

Extension of the Association structure in Joint Models to include Weighted Cumulative Effects: Supplementary Material

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1. Derivation of Equation 11

As per [14], we have in general, that:

$$\int_a^b f(x)dx \approx \frac{(b-a)}{2} \sum \pi f\left(\frac{(b-a)}{2}q + \frac{(b+a)}{2}\right)$$

where π and q are prespecified weights and abscissas respectively. For the survival function, we have:

$$\begin{aligned} S(t) &= \exp\left[-\int_0^{T_i} h_i(s)ds\right] \\ &= \exp\left[-\int_0^{T_i} h_0(s) \exp\left\{\gamma^\top \mathbf{w}_i(s) + \alpha \int_0^s \varpi(s-u)_+ \eta_i(u) du\right\} ds\right] \end{aligned}$$

Defining:

$$\begin{aligned} \tau_m &= \frac{T_i(q_m + 1)}{2}, \\ \psi_{mn} &= \frac{\tau_m(q_n + 1)}{2} \end{aligned}$$

where T_i is the observed failure time, we then have:

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$$\begin{aligned}
 & \exp \left[- \int_0^{T_i} h_0(s) \exp \left\{ \boldsymbol{\gamma}^\top \mathbf{w}_i(s) + \alpha \int_0^s \varpi(s-u)_+ \eta_i(u) du \right\} ds \right] \\
 & \approx \exp \left[- \frac{T_i}{2} \sum_{m=1}^{15} \pi_m h_0(\tau_m) \exp \left\{ \boldsymbol{\gamma}^\top \mathbf{w}_i(\tau_m) + \alpha \int_0^{\tau_m} \varpi(\tau_m - u)_+ \eta_i(u) du \right\} \right] \\
 & \approx \exp \left[- \frac{T_i}{2} \sum_{m=1}^{15} \pi_m h_0(\tau_m) \exp \left\{ \boldsymbol{\gamma}^\top \mathbf{w}_i(\tau_m) + \frac{\alpha \tau_m}{2} \sum_{n=1}^{15} \tilde{\pi}_n \varpi(\tau_m - \psi_{mn}) \eta_i(\psi_{mn}) \right\} \right] \\
 & = \exp \left[- \frac{T_i}{2} \sum_{m=1}^{15} \pi_m h_0(\tau_m) \exp \left\{ \boldsymbol{\gamma}^\top \mathbf{w}_i(\tau_m) + \frac{\alpha \tau_m}{2} \sum_{n=1}^{15} \tilde{\pi}_n \varpi \left(\frac{\tau_m(1 - q_n)}{2} \right) \eta_i(\psi_{mn}) \right\} \right]
 \end{aligned}$$

where π_m and $\tilde{\pi}_n$ denote prespecified weights and q_m and q_n prespecified abscissas.

2. Tables

Table S 1. Baseline Characteristics of N=6294 and subset N=1125 patients

Variable	Mean (SD)/ N = 6294 (%)	Mean (SD)/ N = 1125 (%)
Diabetes duration (years)	2.8 (4.8)	3.2 (5.2)
Age (years)	60.5 (11.8)	59.82 (11.8)
Systolic blood pressure	142.9 (20.7)	143 (20.9)
Diastolic blood pressure	81.1 (10.9)	81.5 (11.1)
Lower grade retinopathy	478 (8%)	134 (11.9%)

Table S 2. Candidate Models for DCS

Model	DIC
Current Value	71159.57
Cumulative	71154.04
Weighted Normal	71168.92
Weighted Skewed Normal	71124.42

Table S 3. Parameter estimates and 95% credibility intervals under the joint modeling analysis for transplantation-free survival (PBC data). Longitudinal outcome is logged serum Bilirubin

	Event Process			
	Current Value		Cumulative Effect	
	Log hazard (2.5% - 97.5%)	p-value	Log hazard (2.5% - 97.5%)	p-value
D-penicillamine	-0.08 (-0.41 - 0.27)	0.59	-0.28 (-0.61 - 0.07)	0.11
Age	0.04 (0.01 - 0.06)	0.00	0.04 (0.01 - 0.06)	0.00
Interaction	0.01 (-0.02 - 0.04)	0.42	0.01 (-0.02 - 0.04)	0.56
Association parameter (α)	1.41 (1.23 - 1.60)	0.00	0.22 (0.18 - 0.27)	0.00
	Weighted Normal		Weighted Skewed Normal	
	Log hazard (2.5% - 97.5%)	p-value	Log hazard (2.5% - 97.5%)	p-value
D-penicillamine	-0.10 (-0.41 - 0.24)	0.56	-0.11 (-0.44 - 0.22)	0.53
Age	0.04 (0.02 - 0.06)	0.00	0.04 (0.02 - 0.06)	0.00
Interaction	0.01 (-0.02 - 0.04)	0.40	0.01 (-0.02 - 0.04)	0.36
Association parameter (α)	1.37 (1.17 - 1.57)	0.00	1.36 (1.19 - 1.56)	0.00
	Weight Function			
	Coefficient (2.5% - 97.5%)	p-value	Coefficient (2.5% - 97.5%)	p-value
Scale parameter (σ/v)	0.10 (0.04 - 0.19)	0.00	0.10 (0.04 - 0.18)	0.00
Shape parameter (κ)			5.73 (0.16 - 9.73)	0.00

Table S 4. Parameter estimates and 95% credibility intervals under the joint modeling analysis for transplantation-free survival (PBC data). Longitudinal outcome is logged serum Bilirubin, $D[i, j]$ denote the ij -element of the covariance matrix for the random effects

Longitudinal Process				
	Current Value		Cumulative Effect	
	Coefficient (2.5% - 97.5%)	p-value	Coefficient (2.5% - 97.5%)	p-value
Intercept	0.51 (0.40 - 0.62)	0.00	0.51 (0.40 - 0.62)	0.00
ns(years, 2)1	2.30 (1.98 - 2.59)	0.00	2.22 (1.94 - 2.51)	0.00
ns(years, 2)2	2.10 (1.80 - 2.42)	0.00	2.05 (1.76 - 2.35)	0.00
σ_ϵ	0.30 (0.29 - 0.32)	0.00	0.30 (0.29 - 0.32)	0.00
D[1, 1]	1.01 (0.86 - 1.20)	0.00	1.02 (0.86 - 1.20)	0.00
D[2, 1]	0.72 (0.37 - 1.11)	0.00	0.69 (0.30 - 1.04)	0.00
D[3, 1]	0.56 (-0.02 - 1.12)	0.05	0.64 (0.16 - 1.18)	0.01
D[2, 2]	4.95 (3.88 - 6.29)	0.00	4.60 (3.53 - 5.86)	0.00
D[3, 2]	2.34 (1.31 - 3.67)	0.00	2.06 (1.10 - 3.17)	0.00
D[3, 3]	4.48 (3.00 - 6.44)	0.00	3.95 (2.68 - 5.71)	0.00
tauBs	453.12 (100.29 - 1103.18)		286.75 (37.35 - 901.96)	
	Weighted Normal		Weighted Skewed Normal	
	Coefficient (2.5% - 97.5%)	p-value	Coefficient (2.5% - 97.5%)	p-value
Intercept	0.51 (0.39 - 0.63)	0.00	0.52 (0.40 - 0.63)	0.00
ns(years, 2)1	2.28 (2.01 - 2.57)	0.00	2.28 (1.99 - 2.58)	0.00
ns(years, 2)2	2.09 (1.80 - 2.38)	0.00	2.08 (1.78 - 2.39)	0.00
σ_ϵ	0.30 (0.29 - 0.32)	0.00	0.30 (0.29 - 0.32)	0.00
D[1, 1]	1.01 (0.86 - 1.19)	0.00	1.01 (0.86 - 1.18)	0.00
D[2, 1]	0.73 (0.39 - 1.11)	0.00	0.72 (0.40 - 1.08)	0.00
D[3, 1]	0.59 (0.12 - 1.07)	0.01	0.56 (0.12 - 1.03)	0.02
D[2, 2]	4.96 (3.84 - 6.26)	0.00	4.86 (3.80 - 6.15)	0.00
D[3, 2]	2.31 (1.22 - 3.66)	0.00	2.21 (1.20 - 3.47)	0.00
D[3, 3]	4.32 (2.88 - 6.24)	0.00	4.37 (2.85 - 6.54)	0.00
tauBs	450.74 (65.81 - 1149.31)		414.04 (74.41 - 1056.09)	

