

Causal mediation analyses with effect modification terms using CANTOS trial data

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```
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

```
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
```

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

2. Mediation analyses

(1) No Effect modification by any covariates

```
fit0.0 <- regmedint(data = anemia3,
                    yvar = "anemiayrs",
                    eventvar = "anemiaev",
                    avar = "canakinumab",
                    mvar = "diff_logCRP",
                    cvar = cvar,
                    ## EMM
                    emm_ac_mreg = NULL,
                    emm_ac_yreg = NULL,
                    emm_mc_yreg = NULL,
                    ##
                    mreg = "linear",
                    yreg = "survAFT_weibull",
                    interaction = TRUE,
                    casecontrol = FALSE,
                    a0 = 0,
                    a1 = 1,
                    m_cde = mean(anemia3$diff_logCRP),
                    c_cond = c_cond0)

summary(fit0.0)
```

```
## ### Mediator model
##
## Call:
## lm(formula = diff_logCRP ~ canakinumab + age + female + base_logCRP +
##     chf + htn + dm, data = data)
##
## Residuals:
##      Min       1Q   Median       3Q      Max
## -4.4422 -0.5246 -0.0366  0.4550  5.6302
##
## Coefficients:
##              Estimate Std. Error t value Pr(>|t|)
## (Intercept)  0.4554245  0.0624193   7.296 3.23e-13 ***
## canakinumab -0.6504159  0.0194098 -33.510 < 2e-16 ***
## age         -0.0006661  0.0009536  -0.698  0.4849
```

```

## female      0.0124121  0.0214418    0.579  0.5627
## base_logCRP -1.4574217  0.0135301 -107.717 < 2e-16 ***
## chf         0.0928082  0.0191562    4.845  1.29e-06 ***
## htn         0.0161637  0.0230710    0.701  0.4836
## dm          0.0427669  0.0229648    1.862  0.0626 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 0.8336 on 8294 degrees of freedom
## Multiple R-squared:  0.6082, Adjusted R-squared:  0.6078
## F-statistic: 1839 on 7 and 8294 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, data = data, dist = "weibull")
##
##              Value Std. Error      z      p
## (Intercept)      7.95064    0.33587  23.67 < 2e-16
## canakinumab       0.08959    0.14936   0.60 0.54860
## diff_logCRP     -0.23037    0.06386  -3.61 0.00031
## age             -0.05624    0.00446 -12.61 < 2e-16
## female          -0.00679    0.09005  -0.08 0.93985
## base_logCRP     -0.73261    0.08947  -8.19 2.6e-16
## chf             -0.63685    0.08163  -7.80 6.1e-15
## htn             -0.06529    0.10624  -0.61 0.53883
## dm             -0.31877    0.09297  -3.43 0.00061
## canakinumab:diff_logCRP -0.04176    0.06238  -0.67 0.50319
## Log(scale)       0.52382    0.02211  23.69 < 2e-16
##
## Scale= 1.69
##
## Weibull distribution
## Loglik(model)= -6073.9  Loglik(intercept only)= -6258.5
##  Chisq= 369.15 on 9 degrees of freedom, p= 5.2e-74
## Number of Newton-Raphson Iterations: 7
## n= 8302
##
## ### Mediation analysis
##
##      est      se      Z      p      lower      upper
## cde 0.1788398 0.08779440 2.037030 4.164704e-02 0.0067659649 0.3509137
## pnde 0.1698583 0.08658498 1.961752 4.979133e-02 0.0001548423 0.3395617
## tnle 0.1769992 0.03295536 5.370878 7.835435e-08 0.1124078731 0.2415905
## tnle 0.1970205 0.09481515 2.077943 3.771461e-02 0.0111862011 0.3828547
## pnle 0.1498370 0.04177719 3.586575 3.350502e-04 0.0679552181 0.2317188
## te  0.3468575 0.08320654 4.168632 3.064328e-05 0.1837756542 0.5099393
## pm  0.5534728 0.13876434 3.988581 6.646960e-05 0.2814997466 0.8254460
##
## 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) = 60.53746 0 1.494902 0 1 0
##
## Note that effect estimates can vary over m_cde and c_cond values when interaction = TRUE.
```

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

a. Specify low and high risk groups' covariate levels

```
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
# c_cond_high_all
```

b. Fit regmedint function

```
fit.emm <- 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)

summary(fit.emm)
```

```
## ### 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(fit.emm, c_cond = c_cond_high_all)
```

```
## ### 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
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##   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 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
## tnle 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
##   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) = 67 0 1.8871 0 1 1
##
## Note that effect estimates can vary over m_cde and c_cond values when interaction = TRUE.

```