates in Cox regression. This procedure frees up and tests the proportional hazard assumption in ordinary Cox regression (Norusis, 2005; Chen et al., 2010). This is not very often verified in research (Bellera et al., 2010). Based on these results, time-restricted Cox proportional models may be chosen. Covariates may be static or time-varying and may have different magnitude in their predictive associations with mortality over time. If time is divided into several restricted interval variables and discrete-time survival models analyzed, predictors may be directly related to mortality in separate time intervals (Muthén and Masyn, 2005; Abbott, 1985).

Proportional hazard models may still be estimated as latent discrete-time survival analyses (Muthén and Muthén, 2007) and used as an approximation to the Cox regression model as long as the categorization of the time variable is sufficiently detailed (Asparouhov et al., 2006). Equal hazards over the entire range of time intervals is then specified with all factor loadings between the latent variable and the mortality status in each time interval specified as one (Muthén and Muthén, 2007). Here, we used two set of models consisting of two- and four year intervals. Using a four year interval will increase the prediction power due to more deaths within each interval, while a more restricted interval is more suitable when shorter time-dependent associations is in focus. The proportional restriction may be freed up in order to analyze different predictive relations in each interval. This is done by removing the latent part of the model and different time intervals are allowed to be predicted by separate logistic regressions (Muthén and Masyn, 2005).

Another test of a non-proportional hazard model could be done by adding predictors over and beyond the latent factor. We have not seen this last procedure used in the literature, but adding parameters to a basis model is used as a strategy in other structural models (Muthén and Curran, 1997). Dependent on the sample size (Kline, 2010), combinations of survival models and other structural equation models may address very flexible research problems (Muthén and Muthén, 2007; Bollen, 1989; Bollen and Curran, 2006; Duncan et al., 2006; Masyn, 2008). Model fit is evaluated with the measures-LogLikelihood, Akaike information criterion (AIC), and the Bayesian information criterion (BIC) (Kline, 2010).

Statistical Package for Social Sciences (SPSS) 18 was used for multilevel analyses (linear mixed model) and Cox survival analyses. Mplus 5.2 was used for multilevel analyses, level and difference models, multilevel Cox regression and discrete-time survival analyses (Muthén and Muthén 2007, Muthén and Masyn 2005).

RESULTS

The mean age is 42.63 (standard deviation (SD) = 9.81) for patients, for controls 42.54 (SD = 9.77). The parametric 95% confidence intervals (CI) are: addicted women: 41.69 to 43.57 and MGPC subjects: 42.11 to 42.96. The stratified 95% bootstrapping of the MGPC group on cluster within the four sequence strata shows a much smaller CI than the parametric CI: 42.53 to 42.55. Mortality was 33.1% in the alcoholic group and 14.6% in the control group ($p < 0.001$; RR = 2.26, OR = 2.89).

Matched data

Multilevel analyses of age in the MGPC group showed the within cluster variation of age to be very small compared to the between cluster variation (SPSS/Mplus: $\sigma_w^2 = 0.09/0.07$, $p < 0.001$); $\sigma_B^2 = 95.05/94.84$, $p < .001$; ICC = 0.999). The standard error of mean (SEM) level-and-difference model confirms between cluster variations in age with equal estimates in an intercept model. A nested model with the age variable constrained to be equal for all within controls and patients shows a better fit than the unrestricted model ($\chi^2 = 33.39$, $df = 24$, $p = 0.096$, root mean square error of approximation (RMSEA) = 0.031, $RMSEA_{close\ fit} = 0.91$; $\Delta\chi^2 = 3.48$, $\Delta df = 5$, $p = 0.63$). This model with control for the statistical stratification effect was only marginally different ($RMSEA_{close\ fit} = 0.92$). Both Mplus and SPSS Cox regression analysis gives identical estimates of the relation between age and time to death (0.09, $p < 0.001$). Mplus multilevel Cox regression analysis show no such within cluster relation between age and mortality (0.08, $p > 0.05$).