Table S 5. Parameter estimates and 95% credibility intervals under the joint modeling analysis for transplantation-free survival (PBC data). Longitudinal outcome is square root serum Cholesterol

	Event Process			
	Current Value		Cumulative Effect	
	Log hazard (2.5% - 97.5%)	p-value	Log hazard (2.5% - 97.5%)	p-value
D-penicillamine	-0.17 (-0.48 - 0.14)	0.28	-0.19 (-0.51 - 0.13)	0.25
Age	0.03 (0.01 - 0.04)	0.00	0.03 (0.01 - 0.04)	0.00
Association parameter (α)	0.02 (-0.02 - 0.09)	0.37	0.01 (0.00 - 0.02)	0.01
	Weighted Normal		Weighted Skewed Normal	
	Log hazard (2.5% - 97.5%)	p-value	Log hazard (2.5% - 97.5%)	p-value
D-penicillamine	-0.23 (-0.55 - 0.09)	0.15	-0.22 (-0.53 - 0.10)	0.17
Age	0.03 (0.02 - 0.05)	0.00	0.03 (0.02 - 0.05)	0.00
Association parameter (α)	0.15 (0.07 - 0.24)	0.00	0.15 (0.09 - 0.22)	0.00
	Weight Function			
	Coefficient (2.5% - 97.5%)	p-value	Coefficient (2.5% - 97.5%)	p-value
Scale parameter (σ/v)	3.13 (1.62 - 4.42)	0.00	3.03 (1.69 - 4.38)	0.00
Shape parameter (κ)			4.81 (0.32 - 9.64)	0.00

Table S 6. Parameter estimates and 95% credibility intervals under the joint modeling analysis for transplantation-free survival (PBC data). Longitudinal outcome is square root serum Cholesterol, $D[i, j]$ denote the ij -element of the covariance matrix for the random effects

	Longitudinal Process			
	Current Value		Cumulative Effect	
	Coefficient (2.5% - 97.5%)	p-value	Coefficient (2.5% - 97.5%)	p-value
Intercept	18.42 (17.92 - 18.90)	0.00	18.42 (17.95 - 18.94)	0.00
Year	-0.25 (-0.39 - -0.11)	0.00	-0.25 (-0.40 - -0.12)	0.00
σ_ϵ	1.92 (1.81 - 2.03)	0.00	1.91 (1.80 - 2.02)	0.00
D[1, 1]	15.44 (12.68 - 18.70)	0.00	15.68 (12.93 - 18.96)	0.00
D[2, 1]	-2.18 (-3.13 - -1.39)	0.00	-2.21 (-3.12 - -1.44)	0.00
D[2, 2]	1.02 (0.72 - 1.39)	0.00	1.01 (0.75 - 1.38)	0.00
	Weighted Normal		Weighted Skewed Normal	
	Coefficient (2.5% - 97.5%)	p-value	Coefficient (2.5% - 97.5%)	p-value
Intercept	18.41 (17.93 - 18.87)	0.00	18.40 (17.93 - 18.88)	0.00
Year	-0.24 (-0.38 - -0.11)	0.00	-0.25 (-0.39 - -0.11)	0.00
σ_ϵ	1.91 (1.80 - 2.02)	0.00	1.91 (1.81 - 2.01)	0.00
D[1, 1]	15.54 (12.78 - 19.02)	0.00	15.72 (12.93 - 19.11)	0.00
D[2, 1]	-2.09 (-2.99 - -1.29)	0.00	-2.15 (-3.15 - -1.37)	0.00
D[2, 2]	0.98 (0.72 - 1.32)	0.00	0.99 (0.71 - 1.37)	0.00

Table S 7. Parameter estimates and 95% credibility intervals under the joint modeling analysis for transplantation-free survival (PBC data). Longitudinal outcome is Hepatomegaly (dichotomous)

	Event Process			
	Current Value		Cumulative Effect	
	Log hazard (2.5% - 97.5%)	p-value	Log hazard (2.5% - 97.5%)	p-value
D-penicillamine	-0.05 (-0.41 - 0.33)	0.80	-0.10 (-0.47 - 0.25)	0.60
Age	0.03 (0.001 - 0.05)	0.05	0.03 (0.002 - 0.05)	0.04
Interaction	-0.001 (-0.04 - 0.04)	0.98	-0.01 (-0.04 - 0.03)	0.60
Association parameter (α)	0.31 (0.22 - 0.40)	0.00	0.07 (0.05 - 0.10)	0.00
	Weighted Normal		Weighted Skewed Normal	
	Log hazard (2.5% - 97.5%)	p-value	Log hazard (2.5% - 97.5%)	p-value
D-penicillamine	-0.08 (-0.42 - 0.27)	0.65	-0.08 (-0.41 - 0.26)	0.65
Age	0.03 (0.001 - 0.05)	0.04	0.03 (0.001 - 0.05)	0.03
Interaction	0.002 (-0.04 - 0.03)	0.92	-0.002 (-0.036 - 0.03)	0.90
Association parameter (α)	0.42 (0.28 - 0.62)	0.00	0.41 (0.29 - 0.58)	0.00
	Weight Function			
	Coefficient (2.5% - 97.5%)	p-value	Coefficient (2.5% - 97.5%)	p-value
Scale parameter (σ/v)	2.11 (0.49 - 4.02)	0.00	1.82 (0.02 - 3.54)	0.00
Shape parameter (κ)			5.08 (0.23 - 9.70)	0.00

Table S 8. Parameter estimates and 95% credibility intervals under the joint modeling analysis for transplantation-free survival (PBC data). Longitudinal outcome is Hepatomegaly (dichotomous), $D[i, j]$ denote the ij -element of the covariance matrix for the random effects

