

# The association of MTHFR C677T genotype and cumulative live birth

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# 1 Load data

```
load("MTHFR_original_data.Rdata")
```

# 2 Baseline characteristics\_Table1

## 2.1 Baseline characteristics comparision stratified by MTHFR C677T genotype using compareGroups package

```
library(compareGroups)
# select patients with first ET cycle
MTHFR <- subset(MTHFR_original, Time=="1", select = c(ID, Indication, MTHFR, MTHFRtype, Age, BMI, Total_Avail
# Baseline characteristics comparison stratified by MTHFR C677T genotype
table1_all <- descrTable(MTHFR~ Age+BMI+InferType+InferYear+Indication+Protocol+EndoThick+EndoPattern+bFSH+bl
# show table
table1_all
```

```
##
## -----Summary descriptives table by 'MTHFR'-----
##
## -----
##              CC              CT              TT              p.overall
##              N=500          N=546          N=127
## -----
## Age              30.52 (4.90)      30.65 (4.89)      30.66 (4.69)      0.892
```

## BMI	21.47 (1.82)	21.39 (1.90)	21.50 (1.86)	0.732
## InferType:				0.695
##     Primary	231 (46.20%)	239 (43.77%)	59 (46.46%)	
##     Secondary	269 (53.80%)	307 (56.23%)	68 (53.54%)	
## InferYear	4.28 (3.49)	4.18 (3.15)	4.31 (3.36)	0.842
## Indication:				0.021
##     Male factor	61 (12.20%)	39 (7.14%)	13 (10.24%)	
##     Female factor	439 (87.80%)	507 (92.86%)	114 (89.76%)	
## Protocol:				0.181
##     Long protocol	297 (59.40%)	348 (63.74%)	85 (66.93%)	
##     Short protocol	203 (40.60%)	198 (36.26%)	42 (33.07%)	
## EndoThick	10.53 (2.20)	10.67 (2.11)	10.64 (2.25)	0.596
## EndoPattern:				0.494
##     A	224 (44.80%)	239 (43.77%)	64 (50.39%)	
##     B	256 (51.20%)	277 (50.73%)	59 (46.46%)	
##     C	20 (4.00%)	30 (5.49%)	4 (3.15%)	
## bFSH	6.59 (1.56)	6.62 (1.70)	6.54 (1.50)	0.841
## bLH	5.85 (3.14)	5.52 (3.19)	5.59 (3.04)	0.229
## GnStart	163.96 (50.44)	165.30 (51.22)	161.52 (52.19)	0.736
## GnTotal	1917.37 (661.68)	1925.40 (661.90)	1844.95 (625.59)	0.455
## GnDay	10.50 (2.47)	10.47 (2.38)	10.43 (2.18)	0.947
## EmOrigin:				0.149
##     IVF	342 (68.40%)	403 (73.81%)	88 (69.29%)	
##     ICSI	153 (30.60%)	132 (24.18%)	37 (29.13%)	
##     IVF+ICSI	5 (1.00%)	11 (2.01%)	2 (1.57%)	
## No_ET:				0.798
##     1	44 (8.80%)	44 (8.06%)	9 (7.09%)	
##     2	456 (91.20%)	502 (91.94%)	118 (92.91%)	
## -----				

```
# export table to docx file
# library(eoffice)
# export2word(table1_all, file='table1_all.docx')
```

## 2.2 Baseline characteristics comparision stratified by MTHFR C677T genotype under different protocols

```
#Baseline characteristics comparison sub-grouped by protocol
table1_protocol <- strataTable(table1_all, "Protocol")
table1_protocol
```

```
##
## -----Summary descriptives table -----
##
## -----
```

LABORATORY OUTCOMES\_Table2

4

##	Long protocol					SH
##						
##	CC	CT	TT	p.overall	CC	0
##	N=297	N=348	N=85		N=203	N=198
##						
## Age	29.57 (4.09)	29.80 (4.23)	30.02 (4.69)	0.623	31.91 (5.62)	32.15 (5.62)
## BMI	21.43 (1.89)	21.30 (1.89)	21.34 (1.90)	0.666	21.52 (1.72)	21.55 (1.72)
## InferType:				0.936		
##     Primary	144 (48.48%)	164 (47.13%)	40 (47.06%)		87 (42.86%)	75 (37.86%)
##     Secondary	153 (51.52%)	184 (52.87%)	45 (52.94%)		116 (57.14%)	123 (62.14%)
## InferYear	3.92 (3.10)	4.19 (3.10)	3.98 (2.49)	0.513	4.81 (3.95)	4.15 (3.10)
## Indication:				0.035		
##     Male factor	38 (12.79%)	24 (6.90%)	7 (8.24%)		23 (11.33%)	15 (7.58%)
##     Female factor	259 (87.21%)	324 (93.10%)	78 (91.76%)		180 (88.67%)	183 (92.42%)
## Protocol:				.		
##     Long protocol	297 (100.00%)	348 (100.00%)	85 (100.00%)		0 (0.00%)	0 (0.00%)
##     Short protocol	0 (0.00%)	0 (0.00%)	0 (0.00%)		203 (100.00%)	198 (100.00%)
## EndoThick	10.92 (2.16)	11.07 (2.21)	10.96 (2.37)	0.675	9.97 (2.14)	9.96 (2.14)
## EndoPattern:				0.912		
##     A	144 (48.48%)	165 (47.41%)	42 (49.41%)		80 (39.41%)	74 (37.86%)
##     B	143 (48.15%)	166 (47.70%)	39 (45.88%)		113 (55.67%)	111 (55.56%)
##     C	10 (3.37%)	17 (4.89%)	4 (4.71%)		10 (4.93%)	13 (6.57%)
## bFSH	6.46 (1.47)	6.57 (1.75)	6.17 (1.30)	0.115	6.77 (1.67)	6.73 (1.67)
## bLH	5.93 (2.95)	5.63 (3.37)	5.60 (2.91)	0.446	5.73 (3.41)	5.32 (2.91)
## GnStart	156.76 (47.24)	160.26 (48.05)	154.85 (49.87)	0.516	174.51 (53.17)	174.18 (53.17)
## GnTotal	1980.09 (638.81)	2008.77 (667.87)	1893.74 (647.07)	0.345	1825.61 (685.08)	1778.86 (647.07)
## GnDay	11.13 (2.37)	11.06 (2.13)	10.99 (2.01)	0.842	9.57 (2.33)	9.41 (2.01)
## EmOrigin:				0.024		
##     IVF	200 (67.34%)	258 (74.14%)	60 (70.59%)		142 (69.95%)	145 (73.74%)
##     ICSI	96 (32.32%)	81 (23.28%)	23 (27.06%)		57 (28.08%)	51 (25.93%)
##     IVF+ICSI	1 (0.34%)	9 (2.59%)	2 (2.35%)		4 (1.97%)	2 (1.01%)
## No_ET:				0.293		
##     1	17 (5.72%)	27 (7.76%)	3 (3.53%)		27 (13.30%)	17 (8.59%)
##     2	280 (94.28%)	321 (92.24%)	82 (96.47%)		176 (86.70%)	181 (91.41%)
##						

