# Extensions to Joint Models

**Day 7**

- Alternative parameterizations
- Residual Diagnostics

# Standard Joint Model

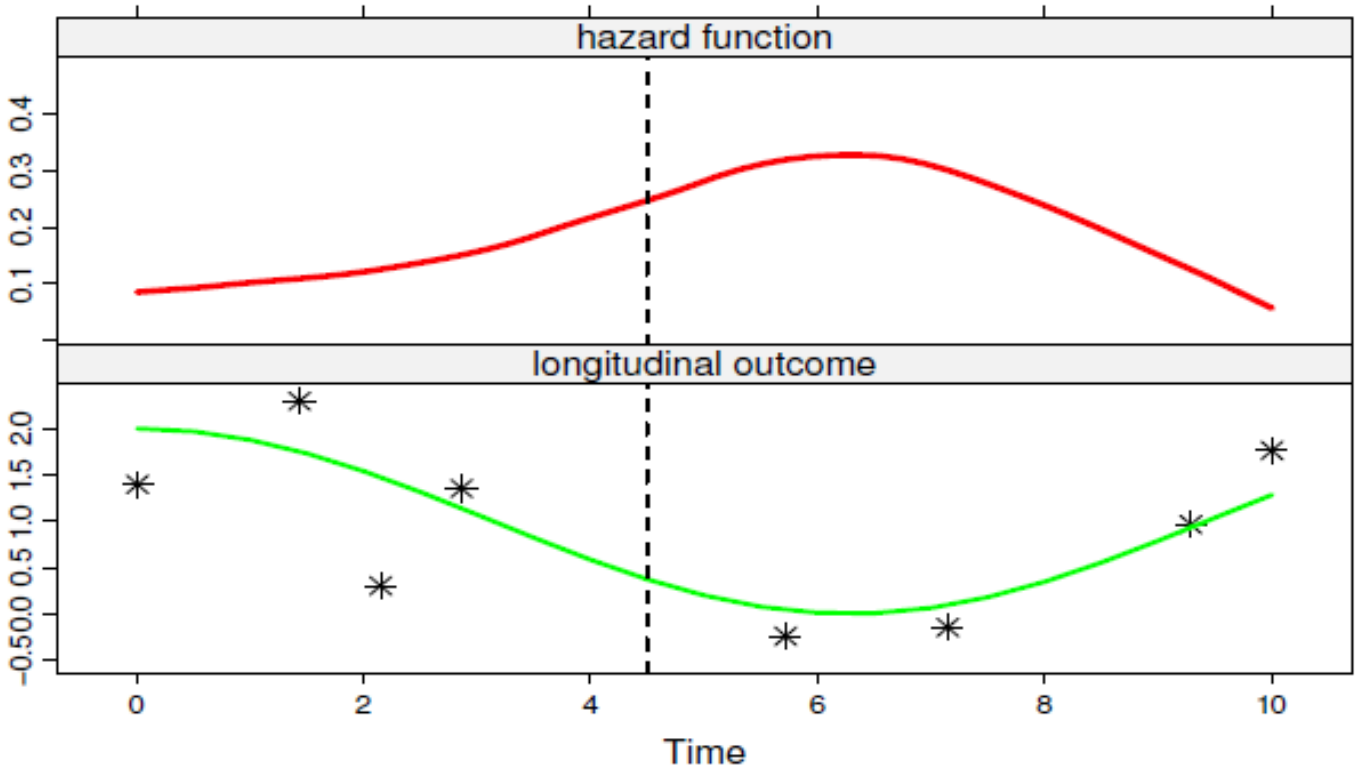
- The standard joint model

$$h_i(t|\mathcal{M}_i(t)) = h_0(t)\exp\{\gamma' w_i + \alpha m_i(t)\}$$
$$y_i(t) = m_i(t) + \epsilon_i(t)$$
$$= x_i'(t)\beta + z_i'(t)b_i + \epsilon_i(t)$$

where $\mathcal{M}_i(t) = \{m_i(s), 0 \leq s < t\}$

- $\alpha m_i(t)$ is the current value parameterization
- $m_i(t)$ is a function of time, rather than observed values at specific time points

# Standard Joint Model




- Is this the only option?
- Is this the most optimal choice?

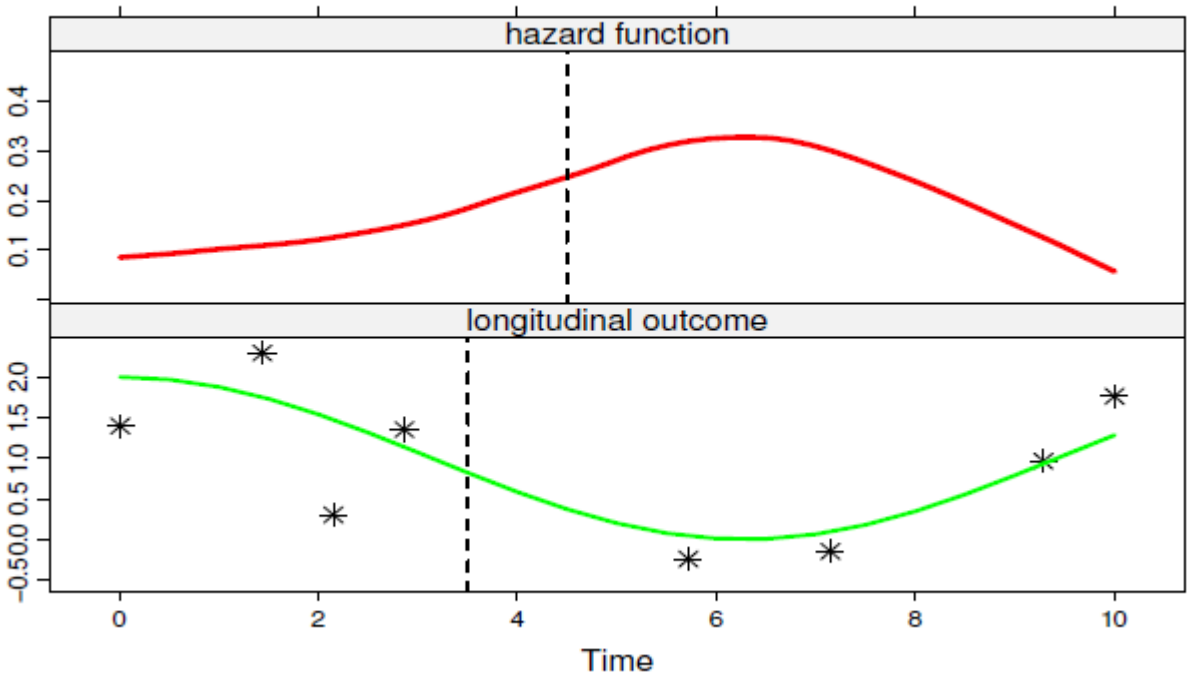
# Alternative Parameterizations

- Inappropriate modeling of time-dependent covariates may result in surprising results
- Cavender et al. (1992) conducted an analysis to test the effect of cigarette smoking on survival of patients who underwent coronary artery surgery
  - Found that the association was that patients who smoked had a higher probability of survival (although not significant)
  - Most of those who had died were smokers but many stopped smoking at the last follow-up before their death
- Need to carefully consider the functional form of time-dependent covariates