	Longitudinal Process			
	Current Value		Cumulative Effect	
	Coefficient (2.5% - 97.5%)	p-value	Coefficient (2.5% - 97.5%)	p-value
Intercept	0.15 (-0.27 - 0.56)	0.50	0.13 (-0.34 - 0.61)	0.55
Years	0.19 (0.09 - 0.31)	0.00	0.14 (0.03 - 0.26)	0.02
D[1, 1]	10.87 (7.23 - 15.40)	0.00	14.10 (9.69 - 19.60)	0.00
D[2, 1]	-0.38 (-1.06 - 0.24)	0.22	-1.24 (-2.21 - -0.40)	0.00
D[2, 2]	0.53 (0.35 - 0.78)	0.00	0.60 (0.40 - 0.86)	0.00
tauBs	407.51 (66.45 - 1106.75)		251.81 (21.27 - 770.66)	
	Weighted Normal		Weighted Skewed Normal	
	Coefficient (2.5% - 97.5%)	p-value	Coefficient (2.5% - 97.5%)	p-value
Intercept	0.13 (-0.32 - 0.56)	0.59	0.12 (-0.31 - 0.58)	0.60
Years	0.16 (0.05 - 0.27)	0.00	0.16 (0.06 - 0.27)	0.00
D[1, 1]	12.22 (8.49 - 17.11)	0.00	12.46 (8.38 - 17.69)	0.00
D[2, 1]	-0.83 (-1.60 - -0.17)	0.02	-0.86 (-1.74 - -0.10)	0.02
D[2, 2]	0.53 (0.36 - 0.77)	0.00	0.54 (0.35 - 0.77)	0.00
tauBs	453.92 (61.80 - 1169.10)		443.67 (88.74 - 1142.21)	

3. Figures

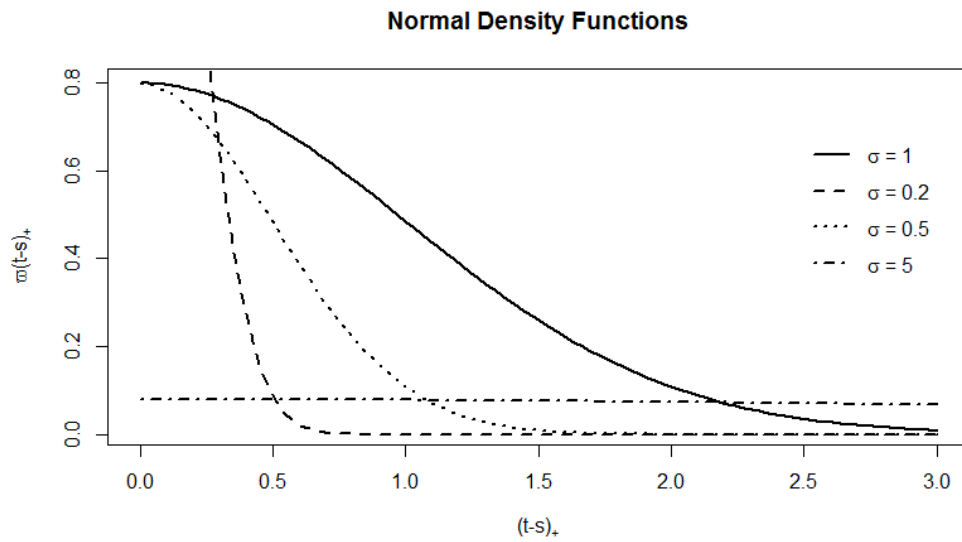


Figure S 1. Normal density functions for varying values of σ

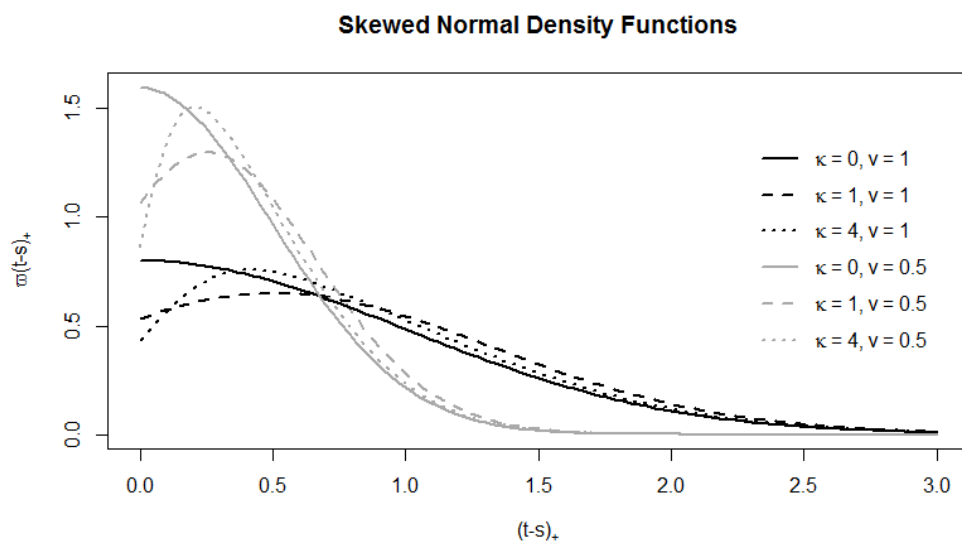


Figure S 2. Skewed normal density functions for varying values of the shape (κ) and scale (v) parameters

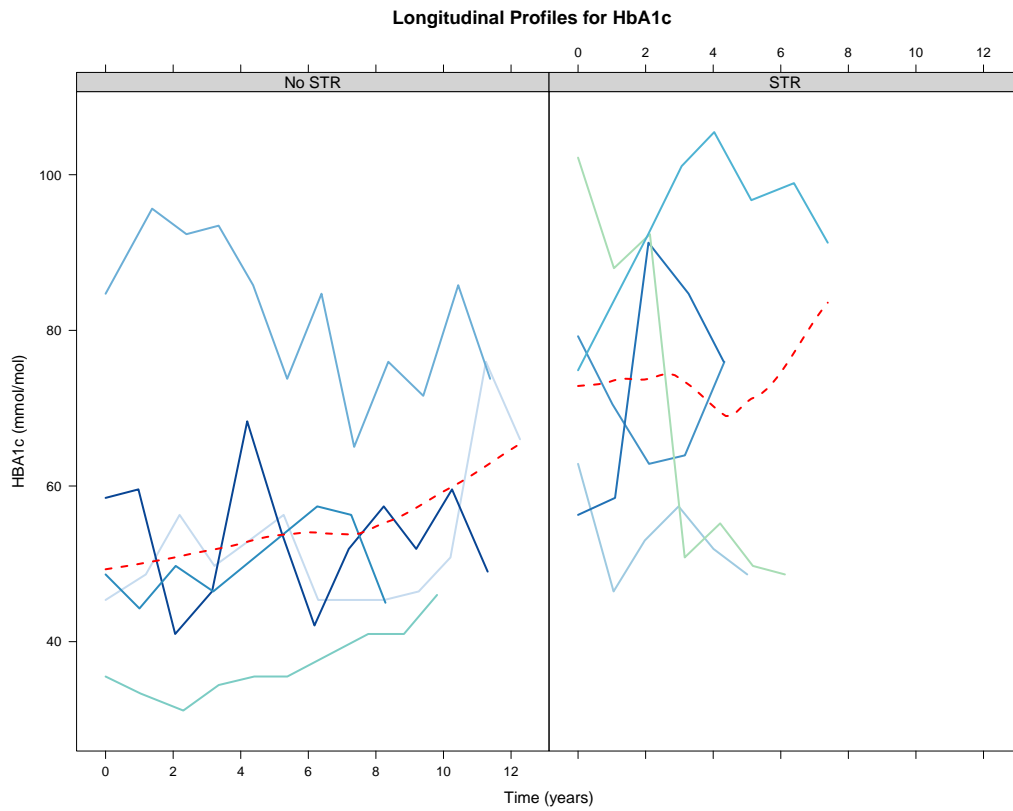


Figure S 3. Subject-specific longitudinal profiles for HbA1c for a random sample of patients with and without the event of interest (STR). The red line represents the loess smoother