# export table to docx file

# export2word(table1\_protocol, file='table1\_protocol.docx')

3 Laboratory outcomes\_Table2

### 3.1 Laboratory outcomes stratified by MTHFR C677T genotype using compareGroups package

```
# Laboratory outcomes comparison stratified by MTHFR C677T genotype
table2_all <- descrTable(MTHFR~ Oocyte+Total_AvailableEm+Total_GoodEm, data=MTHFR, digits = 2)
# show table
table2_all
```

```
##
## -----Summary descriptives table by 'MTHFR'-----
##
## -----
##              CC              CT              TT              p.overall
##              N=500              N=546              N=127
## -----
## Oocyte          10.33 (4.41) 10.14 (4.24) 9.83 (4.00)    0.463
## Total_AvailableEm 4.28 (2.57) 4.17 (2.41) 3.88 (2.21)    0.254
## Total_GoodEm      3.88 (2.35) 3.80 (2.23) 3.40 (1.92)    0.102
## -----
```

```
# export table to docx file
# export2word(table2_all, file='table2_all.docx')
```

### 3.2 Laboratory outcomes comparison stratified by MTHFR C677T genotype under different protocols

```
#Laboratory outcomes comparison sub-grouped by protocol
table2_protocol <- strataTable(table2_all, "Protocol")
table2_protocol
```

```
##
## -----Summary descriptives table -----
##
## -----
##              Long protocol              Short protocol
##              -----
##              CC              CT              TT              p.overall              CC              CT              TT              p
##              N=297              N=348              N=85              N=203              N=198              N=42
## -----
## Oocyte          10.64 (4.39) 10.53 (4.22) 10.33 (4.08)    0.838    9.89 (4.41) 9.44 (4.20) 8.81 (3.65)
## Total_AvailableEm 4.23 (2.54) 4.09 (2.31) 4.20 (2.38)    0.763    4.36 (2.62) 4.31 (2.58) 3.24 (1.66)
## Total_GoodEm      3.85 (2.30) 3.74 (2.14) 3.76 (2.06)    0.796    3.92 (2.42) 3.90 (2.40) 2.67 (1.34)
## -----
```

```
# export table to docx file
# export2word(table2_protocol, file='table2_protocol.docx')
```

### 3.3 Post-hoc multiple comparisons under GnRHa short protocol for the number of transferable embryos:

```
MTHFR_short <- subset(MTHFR, Protocol=="Short protocol", select = c(Indication, MTHFR, MTHFRtype, Age, BMI, T
descrTable(MTHFR~Total_AvailableEm, data=MTHFR_short, digits = 2, show.p.mul=T, p.corrected = F)#multiple compari

##
## -----Summary descriptives table by 'MTHFR'-----
##
## -----
##          CC          CT          TT          p.overall p.CC vs CT p.CC vs TT p.CT vs TT
##          N=203      N=198      N=42
## -----
## Total_AvailableEm 4.36 (2.62) 4.31 (2.58) 3.24 (1.66) 0.028      0.858      0.001      0.001
## -----
```

### 3.4 Post-hoc multiple comparisons under GnRHa short protocol for the number of good-quality embryos:

```
MTHFR_short <- subset(MTHFR, Protocol=="Short protocol", select = c(Indication, MTHFR, MTHFRtype, Age, BMI, T
descrTable(MTHFR~Total_GoodEm, data=MTHFR_short, digits = 2, show.p.mul=T, p.corrected = F)#multiple compari

##
## -----Summary descriptives table by 'MTHFR'-----
##
## -----
##          CC          CT          TT          p.overall p.CC vs CT p.CC vs TT p.CT vs TT
##          N=203      N=198      N=42
## -----
## Total_GoodEm 3.92 (2.42) 3.90 (2.40) 2.67 (1.34) 0.005      0.943      <0.001      <0.001
## -----
```

## 4 Clinical outcomes\_\_Table3

### 4.1 Clinical outcomes stratified by MTHFR C677T genotype using compareGroups package

```
# Clinical outcomes comparison stratified by MTHFR C677T genotype
table3_all <- descrTable(MTHFR~ BiochemicalPregnancy+ClinicalPregnancy+Miscarriage+LiveBirth+CLB, data=MTHFR,
# show table
table3_all

##
## -----Summary descriptives table by 'MTHFR'-----
```

```
##
## -----
##               CC           CT           TT           p.overall
##               N=500       N=546       N=127
## -----
## BiochemicalPregnancy:                                0.855
##   No                199 (39.80%) 221 (40.48%) 54 (42.52%)
##   Yes                301 (60.20%) 325 (59.52%) 73 (57.48%)
## ClinicalPregnancy:                                0.941
##   No                244 (48.80%) 266 (48.72%) 64 (50.39%)
##   Yes                256 (51.20%) 280 (51.28%) 63 (49.61%)
## Miscarriage:                                0.639
##   No                469 (93.80%) 519 (95.05%) 119 (93.70%)
##   Yes                31 (6.20%)   27 (4.95%)   8 (6.30%)
## LiveBirth:                                0.694
##   No                275 (55.00%) 301 (55.13%) 75 (59.06%)
##   Yes                225 (45.00%) 245 (44.87%) 52 (40.94%)
## CLB:                                0.263
##   No                213 (42.60%) 259 (47.44%) 60 (47.24%)
##   Yes                287 (57.40%) 287 (52.56%) 67 (52.76%)
## -----
```

```
# export table to docx file
# export2word(table3_all, file='table3_all.docx')
```

## 4.2 Clinical outcomes comparision stratified by MTHFR C677T genotype under different protocols

```
#Clinical outcomes comparison sub-grouped by protocol
table3_protocol <- strataTable(table3_all, "Protocol")
table3_protocol
```

```
##
## -----Summary descriptives table -----
##
## -----
##               Long protocol                               Short protocol
##               -----
##               CC           CT           TT           p.overall       CC           CT           TT
##               N=297       N=348       N=85              N=203       N=198       N=42
## -----
## BiochemicalPregnancy:                                0.635
##   No                97 (32.66%) 126 (36.21%) 30 (35.29%)          102 (50.25%) 95 (47.98%) 24 (57.14%)
##   Yes                200 (67.34%) 222 (63.79%) 55 (64.71%)          101 (49.75%) 103 (52.02%) 18 (42.86%)
## ClinicalPregnancy:                                0.853
##   No                120 (40.40%) 148 (42.53%) 36 (42.35%)          124 (61.08%) 118 (59.60%) 28 (66.67%)
```

```
##      Yes      177 (59.60%) 200 (57.47%) 49 (57.65%)      79 (38.92%) 80 (40.40%) 14 (33.33%)
## Miscarriage:      0.843
##      No      279 (93.94%) 329 (94.54%) 79 (92.94%)      190 (93.60%) 190 (95.96%) 40 (95.24%)
##      Yes      18 (6.06%) 19 (5.46%) 6 (7.06%)      13 (6.40%) 8 (4.04%) 2 (4.76%)
## LiveBirth:      0.706
##      No      142 (47.81%) 170 (48.85%) 45 (52.94%)      133 (65.52%) 131 (66.16%) 30 (71.43%)
##      Yes      155 (52.19%) 178 (51.15%) 40 (47.06%)      70 (34.48%) 67 (33.84%) 12 (28.57%)
## CLB:      0.725
##      No      112 (37.71%) 140 (40.23%) 31 (36.47%)      101 (49.75%) 119 (60.10%) 29 (69.05%)
##      Yes      185 (62.29%) 208 (59.77%) 54 (63.53%)      102 (50.25%) 79 (39.90%) 13 (30.95%)
## -----
```

```
# export table to docx file
# export2word(table3_protocol, file='table3_protocol.docx')
```