# Alternative Parameterizations

- **Lagged Effects:** The hazard of an event at $t$ is associated with the level of the marker at a previous time point

$$h_i(t|\mathcal{M}_i(t)) = h_0(t)\exp\{\gamma' w_i + \alpha m_i(t_+^c)\}, \qquad t_+^c = \max(t-c, 0)$$



# Lagged Effects

```
jointFit.lag1 <- jointModel(lmeFit, survFit, timeVar="year", method = "piecewise-PH-aGH", lag=1)
jointFit.lag2 <- jointModel(lmeFit, survFit, timeVar="year", method = "piecewise-PH-aGH", lag=2)
AIC(jointFit.lag1)
```

```
## [1] 3873.239
```

```
AIC(jointFit.lag2)
```

```
## [1] 3885.132
```

```
AIC(jointFit)
```

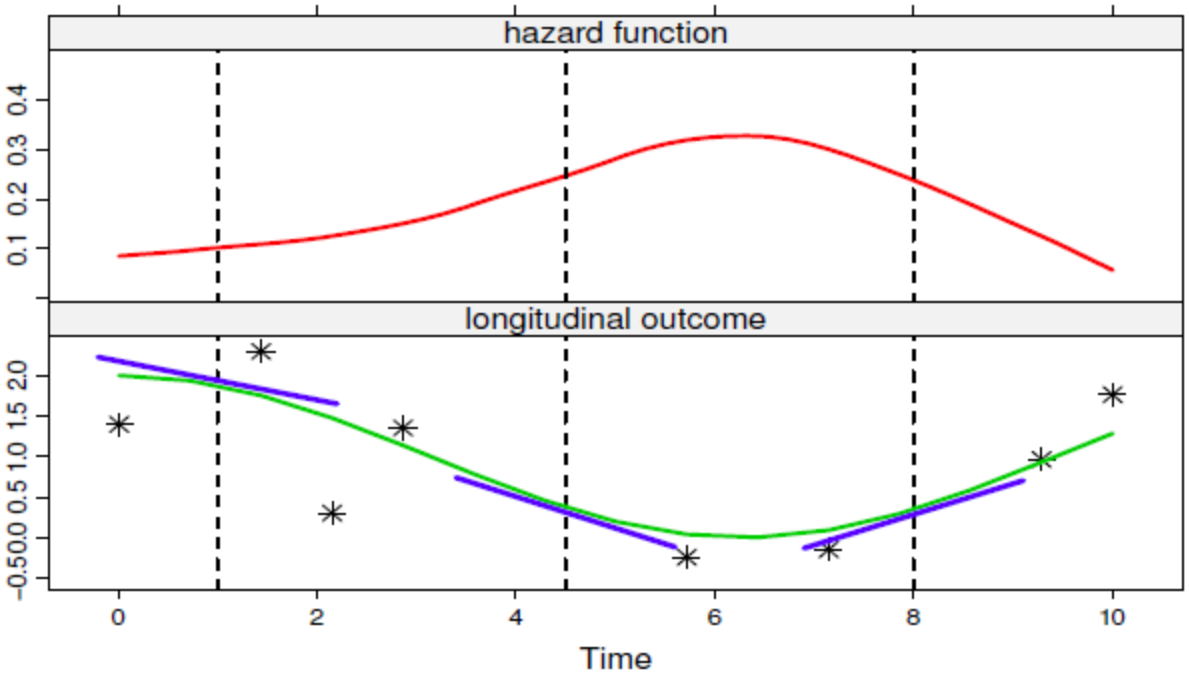
```
## [1] 3864.727
```

# Alternative Parameterizations

- **Time-dependent Slopes:** The hazard of an event at $t$ is associated with both the current value and the slope of the trajectory at $t$ *(Ye et al., 2008, Biometrics)*

$$h_i(t|\mathcal{M}_i(t)) = h_0(t)\exp\{\gamma' w_i + \alpha_1 m_i(t) + \alpha_2 m_i'(t)\}$$

$$m_i'(t) = \frac{d}{dt}\{x_i'(t)\beta + z_i'(t)b_i\}$$



# Time-dependent Slope

- The true value of the marker has the form

$$m_i(t) = \beta_0 + \beta_1 t + \beta_2\{t \times \text{D-penecil}_i\} + b_{i0} + b_{i1}t$$

- We take the derivative with respect to t

$$m_i'(t) = \beta_1 + \beta_2 \text{D-penecil}_i + b_{i1}$$

- We can write this derivative in the form

$$m_i'(t) = [x_i^*(t)]'\beta^* + [z_i^*(t)]'b_i^*$$

where

$$x_i^*(t) = [1, \text{D-penecil}_i], z_i^*(t) = [1]$$

$$\beta^* = [\beta_1, \beta_2], b_i^* = [b_{i1}]$$

# Time-dependent Slope

- We use the parameterization argument to indicate that we are including a slope
- Options: “value” (default), “slope”, “both” (current marker + marker slope)

```
lmeFit <- lme(log(serBilir) ~ year + year:drug, data = pbc2, random = ~ year | id)
survFit <- coxph(Surv(years, status2) ~ drug, data = pbc2.id, x = TRUE)
jointFit <- jointModel(lmeFit, survFit, timeVar="year", method = "piecewise-PH-aGH")

dform <- list(fixed = ~ 1 + drug, indFixed = 2:3,
              random = ~ 1, indRandom = 2)

jointFit.slope <- update(jointFit, parameterization = "both", derivForm = dform)
```

# Time-dependent Slope

- We then use the derivForm argument, which is a named list with four components:
  - fixed: formula representing the derivative of the fixed effects parts
  - indFixed: numeric vector indicating which fixed effects of the lme object correspond to the derivative
  - random: formula representing the derivative of the random effects parts
  - indRandom: numeric vector indicating which random effects of the lme object correspond to the derivative

$$x_i^*(t) = [1, \text{D-penecil}_i], z_i^*(t) = [1] \qquad \beta^* = [\beta_1, \beta_2], b_i^* = [b_{i1}]$$

```
lmeFit <- lme(log(serBilir) ~ year + year:drug, data = pbc2, random = ~ year | id)
survFit <- coxph(Surv(years, status2) ~ drug, data = pbc2.id, x = TRUE)
jointFit <- jointModel(lmeFit, survFit, timeVar="year", method = "piecewise-PH-aGH")

dform <- list(fixed = ~ 1 + drug, indFixed = 2:3,
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jointFit.slope <- update(jointFit, parameterization = "both", derivForm = dform)
```

