

# Overall Results

*Hamza*

*30 September 2019*

## Meta-analysis

### Calculating effect sizes

Here, we calculated our effect sizes (log response ratio lnRR) for our complete data set (all traits).

### Meta-analysis overall results (lnRR)

#### 1. Calculating effect sizes (Done)

We calculated our effect sizes (log response ratio lnRR) for our complete data set (all traits).

#### 2. Deciding random effects (Done)

We used AIC values to decide which random effects to use. Combining “Trait”, “ES\_ID”, “Paper\_ID” and “Cohort\_ID” yielded the lowest AIC values.

#### 3. Running meta-analysis (overall, with and without moderators)

I conducted meta-analysis, first on the complete dataset, with and without moderators.

### Meta Regression for Traits and Exposure Type

```
### Meta Regression
```

```
#Traits meta-regression
```

```
All_Traits_Analysis_traits <- rma.mv(yi, vi, mods= ~Trait-1, random = list(~1|Paper_ID,~1|Cohort_ID,~1|
```

```
summary(All_Traits_Analysis_traits)
```

```
##
```

```
## Multivariate Meta-Analysis Model (k = 341; method: REML)
```

```
##
```

```
##   logLik  Deviance      AIC      BIC      AICc
```

```
## -58.2107  116.4215  138.4215  180.3110  139.2439
```

```
##
```

```
## Variance Components:
```

```
##
```

```
##           estim      sqrt  nlvls  fixed      factor
```

```
## sigma^2.1  0.0840  0.2898    25    no  Paper_ID
```

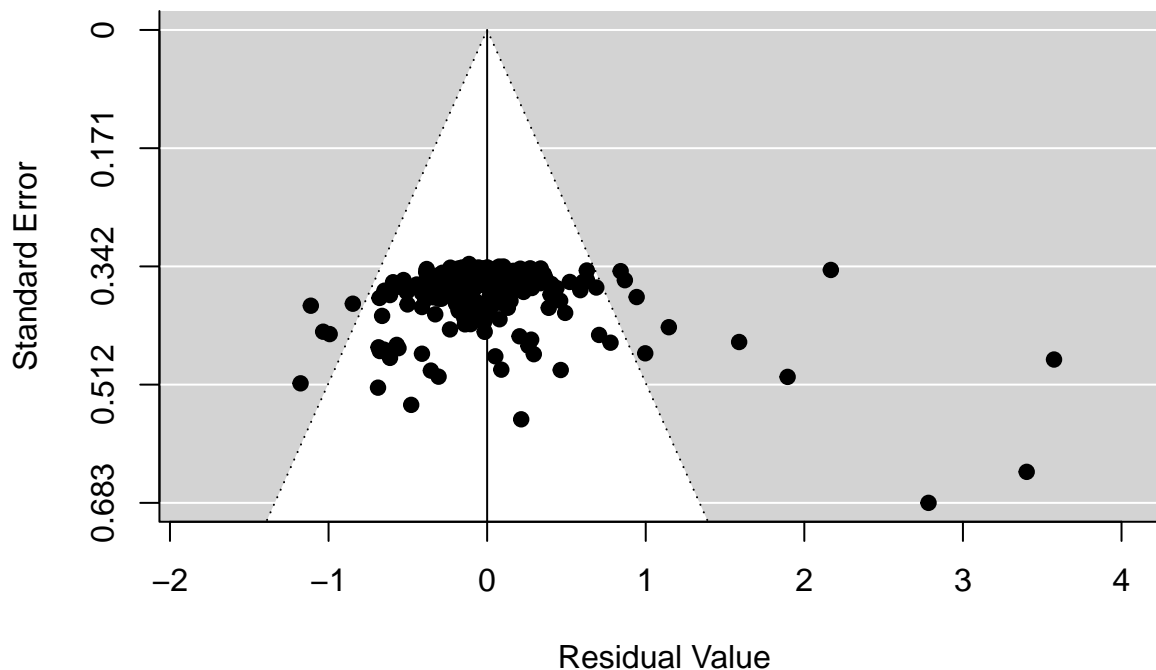
```
## sigma^2.2  0.0084  0.0919    74    no  Cohort_ID
```

```
## sigma^2.3  0.0302  0.1738   341    no    ES_ID
```

```
##
```

```
## Test for Residual Heterogeneity:
## QE(df = 333) = 6097.4737, p-val < .0001
##
## Test of Moderators (coefficient(s) 1:8):
## QM(df = 8) = 84.5884, p-val < .0001
##
## Model Results:
##
##               estimate      se    zval    pval    ci.lb    ci.ub
## TraitAdiposity      0.4111 0.0705  5.8341 <.0001   0.2730   0.5492 ***
## TraitBody_Weight     0.1076 0.0627  1.7166  0.0861  -0.0153   0.2304 .
## TraitGlucose_FBG     0.0404 0.0862  0.4687  0.6393  -0.1286   0.2094
## TraitGlucose_TT      0.1349 0.0731  1.8455  0.0650  -0.0084   0.2782 .
## TraitInsulin_FI      0.2527 0.0815  3.1025  0.0019   0.0931   0.4123 **
## TraitInsulin_TT      0.1307 0.0858  1.5241  0.1275  -0.0374   0.2988
## TraitLeptin          0.4073 0.0961  4.2371 <.0001   0.2189   0.5957 ***
## TraitTriglycerides   0.2457 0.0746  3.2918  0.0010   0.0994   0.3920 ***
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
funnel(All_Traits_Analysis_traits)
```



```
k_traits <- Effect_Size_All_Traits %>% group_by(Trait) %>% count()
```

```
## Warning: The `printer` argument is deprecated as of rlang 0.3.0.
```

```
## This warning is displayed once per session.
```