### 4.3 Post-hoc multiple comparisons under GnRHa short protocol for the cumulative live birth rate:

```
MTHFR_short <- subset(MTHFR, Protocol=="Short protocol", select = c(Indication, MTHFR, MTHFRtype, Age, BMI, T
descrTable(MTHFR~CLB, data=MTHFR_short, digits = 2, show.p.mul=T, p.corrected = F)#multiple comparison
```

```
##
## -----Summary descriptives table by 'MTHFR'-----
##
## -----
##      CC      CT      TT      p.overall p.CC vs CT p.CC vs TT p.CT vs TT
##      N=203      N=198      N=42
## -----
## CLB:      0.024      0.048      0.035      0.364
##      No 101 (49.75%) 119 (60.10%) 29 (69.05%)
##      Yes 102 (50.25%) 79 (39.90%) 13 (30.95%)
## -----
```

## 5 Interactive analysis and Multivariate analysis

### 5.1 Interactive analysis for the number of transferable embryos:

#### 5.1.1 Poisson multivariate analysis without considering the interactive effect with protocol

```
fit_AvailableEm1 <- glm(Total_AvailableEm~MTHFR+Cat_age+Cat_BMI+Indication+InferType+Protocol, data=MTHFR, fa
summary(fit_AvailableEm1)
```

```
##
## Call:
## glm(formula = Total_AvailableEm ~ MTHFR + Cat_age + Cat_BMI +
```



```
##      Indication + InferType + Protocol, family = poisson(), data = MTHFR)
##
## Deviance Residuals:
##      Min        1Q    Median        3Q        Max
## -2.1442  -1.1307  -0.2283   0.8171   3.7283
##
## Coefficients:
##              Estimate Std. Error z value Pr(>|z|)
## (Intercept)      1.39132    0.05673  24.526 < 2e-16 ***
## MTHFRCT          -0.03251    0.03024  -1.075  0.28237
## MTHFRTT          -0.09612    0.05005  -1.920  0.05481 .
## Cat_age>=35      -0.05536    0.03756  -1.474  0.14050
## Cat_BMI20-23     -0.05976    0.03423  -1.746  0.08083 .
## Cat_BMI23-25     -0.13471    0.04122  -3.268  0.00108 **
## IndicationFemale factor  0.09985    0.05135   1.944  0.05185 .
## InferTypeSecondary  0.06984    0.03026   2.308  0.02100 *
## ProtocolShort protocol  0.02518    0.03012   0.836  0.40319
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## (Dispersion parameter for poisson family taken to be 1)
##
##      Null deviance: 1623.7  on 1172  degrees of freedom
## Residual deviance: 1597.9  on 1164  degrees of freedom
## AIC: 5309.4
##
## Number of Fisher Scoring iterations: 5
```

### 5.1.2 Poisson multivariate analysis considering the interactive effect with protocol

```
fit_AvailableEm2 <- glm(Total_AvailableEm~MTHFR+Cat_age+Cat_BMI+Indication+InferType+Protocol+MTHFR:Protocol,
summary(fit_AvailableEm2)
```

```
##
## Call:
## glm(formula = Total_AvailableEm ~ MTHFR + Cat_age + Cat_BMI +
##      Indication + InferType + Protocol + MTHFR:Protocol, family = poisson(),
##      data = MTHFR)
##
## Deviance Residuals:
##      Min        1Q    Median        3Q        Max
## -2.1510  -1.1300  -0.2256   0.8087   3.7421
##
## Coefficients:
```

```
##              Estimate Std. Error z value Pr(>|z|)
## (Intercept)      1.38795    0.05815  23.867 < 2e-16 ***
## MTHFRCT          -0.04210    0.03882  -1.084  0.27824
## MTHFRTT          -0.01213    0.06008  -0.202  0.83992
## Cat_age>=35      -0.05642    0.03754  -1.503  0.13282
## Cat_BMI20-23     -0.05616    0.03425  -1.640  0.10104
## Cat_BMI23-25     -0.13245    0.04124  -3.211  0.00132 **
## IndicationFemale factor  0.09653    0.05138   1.878  0.06031 .
## InferTypeSecondary  0.06870    0.03026   2.271  0.02318 *
## ProtocolShort protocol  0.03677    0.04434   0.829  0.40697
## MTHFRCT:ProtocolShort protocol  0.02808    0.06169   0.455  0.64894
## MTHFRTT:ProtocolShort protocol -0.27242    0.11005  -2.475  0.01331 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## (Dispersion parameter for poisson family taken to be 1)
##
##      Null deviance: 1623.7  on 1172  degrees of freedom
## Residual deviance: 1590.1  on 1162  degrees of freedom
## AIC: 5305.6
##
## Number of Fisher Scoring iterations: 5
```

### 5.1.3 P for interaction for the number of transferable embryos

```
library(lmtest)
lrtest(fit_AvailableEm1, fit_AvailableEm2)

## Likelihood ratio test
##
## Model 1: Total_AvailableEm ~ MTHFR + Cat_age + Cat_BMI + Indication +
##      InferType + Protocol
## Model 2: Total_AvailableEm ~ MTHFR + Cat_age + Cat_BMI + Indication +
##      InferType + Protocol + MTHFR:Protocol
##      #Df  LogLik Df  Chisq Pr(>Chisq)
## 1    9 -2645.7
## 2   11 -2641.8  2  7.8405   0.01984 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

## 5.2 Poisson Multivariate analysis revealed the association of MTHFR C677T genotype with the number of transferable embryos under different protocols

### 5.2.1 Poisson Multivariate analysis revealed the association of MTHFR C677T genotype with the number of transferable embryos under GnRHa short protocol

```
fit_AvailableEm_short <- glm(Total_AvailableEm~MTHFR+Cat_age+Cat_BMI+Indication+InferType, data=MTHFR_short,
summary(fit_AvailableEm_short)
```

```
##
## Call:
## glm(formula = Total_AvailableEm ~ MTHFR + Cat_age + Cat_BMI +
##      Indication + InferType, family = poisson(), data = MTHFR_short)
##
## Deviance Residuals:
##      Min        1Q    Median        3Q        Max
## -2.1172  -1.2356  -0.1901   0.7787   3.3162
##
## Coefficients:
##              Estimate Std. Error z value Pr(>|z|)
## (Intercept)      1.492590    0.087088  17.139 < 2e-16 ***
## MTHFRCT          -0.007332    0.048163  -0.152  0.87900
## MTHFR TT         -0.286071    0.092240  -3.101  0.00193 **
## Cat_age>=35      -0.088398    0.052917  -1.671  0.09482 .
## Cat_BMI20-23     -0.019391    0.058754  -0.330  0.74138
## Cat_BMI23-25     -0.150179    0.069917  -2.148  0.03172 *
## IndicationFemale factor  0.013978    0.080179   0.174  0.86160
## InferTypeSecondary  0.064655    0.050309   1.285  0.19873
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## (Dispersion parameter for poisson family taken to be 1)
##
##      Null deviance: 657.92  on 442  degrees of freedom
## Residual deviance: 636.21  on 435  degrees of freedom
## AIC: 2045.5
##
## Number of Fisher Scoring iterations: 5
```

### 5.2.2 Poisson Multivariate analysis revealed the association of MTHFR C677T genotype with the number of transferable embryos under GnRHa long protocol