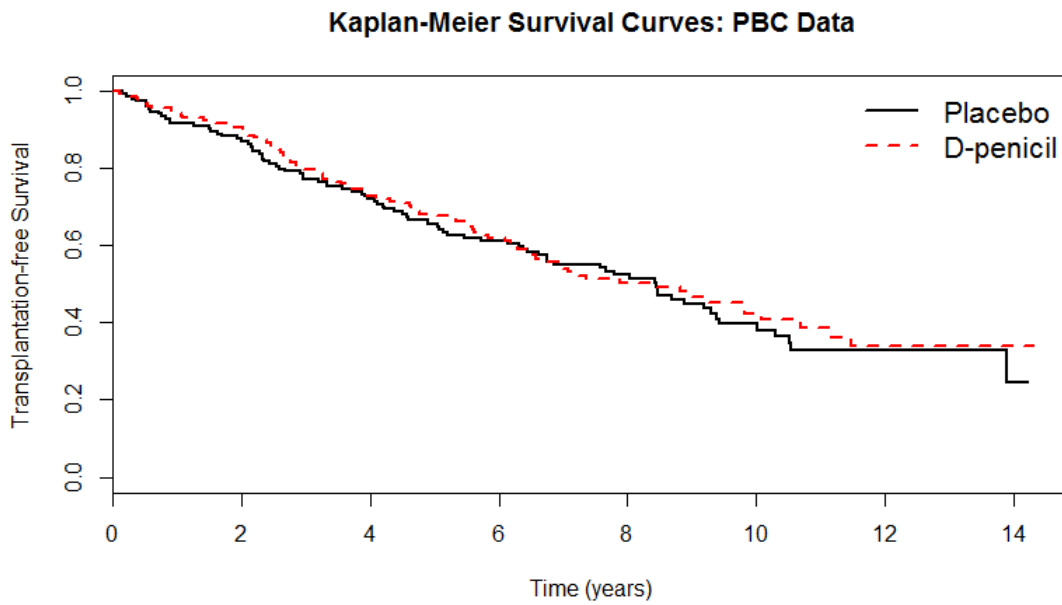


Figure S 4. Kaplan-Meier Survival Curves for the two treatment groups in the PBC data

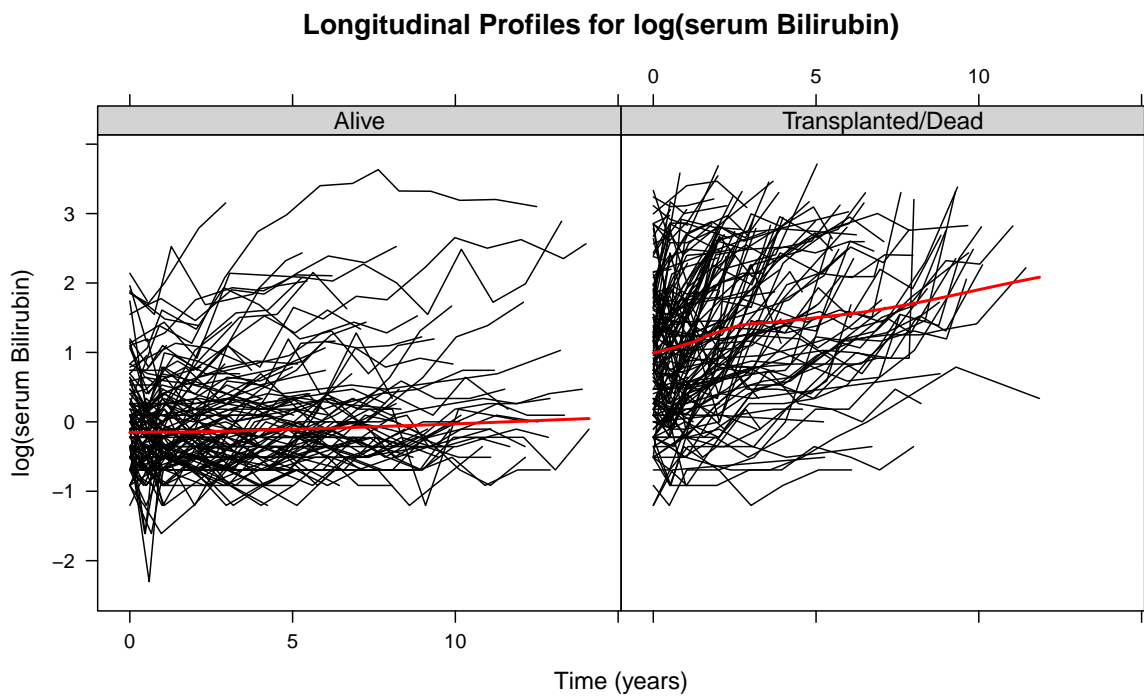


Figure S 5. Subject-specific longitudinal profiles for log(serum Bilirubin) for patients with and without the event of interest. The red line represents the loess smoother