Group difference in mortality dependent on age: The interaction effect

A Cox regression analysis shows the mortality risk among patients relative to controls to be 2.61. After accounting for the variable age, this estimate is 2.67 (Exp(B), $p < 0.001$). When the interaction term with centered age variable is included, this group estimate is 3.31 ($p < 0.001$), which indicate the group mortality difference at mean age level. The hazard ratio of the interaction term was 0.96 ($p < 0.001$). Figure 1 and Appendix 1 illustrates how the interaction effect influences the survival plot, with stronger mortality difference for younger than older patients.

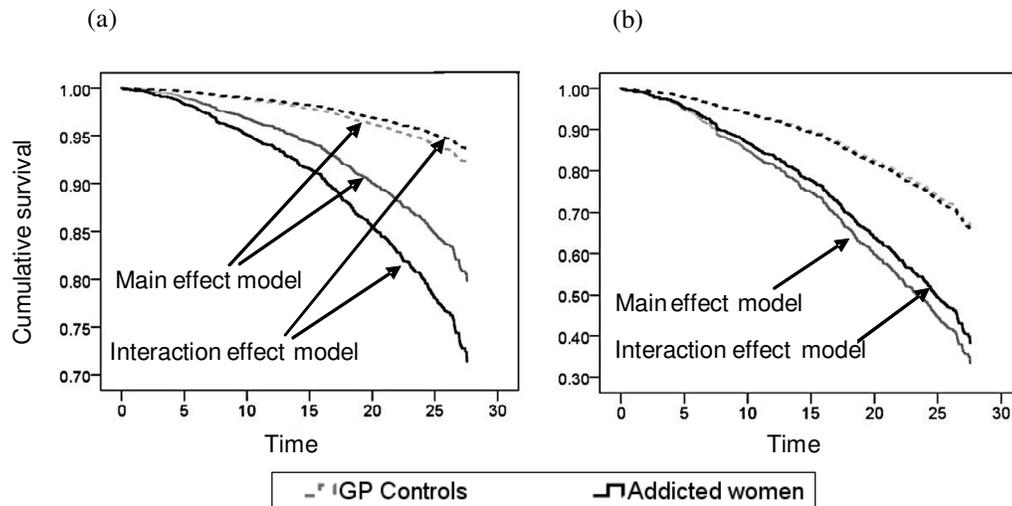


Figure 1. Age adjusted survival plots for addicted women and matched controls (MGPC). The plots are based on one standard Cox regression without interaction terms between group and age and one interaction model within this effect included. The expected survival is illustrated for younger and older women, set to (a) 30 or (b) 50 years.

Table 1. Survival analyses results for addicted women (ALC) and matched general population controls (MGPC) with age and group as time varying covariates. The variable age is centered.

Variable	b	Exp(B)	95% CI (lower)	95% CI (upper)	p
Group (ALC - MGPC)	1.161	3.19	2.56	3.98	***
Age	0.065	1.07	1.04	1.09	***
Age × Time	0.002	1.00	1.00	1.00	*
Age × Group × Time	-0.002	1.00	1.00	1.00	***

*p < 0.05 **p < 0.01, ***p < 0.001, b = unstandardized regression weight.

Analyzing group differences over a long follow-up time

Inspection of the log minus log plots of patients and controls as strata effects show parallel lines and confirm the assumption of proportional hazard. Further exploration of this assumption was done by entering the variables group and age (centered) as time dependent covariates. Table 1 shows age and the interaction between age and group to be statistically significant.

Since the coding for the patient group is one, the last time interaction effect in the table will even out the interaction effect of age and time. An increasing relative mortality risk for patients compared to controls is found among younger females over time, while relative mortality risk is decreasing among older women.

