T2D Scenarios and Estimators

2024-10-18

The Aim

The overall aim of the project is to investigate how to analyse if a drug which has an established beneficial effect on an intermediate event (onset of diabetes is delayed for people taking the drug) has an additional benefit on a terminal event (death).

Intuitively it seems that we have answered this question by answering the specific question

- What is the effect of the drug on the probability of death among T2D subjects?

However, assume that it is also well-known that the intermediate event is a risk factor for the terminal event. Then the effect of the drug on the terminal event could be 100% mediated through the intermediate event. The (naively asked) question is if using and having used the drug helps people when they get diabetes. The major challenge is the selection of the people in the study over time: people are randomized at the start of the study but at the onset of diabetes they are not randomized anymore:

- people who are already dead are not there anymore but if the drug has an effect on death then the people who take the drug live longer and hence are more likely to get diabetes.
- people are older in the treatment arm at the onset of diabetes due to the beneficial effect of the drug on preventing diabetes.

The set up

Simulations are carried out in a setting where patients can experience 2 different events: Death (1) and Type-2-Diabetes (2). We have omitted censoring. Death is a terminal events and each individual can be diagnosed with T2D once. There is a baseline covariate L_0, and a baseline treatment A_0. The covariate L_0 is uniform on $(40, 60)$ and represents age. Effects of covariates L_0, A_0 and T2D on the intensities of the events can be specified by the user by the beta arguments of the simulation function. The intensities of the different events follow the form

$$\lambda_x(t) = R^x(t)\lambda_0(x,t)\phi(x,t)$$

The function $R^x(t)$ is an at risk indicator. The baseline hazard is specified as

$$\lambda_0(x,t) = \eta_x \nu_x t^{\nu_x - 1}$$

The death process has $\eta_{death} = 0.3$ and $\nu_{death} = 1.3$, while T2D has $\eta_{T2D} = 0.1$ and $\nu_{T2D} = 1.1$. The $\phi(x,t)$ function is defined as

$$\phi(x,t) = \exp\left(\frac{\beta_{L_0,x}}{50}L_0 + \beta_{L_1,x}L_1 + \beta_{A_0,x}A_0 + \beta_{L,x}L\right)$$

Below we will for two different settings look at three different ways of evaluating the effect of treatment on death. We will look at

- Proportion of dead treatment and placebo patients a year after T2D diagnose
- Kaplan-Meier estimated survival probability a year after T2D diagnose for respectively treatment and placebo patients.
- An intervention based estimate

We simulate $2 \cdot 10^4$ individuals per estimate.