```
MTHFR_long <- subset(MTHFR, Protocol=="Long protocol", select = c(Indication, MTHFR, MTHFRtype, Age, BMI, Tot
fit_AvailableEm_long <- glm(Total_AvailableEm~MTHFR+Cat_age+Cat_BMI+Indication+InferType, data=MTHFR_long, fa
summary(fit_AvailableEm_long)
```

```
##
```

```
## Call:
## glm(formula = Total_AvailableEm ~ MTHFR + Cat_age + Cat_BMI +
##      Indication + InferType, family = poisson(), data = MTHFR_long)
##
## Deviance Residuals:
##      Min       1Q   Median       3Q      Max
## -2.1032  -1.1247  -0.2123   0.8026   3.6707
##
## Coefficients:
##              Estimate Std. Error z value Pr(>|z|)
## (Intercept)      1.33984    0.07303  18.346  <2e-16 ***
## MTHFRCT          -0.04578    0.03889  -1.177   0.2392
## MTHFR TT         -0.01803    0.06014  -0.300   0.7643
## Cat_age>=35      -0.01861    0.05323  -0.350   0.7267
## Cat_BMI20-23     -0.07696    0.04254  -1.809   0.0704 .
## Cat_BMI23-25     -0.11822    0.05137  -2.301   0.0214 *
## IndicationFemale factor  0.15075    0.06738   2.237   0.0253 *
## InferTypeSecondary  0.07281    0.03794   1.919   0.0550 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## (Dispersion parameter for poisson family taken to be 1)
##
##      Null deviance: 965.47  on 729  degrees of freedom
## Residual deviance: 948.95  on 722  degrees of freedom
## AIC: 3265.2
##
## Number of Fisher Scoring iterations: 5
```

## 5.3 Interactive analysis for the number of good-quality embryos:

### 5.3.1 Poisson multivariate analysis without considering the interactive effect with protocol

```
fit_Goodembryo1 <- glm(Total_GoodEm~MTHFR+Cat_age+Cat_BMI+Indication+Protocol+InferType, data=MTHFR, family = poisson(), data.as.factor=T)
summary(fit_Goodembryo1)
```

```
##
## Call:
## glm(formula = Total_GoodEm ~ MTHFR + Cat_age + Cat_BMI + Indication +
##      Protocol + InferType, family = poisson(), data = MTHFR)
##
## Deviance Residuals:
##      Min       1Q   Median       3Q      Max
## -1.9557  -0.9958  -0.3420   0.6527   3.9882
```

```
##
## Coefficients:
##              Estimate Std. Error z value Pr(>|z|)
## (Intercept)      1.28856    0.05993  21.503 < 2e-16 ***
## MTHFRCT          -0.02925    0.03174  -0.922 0.356762
## MTHFRTT          -0.12981    0.05330  -2.435 0.014879 *
## Cat_age>=35      -0.06453    0.03966  -1.627 0.103704
## Cat_BMI20-23     -0.05728    0.03592  -1.595 0.110807
## Cat_BMI23-25     -0.14796    0.04346  -3.405 0.000662 ***
## IndicationFemale factor  0.12146    0.05433   2.235 0.025388 *
## ProtocolShort protocol  0.01284    0.03172   0.405 0.685630
## InferTypeSecondary  0.05699    0.03177   1.794 0.072858 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## (Dispersion parameter for poisson family taken to be 1)
##
##      Null deviance: 1452.5  on 1172  degrees of freedom
## Residual deviance: 1424.0  on 1164  degrees of freedom
## AIC: 5032.4
##
## Number of Fisher Scoring iterations: 5
```

```
exp1<-exp(coef(fit_Goodembryo1))
confint1 <- exp(confint(fit_Goodembryo1))
```

### 5.3.2 Poisson multivariate analysis considering the interactive effect with protocol

```
fit_Goodembryo2 <- glm(Total_GoodEm~MTHFR+Cat_age+Cat_BMI+Indication+Protocol+InferType+MTHFR:Protocol, data=
summary(fit_Goodembryo2)
```

```
##
## Call:
## glm(formula = Total_GoodEm ~ MTHFR + Cat_age + Cat_BMI + Indication +
##      Protocol + InferType + MTHFR:Protocol, family = poisson(),
##      data = MTHFR)
##
## Deviance Residuals:
##      Min       1Q   Median       3Q      Max
## -1.9635  -1.0231  -0.3574   0.6490   4.0043
##
## Coefficients:
##              Estimate Std. Error z value Pr(>|z|)
## (Intercept)      1.28460    0.06139  20.924 < 2e-16 ***
## MTHFRCT          -0.04077    0.04067  -1.002 0.316188
```

```
## MTHFRTT          -0.02715    0.06335  -0.429  0.668247
## Cat_age>=35      -0.06583    0.03963  -1.661  0.096688 .
## Cat_BMI20-23     -0.05296    0.03594  -1.473  0.140619
## Cat_BMI23-25     -0.14525    0.04347  -3.341  0.000834 ***
## IndicationFemale factor    0.11748    0.05437   2.161  0.030707 *
## ProtocolShort protocol    0.02665    0.04664   0.572  0.567652
## InferTypeSecondary    0.05560    0.03177   1.750  0.080078 .
## MTHFRCT:ProtocolShort protocol  0.03396    0.06482   0.524  0.600381
## MTHFRTT:ProtocolShort protocol -0.34449    0.11924  -2.889  0.003864 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## (Dispersion parameter for poisson family taken to be 1)
##
##      Null deviance: 1452.5  on 1172  degrees of freedom
## Residual deviance: 1413.3  on 1162  degrees of freedom
## AIC: 5025.7
##
## Number of Fisher Scoring iterations: 5
```

### 5.3.3 P for interaction for the number of good-quality embryos

```
library(lmtest)
lrtest(fit_Goodembryo1, fit_Goodembryo2)

## Likelihood ratio test
##
## Model 1: Total_GoodEm ~ MTHFR + Cat_age + Cat_BMI + Indication + Protocol +
##      InferType
## Model 2: Total_GoodEm ~ MTHFR + Cat_age + Cat_BMI + Indication + Protocol +
##      InferType + MTHFR:Protocol
##      #Df  LogLik Df  Chisq Pr(>Chisq)
## 1    9 -2507.2
## 2   11 -2501.8  2 10.703   0.00474 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

## 5.4 Poisson Multivariate analysis revealed the association of MTHFR C677T genotype with the number of good-quality embryos under different protocols