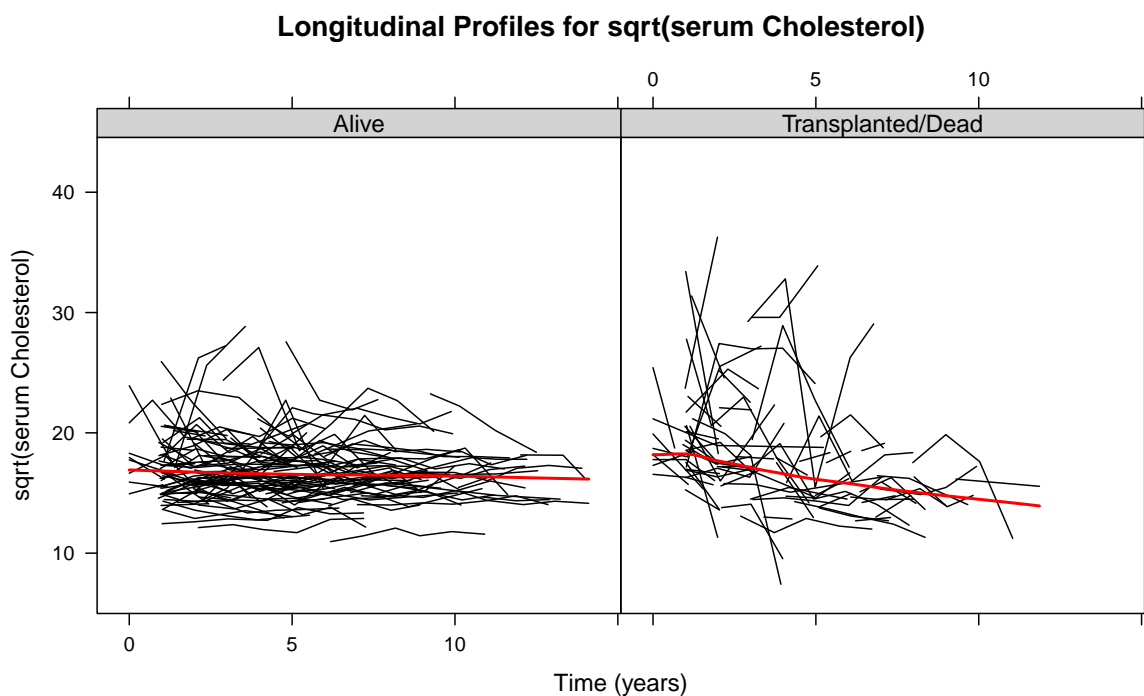


Figure S 6. Subject-specific longitudinal profiles for sqrt(serum Cholesterol) for patients with and without the event of interest. The red line represents the loess smoother

Longitudinal Profiles for PBC Subjects: Weighted Cumulative Association

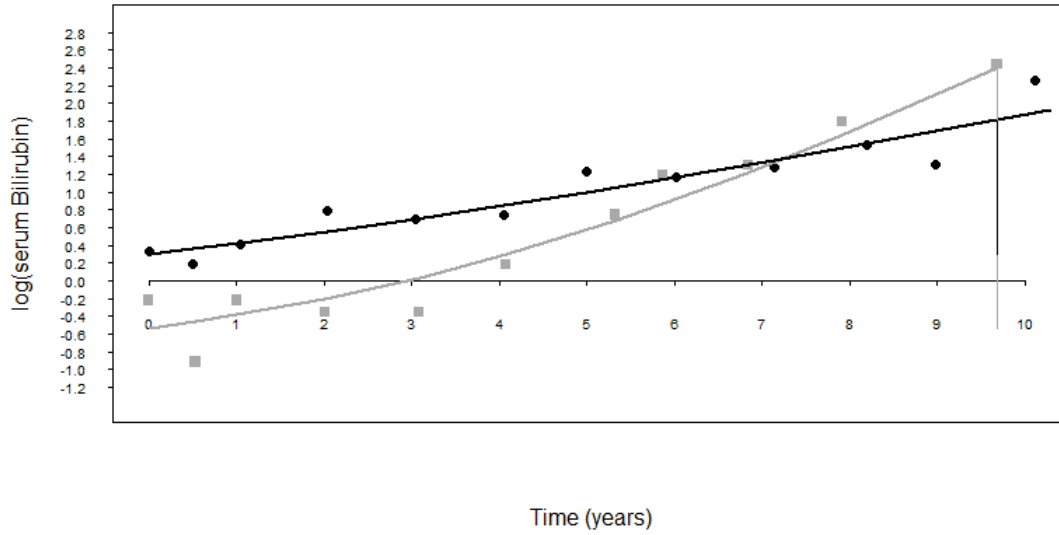


Figure S 7. Longitudinal profiles for randomly selected subjects from PBC data, with weighted cumulative effect

Longitudinal Profiles for PBC Subjects: Cumulative Association

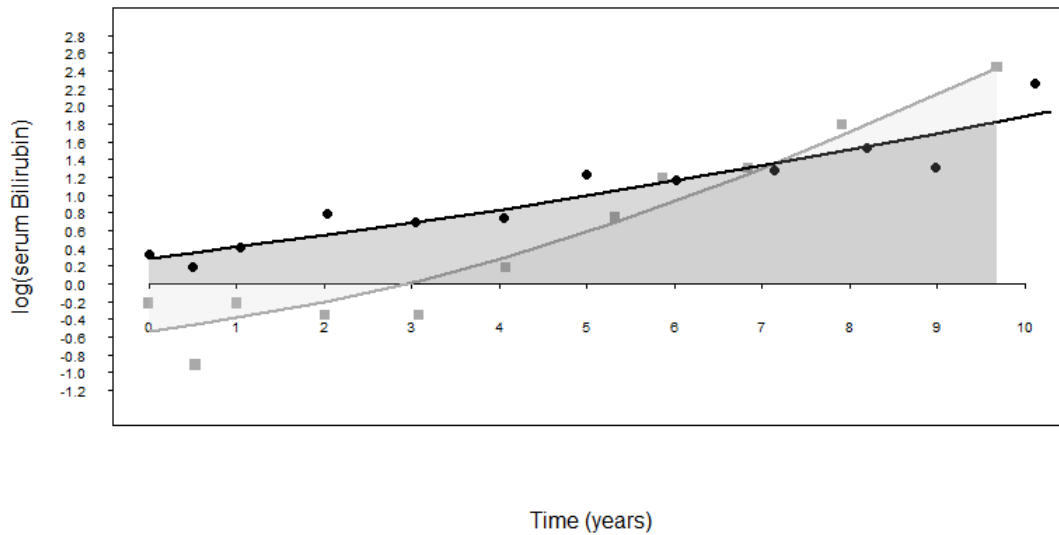


Figure S 8. Longitudinal profiles for randomly selected subjects from PBC data, with un-weighted cumulative effect

Comparison of Estimated Weight functions for PBC Analysis: Normal Density

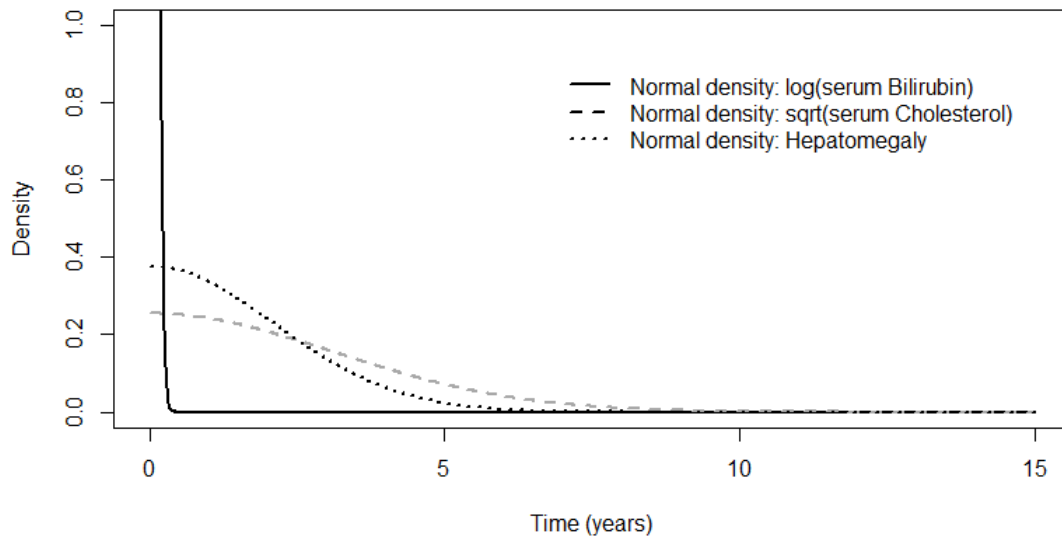


Figure S 9. Estimated normal density weight function under the joint model specification for the risk of transplantation-free survival