Setting A

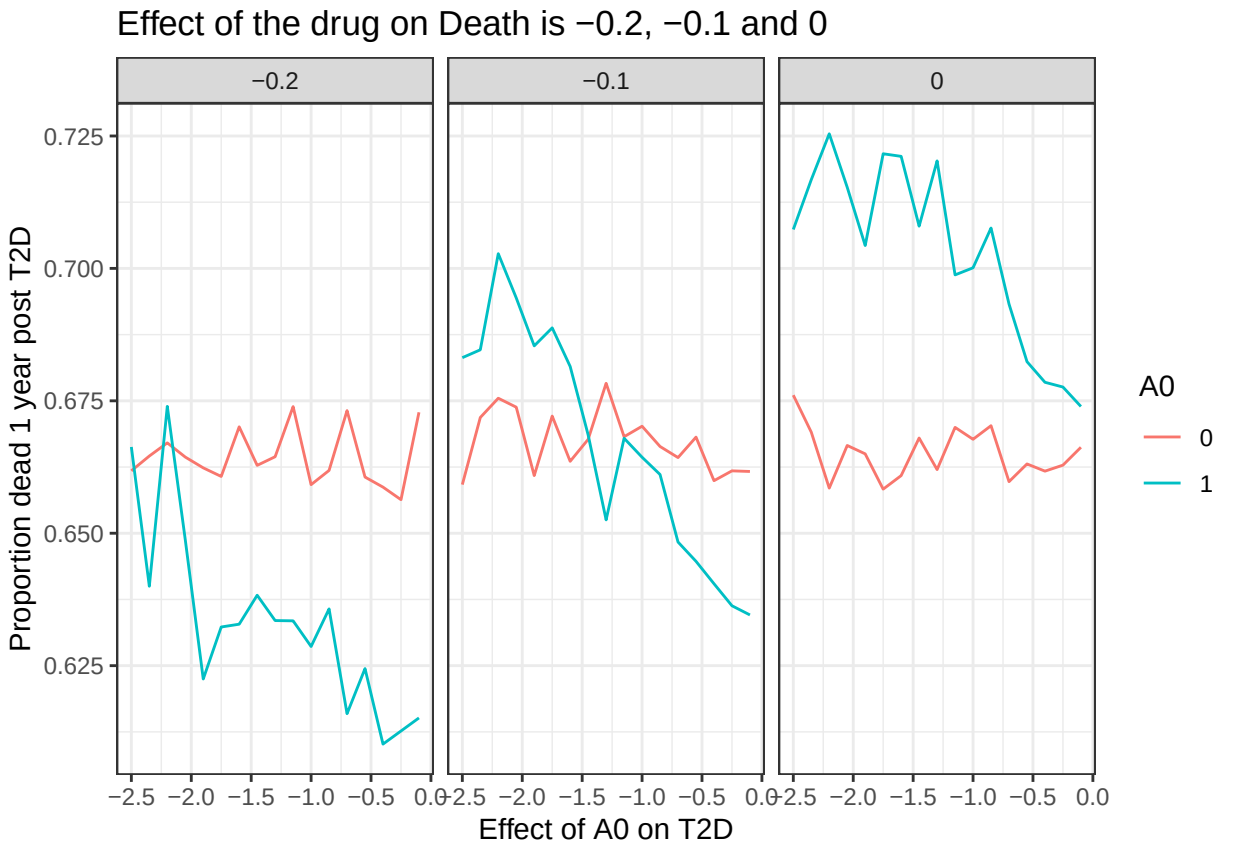
Below we estimate the proportion and survival probability in three different scenarios: where the effect of the drug on Death is 0, -0.1 and -0.2. The effect of A_0 on T2D is let to vary from -2.5 to 0 by 0.15. The effect of L_0 on T2D is large ($= 2$). And the effect of T2D on death is moderate ($= 1$). There is no effect of L_0 directly on death.

```
N <- 2 * 10^4

estimator1 <- function(data, N) {
  # T2D events
  T2D_events <- data[Delta == 3]
  # T2D people
  T2D_peeps <- data[ID %in% T2D_events$ID]

  # Setting T_0 to debut time of diabetes
  T2D_peeps[, Time_T2D := Time - min(Time), by = ID]

  # Removing the new Time 0
  T2D_peeps <- T2D_peeps[Delta != 3]

  # Proportion of treatment and placebo patients who have died before 1 year after T2D diagnose
  prop_treat <- nrow(T2D_peeps[Time_T2D < 1 & Delta == 1 & A0 == 1]) / length(unique(T2D_peeps[A0 == 1]$
  prop_plac <- nrow(T2D_peeps[Time_T2D < 1 & Delta == 1 & A0 == 0]) / length(unique(T2D_peeps[A0 == 0]$

  # Kaplan meyer fit
  fit <- survfit(Surv(Time_T2D, Delta == 1) ~ A0, data = T2D_peeps)

  # Save estimate of survival probability, and confidence limits
  preds <- summary(fit, times = 1, data.frame = TRUE)

  # The proportion dead, the KM estimate, SE's, lower CI, and upper CI is returned
  return(c(prop_plac, prop_treat, preds[,5], preds[,7], preds[,9], preds[,10]))
}

res1 <- compare_effects(estimator = estimator1,
                        N = N,
                        eta = c(0.1,0.3,0.1,0.1),
                        nu = c(1.1,1.3,1.1,1.1),
                        beta_L0_L = 2,
                        beta_A0_L = seq(-2.5, 0, by = 0.15),
                        beta_L_D = 1,
                        beta_L0_D = 0)
```

Proportion Dead

Below the plots show the proportion dead for different effects of the drug on death.

```
plot_compare(res1[,c(1,2,11,12,21,22)], diff_betas = seq(-2.5, 0, by = 0.15))+
  ylab("Proportion dead 1 year post T2D")+
  xlab("Effect of A0 on T2D")+
  labs(title = "Effect of the drug on Death is -0.2, -0.1 and 0")
```