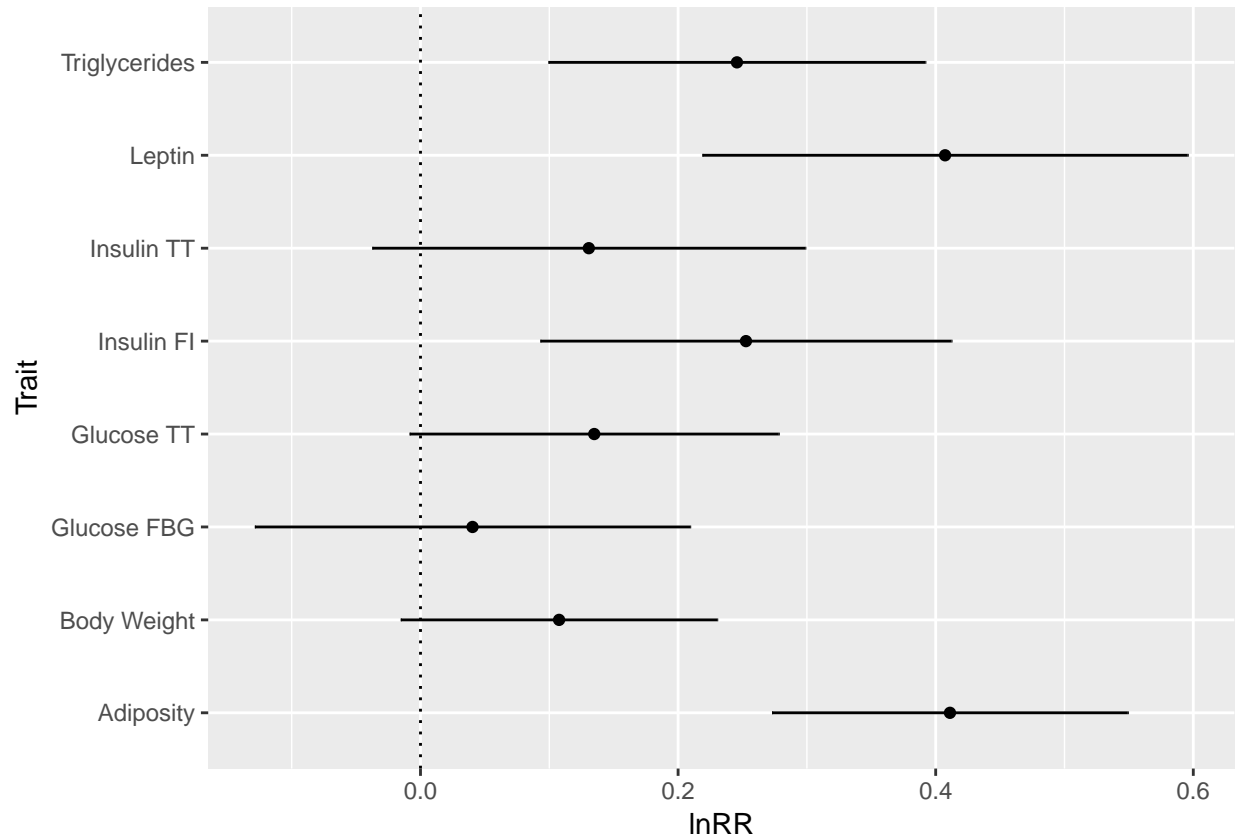
```
k_traits
```

```
## # A tibble: 8 x 2
## # Groups:   Trait [8]
##   Trait      n
##   <fct>    <int>
## 1 Adiposity    65
## 2 Body_Weight  146
## 3 Glucose_FBG   12
## 4 Glucose_TT   28
## 5 Insulin_FI   26
## 6 Insulin_TT   19
## 7 Leptin      12
## 8 Triglycerides 33
```

```
Traits_overall_lnRR <- tibble(
  Trait = c("Adiposity", "Body Weight", "Glucose FBG", "Glucose TT", "Insulin FI", "Insulin TT", "Leptin"),
  lnRR = c(0.4111, 0.1076, 0.0404, 0.1349, 0.2527, 0.1307, 0.4073, 0.2457),
  ci.lb = c(0.2730, -0.0153, -0.1286, -0.0084, 0.0931, -0.0374, 0.2189, 0.0994),
  ci.ub = c(0.5492, 0.2304, 0.2094, 0.2782, 0.4123, 0.2988, 0.5957, 0.3920),
  k = c(k_traits$n[1], k_traits$n[2], k_traits$n[3], k_traits$n[4], k_traits$n[5], k_traits$n[6], k_traits$n[7], k_traits$n[8])
)
Traits_overall_lnRR
```

```
## # A tibble: 8 x 5
##   Trait      lnRR   ci.lb ci.ub    k
##   <chr>    <dbl>   <dbl> <dbl> <int>
## 1 Adiposity  0.411  0.273  0.549   65
## 2 Body Weight 0.108 -0.0153 0.230  146
## 3 Glucose FBG 0.0404 -0.129  0.209   12
## 4 Glucose TT  0.135 -0.0084 0.278   28
## 5 Insulin FI  0.253  0.0931 0.412   26
## 6 Insulin TT  0.131 -0.0374 0.299   19
## 7 Leptin     0.407  0.219  0.596   12
## 8 Triglycerides 0.246  0.0994 0.392   33
```

```
plot_lnRR_overall_traits <- ggplot(Traits_overall_lnRR, aes(x=Trait, y=lnRR)) +
  geom_errorbar(aes(ymin=ci.lb, ymax=ci.ub), width = 0, position = position_dodge(0.3)) +
  geom_point(aes(x = Trait, y = lnRR), position = position_dodge(0.3)) +
  geom_hline(yintercept = 0, lty = "dotted") +
  labs(x = "Trait", y = "lnRR") +
  coord_flip()
plot_lnRR_overall_traits
```