Comparison of Estimated Weight functions for PBC Analysis: Skewed Normal Density

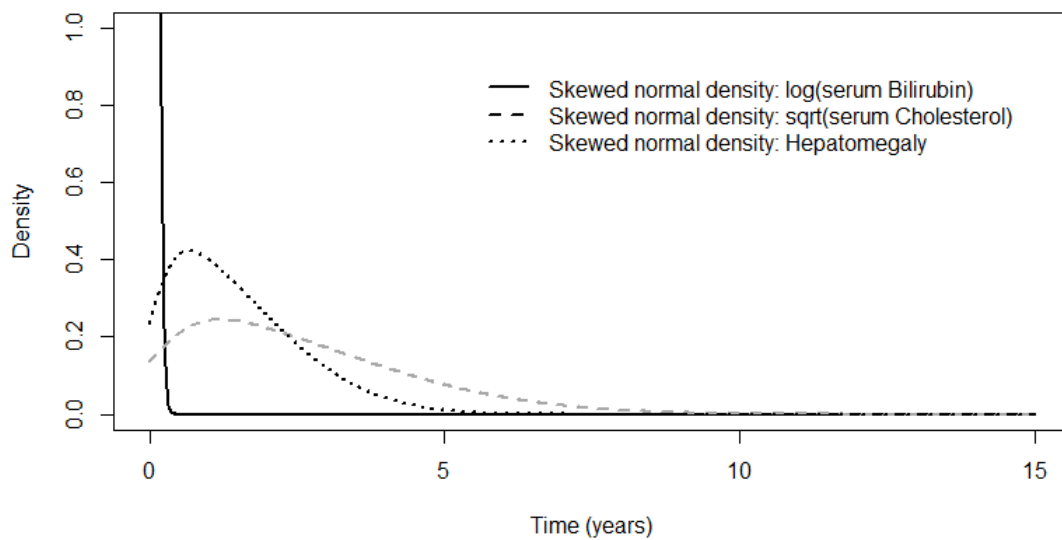


Figure S 10. Estimated skewed normal density weight function under the joint model specification for the risk of transplantation-free survival

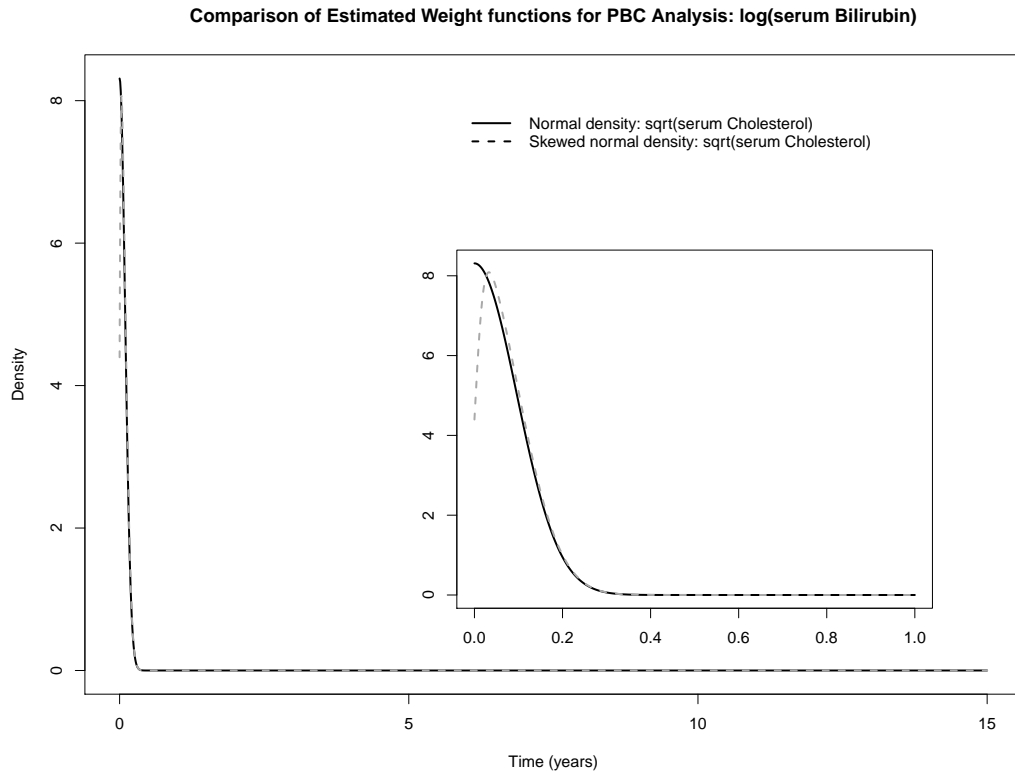


Figure S 11. Estimated weight function for logged serum Bilirubin under the joint model specification for the risk of transplantation-free survival

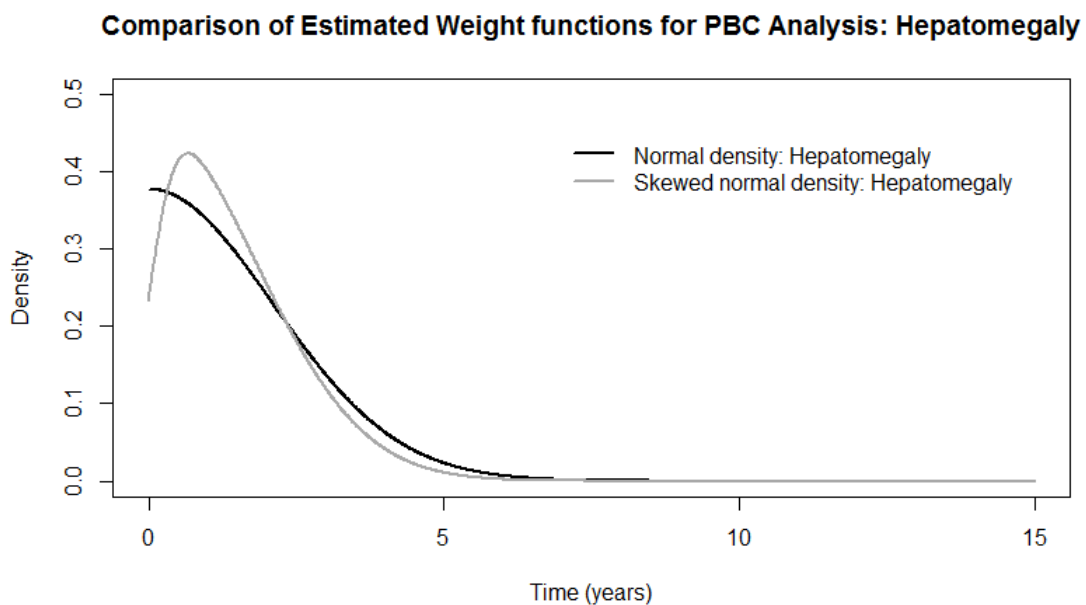


Figure S 12. Estimated weight function for Hepatomegaly under the joint model specification for the risk of transplantation-free survival