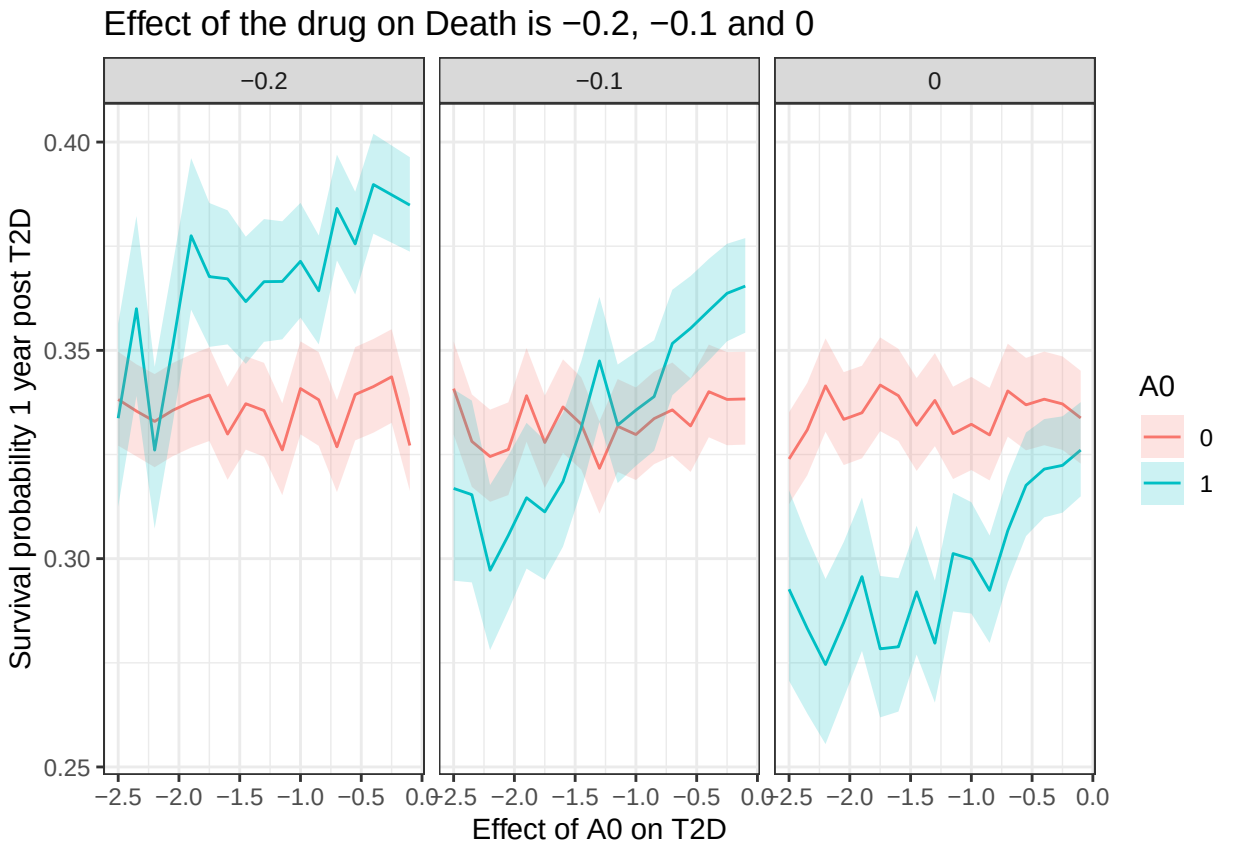


We see that the proportion of dead is larger in the treatment group than the placebo group, when the drug does not have an effect on death. When the drug has a small effect the proportions are equally large. And only when the beneficial effect of the drug is large, the proportion of dead is smaller. It seems our hypothesis about the selection of individuals is true. It further seems, in all three scenarios, as if the proportion of dead in the treatment group is decreasing as the effect of A_0 on T2D decreases, further supporting the selection hypothesis.

Survival Probability

Below the Kaplan-Meier estimates as well as the .95 CI's of the survival probability 1 year after T2D diagnose are plotted.

```
estimates <- res1[,c(3,4,13,14,23,24)]
lower <- res1[,c(7,8,17,18,27,28)]
upper <- res1[,c(9,10,19,20,29,30)]

plot_compare(estimates = estimates, diff_betas = seq(-2.5, 0, by = 0.15),
             lower = lower, upper = upper)+
  ylab("Survival probability 1 year post T2D")+
  xlab("Effect of A0 on T2D")+
  labs(title = "Effect of the drug on Death is -0.2, -0.1 and 0")
```