# Time-dependent Slope

```
## Event Process
##                  Value Std.Err  z-value p-value
## drugD-penicil   0.0454  0.1930   0.2349  0.8143
## Assoct          1.0009  0.1250   8.0070 <0.0001
## Assoct.s        3.3387  1.0342   3.2281  0.0012
## log(xi.1)      -5.1424  0.3920 -13.1195
## log(xi.2)      -4.8199  0.3490 -13.8105
## log(xi.3)      -5.0011  0.3682 -13.5824
## log(xi.4)      -4.8856  0.4060 -12.0331
## log(xi.5)      -4.4528  0.3626 -12.2807
## log(xi.6)      -3.9471  0.3710 -10.6383
## log(xi.7)      -4.6314  0.5085  -9.1077
```

```
anova(jointFit.slope, process = "Event")
```

```
##
## Marginal Wald Tests Table
##
## Event Process
##                   Chisq df Pr(>|Chi|)
## drug             0.0552  1     0.8143
## Assoct(all) 160.4073  2     <1e-04
## Assoct        64.1114  1     <1e-04
## Assoct.s      10.4207  1     0.0012
```

- The "Assoct" parameter is our $\alpha_1$ parameter and represents the association between $m_i(t)$ (true log-bilirubin) and the risk of death
- The "Assoct.s" parameter is our $\alpha_2$ parameter for the association between $m_i'(t)$ (slope) and the risk of death

# Time-dependent Slope

```
## Event Process
##                 Value Std.Err  z-value p-value
## drugD-penicil  0.0454  0.1930   0.2349  0.8143
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## Assoct(all) 160.4073  2     <1e-04
## Assoct       64.1114  1     <1e-04
## Assoct.s     10.4207  1     0.0012
```
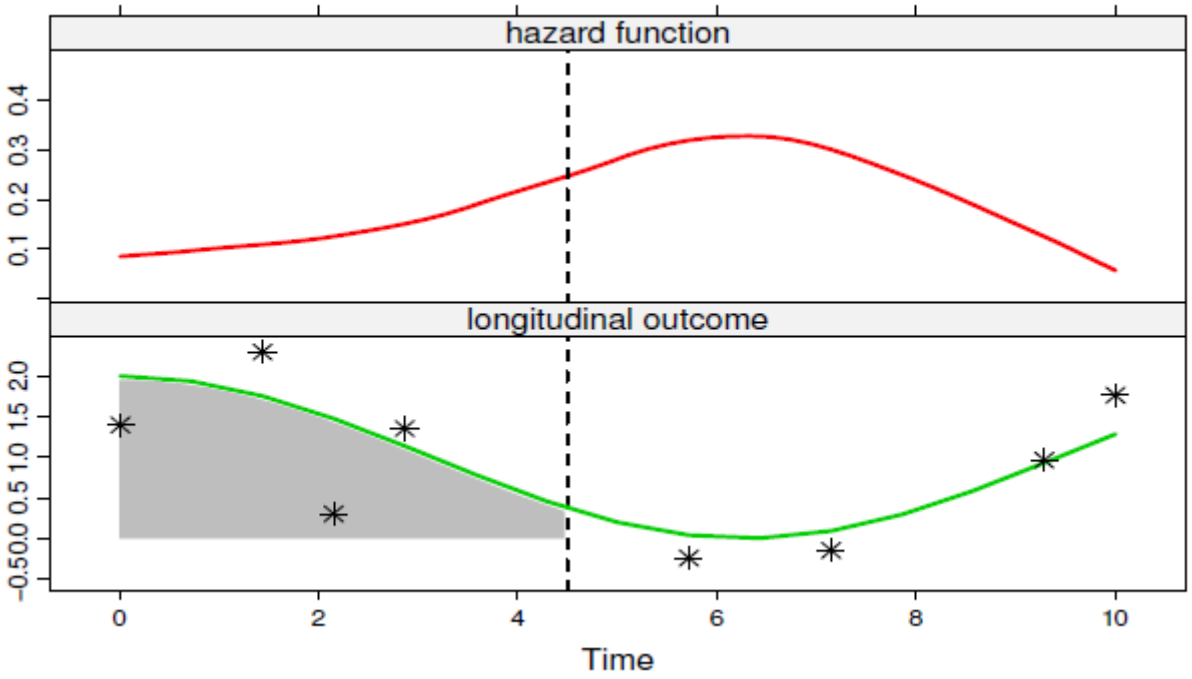

- For patients having the same level of log serum bilirubin, the log hazard ratio for a unit increase in the current slope of the bilirubin trajectory is 3.34 (95% CI: 1.31-5.37).
- For PBC patients the current value of log serum bilirubin and the slope of the bilirubin trajectory are highly associated with the hazard for death ($p<0.001$).

# Alternative Parameterizations

- **Cumulative Effects:** The hazard of an event at $t$ is associated with the whole area under the trajectory up to $t$

$$h_i(t|\mathcal{M}_i(t)) = h_0(t)\exp\left\{\gamma' w_i + \alpha\int_0^t m_i(s)ds\right\}$$



# Cumulative Effects

- The true value of the marker has the form

$$m_i(t) = \beta_0 + \beta_1 t + \beta_2\{t \times \text{D-penecil}_i\} + b_{i0} + b_{i1}t$$

- We take the integral with respect to t

$$\int_0^t m_i(s)ds = \beta_0 t + \beta_1 t^2/2 + \beta_2 \text{D-penecil}_i t^2/2 + b_{i0}t + b_{i1}t^2/2$$

- We can write this integral in the form

$$\int_0^t m_i(s)ds = [x_i^*(t)]'\beta^* + [z_i^*(t)]'b_i^*$$

where

$x_i^*(t) = [t, t^2/2, \text{D-penecil}_i t^2/2], z_i^*(t) = [t, t^2/2]$

$\beta^* = [\beta_0, \beta_1, \beta_2], b_i^* = [b_{i0}, b_{i1}]$

# Cumulative Effects

$$x_i^*(t) = [t, t^2/2, \text{D-penecil}_i t^2/2], z_i^*(t) = [t, t^2/2]$$

$$\beta^* = [\beta_0, \beta_1, \beta_2], b_i^* = [b_{i0}, b_{i1}]$$

```
lmeFit <- lme(log(serBilir) ~ year + year:drug, data = pbc2, random = ~ year | id)
survFit <- coxph(Surv(years, status2) ~ drug, data = pbc2.id, x = TRUE)
jointFit <- jointModel(lmeFit, survFit, timeVar="year", method = "piecewise-PH-aGH")

iform <- list(fixed = ~ -1 + year + I(year^2/2) + I(year^2/2*(drug=="D-penecil")), indFixed = 1:3,
              random = ~ -1 + year + I(year^2/2), indRandom = 1:2)

jointFit.cumulative <- update(jointFit, parameterization = "slope", derivForm = iform)

summary(jointFit.cumulative)
```

```
Event Process
                Value Std.Err  z-value p-value
drugD-penicil -0.0113  0.1829  -0.0616  0.9509
Assoct.s       0.2082  0.0221   9.4230 <0.0001
log(xi.1)     -2.9211  0.1807 -16.1610
log(xi.2)     -2.9892  0.2045 -14.6171
log(xi.3)     -3.5632  0.2804 -12.7087
log(xi.4)     -3.7422  0.3531 -10.5987
log(xi.5)     -3.6700  0.3340 -10.9873
log(xi.6)     -3.5760  0.3950  -9.0533
log(xi.7)     -5.2938  0.6458  -8.1968
```