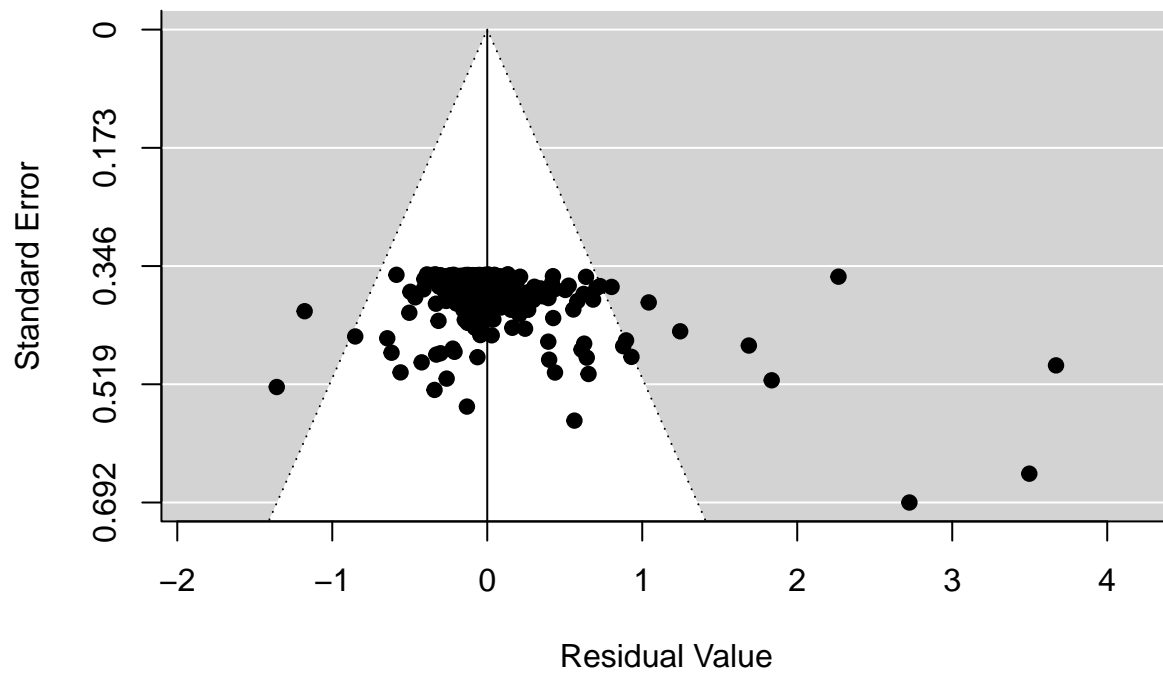


```
#Exposure type meta-regression
All_Traits_Analysis_Exp <- rma.mv(yi, vi, mods= ~Exposure_Type-1, random = list(~1|Paper_ID,~1|Cohort_ID,~1|ES_ID))
summary(All_Traits_Analysis_Exp)
```

```
##
## Multivariate Meta-Analysis Model (k = 341; method: REML)
##
##   logLik  Deviance      AIC      BIC      AICc
## -82.0467  164.0934  174.0934  193.2234  174.2736
##
## Variance Components:
##
##      estim  sqrt  nlvls  fixed  factor
## sigma^2.1 0.0885 0.2975   25    no  Paper_ID
## sigma^2.2 0.0032 0.0561   74    no  Cohort_ID
## sigma^2.3 0.0415 0.2037  341    no    ES_ID
##
## Test for Residual Heterogeneity:
## QE(df = 339) = 6278.3587, p-val < .0001
##
## Test of Moderators (coefficient(s) 1:2):
## QM(df = 2) = 27.8895, p-val < .0001
##
## Model Results:
##
```

```
##               estimate      se   zval   pval   ci.lb
## Exposure_TypeMultigenerational  0.3121 0.0705 4.4287 <.0001 0.1740
## Exposure_TypeOne off            0.0632 0.0669 0.9451 0.3446 -0.0679
##               ci.ub
## Exposure_TypeMultigenerational 0.4502 ***
## Exposure_TypeOne off           0.1943
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
funnel(All_Traits_Analysis_Exp)
```



```
k_exp <- Effect_Size_All_Traits %>% group_by(Exposure_Type) %>% count()
k_exp
```

```
## # A tibble: 2 x 2
## # Groups:   Exposure_Type [2]
##   Exposure_Type      n
##   <fct>          <int>
## 1 Multigenerational 118
## 2 One off          223
```

```
Overall_Exp_meta_lnRR <- tibble(
  Exposure_Type = c("Multigenerational", "One off"),
```

```

lnRR = c(0.3121,0.0632),
ci.lb = c(0.1740,-0.0679),
ci.ub = c(0.4502,0.1943),
k = c(k_exp$n[1],k_exp$n[2])
)
Overall_Exp_meta_lnRR