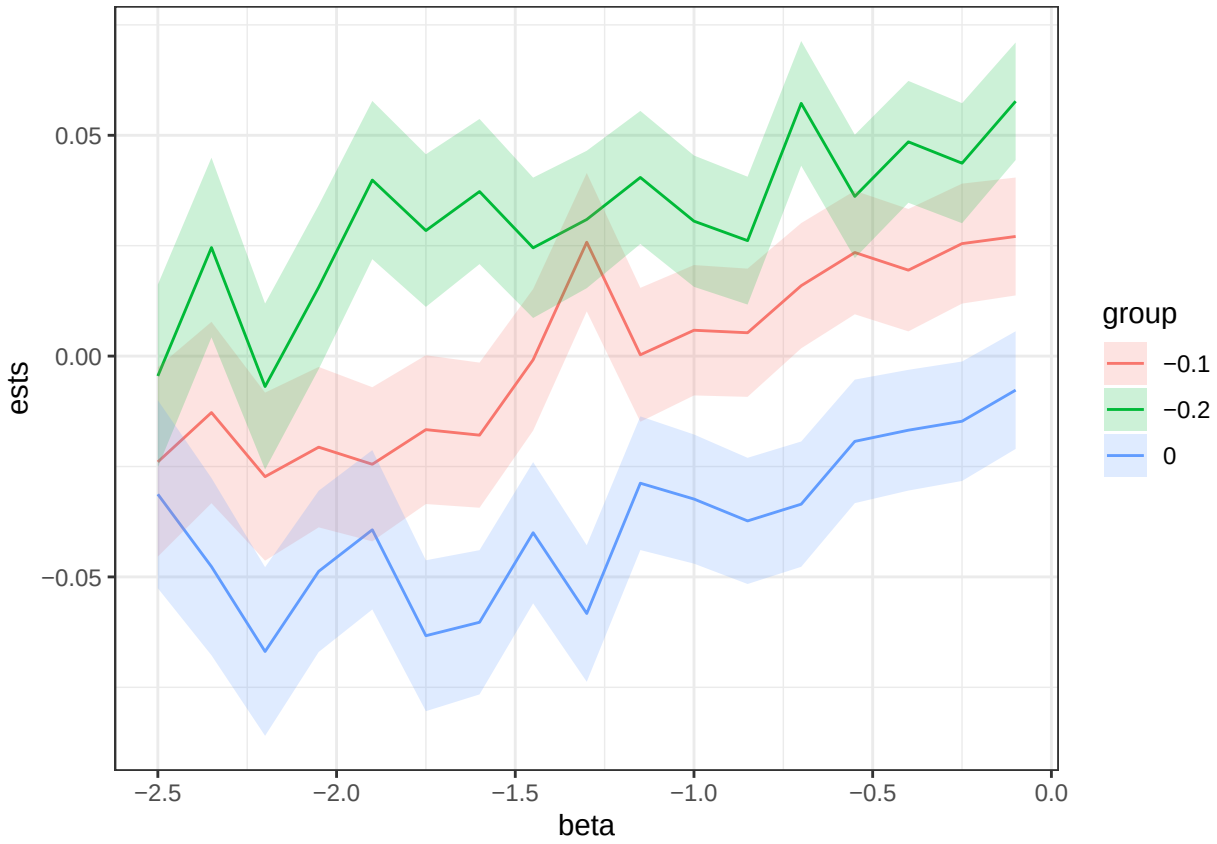
The Kaplan-Meier estimates tell the same story as the proportions.

We now plot the estimated differences in survival probabilities between treatment and placebo group. We calculate the standard error of the difference in survival probability between the two groups as $SE_{diff} = \sqrt{Var(\hat{S}(t|A_0 = 1)) + Var(\hat{S}(t|A_0 = 0))}$, where the two standard errors are obtained from the KM fit from the survival package, and calculate the confidence interval as

$$\hat{S}(t|A_0 = 1) - \hat{S}(t|A_0 = 0) \pm \alpha_{0.05} SE_{diff}$$

using a normal approximation.

```
diffs <- res1[,c(4,14,24)] - res1[,c(3,13,23)]
se <- sqrt(res1[,c(5,15,25)]^2 + res1[,c(6,16,26)]^2)
upper <- diffs + qnorm(0.05)*se
lower <- diffs - qnorm(0.05)*se

plot.data <- data.table(ests = c(diffs),
           beta = rep(seq(-2.5, 0, by = 0.15), 3),
           group = c(rep("0", 17), rep("-0.1", 17), rep("-0.2", 17)),
           upper = c(upper),
           lower = c(lower))



ggplot(plot.data)+
  geom_line(aes(x = beta, y = ests, color = group))+
  geom_ribbon(aes(x = beta, ymin = lower, ymax = upper, fill = group), alpha = 0.2)
```



(Må jeg gerne det her? 1) de to estimater er jo nok ikke uafhængige… eller er de? og to, er normal fordelings antagelsen ok?)

Interventions

We want to see whether we can estimate the effect of the drug on death more correctly with interventions. The idea is to generate a large data set. Estimate the intensity of the T2D event for the non treatment group. Generate two new data sets: one with the estimated intensity of the T2D event and one simulated as before. And at last, compare the proportion of dead people in the treatment group τ years after beginning of trial.