- A unit increase in the area under the log serum bilirubin longitudinal profile corresponds to a 1.23-fold increase in the risk of death (95% CI: 1.18-1.29; p<0.0001)

# Comparison of association structures

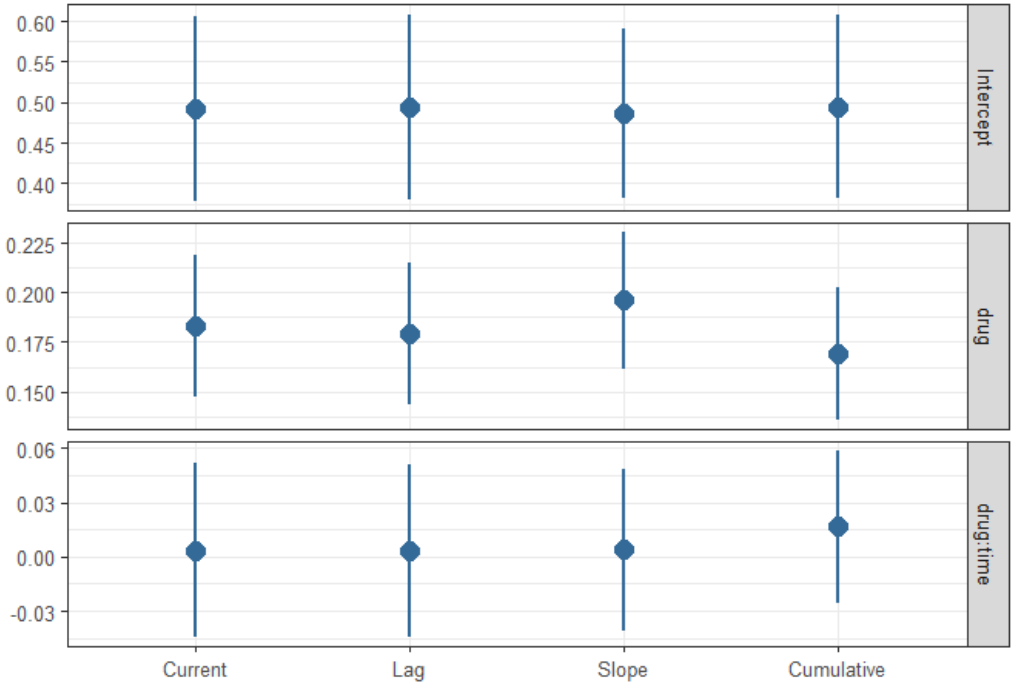
- Can compare the non-nested models using AIC/BIC

| Model | AIC | BIC |
|---|---|---|
| Current | 3864.7 | 3924.6 |
| Lag (1 year) | 3873.2 | 3933.1 |
| Slope | 3855.2 | 3918.8 |
| Cumulative | 3983.3 | 4043.2 |

- These association structures can be though of time-dependent association structures
- The risk of the event at time $t$ is linked to a value (or transformation) of the marker at time $t$

# Alternative Parameterizations

- We will see sensitivities for the longitudinal processes depending on the choice of parameterization
- Thus, a sensitivity analysis should not stop at the standard joint model parameterization, but should also consider alternative association structures



# Model Diagnostics

- **Standard tool:** residual plots
- Evaluate validity of statistical model assumptions
- Help in model selection
- Focus on separate types of residuals for the survival and longitudinal parts
- These residuals can be affected by the nonrandom dropout

# Residuals for Longitudinal Submodel

- Subject-specific (conditional) residuals: validate the assumptions of the hierarchical version of the model
  - Homoskedasticity (homogeneity of variance)
  - Normality assumptions

$$y_i = X_i\beta + Z_i b_i + \epsilon_i$$
$$b_i \sim N(0, D), \epsilon_i \sim N(0, \sigma^2)$$

$$r_i^{ys}(t) = \{y_i(t) - x_i'(t)\hat{\beta} - z_i'(t)\hat{b}_i\}$$
$$r_i^{yss}(t) = \{y_i(t) - x_i'(t)\hat{\beta} - z_i'(t)\hat{b}_i\}/\hat{\sigma}$$

- $\hat{b}_i$ is the empirical Bayes estimates for the random effects

# Residuals for Longitudinal Submodel

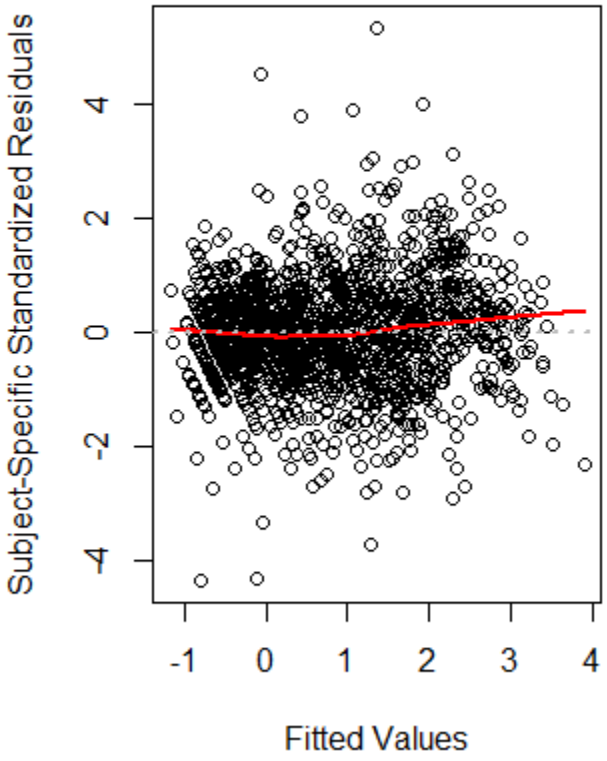
- Marginal (population averaged) residuals: focuses on marginal model
  - Investigate the misspecification of the mean structure $X\beta$
  - Validate assumptions for the within-subjects covariance structure