```

```

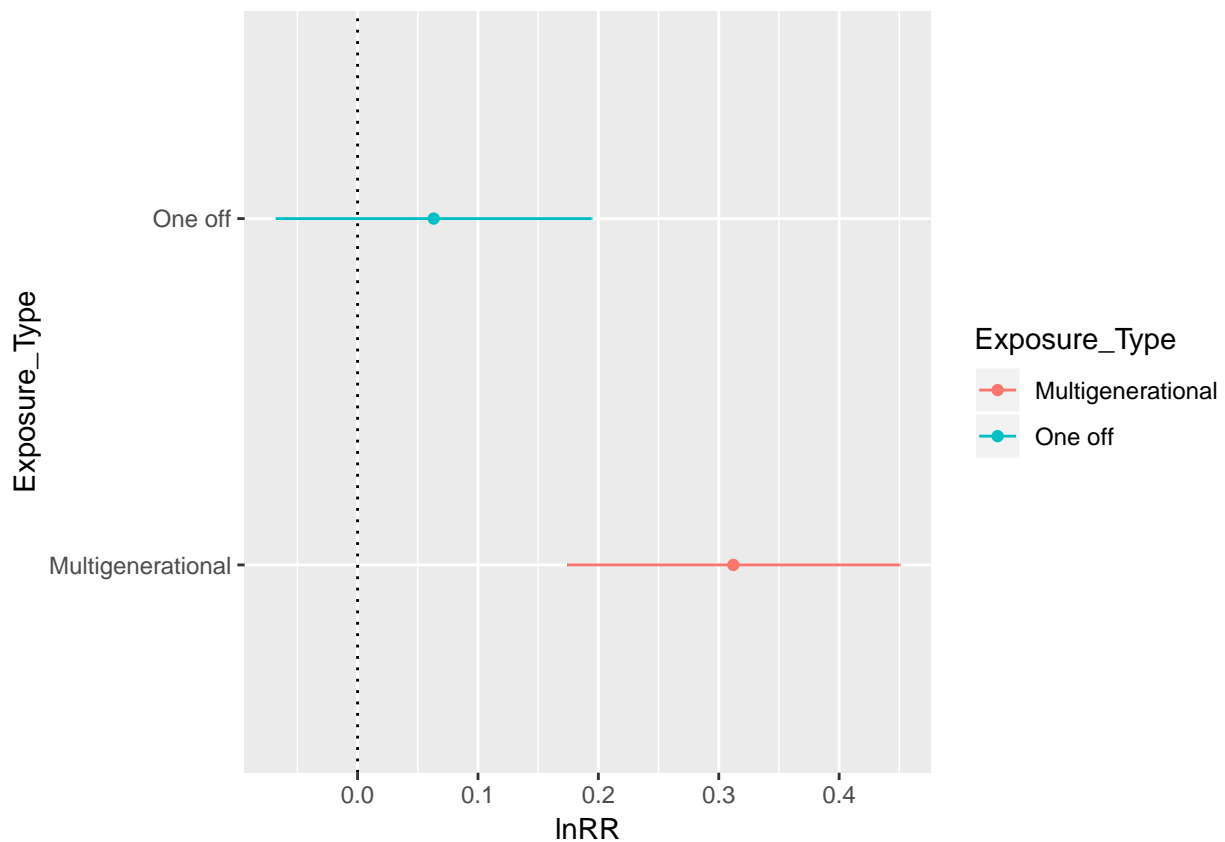
## # A tibble: 2 x 5
##   Exposure_Type      lnRR   ci.lb ci.ub    k
##   <chr>          <dbl>   <dbl> <dbl> <int>
## 1 Multigenerational 0.312   0.174  0.450   118
## 2 One off          0.0632 -0.0679 0.194   223