Generate large data

```
data_A <- sim_data_setting2(N,
                            eta = c(0.1,0.3,0.1,0.1),
                            nu = c(1.1,1.3,1.1,1.1),
                            beta_A0_D = -0.1,
                            beta_L0_L = 2,
                            beta_A0_L = -1,
                            beta_L_D = 1,
                            beta_L0_D = 0,
                            cens = 0)
```

Grouping data based on treatment

```
no_treat_group <- data_A[A0 == 0]
treat_group <- data_A[A0 == 1]
```

Fit Weibull

```
survfit <- survreg(Surv(Time, Delta == 3) ~ 1,
                   data = no_treat_group[L == 0],
                   cluster = ID,
                   dist='weibull')
```

Estimates in no treatment group

```
nu_est <- 1/survfit$scale; nu_est
```

```
## [1] 1.004196
```

```
eta_est <- 1/(exp(survfit$coefficients[1]))^nu_est; eta_est
```

```
## (Intercept)
##    0.740035
```

Generate large data set under the intervened intensity

```
data_new <- sim_data_setting2(N = N,
                              cens = 0,
                              eta = c(0.1,0.3,0.1,eta_est),
                              nu = c(1.1,1.3,1.1,nu_est),
                              beta_A0_D = 0,
                              beta_L_D = 1,
                              beta_L0_D = 0,
                              beta_L0_L = 0,
                              beta_A0_L = 0)
```

Generate large data set without intervened intensity

```
data_new_no_int <- sim_data_setting2(N = N,
                                     eta = c(0.1,0.3,0.1,0.1),
                                     nu = c(1.1,1.3,1.1,1.1),
                                     beta_A0_D = 0,
                                     beta_L0_L = 2,
                                     beta_A0_L = -1,
                                     beta_L_D = 1,
                                     beta_L0_D = 0,
                                     cens = 0)
```

Proportion of subjects dying before some time τ in treatment group

```
tau <- 2
mean(data_new[Delta == 1 & A0 == 1, Time] < tau) # with intervention
```

```
## [1] 0.7229995
```

```
mean(data_new_no_int[Delta == 1 & A0 == 1, Time] < tau) # without intervention
```

```
## [1] 0.6376258
```

The proportion of people dead under intervention is larger. The intervention approach seems to capture the beneficial effect of the drug on death that the two previous approaches did not.

Setting B

We now turn to a similar setting. Three different scenarios are considered: 1) no effect of T2D on death (0), 2) moderate effect of T2D on death (0.5), 3) larger effect of T2D on death (1). And no effect of drug on