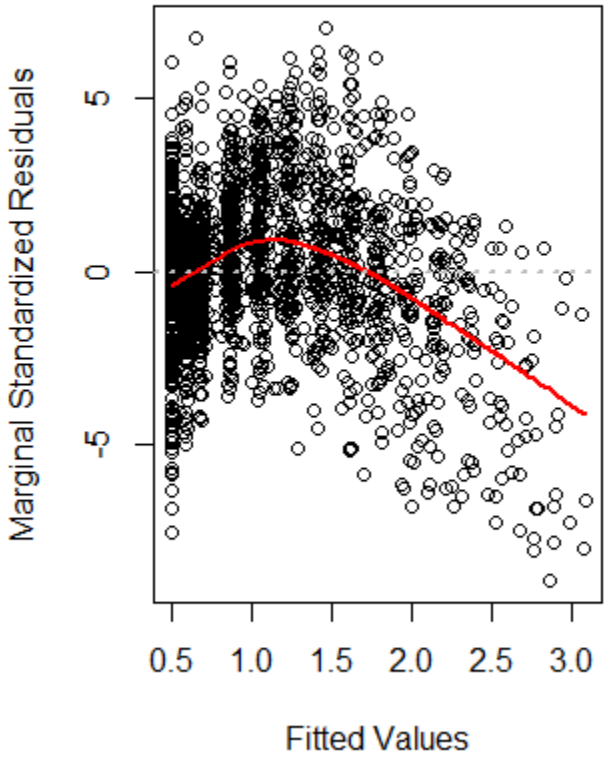
$$y_i = X_i\beta + \epsilon_i^*$$
$$\epsilon_i^* \sim N(0, Z_i D Z_i' + \sigma^2 I_{n_i})$$

$$r_i^{ym}(t) = y_i(t) - X_i'\hat{\beta}$$
$$r_i^{ysm}(t) = \hat{V}_i^{1/2}(y_i - X_i'\hat{\beta})$$

- $\hat{b}_i$ is the empirical Bayes estimates for the random effects
- $\hat{V}_i = Z_i \hat{D} Z_i' + \hat{\sigma}^2 I_{n_i}$ is the estimated marginal covariance matrix

# Residuals for Longitudinal Submodel



# Residuals for Survival Submodel

- Martingale residuals (based on counting process)
  - Used to evaluate whether the functional form is appropriate
  - Used to identify subjects that are poorly fit by the model
  - Can plot the martingale residuals from a null model versus a predictor to reveal to the functional form for that predictor

$$r_i^{tm}(t) = N_i(t) - \int_0^t R_i(s) h_i(s \mid \hat{\mathcal{M}}_i(s); \hat{\theta})\, ds$$

$$= N_i(t) - \int_0^t R_i(s) \hat{h}_0(s) \exp\{\hat{\gamma}^\top w_i + \hat{\alpha} \hat{m}_i(s)\}\, ds$$

- $N_i(t)$ is the counting process denoting the number of events for subject $i$ by time $t$, $R_i(t)$ is the left continuous at-risk process

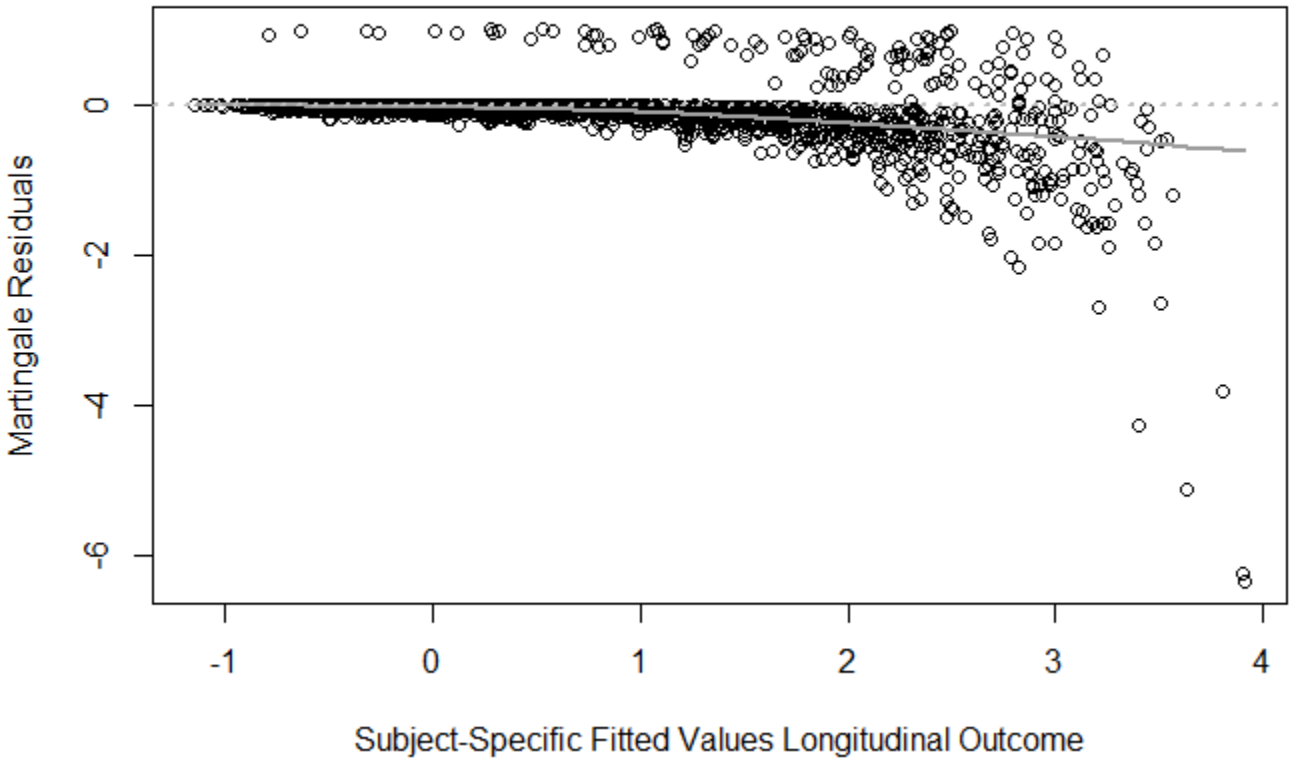
# Residuals for Survival Submodel

- Cox-Snell residuals
  - Used to assess how well the model fits the data
  - Calculated as the estimated cumulative risk function evaluated at $T_i$
  - If the model is a good fit then the cumulative hazard will have a unit exponential distribution
  - Idea: If $T_i \sim S_i(t)$ then $S_i(T_i) \sim Unif[0,1]$ and $\Lambda_i(T_i) = -\log[S_i(T_i)] \sim Exp(1)$