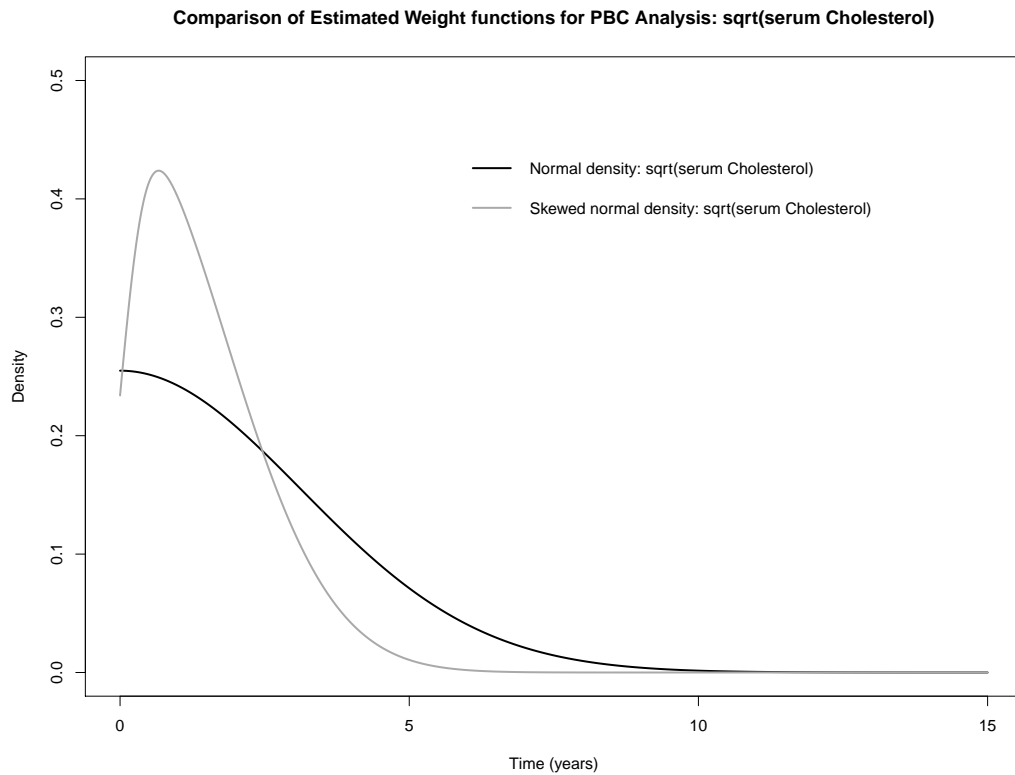


Figure S 13. Estimated weight function for square rooted serum Cholesterol under the joint model specification for the risk of transplantation-free survival

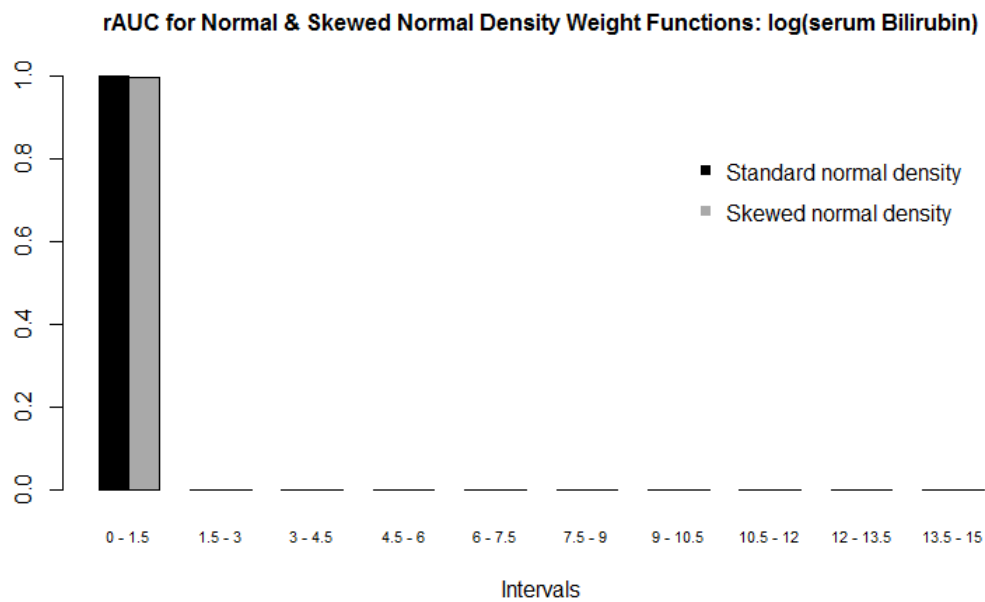


Figure S 14. Relative AUC calculated for logged serum Bilirubin over several intervals