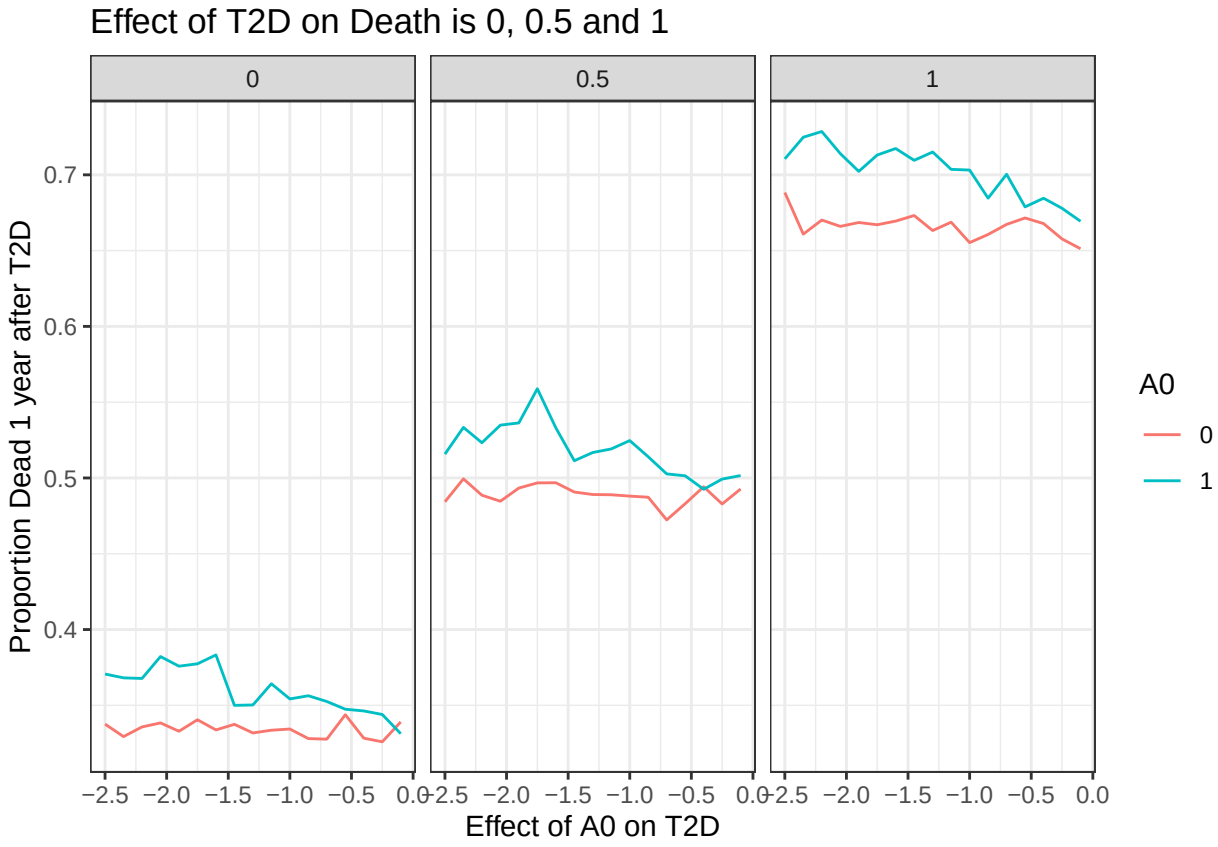
death. All other parameters are the same. The effect of A_0 on T2D is again let to vary from -2.5 to 0 by 0.15.

```
res2 <- compare_effects(estimator = estimator1,
                        N = N,
                        eta = c(0.1,0.3,0.1,0.1),
                        nu = c(1.1,1.3,1.1,1.1),
                        beta_L0_L = 2,
                        beta_A0_L = seq(-2.5, 0, by = 0.15),
                        beta_L0_D = 0,
                        setting = 2)
```

Proportion dead

Below the plots show the proportion dead for different effects of the drug on death.

```
plot_compare(res2[,c(1,2,11,12,21,22)], diff_betas = seq(-2.5, 0, by = 0.15), groups = c(0, 0.5, 1))+
  ylab("Proportion Dead 1 year after T2D")+
  xlab("Effect of A0 on T2D")+
  labs(title = "Effect of T2D on Death is 0, 0.5 and 1")
```