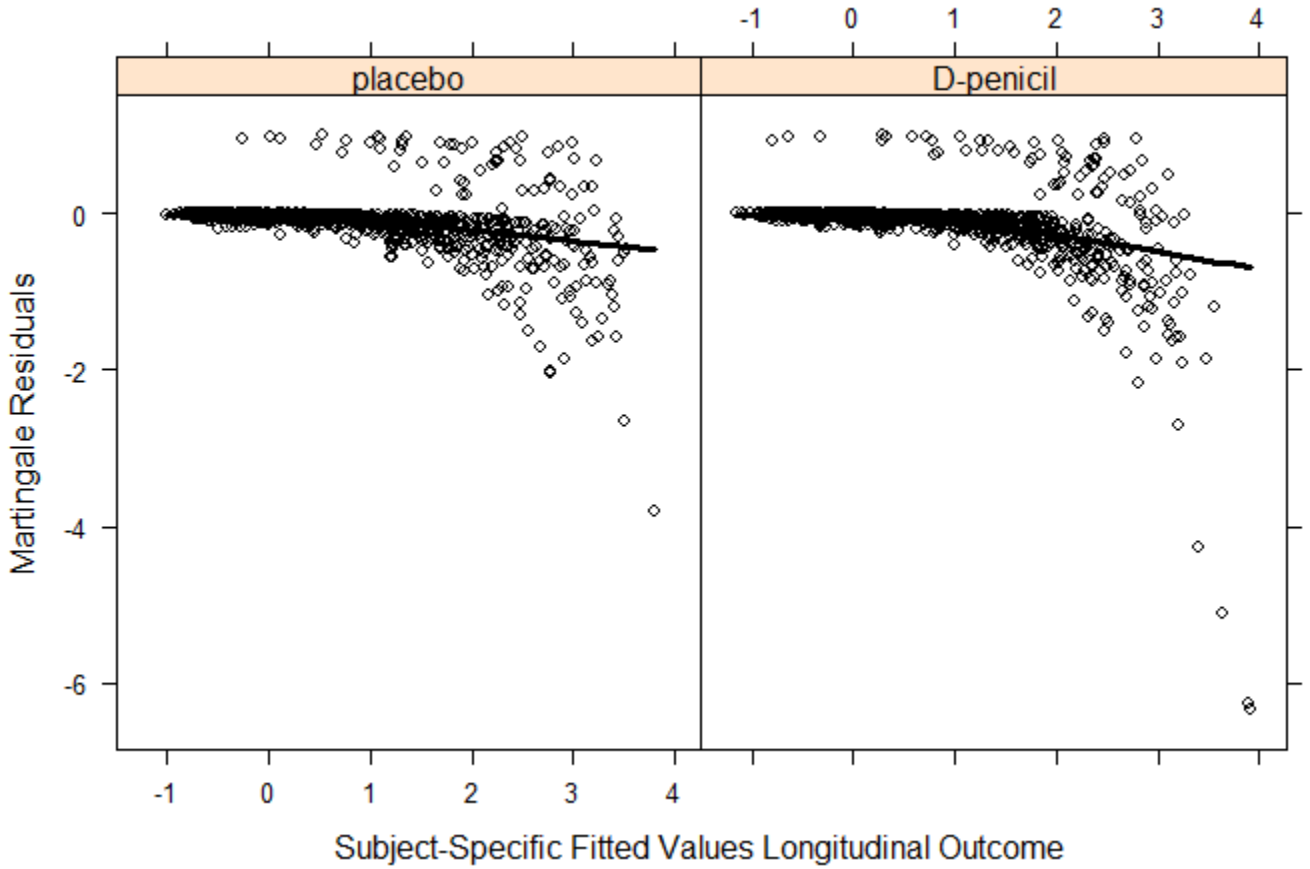
$$r_i^{tcs} = \int_0^{T_i} h_i(s \mid \hat{\mathcal{M}}_i(s); \hat{\theta})\, ds$$

$$= \int_0^{T_i} \hat{h}_0(s) \exp\{\hat{\gamma}^\top w_i + \hat{\alpha}\hat{m}_i(s)\}\, ds$$

# Residuals for Survival Submodel



# Residuals for Survival Submodel



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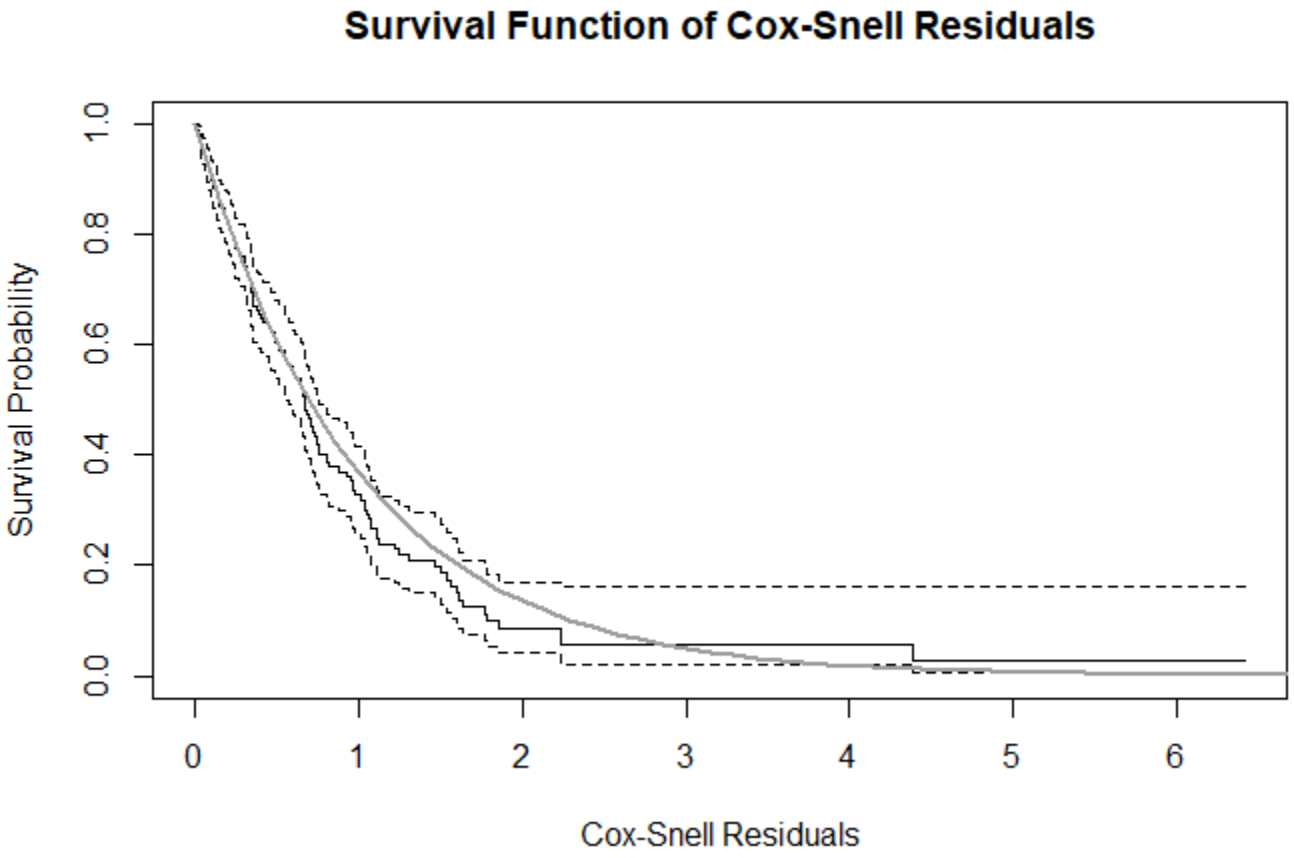
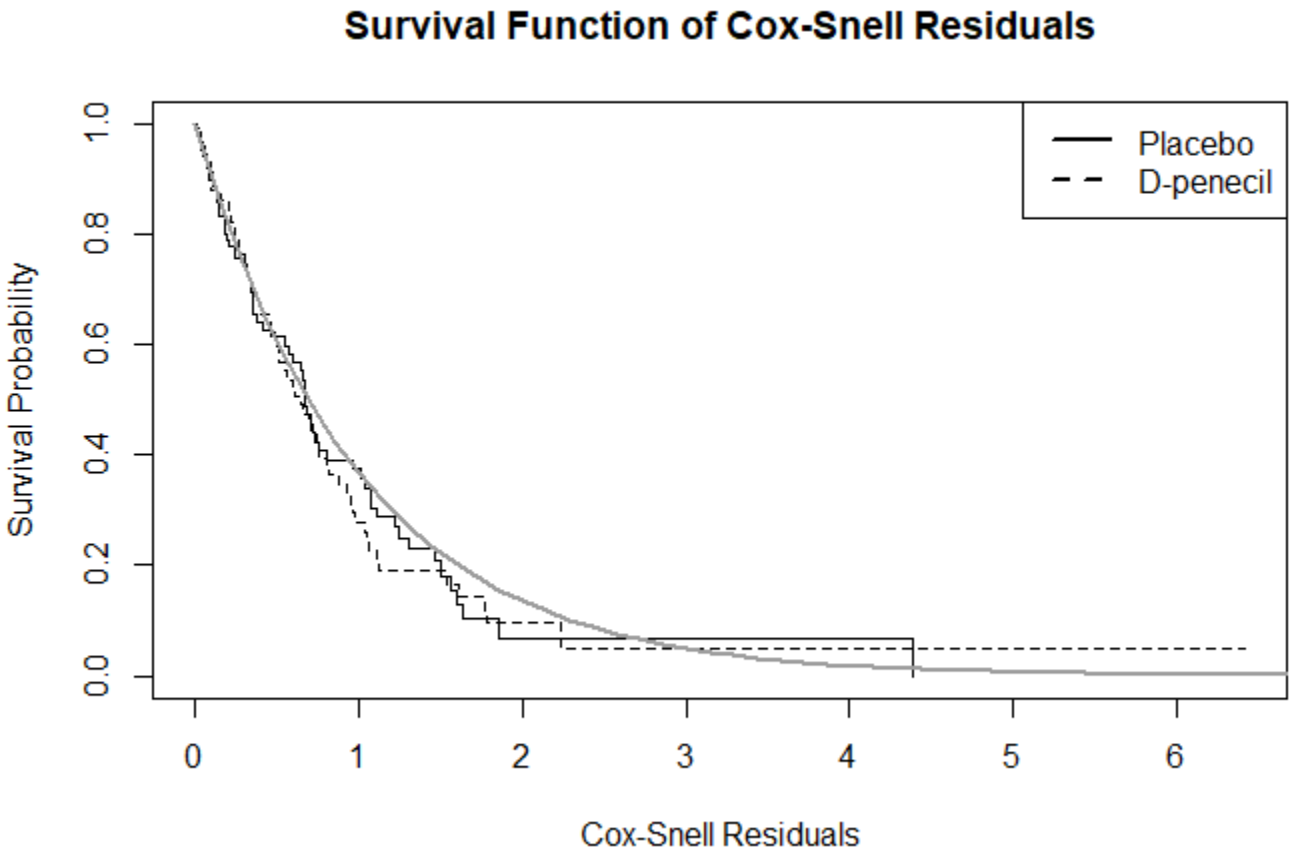