#### 5.4.1 Poisson Multivariate analysis revealed the association of MTHFR C677T genotype with the number of good-quality embryos under GnRHa long protocol

```
MTHFR_long <- subset(MTHFR, Protocol=="Long protocol", select = c(Indication, MTHFR, MTHFRtype, Age, BMI, TotalGoodEm))
fit_Goodembryo_long <- glm(Total_GoodEm~MTHFR+Cat_age+Cat_BMI+Indication+InferType, data=MTHFR_long, family = poisson())
summary(fit_Goodembryo_long)
```

```
##
## Call:
## glm(formula = Total_GoodEm ~ MTHFR + Cat_age + Cat_BMI + Indication + InferType, family = poisson(), data = MTHFR_long)
##
## Deviance Residuals:
##      Min       1Q   Median       3Q      Max
## -1.9249  -1.0018  -0.3537   0.6659   3.9354
##
## Coefficients:
##              Estimate Std. Error z value Pr(>|z|)
## (Intercept)      1.22931    0.07706  15.953  <2e-16 ***
## MTHFRCT          -0.04422    0.04074  -1.085   0.2778
## MTHFRTT          -0.03228    0.06341  -0.509   0.6107
## Cat_age>=35      -0.03180    0.05613  -0.567   0.5710
## Cat_BMI20-23     -0.06435    0.04456  -1.444   0.1487
## Cat_BMI23-25     -0.12621    0.05409  -2.333   0.0196 *
## IndicationFemale factor  0.17537    0.07115   2.465   0.0137 *
## InferTypeSecondary  0.05734    0.03975   1.443   0.1492
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## (Dispersion parameter for poisson family taken to be 1)
##
##      Null deviance: 853.64  on 729  degrees of freedom
## Residual deviance: 838.15  on 722  degrees of freedom
## AIC: 3094.9
##
## Number of Fisher Scoring iterations: 5
```

```
exp_Goodembryo_long <- exp(coef(fit_Goodembryo_long))
conf_Goodembryo_long <- exp(confint(fit_Goodembryo_long))
OR_Goodembryo_long <- data.frame(exp_Goodembryo_long, conf_Goodembryo_long)
write.table(OR_Goodembryo_long, "OR_GoodEm_long.csv", row.names = T, sep = "\t")
```

## 5.4.2 Poisson Multivariate analysis revealed the association of MTHFR C677T genotype with the number of good-quality embryos under GnRHa short protocol

```
MTHFR_short <- subset(MTHFR, Protocol=="Short protocol", select = c(Indication, MTHFR, MTHFRtype, Age, BMI, T
fit_Goodembryo_short <- glm(Total_GoodEm~MTHFR+Cat_age+Cat_BMI+Indication+InferType, data=MTHFR_short, family
summary(fit_Goodembryo_short)
```

```
##
## Call:
## glm(formula = Total_GoodEm ~ MTHFR + Cat_age + Cat_BMI + Indication +
##     InferType, family = poisson(), data = MTHFR_short)
##
## Deviance Residuals:
##      Min       1Q   Median       3Q      Max
## -1.9513  -1.0424  -0.2673   0.6951   3.2127
##
## Coefficients:
##              Estimate Std. Error z value Pr(>|z|)
## (Intercept)      1.3917686   0.0921584  15.102  < 2e-16 ***
## MTHFRCT          -0.0008916   0.0507007  -0.018  0.985969
## MTHFRTT          -0.3726438   0.1010613  -3.687  0.000227 ***
## Cat_age>=35      -0.0950380   0.0559415  -1.699  0.089342 .
## Cat_BMI20-23     -0.0324895   0.0617385  -0.526  0.598719
## Cat_BMI23-25     -0.1734974   0.0737764  -2.352  0.018690 *
## IndicationFemale factor  0.0307355   0.0850712   0.361  0.717882
## InferTypeSecondary  0.0547754   0.0530385   1.033  0.301722
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## (Dispersion parameter for poisson family taken to be 1)
##
##      Null deviance: 598.89  on 442  degrees of freedom
## Residual deviance: 571.24  on 435  degrees of freedom
## AIC: 1936.8
##
## Number of Fisher Scoring iterations: 5
```

## 5.5 Iterative analysis for cumulative live birth:

### 5.5.1 Cox multivariate analysis without considering the interactive effect with protocol

```
# select the dataframe for Cox regression
MTHFR_cox <- subset(MTHFR_original, select = c(ID, Indication, MTHFR, Age, BMI, CLB, Time, Status, InferType,
# library packages
```



```
library(survival)
library(survminer)
# Cox regression
mycox_1 <- coxph(Surv(Time,Status)~MTHFR+Cat_age+Cat_BMI+Indication+Protocol+InferType, data=MTHFR_cox, id=ID)
summary(mycox_1)
```

```
## Call:
## coxph(formula = Surv(Time, Status) ~ MTHFR + Cat_age + Cat_BMI +
##       Indication + Protocol + InferType, data = MTHFR_cox, id = ID)
##
##      n= 1710, number of events= 953
##
##              coef exp(coef) se(coef) robust se      z Pr(>|z|)
## MTHFRCT          0.17803   1.19486  0.06992   0.07073  2.517  0.01183
## MTHFRTT          0.20709   1.23009  0.11187   0.10992  1.884  0.05957
## Cat_age>=35       0.16020   1.17374  0.07750   0.07585  2.112  0.03469
## Cat_BMI20-23     -0.04129   0.95955  0.07919   0.07700 -0.536  0.59179
## Cat_BMI23-25      0.01378   1.01388  0.09459   0.09168  0.150  0.88052
## IndicationFemale factor 0.02356   1.02384  0.12906   0.13177  0.179  0.85807
## ProtocolShort protocol 0.18726   1.20595  0.06763   0.06779  2.762  0.00574
## InferTypeSecondary  0.06424   1.06635  0.07190   0.07175  0.895  0.37062
##
## MTHFRCT          *
## MTHFRTT          .
## Cat_age>=35       *
## Cat_BMI20-23
## Cat_BMI23-25
## IndicationFemale factor
## ProtocolShort protocol **
## InferTypeSecondary
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## MTHFRCT          1.1949    0.8369    1.0402    1.373
## MTHFRTT          1.2301    0.8129    0.9917    1.526
## Cat_age>=35       1.1737    0.8520    1.0116    1.362
## Cat_BMI20-23      0.9595    1.0422    0.8251    1.116
## Cat_BMI23-25      1.0139    0.9863    0.8471    1.213
## IndicationFemale factor 1.0238    0.9767    0.7908    1.326
## ProtocolShort protocol 1.2059    0.8292    1.0559    1.377
## InferTypeSecondary  1.0663    0.9378    0.9265    1.227
##
## Concordance= 0.56 (se = 0.013 )
## Likelihood ratio test= 27.01 on 8 df,  p=7e-04
```

```
## Wald test          = 26.73  on 8 df,    p=8e-04
## Score (logrank) test = 27.35  on 8 df,    p=6e-04,    Robust = 27.06  p=7e-04
##
## (Note: the likelihood ratio and score tests assume independence of
## observations within a cluster, the Wald and robust score tests do not).
```