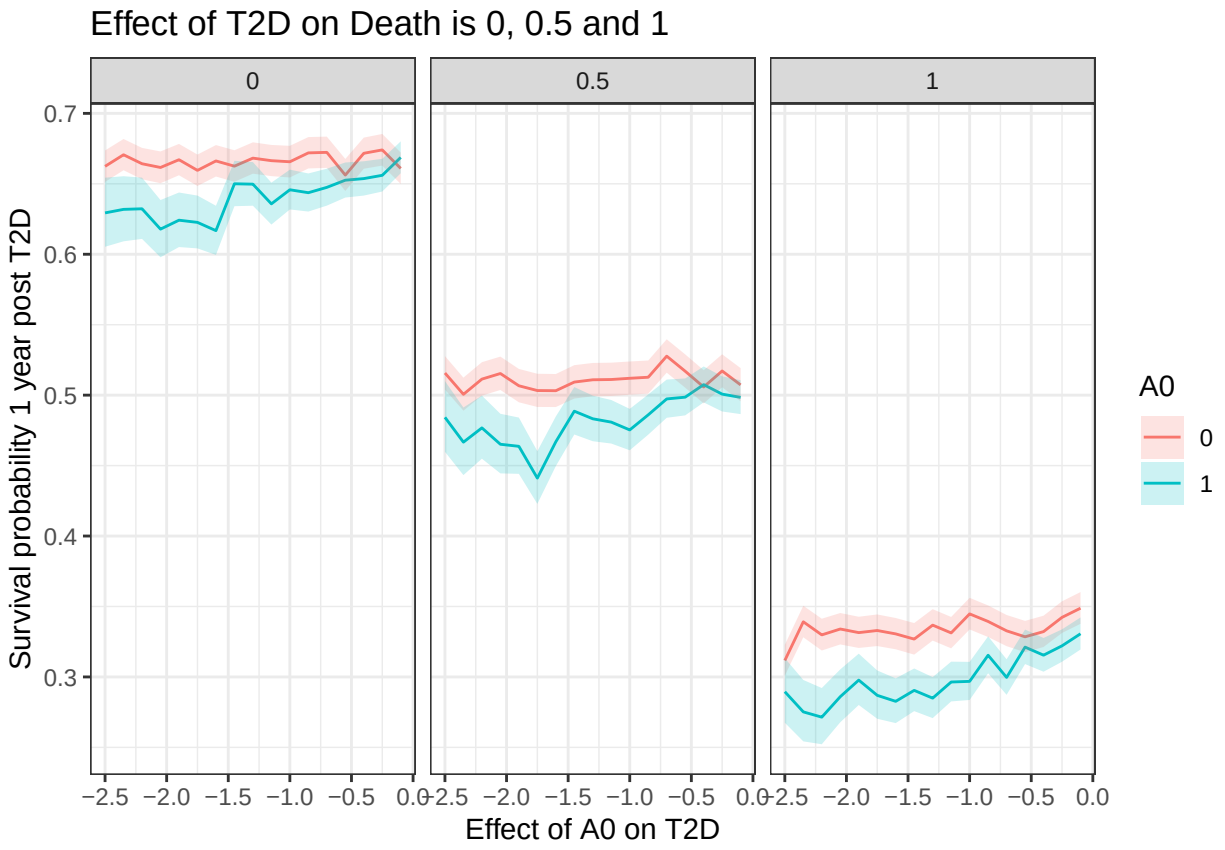


For all three scenarios we see that the proportion of dead is larger in the treatment group than in the placebo group when there is an effect of $A0$ on T2D. This is again due to the selection of individuals. Since $A0$ decreases the risk of T2D, the people in the treatment group that end up diagnosed with T2D are older, and thus more likely to die. It seems the difference is increasing as the effect of T2D on death increases.

Survival Probability

Below the Kaplan-Meier estimates as well as the .95 CI's of the survival probability 1 year after T2D diagnose are plotted.

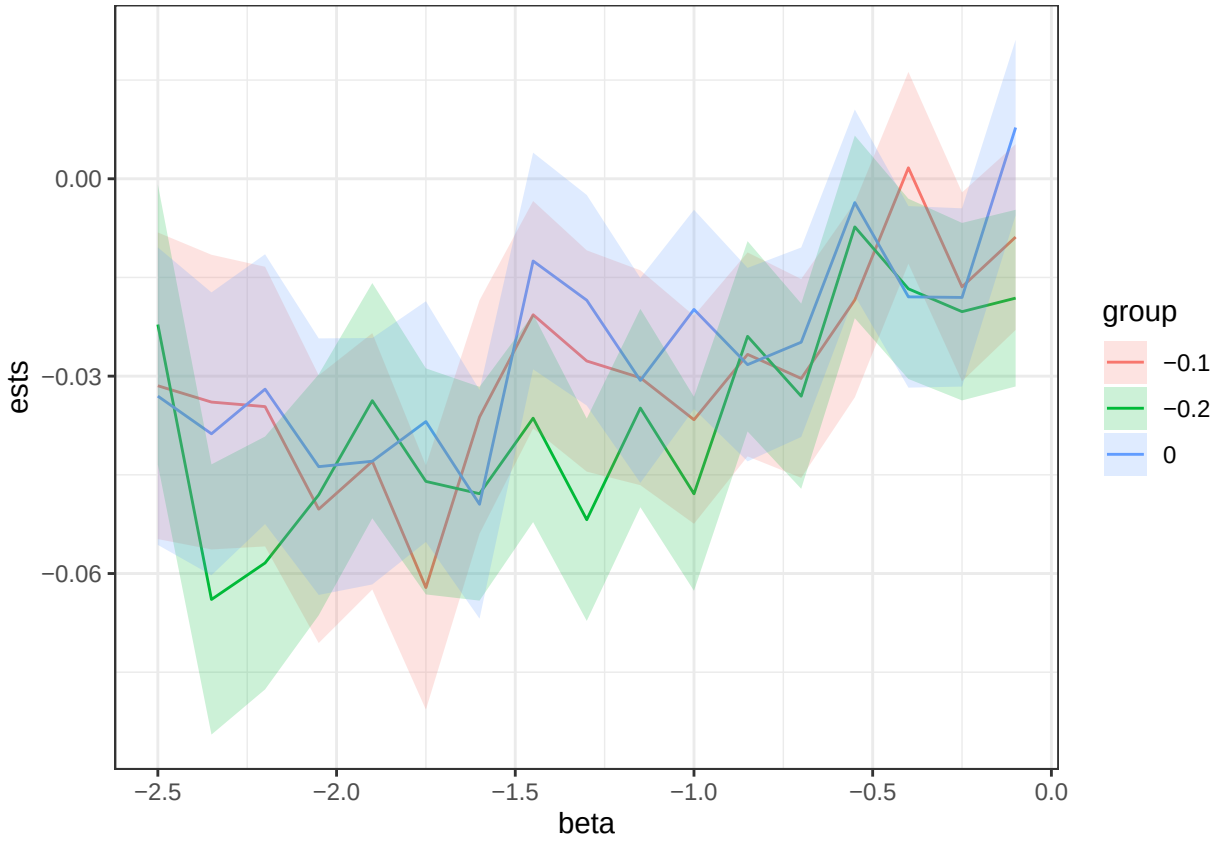
```
estimates <- res2[,c(3,4,13,14,23,24)]
lower <- res2[,c(7,8,17,18,27,28)]
upper <- res2[,c(9,10,19,20,29,30)]

plot_compare(estimates = estimates, diff_betas = seq(-2.5, 0, by = 0.15),
             lower = lower, upper = upper, groups = c(0, 0.5, 1)) +
  ylab("Survival probability 1 year post T2D")+
  xlab("Effect of A0 on T2D")+
  labs(title = "Effect of T2D on Death is 0, 0.5 and 1")
```