Latent discrete-time survival models based on these two-year intervals show identical results compared to the SPSS Cox regression analysis (Group = 1.21, age = 0.09, and Group × age = -0.04, all p-values < 0.001) (Model fit: LogLikelihood = -3150.41, akaike information criterion (AIC) = 6336.82, Bayesian information criterion

(BIC) = 6441.33). A multilevel latent discrete-time analysis, with the cluster variation in relationship between age and mortality accounted for, gives almost identical results. Another discrete-time survival model allows for direct group predictions of mortality within separate time intervals in addition to the already specified proportional hazard model accounted for by the latent factor. This shows the time interval 2 to 4 years to be statistically significantly predicted (b = 1.12, Exp(B) = 3.06, p < 0.05). This adds more evidence of non-proportionality in mortality between the groups over time. After accounting for educational level associations, the mortality ratio between cases and controls is found to be 3.65 (Exp(B)) for women at average age level and over all education levels. Education levels are found to be statistically significant related to mortality (Mplus results: Group = 1.30, age = 0.10, Group × age = -0.04, Edu_H1 = 0.32, and Edu_H2 = 0.28, all p-values < 0.01; Model fit: LogLikelihood = -2545.12, AIC = 5130.24, BIC = 5243.12).

In order to explore different mortality ratios in different time intervals, the latent variable is removed from the model. Table 2 shows no group differences for 3 intervals

Table 2. Prediction of mortality within discrete-time intervals (2 year). Predictors are group (addicted women versus matched general population control women - MGPC), age, and interaction between group and age. Fit statistics are given for full (M_0) and restricted (M_1) models with difference between these models.

Variable	Group		Age		G × A	
	b	OR	b	OR	b	OR
Time interval						
0-2	1.36*	3.91	0	1	-	
2-4	2.01***	7.45	0.04	1.05	-	
4-6	0.46	1.58	0.08**	1.08	-	
6-8	0.74*	2.1	0.09***	1.09	-	
8-10	1.87***	6.5	0.14***	1.15	-0.08*	0.92
10-12	0.85*	2.35	0.07**	1.07	-	
12-14	0.72	2.06	0.06**	1.06	-	
14-16	0.90*	2.46	0.11***	1.12	-0.09*	0.92
16-18	1.32***	3.76	0.08***	1.09	-	
18-20	1.17**	3.23	0.10***	1.1	-	
20-22	1.03**	2.79	0.08***	1.09	-	
22-24	0.62	1.86	0.10***	1.11	-	
24-26	1.41***	4.1	0.11***	1.12	-	
26-28	1.35**	3.84	0.02	1.02	-	
LogLikelihood	M_0	-3126.64	M_1	-3134.84	$\Delta M_1 M_0$	8.2
AIC		6367.28		6359.68		-7.6
BIC		6698.24		6477.98		-220.26

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. M_0 = full model, M_1 = restricted model without non-significant interaction effects, OR = odd ratio based on logistic regression, AIC: Akaike information criterion, BIC: Bayesian information criterion, b = unstandardized regression weight.

intervals and relatively large variation in the other time-dependent group estimates. Two interaction effects between group and age are found. The results from the four year interval model confirm the group mortality difference to be quite different in different periods (odds ratio: 1.82 to 5.88). Educational level contrast variables were added to the analyses of four year intervals. The difference between patients and matched controls is now statistically significant in all intervals except the second (4 to 8 years) and the interval 12 to 16 years (mortality estimates: 5.54, 1.00, 4.04, 1.00, 5.33, 3.09, and 4.64). The education level variables (Edu_H1 and H2) are statistically significant, related to mortality in the intervals 4 to 8 (Edu_H2 = 1.52) and in the interval 8 to 12 (Edu_H1 = 1.90 and Edu_H2 = 1.76).