### 5.5.2 Cox multivariate analysis considering the interactive effect with protocol

```
mycox_2 <- coxph(Surv(Time,Status)~MTHFR+Cat_age+Cat_BMI+Indication+Protocol+InferType+MTHFR:Protocol, data=MTHFR_cox,
summary(mycox_2)
```

```
## Call:
## coxph(formula = Surv(Time, Status) ~ MTHFR + Cat_age + Cat_BMI +
## Indication + Protocol + InferType + MTHFR:Protocol, data = MTHFR_cox,
## id = ID)
##
## n= 1710, number of events= 953
##
##               coef exp(coef) se(coef) robust se      z
## MTHFRCT          0.13376   1.14312  0.09860   0.10295  1.299
## MTHFR TT        -0.06253   0.93938  0.15206   0.15863 -0.394
## Cat_age>=35       0.16216   1.17605  0.07771   0.07575  2.141
## Cat_BMI20-23     -0.05193   0.94939  0.07941   0.07600 -0.683
## Cat_BMI23-25      0.00296   1.00297  0.09496   0.09161  0.032
## IndicationFemale factor  0.02818   1.02858  0.12912   0.12983  0.217
## ProtocolShort protocol  0.07632   1.07931  0.10440   0.10919  0.699
## InferTypeSecondary  0.05775   1.05945  0.07200   0.07149  0.808
## MTHFRCT:ProtocolShort protocol  0.08503   1.08875  0.13920   0.14076  0.604
## MTHFR TT:ProtocolShort protocol  0.65301   1.92132  0.22233   0.20856  3.131
##
##               Pr(>|z|)
## MTHFRCT          0.19385
## MTHFR TT          0.69343
## Cat_age>=35       0.03231 *
## Cat_BMI20-23      0.49440
## Cat_BMI23-25      0.97422
## IndicationFemale factor  0.82814
## ProtocolShort protocol  0.48459
## InferTypeSecondary  0.41920
## MTHFRCT:ProtocolShort protocol  0.54579
## MTHFR TT:ProtocolShort protocol  0.00174 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
```

```
## MTHFRCT                1.1431    0.8748    0.9342    1.399
## MTHFRTT                0.9394    1.0645    0.6884    1.282
## Cat_age>=35            1.1760    0.8503    1.0138    1.364
## Cat_BMI20-23           0.9494    1.0533    0.8180    1.102
## Cat_BMI23-25           1.0030    0.9970    0.8381    1.200
## IndicationFemale factor 1.0286    0.9722    0.7975    1.327
## ProtocolShort protocol 1.0793    0.9265    0.8714    1.337
## InferTypeSecondary      1.0595    0.9439    0.9209    1.219
## MTHFRCT:ProtocolShort protocol 1.0887    0.9185    0.8263    1.435
## MTHFRTT:ProtocolShort protocol 1.9213    0.5205    1.2767    2.892
##
## Concordance= 0.568 (se = 0.013 )
## Likelihood ratio test= 35.63 on 10 df, p=1e-04
## Wald test              = 44.89 on 10 df, p=2e-06
## Score (logrank) test = 38.81 on 10 df, p=3e-05, Robust = 38.16 p=4e-05
##
## (Note: the likelihood ratio and score tests assume independence of
## observations within a cluster, the Wald and robust score tests do not).
```

### 5.5.3 P for interaction for cumulative live birth

```
library(lmtest)
lrtest(mycox_1, mycox_2)

## Likelihood ratio test
##
## Model 1: Surv(Time, Status) ~ MTHFR + Cat_age + Cat_BMI + Indication +
## Protocol + InferType
## Model 2: Surv(Time, Status) ~ MTHFR + Cat_age + Cat_BMI + Indication +
## Protocol + InferType + MTHFR:Protocol
## #Df LogLik Df Chisq Pr(>Chisq)
## 1 8 -6155.7
## 2 10 -6151.3 2 8.6257 0.0134 *
## ---
## Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

## 5.6 Cox Multivariate analysis revealed the association of MTHFR C677T genotype with cumulative live birth under different protocols

### 5.6.1 Cox Multivariate analysis revealed the association of MTHFR C677T genotype with cumulative live birth under GnRHa short protocol

```
MTHFR_cox_short <- subset(MTHFR_cox, Protocol=="Short protocol")
mycox_short <- coxph(Surv(Time,Status)~MTHFR+Cat_age+Cat_BMI+Indication+InferType, data=MTHFR_cox_short, id=
```

```
summary(mycox_short)
```

```
## Call:
## coxph(formula = Surv(Time, Status) ~ MTHFR + Cat_age + Cat_BMI +
##      Indication + InferType, data = MTHFR_cox_short, id = ID)
##
##      n= 708, number of events= 471
##
##
##              coef exp(coef) se(coef) robust se      z Pr(>|z|)
## MTHFRCT          0.21060   1.23442  0.09959   0.09642  2.184  0.02895
## MTHFRCTT          0.57638   1.77958  0.16336   0.13385  4.306 1.66e-05
## Cat_age>=35       0.24826   1.28179  0.10094   0.09312  2.666  0.00768
## Cat_BMI20-23      -0.12838   0.87952  0.11795   0.10907 -1.177  0.23918
## Cat_BMI23-25       0.03581   1.03646  0.13850   0.12525  0.286  0.77497
## IndicationFemale factor -0.14266  0.86705  0.17086   0.15723 -0.907  0.36423
## InferTypeSecondary  0.04674   1.04785  0.10740   0.09992  0.468  0.63993
##
## MTHFRCT          *
## MTHFRCTT          ***
## Cat_age>=35       **
## Cat_BMI20-23
## Cat_BMI23-25
## IndicationFemale factor
## InferTypeSecondary
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##
##              exp(coef) exp(-coef) lower .95 upper .95
## MTHFRCT          1.2344    0.8101    1.0219    1.491
## MTHFRCTT          1.7796    0.5619    1.3689    2.313
## Cat_age>=35       1.2818    0.7802    1.0680    1.538
## Cat_BMI20-23      0.8795    1.1370    0.7102    1.089
## Cat_BMI23-25      1.0365    0.9648    0.8108    1.325
## IndicationFemale factor 0.8670    1.1533    0.6371    1.180
## InferTypeSecondary 1.0479    0.9543    0.8615    1.275
##
## Concordance= 0.59 (se = 0.018 )
## Likelihood ratio test= 25.07 on 7 df,  p=7e-04
## Wald test          = 34 on 7 df,  p=2e-05
## Score (logrank) test = 26.29 on 7 df,  p=4e-04,  Robust = 26.95 p=3e-04
##
## (Note: the likelihood ratio and score tests assume independence of
##      observations within a cluster, the Wald and robust score tests do not).
```

## 5.6.2 Cox Multivariate analysis revealed the association of MTHFR C677T genotype with cumulative live birth under GnRHa long protocol

```
MTHFR_cox_long <- subset(MTHFR_cox, Protocol=="Long protocol")
mycox_long <- coxph(Surv(Time,Status)~MTHFR+Cat_age+Cat_BMI+Indication+InferType, data=MTHFR_cox_long, id=ID)
summary(mycox_long)
```