Again the Kaplan-Meier estimates tell the same story. We now plot the estimated differences in survival probabilities between treatment and placebo group, as well as confidence bands.

```
diffs <- res2[,c(4,14,24)] - res2[,c(3,13,23)]
se <- sqrt(res2[,c(5,15,25)]^2 + res2[,c(6,16,26)]^2)
upper <- diffs + qnorm(0.05)*se
lower <- diffs - qnorm(0.05)*se

plot.data <- data.table(ests = c(diffs),
           beta = rep(seq(-2.5, 0, by = 0.15), 3),
           group = c(rep("0", 17), rep("-0.1", 17), rep("-0.2", 17)),
           upper = c(upper),
           lower = c(lower))
```

```
ggplot(plot.data)+
  geom_line(aes(x = beta, y = ests, color = group))+
  geom_ribbon(aes(x = beta, ymin = lower, ymax = upper, fill = group), alpha = 0.2)
```



Interventions

As before we want to see whether we can estimate the effect of the drug on death more correctly with an interventions. The same procedure as before is applied.

Generate large data

```
data_A <- sim_data_setting2(N,
                            eta = c(0.1,0.3,0.1,0.1),
                            nu = c(1.1,1.3,1.1,1.1),
                            beta_A0_D = 0,
                            beta_L0_L = 2,
                            beta_A0_L = -1,
                            beta_L_D = 0.5,
                            beta_L0_D = 0,
                            cens = 0)
```

Grouping data based on treatment

```
no_treat_group <- data_A[A0 == 0]
treat_group <- data_A[A0 == 1]
```

Fit Weibull

```
survfit <- survreg(Surv(Time, Delta == 3) ~ 1,
                   data = no_treat_group[L == 0],
                   cluster = ID,
                   dist='weibull')
```

Estimates in no treatment group

```
nu_est <- 1/survfit$scale; nu_est
```

```
## [1] 1.022935
```

```
eta_est <- 1/(exp(survfit$coefficients[1]))^nu_est; eta_est
```

```
## (Intercept)
##    0.734606
```

Generate large data set under the intervened intensity

```
data_new <- sim_data_setting2(N = N,
                              cens = 0,
                              eta = c(0.1,0.3,0.1,eta_est),
                              nu = c(1.1,1.3,1.1,nu_est),
                              beta_A0_D = 0,
                              beta_L_D = 0.5,
                              beta_L0_D = 0,
                              beta_L0_L = 0,
                              beta_A0_L = 0)
```

Generate large data set without intervened intensity

```
data_new_no_int <- sim_data_setting2(N,
                                     eta = c(0.1,0.3,0.1,0.1),
                                     nu = c(1.1,1.3,1.1,1.1),
                                     beta_A0_D = 0,
                                     beta_L0_L = 2,
                                     beta_A0_L = -1,
                                     beta_L_D = 0.5,
                                     beta_L0_D = 0,
                                     cens = 0)
```

Proportion of subjects dying before some time τ in treatment group

```
tau <- 2
mean(data_new[Delta == 1 & A0 == 1, Time] < tau) # with intervention
```

```
## [1] 0.6259827
```

```
mean(data_new_no_int[Delta == 1 & A0 == 1, Time] < tau) # without intervention
```

```
## [1] 0.5665395
```

Again the proportion of people dead under intervention is larger. And it seems this approach catches the effect better than the two previous methods.