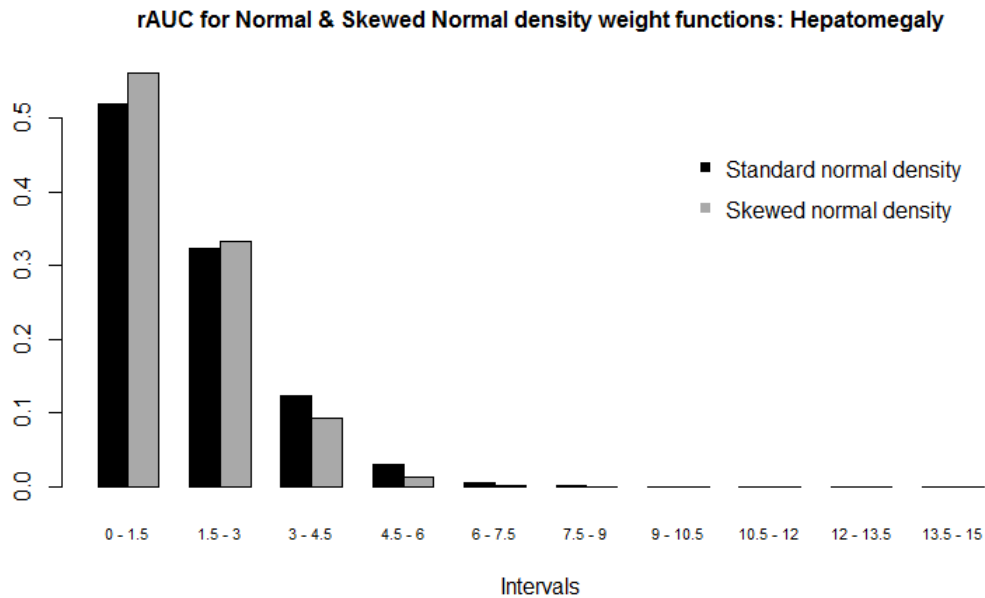


Figure S 15. Relative AUC calculated for Hepatomegaly over several intervals

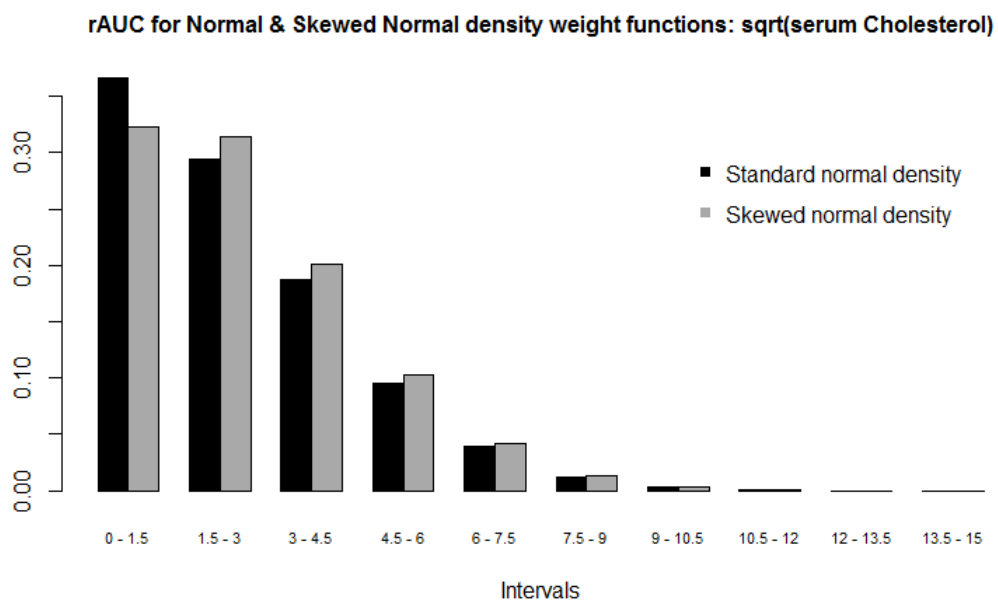


Figure S 16. Relative AUC calculated for logged serum Cholesterol over several intervals

4. Simulation Study

Table S 9. Details of simulation study

Longitudinal Process			
Coefficient	Input	Bias	RMSE
Intercept	0.540	0.050	0.068
ns(years, 3)1	0.772	-0.195	0.217
ns(years, 3)2	0.977	0.106	0.207
ns(years, 3)3	0.805	0.512	0.624
σ_e	0.286	0.000	0.004

Table S 10. Details of simulation study. $D[i, j]$ denote the square root of the ij -element of the (diagonal) covariance matrix for the random effects

Event Process			
Coefficient	Input	Bias	RMSE
Drug	-0.088	0.042	0.242
Association parameter (α)	2.503	-0.005	0.496
Scale parameter (σ)	1.000	0.175	0.463
D[1, 1]	1.002	0.003	0.036
D[2, 2]	1.254	-0.182	0.202
D[3, 3]	1.049	0.537	0.571
D[4, 4]	0.867	2.637	2.680

5. R Code

```
# LIBRARIES

library(lattice)
library(JMbayes)
library(sn)

# LONGITUDINAL SUB MODEL

lmeFit.origREML <- lme(hb1c_nw ~ ns(fu_years, 2) + diabetesduur + agen +
                      base_ret + base_sbpn,
                      data = subset_long,
                      random = ~ ns(fu_years, 2) | patientnr,
                      method = "REML")

# SURVIVAL SUB MODEL

coxFit.2 <- coxph(Surv(year_event, STR_first) ~ 1, data = subset_surv,
                 x = TRUE)
summary(coxFit.2)

# INITIAL JOINT MODEL: CURRENT VALUE SPECIFICATION

jointFit.origREML <- jointModelBayes(lmeFit.origREML, coxFit.2,
                                    timeVar = "fu_years",
                                    n.iter = 100000)

plot(jointFit.rootREML)

# CUMULATIVE SPECIFICATION (NO WEIGHTS)

iForm <- list(fixed = ~ 0 + fu_years + ins(fu_years, 2),
             random = ~ 0 + fu_years + ins(fu_years, 2),
             indFixed = 1:3, indRandom = 1:3)

jointFit.str_c <- update(jointFit.origREML, param = "td-extra",
                       extraForm = iForm)

summary(jointFit.str_c)
plot(jointFit.str_c)

# WEIGHTED CUMULATIVE ASSOCIATION
```

```
# NORMAL DISTRIBUTION SINGLE PARAMETER

wf <- function(u, parms, t.max)
  num <- dnorm(x = u, sd = parms)
  den <- pnorm(q = c(0, t.max), sd = parms)
  num / (den[2L] - den[1L])

jointFit.strw_o <- update(jointFit.origREML, estimateWeightFun = TRUE,
  weightFun = wf,
  priorShapes = list(shapel = dunif),
  priors = list(priorshapel = c(0, 5)))
summary(jointFit.strw_o)
plot(jointFit.strw_o, which = "weightFun", max.t = max(subset_surv$year_event))
plot(jointFit.strw_o)

# SKEWED NORMAL

wfsn <- function(u, parms, t.max)
  num <- dst(x = u, omega = parms[1], alpha = parms[2])
  den <- pst(x = c(0, t.max), omega = parms[1], alpha = parms[2])
  num / (den[2L] - den[1L])

jointFitsn.strw_o <- update(jointFit.origREML, estimateWeightFun = TRUE,
  weightFun = wfsn,
  priorShapes = list(shapel = dunif, shape2 = dunif),
  priors = list(priorshapel = c(0, 5),
  priorshape2 = c(0, 10)))
summary(jointFitsn.strw_o)
plot(jointFitsn.strw_o, which = "weightFun", max.t = max(subset_surv$year_event))
plot(jointFitsn.strw_o)

# CODE FOR HEPATOMEGALY (DICHOTOMOUS RESPONSE IN PBC DATA)

# SURVIVAL & LONGITUDINAL SUB MODELS

lmeFit.hep1 <- glmmPQL(hepatomegaly ~ year, random = ~ year | id,
  family = binomial, data = pbc2.na)
coxFit.hep1n <- coxph(Surv(years, status2) ~ drug * agenew, data = pbc2.id.na,
  x = TRUE)

# INITIAL JOINT MODEL: CURRENT VALUE SPECIFICATION

dLongBin <- function(y, eta.y, scale, log = FALSE, data)
```

```
dbinom(x = y, size = 1, prob = plogis(eta.y), log = log)

jointFit.hep2n <- jointModelBayes(lmeFit.hep1, coxFit.hep1n, timeVar = "year",
                                densLong = dLongBin, n.iter = 60000)

# CUMULATIVE SPECIFICATION (NO WEIGHTS)
iForm <- list(fixed = ~ 0 + year + I((year^2)/2),
             random = ~ 0 + year + I((year^2)/2),
             indFixed = 1:2, indRandom = 1:2)

jointFit.hep_c <- update(jointFit.hep2n, param = "td-extra",
                       extraForm = iForm)

# WEIGHTED CUMULATIVE ASSOCIATION
# NORMAL DISTRIBUTION SINGLE PARAMETER

wf <- function(u, parms, t.max)
  num <- dnorm(x = u, sd = parms)
  den <- pnorm(q = c(0, t.max), sd = parms)
  num / (den[2L] - den[1L])

jointFit.hepw <- update(jointFit.hep2n, estimateWeightFun = TRUE,
                      weightFun = wf,
                      priorShapes = list(shapel = dunif),
                      priors = list(priorshapel = c(0, 4.5)))
```