```

```

plot_lnRR_overall_expmeta <- ggplot(Overall_Exp_meta_lnRR, aes(x=Exposure_Type, y=lnRR, colour=Exposure_Type)) +
  geom_errorbar(aes(ymin=ci.lb, ymax=ci.ub), width = 0, position = position_dodge(0.3)) +
  geom_point(aes(x = Exposure_Type, y = lnRR), position = position_dodge(0.3)) +
  geom_hline(yintercept = 0, lty = "dotted") +
  labs(x = "Exposure_Type", y = "lnRR") +
  coord_flip()
plot_lnRR_overall_expmeta

```



## Meta-regression of overall dataset for F0 parent and offspring sex

```
All_Data_Analysis_f0 <- rma.mv(yi, vi, mods = ~F0_Parent_Exposed-1, random = list(~1|Trait, ~1|Paper_ID)
summary(All_Data_Analysis_f0)
```

```
##
## Multivariate Meta-Analysis Model (k = 341; method: REML)
##
##   logLik  Deviance      AIC      BIC      AICc
## -64.9505  129.9010  143.9010  170.6623  144.2404
##
## Variance Components:
##
##           estim      sqrt  nlvls  fixed      factor
## sigma^2.1  0.0157  0.1252      8     no      Trait
## sigma^2.2  0.0863  0.2937     25     no  Paper_ID
## sigma^2.3  0.0084  0.0915     74     no Cohort_ID
## sigma^2.4  0.0301  0.1734    341     no      ES_ID
##
## Test for Residual Heterogeneity:
## QE(df = 338) = 7056.6821, p-val < .0001
##
## Test of Moderators (coefficient(s) 1:3):
## QM(df = 3) = 8.7540, p-val = 0.0327
##
## Model Results:
##
##              estimate      se    zval    pval    ci.lb    ci.ub
## F0_Parent_ExposedBoth    0.2747  0.1660  1.6551  0.0979   -0.0506   0.5999
## F0_Parent_ExposedFemale    0.2242  0.0794  2.8223  0.0048    0.0685   0.3799
## F0_Parent_ExposedMale    0.1427  0.1199  1.1900  0.2341   -0.0923   0.3777
##
## F0_Parent_ExposedBoth      .
## F0_Parent_ExposedFemale    **
## F0_Parent_ExposedMale
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
k_All_Data_Analysis_f0 <- Effect_Size_All_Traits %>% group_by(F0_Parent_Exposed) %>% count()
k_All_Data_Analysis_f0
```

```
## # A tibble: 3 x 2
## # Groups:   F0_Parent_Exposed [3]
##   F0_Parent_Exposed     n
##   <fct>              <int>
## 1 Both                4
## 2 Female             262
## 3 Male                75
```

```
All_Data_Analysis_sex <- rma.mv(yi, vi, mods = ~Sex-1, random = list(~1|Trait, ~1|Paper_ID, ~1|Cohort_ID)
summary(All_Data_Analysis_sex)
```

