

EMM CANTOS

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24/09/2022

```
library(regmedint)
```

```
## Warning: package 'regmedint' was built under R version 4.1.2
```

0. Data Source

Original paper: Vallurupalli M, MacFadyen JG, Glynn RJ, et al. Effects of Interleukin-1 β Inhibition on Incident Anemia: Exploratory Analyses From a Randomized Trial. Ann Intern Med. 2020;172(8):523. doi:10.7326/M19-2945

```
setwd("/Users/yili/Desktop/_cantos_analyses/Anemia outcome")

anemia3 <- read.csv("~/Desktop/_cantos_analyses/Anemia outcome/anemia3.csv", header = FALSE)

colnames(anemia3) <- c("canakinumab", "age", "female", "base_logCRP",
                      "chf", "htn", "dm", "egfrlo", "3mo_logCRP_100",
                      "anemiaev", "anemiayrs"
                      )

anemia3$diff_logCRP <- anemia3$`3mo_logCRP_100`/100 - anemia3$base_logCRP
```

1. Variables

Treatment: canakinumab use (binary)

Mediator: change in log CRP (continuous)

Outcome: anemia (survival time)

Baseline confounders: age, sex, baseline log CRP, heart failure, hypertension, diabetes

2. Directed Acyclic Graph

```
c_cond0_mean <- sapply(anemia3[, c("age", "female", "base_logCRP",
                                   "chf", "htn", "dm")], mean)
c_cond0_mean
```

```
##      age      female base_logCRP      chf      htn      dm
## 60.5374609 0.2471694 1.4949021 0.3819562 0.7898097 0.2033245
```

```
# Condition on other non-EMM covariates:
# female = 0, chf (heart failure) = 0, htn (hypertention) = 1
c_cond0 <- c(mean(anemia3$age), 0, mean(anemia3$base_logCRP), 0, 1, 0)
c_cond0
```

```
## [1] 60.537461 0.000000 1.494902 0.000000 1.000000 0.000000
```

3. Mediation analyses

Effect modification by baseline logCRP in mediator model, and age & diabetes in outcome model

```
c_cond_low_all <- c_cond_high_all <- c_cond0
c_cond_low_all[c(1, 3, 6)] <- c(quantile(anemia3$age, 0.25),
                                quantile(anemia3$base_logCRP, 0.25),
                                0)
c_cond_high_all[c(1, 3, 6)] <- c(quantile(anemia3$age, 0.75),
                                quantile(anemia3$base_logCRP, 0.75),
                                1)

c_cond_low_all
```

1. Specify low and high risk groups' covariate levels

```
## [1] 54.0000 0.0000 1.0116 0.0000 1.0000 0.0000
```

```
c_cond_high_all
```

```
## [1] 67.0000 0.0000 1.8871 0.0000 1.0000 1.0000
```

```
cvar = c("age", "female", "base_logCRP",
          "chf", "htn", "dm")

fit1.1 <- regmedint(data = anemia3,
                    yvar = "anemiayrs",
                    eventvar = "anemiaev",
                    avar = "canakinumab",
                    mvar = "diff_logCRP",
                    cvar = cvar,
                    ## EMM
                    emm_ac_mreg = c("base_logCRP"),
                    emm_ac_yreg = NULL,
                    emm_mc_yreg = c("age", "dm"),
                    ##
                    mreg = "linear",
                    yreg = "survAFT_weibull",
```

```

interaction = TRUE,
casecontrol = FALSE,
a0 = 0,
a1 = 1,
m_cde = mean(anemia3$diff_logCRP),
c_cond = c_cond_low_all)

fit1.2 <- regmedint(data = anemia3,
  yvar = "anemiayrs",
  eventvar = "anemiaev",
  avar = "canakinumab",
  mvar = "diff_logCRP",
  cvar = cvar,
  ## EMM
  emm_ac_mreg = c("base_logCRP"),
  emm_ac_yreg = NULL,
  emm_mc_yreg = c("age", "dm"),
  ##
  mreg = "linear",
  yreg = "survAFT_weibull",
  interaction = TRUE,
  casecontrol = FALSE,
  a0 = 0,
  a1 = 1,
  m_cde = mean(anemia3$diff_logCRP),
  c_cond = c_cond_high_all)

summary(fit1.1)

```

2. Fit regmedint function

```

## ### Mediator model
##
## Call:
## lm(formula = diff_logCRP ~ canakinumab + age + female + base_logCRP +
##     chf + htn + dm + canakinumab:base_logCRP, data = data)
##
## Residuals:
##      Min       1Q   Median       3Q      Max
## -4.4475 -0.5258 -0.0350  0.4525  5.6261
##
## Coefficients:
##              Estimate Std. Error t value Pr(>|t|)
## (Intercept)    0.4228295   0.0690623    6.122 9.63e-10 ***
## canakinumab   -0.6036174   0.0466630   -12.936 < 2e-16 ***
## age          -0.0006421   0.0009539    -0.673  0.5008
## female        0.0126025   0.0214422    0.588  0.5567
## base_logCRP   -1.4365841   0.0232393   -61.817 < 2e-16 ***
## chf           0.0928445   0.0191560    4.847 1.28e-06 ***
## htn           0.0163260   0.0230711    0.708  0.4792
## dm            0.0427971   0.0229645    1.864  0.0624 .
## canakinumab:base_logCRP -0.0314079  0.0284792   -1.103  0.2701
## ---