```
## Call:
## coxph(formula = Surv(Time, Status) ~ MTHFR + Cat_age + Cat_BMI +
##       Indication + InferType, data = MTHFR_cox_long, id = ID)
##
##      n= 1002, number of events= 482
##
##              coef exp(coef) se(coef) robust se      z Pr(>|z|)
## MTHFRCT          0.13293   1.14217  0.09908   0.10239  1.298   0.194
## MTHFRCTT        -0.05200   0.94933  0.15280   0.15892 -0.327   0.743
## Cat_age>=35       0.04602   1.04710  0.12531   0.12760  0.361   0.718
## Cat_BMI20-23      0.03478   1.03539  0.10834   0.10789  0.322   0.747
## Cat_BMI23-25     -0.03954   0.96123  0.13256   0.13652 -0.290   0.772
## IndicationFemale factor 0.24342   1.27560  0.19841   0.22120  1.100   0.271
## InferTypeSecondary  0.05990   1.06173  0.09789   0.10201  0.587   0.557
##
##              exp(coef) exp(-coef) lower .95 upper .95
## MTHFRCT          1.1422     0.8755     0.9345     1.396
## MTHFRCTT          0.9493     1.0534     0.6952     1.296
## Cat_age>=35       1.0471     0.9550     0.8154     1.345
## Cat_BMI20-23      1.0354     0.9658     0.8381     1.279
## Cat_BMI23-25      0.9612     1.0403     0.7356     1.256
## IndicationFemale factor 1.2756     0.7839     0.8269     1.968
## InferTypeSecondary 1.0617     0.9419     0.8693     1.297
##
## Concordance= 0.543 (se = 0.018 )
## Likelihood ratio test= 5.75 on 7 df,  p=0.6
## Wald test            = 4.89 on 7 df,  p=0.7
## Score (logrank) test = 5.6 on 7 df,  p=0.6, Robust = 5.01 p=0.7
##
## (Note: the likelihood ratio and score tests assume independence of
##       observations within a cluster, the Wald and robust score tests do not).
```

## 6 Statistical power estimation

```
#pwr 包
# install.packages("pwr")
```

```

# library package
library(pwr)

# data<-c(0.23,0.228,0.178,0.269,0.029,0.065)
# prob<-matrix(data,byrow = TRUE,nrow = 3)
# ES.w2(prob)

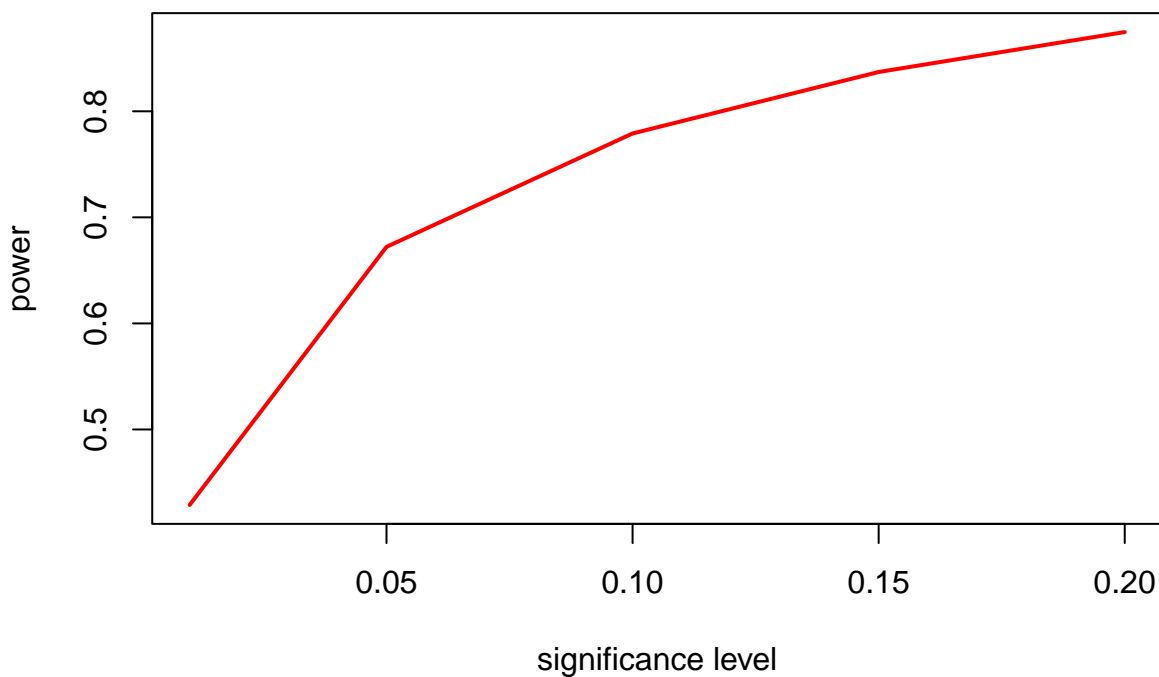
# pwr.chisq.test(w=0.13, N=443, df=2, sig.level = .1)
# pwr.chisq.test(w=0.13, df=2, sig.level = 0.05, power = 0.75)
# pwr.t2n.test(n1=203,n2=43, sig.level=0.05, d=0.2)

# Statistical power curve
library(pwr)
sig <- c(0.01, 0.05, 0.10, 0.15, 0.20)
length_sig <- length(sig)

power <- NULL
for (i in 1:length_sig){
  result <- pwr.anova.test(k=3, f=0.24, sig.level=sig[i], n=43)
  power[i] <- result$power
}

plot(sig, power, type="l", lwd=2, col="red",
      xlab="significance level",
      ylab="power",
      main = ""
)

```

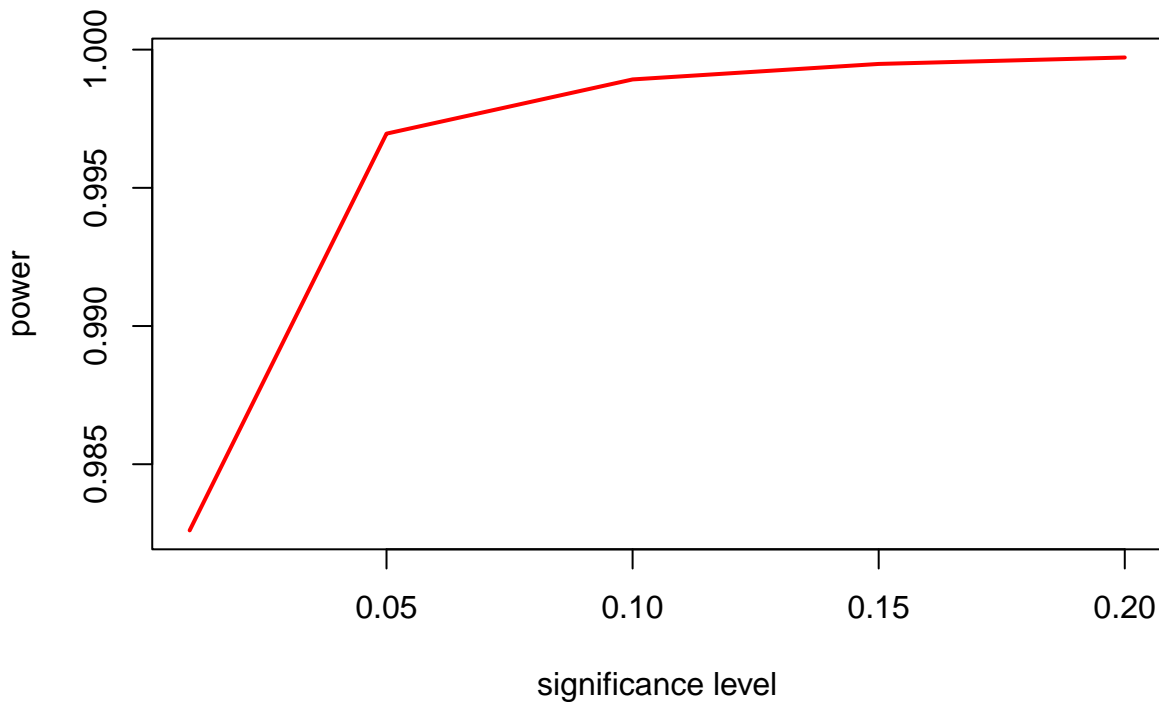