DISCUSSION

The mortality ratio between patients and controls is found to be 2.3/2.9. The estimate is 2.67 when time to death and age is included in the analyses. The interaction result between group and age shows the risk estimate to be 3.31 at the average age level, while it is 3.65 when accounting for education levels. Higher educational level

is associated with lower mortality risk. Thus, educational level is a factor to include when analyzing patient and control difference in mortality (Rogers et al., 2010; Thygesen et al., 2008; Saarni et al., 2008). Discrete two and four year intervals show varying mortality ratios between the groups, with estimates up to 7.45. These findings illustrate how mortality estimates depend on how time and event related variables are treated and analyzed.

Clustered data

The small within cluster variation of age does not contribute statistically significantly regarding mortality. Finding equal results when accounting for the multilevel data structure are not obvious in all studies and such statistical models are well suited for checking how the matching procedure turned out. Significant within cluster variation in predictor levels and their relations with the outcome variable would indicate problems with this sampling procedure of matched controls. Multilevel analyses, controlling for cluster and stratification variations, give additional information about data (Muthén and Satorra, 1995).

Interaction effects

Mortality differences between patients and controls are found to be stronger for younger than older women. This finding illustrates the importance of considering the inclusion of interaction terms in time-to-event analyses and thereby account for important within group heterogeneity. A model including interaction effects may be misinterpreted, as the interpretation of main effects is changed in contrast to the model with main effects only. In interaction models, one main effect is tested when the other main effect is zero, while a model without interaction terms is testing one main effect over all levels in the other variable (Hair et al., 1998). Centering reduces the multicollinearity problem and makes the interpretation easier. In our case, the uncentered interaction model tested the group effect when age was zero, while in the centered interaction model the group difference was tested when age was at the average level. The last model is of course most relevant. However, the total model will in both cases give identical pictures, as main effects or lack of such effects only should be interpreted in relation to the interaction effect (Pedhazur and Schmelkin, 1991; Hair et al., 1998).

In the present study, age is important to include both as a main effect and in the interaction term with group membership. We have elsewhere documented reduced mortality for addicted women who received a specialized treatment relative to mortality among women who received "treatment as usual" (Gjestad et al., 2011). In that study, no effects were found without including interaction terms into the analyses. Then, a stronger mortality difference was found among younger than older women and early in the follow-up period than later on. This illustrates how an exclusive focus on the main effects not always gives the complete picture.

Time-dependent relations in long term follow-up intervals

Results from Cox regression analyses with time dependent covariates and discrete-time survival analyses show that the mortality difference between the groups is varying over time. These findings illustrate how non-proportional hazard models may give other results than proportional hazard models. The non-proportional hazard discrete-time survival analyses based on two-year intervals reveal that patients in our study do not differ from controls regarding mortality in the two-year interval after treatment, which could imply the possibility of a time limited treatment effect (Cuijpers et al., 2004). In this way, to specify a latent discrete-time survival analysis gives the possibility of analyzing the effect of a set of predictors directly on mortality in all time-intervals, the non-proportional

hazard model, in addition to the predictive relationship through the latent factor, giving the proportional hazard part of the model. This method increases the flexibility in model specification.

Conclusions

This paper illustrates how results obtained from mortality data are affected by the statistical procedures used. Differences in follow-up time, the selection of control samples, and the handling of variables contribute independently and together to reported mortality differences. Mortality estimates reported in epidemiological and clinical studies may be affected by factors that may be accounted for when groups are being made equal by matching variables (for example age, gender, and geographic location). However, other left out variables from the matching procedure may still contribute to some biases in the estimated risks. Applying different statistical models showed varying risk estimates, higher for the younger than for older women, and higher estimates early than later in the follow-up period. Thus, the overall estimate is only one way of reporting this group difference. Other studies have found mortality risks among women alcoholics to be about 6 (Dahlgren and Myrhed, 1977), 5 (Lindberg and Ågren, 1988), 5 (Berglund, 1984), 4 (Smith et al., 1994), and 3 (Schmidt and Popham, 1980). These studies did not use matched controls or control for confounding factors, they were of very different follow-up duration, and different statistical models were used. Such differences between studies come in addition to differences related to the samples involved as explanations for the findings and are relevant methodological aspects for other time-to-event analyses as well, for example treatment termination, relapse, drop-out, and hospital readmission.