```

```

## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 0.8336 on 8293 degrees of freedom
## Multiple R-squared:  0.6082, Adjusted R-squared:  0.6078
## F-statistic: 1609 on 8 and 8293 DF,  p-value: < 2.2e-16
##
## ### Outcome model
##
## Call:
## survival::survreg(formula = Surv(anemiayrs, anemiaev) ~ canakinumab +
##   diff_logCRP + canakinumab:diff_logCRP + age + female + base_logCRP +
##   chf + htn + dm + diff_logCRP:age + diff_logCRP:dm, data = data,
##   dist = "weibull")
##
##              Value Std. Error      z      p
## (Intercept)      7.40059    0.53565 13.82 < 2e-16
## canakinumab       0.08224    0.14929  0.55  0.582
## diff_logCRP     -0.48373    0.20525 -2.36  0.018
## age             -0.04799    0.00802 -5.98 2.2e-09
## female          -0.00885    0.09005 -0.10  0.922
## base_logCRP     -0.73354    0.08943 -8.20 2.4e-16
## chf             -0.63861    0.08165 -7.82 5.2e-15
## htn             -0.06670    0.10627 -0.63  0.530
## dm             -0.21359    0.17003 -1.26  0.209
## canakinumab:diff_logCRP -0.04483    0.06241 -0.72  0.473
## diff_logCRP:age   0.00376    0.00307  1.23  0.220
## diff_logCRP:dm    0.04716    0.06412  0.74  0.462
## Log(scale)       0.52366    0.02211 23.69 < 2e-16
##
## Scale= 1.69
##
## Weibull distribution
## Loglik(model)= -6072.8  Loglik(intercept only)= -6258.5
## Chisq= 371.37 on 11 degrees of freedom, p= 7.2e-73
## Number of Newton-Raphson Iterations: 7
## n= 8302
##
## ### Mediation analysis
##      est      se      Z      p      lower      upper
## cde 0.1780520 0.08776683 2.028693 4.248956e-02 0.006032135 0.3500718
## pnde 0.1387042 0.09665386 1.435061 1.512698e-01 -0.050733912 0.3281422
## tnle 0.2068696 0.03998078 5.174225 2.288590e-07 0.128508667 0.2852305
## tnle 0.1671901 0.08655933 1.931508 5.342023e-02 -0.002463110 0.3368432
## pnle 0.1783837 0.04636945 3.847009 1.195687e-04 0.087501223 0.2692661
## te  0.3455737 0.09103109 3.796216 1.469213e-04 0.167156063 0.5239914
## pm  0.6395734 0.17300163 3.696921 2.182302e-04 0.300496404 0.9786503
##
## Evaluated at:
## avar: canakinumab
## a1 (intervened value of avar) = 1
## a0 (reference value of avar) = 0
## mvar: diff_logCRP
## m_cde (intervend value of mvar for cde) = -2.137102
## cvar: age female base_logCRP chf htn dm
## c_cond (covariate vector value) = 54 0 1.0116 0 1 0

```

```
##
## Note that effect estimates can vary over m_cde and c_cond values when interaction = TRUE.
```

```
summary(fit1.2)
```

```
## ### Mediator model
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## Call:
## lm(formula = diff_logCRP ~ canakinumab + age + female + base_logCRP +
##     chf + htn + dm + canakinumab:base_logCRP, data = data)
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## F-statistic: 1609 on 8 and 8293 DF, p-value: < 2.2e-16
##
## ### Outcome model
##
## Call:
## survival::survreg(formula = Surv(anemia yrs, anemia ev) ~ canakinumab +
##     diff_logCRP + canakinumab:diff_logCRP + age + female + base_logCRP +
##     chf + htn + dm + diff_logCRP:age + diff_logCRP:dm, data = data,
##     dist = "weibull")
##
##              Value Std. Error      z      p
## (Intercept)    7.40059    0.53565 13.82 < 2e-16
## canakinumab     0.08224    0.14929  0.55  0.582
## diff_logCRP    -0.48373    0.20525 -2.36  0.018
## age            -0.04799    0.00802 -5.98 2.2e-09
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## cde  0.1780520  0.08776683  2.028693  0.0424895616  0.006032135  0.3500718
## pnde 0.1905550  0.09129110  2.087334  0.0368579399  0.011627762  0.3694823
## tnle 0.1521701  0.04534835  3.355582  0.0007919818  0.063288972  0.2410512
## tnde 0.2202737  0.11154304  1.974787  0.0482923802  0.001653350  0.4388940
## pnle 0.1224514  0.05256308  2.329609  0.0198268189  0.019429688  0.2254732
## te   0.3427251  0.09821450  3.489557  0.0004838213  0.150228244  0.5352220
## pm   0.4864715  0.14075463  3.456167  0.0005479164  0.210597461  0.7623455
##
## Evaluated at:
## avar: canakinumab
##   a1 (intervened value of avar) = 1
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## mvar: diff_logCRP
##   m_cde (intervend value of mvar for cde) = -2.137102
## cvar: age female base_logCRP chf htn dm
##   c_cond (covariate vector value) = 67 0 1.8871 0 1 1
##
## Note that effect estimates can vary over m_cde and c_cond values when interaction = TRUE.

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