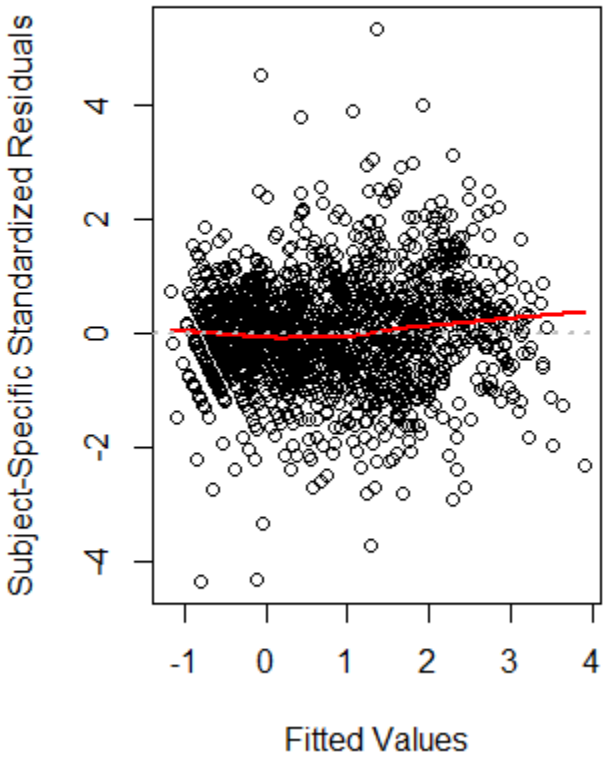
# Residuals for Survival Submodel

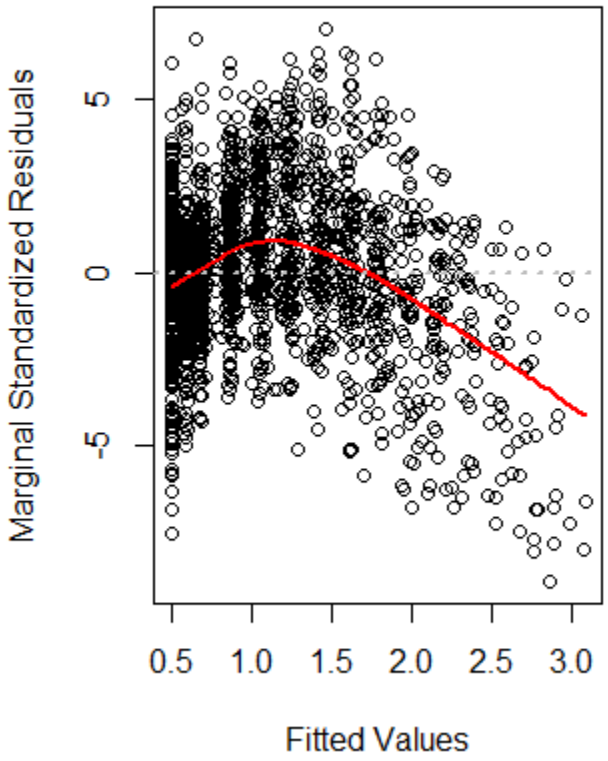


# Residuals and Dropout

- So far we have looked at residual plots used when mixed models and relative risk models are fitted separately
- The issue that arises in joint models is that we have dropout caused by the event process
- The nonrandom nature of the dropout mechanism (MNAR) is that the observed data upon which we calculate the residuals do not constitute a random sample of the target population
- So residuals should not be expected to exhibit standard properties (zero mean and independence)