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APPENDIX

Analysis syntax

Appendix 1. Age adjusted survival plots for addicted women and matched controls (MGPC). The plots are based on one standard Cox regression without interaction terms between group and age and one interaction model within this effect included. The expected survival is illustrated for younger and older women, set to 30 or 50 years.

A1: SPSS syntax: COX regression with interaction effects plotting survival for 30 and 50 years old subjects. Age is treated as a continuous variable.

```
COXREG TIME
/STATUS=DEAD(1)
/PATTERN age(30) BY Group
/PATTERN age(50) BY Group
/CONTRAST (Group)=Indicator(1)
/METHOD=ENTER Age Group Age*Group
/PLOT SURVIVAL
/PRINT=CI(95) CORR BASELINE
/CRITERIA=PIN(.05) POUT(.10) ITERATE(20).
```

A2: COX regression with time-dependent covariates

```
TIME PROGRAM.
COMPUTE T_COV = T_.
COXREG TIME
/STATUS=DEAD(1)
/METHOD=ENTER AGEc Group AGEc*Group
/method=enter AGEc*T_COV Group*T_COV
/method= enter AGEc*Group*T_COV
/PRINT=CI(95) CORR
/CRITERIA=PIN(.05) POUT(.10) ITERATE(20).
```

A3: Mplus Multilevel Cox regression

```
TITLE: Multilevel Cox regression
DATA: FILE = alc_mgpc_survival.dat;
VARIABLE:
NAMES = Case EWAAnr Ewanr2 Sequence
Seq_2 Group Group8 Age G_x_A Age_L2
Age_L1 Dead Time ;
USEVARIABLES = Age_L1 Age_L2 Group
Dead Time EWAAnr2 G_x_A ;
```

```
Cluster = EWAAnr2 ;
Categorical = Group ;
within = Age_L1 ;
between = Age_L2 Group G_x_A ;
Survival = Time (ALL);
Timecensored = Dead (1 = NOT 0 = Right) ;
```

ANALYSIS:

```
Type = twolevel ;
Basehazard = off ;
```

MODEL:

```
%within%
Time on Age_L1 ;
%between%
Time on Age_L2 ;
Time on Group ;
Time on G_x_A ;
```

Output:

```
Sampstat ;
cinterval ;
```

A4: Mplus Time-discrete survival analysis

```
TITLE: Latent time-discrete survival model
DATA: FILE = survival.dat ;
VARIABLE:
NAMES = Case EWAAnr Ewanr2 Sequence Seq_2 Group Group8 Age G_x_A
Age_L2 Age_L1 Dead Time D1-D14 DB1-DB7 ;
USEVARIABLES = D1-D14 Age ;
Categorical = D1-D14 ;
Missing = all (999) ;
```

ANALYSIS:

```
Estimator = MLR ;
```

MODEL:

```
f by D1-D14@1 ;
f on Age ;
f@0 ;
```

Output:

```
Sampstat ;
cinterval ;
```

The two-year intervals D1-D14 is coded 0 if subject is alive and 1 if a person dies in that actual period. After that point of time, intervals are coded missing data (999). D1-D14 is declared as categorical variables. The latent factor f with factor loadings pre-specified as 1 on all periods constitutes a proportional hazard time-discrete model. In this case, the survival function is regressed on the variable *age*.

The model may be expanded in order to include a multilevel time-discrete survival model including group, age and the interaction term group x age

MODEL:

```
%within%
D1-D14 on Age_L1 ;
%between%
F by D1-D14@1 ;
F@0 ;
F on Age_L2 Group G_x_A ;
D1-D14 on Group ;
```