```

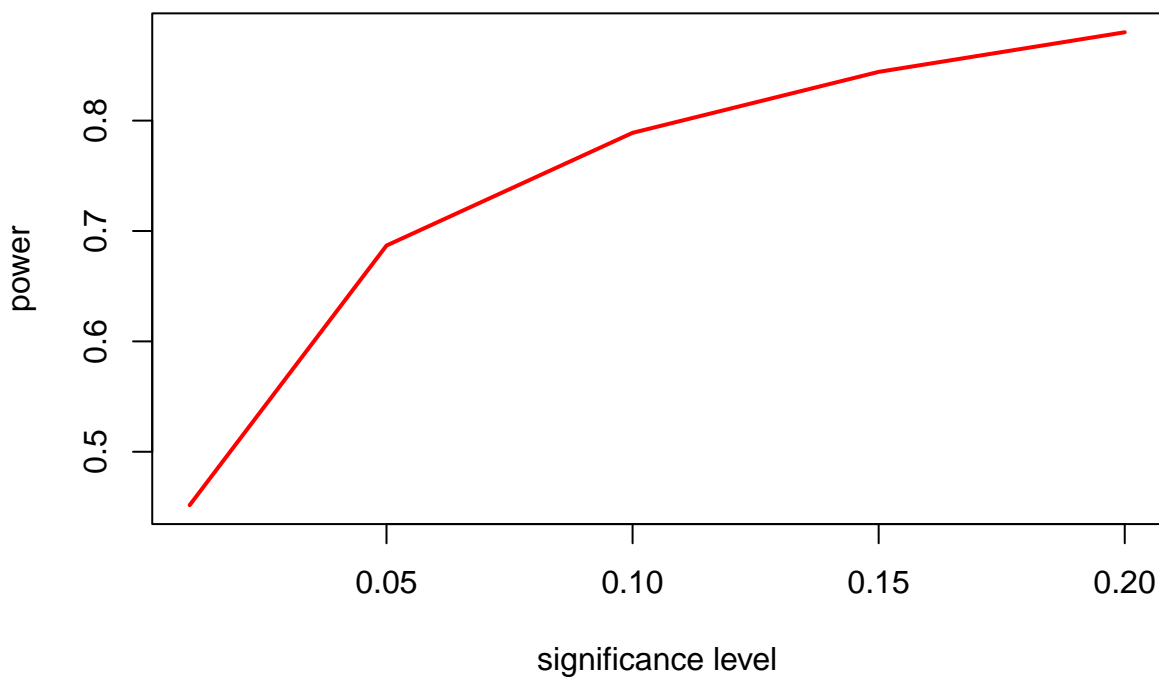
power_2 <- NULL
for (i in 1:length_sig){
  result <- pwr.anova.test(k=3, f=0.45, sig.level=sig[i], n=43)

```

```
power_2[i] <- result$power
}  
  
plot(sig, power_2, type="l", lwd=2, col="red",  
      xlab="significance level",  
      ylab="power",  
      main = ""  
)
```

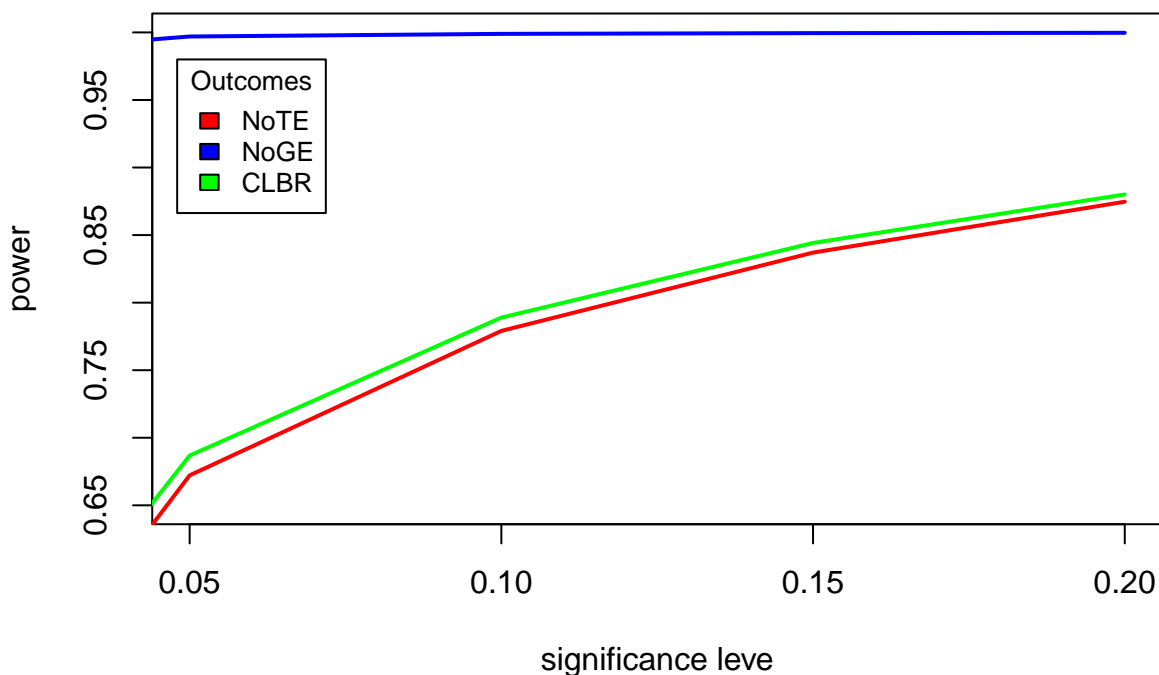


```
power_3<- NULL  
for (i in 1:length_sig){  
  result <- pwr.chisq.test(w=0.13, N=443, df=2, sig.level = sig[i])  
  power_3[i] <- result$power  
}  
  
plot(sig, power_3, type="l", lwd=2, col="red",  
      xlab="significance level",  
      ylab="power",  
      main = ""  
)
```



```
xrange <- c(0.05,0.20)
yrange <- c(0.65,1)
plot(xrange, yrange, type="n",
     xlab="significance leve",
     ylab="power" )
lines(sig, power, type = "l", lwd=2, col="red")
lines(sig, power_2, type = "l", lwd=2, col="blue")
lines(sig, power_3, type = "l", lwd=2, col="green")
title("Statistical Power Estimation\n Curve for Each Outcome")
legend(x=0.048, y=0.98, title="Outcomes", legend = c("NoTE", "NoGE", "CLBR"),fill = c("red", "blue", "green"))
```

### Statistical Power Estimation Curve for Each Outcome





```
dev.off()
```

```
## null device
```

```
##          1
```