# Residuals for Longitudinal Submodel

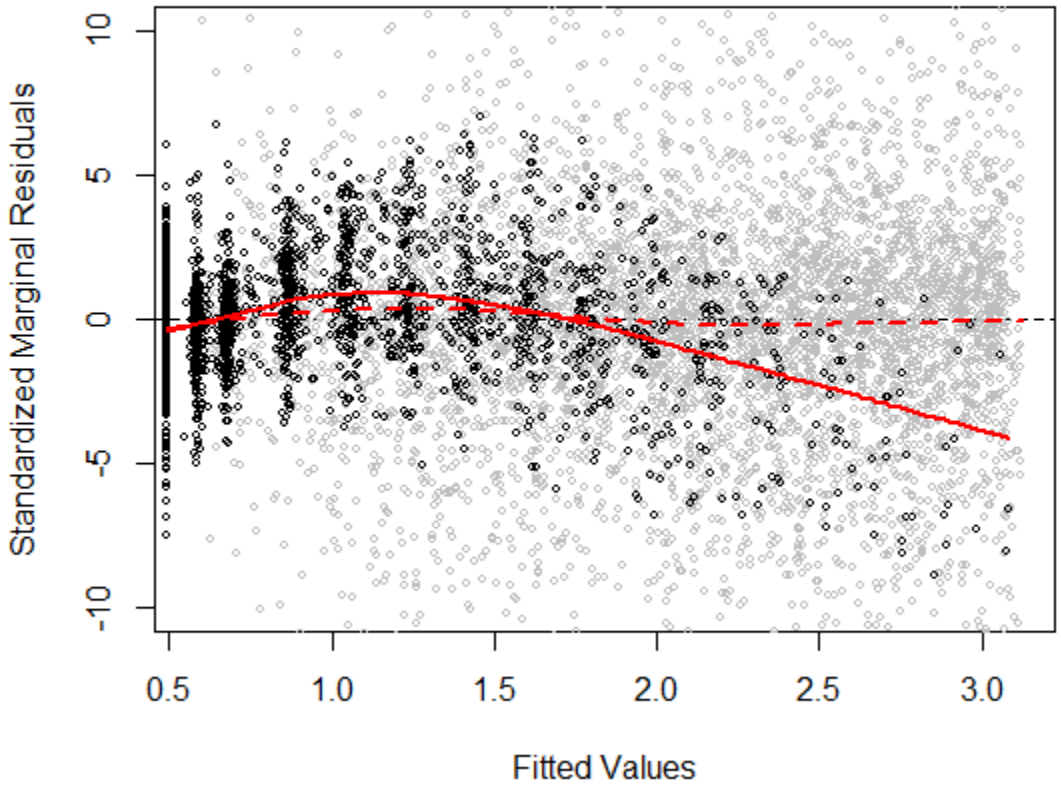


# Multiple Imputation Residuals

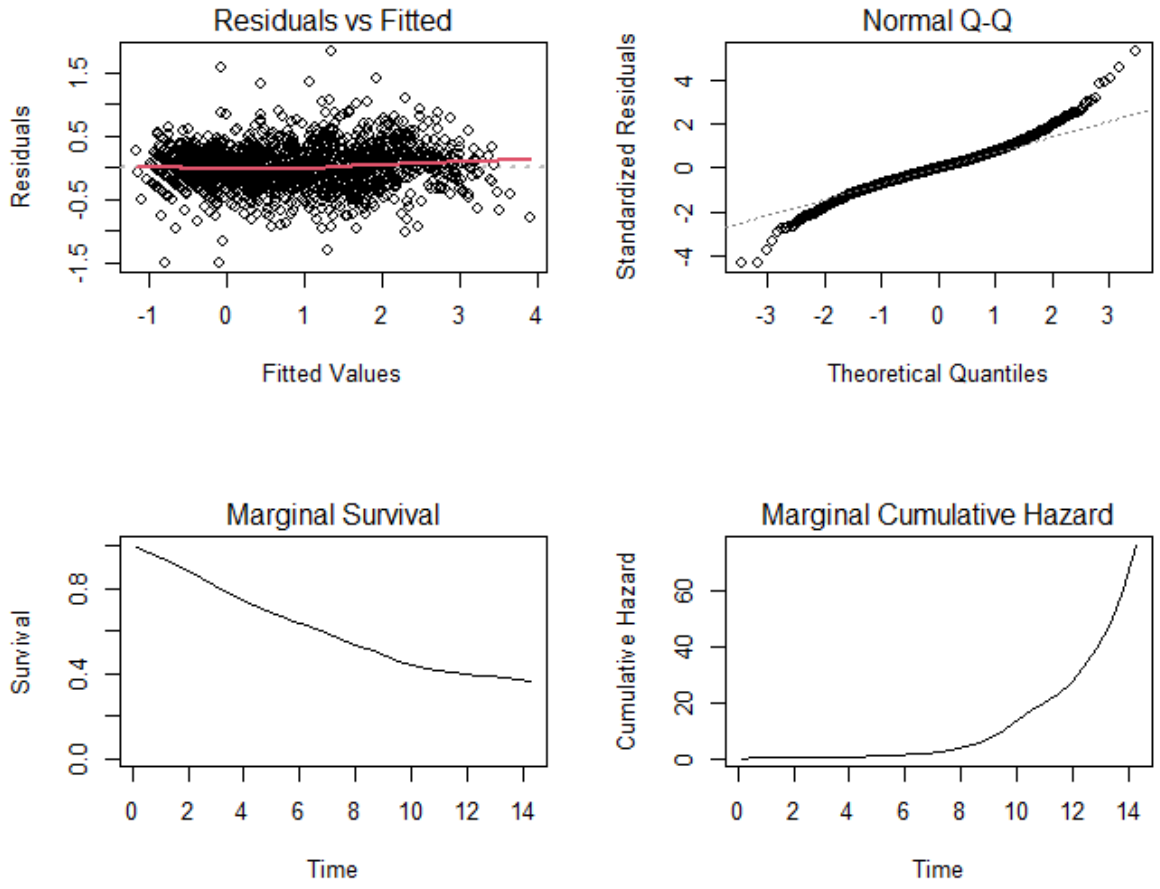
- Need to overcome the problems caused by nonrandom dropout and produce appropriate residuals for the longitudinal process to use in diagnostic plots
- Solution (Rizopoulos et al, 2010): Augment the observed data with randomly imputed longitudinal responses under the complete data model that would correspond to longitudinal outcomes that would have been observed if the patients had not dropped out
- Uses a Bayesian framework
- Random visit times: need to specify a model for the visiting process (can't use arbitrary points) – Weibull model with a multiplicative Gamma frailty

# Multiple Imputation Residuals



# Simple Joint Model Diagnostics

- Use the plot function on your jointModel() object



# Robustness

- Shared random effects joint models enjoy a certain level of robustness
- Robustness of the MLE to random effects model misspecification when there is enough information from the longitudinal data (Hsieh et al, 2006; Rizopoulos et al, 2008; Huang et al, 2009)

# Example Paper

- Abdi, Z.D., Essig, M., Rizopoulos, D., Le Meur, Y., Prémaud, A., Woillard, J.B., Rerolle, J.P., Marquet, P. and Rousseau, A., 2013. Impact of longitudinal exposure to mycophenolic acid on acute rejection in renal-transplant recipients using a joint modeling approach. *Pharmacological research*, *72*, pp.52-60.