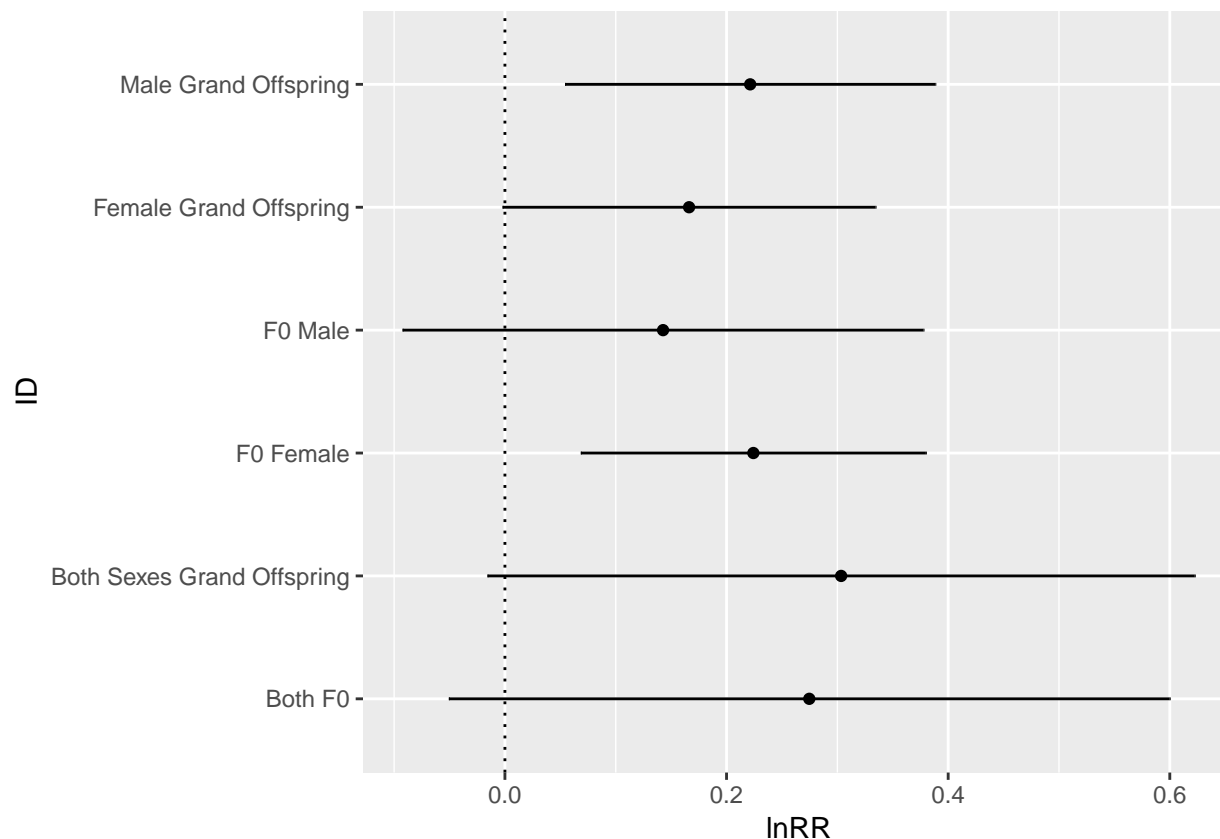
```
##
## Multivariate Meta-Analysis Model (k = 341; method: REML)
##
##   logLik  Deviance      AIC      BIC      AICc
## -64.2506  128.5012  142.5012  169.2625  142.8406
##
## Variance Components:
##
##      estim      sqrt  nlvls  fixed      factor
## sigma^2.1  0.0153  0.1238     8     no      Trait
## sigma^2.2  0.0992  0.3150    25     no    Paper_ID
## sigma^2.3  0.0081  0.0898    74     no    Cohort_ID
## sigma^2.4  0.0299  0.1729   341     no      ES_ID
##
## Test for Residual Heterogeneity:
## QE(df = 338) = 6794.7529, p-val < .0001
##
## Test of Moderators (coefficient(s) 1:3):
## QM(df = 3) = 10.0671, p-val = 0.0180
##
## Model Results:
##
##      estimate      se      zval      pval      ci.lb      ci.ub
## SexBoth      0.3034  0.1628  1.8634  0.0624  -0.0157  0.6225  .
## SexFemale    0.1662  0.0859  1.9355  0.0529  -0.0021  0.3345  .
## SexMale      0.2213  0.0852  2.5964  0.0094   0.0543  0.3884  **
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
Overall_effects_not_split_f0_sex <- tibble(
  ID = c("Both F0", "F0 Female", "F0 Male", "Both Sexes Grand Offspring", "Female Grand Offspring", "Male Grand Offspring"),
  lnRR = c(All_Data_Analysis_f0$b[1], All_Data_Analysis_f0$b[2], All_Data_Analysis_f0$b[3], All_Data_Analysis_f0$b[4], All_Data_Analysis_f0$b[5], All_Data_Analysis_f0$b[6]),
  ci.lb = c(All_Data_Analysis_f0$ci.lb[1], All_Data_Analysis_f0$ci.lb[2], All_Data_Analysis_f0$ci.lb[3], All_Data_Analysis_f0$ci.lb[4], All_Data_Analysis_f0$ci.lb[5], All_Data_Analysis_f0$ci.lb[6]),
  ci.ub = c(All_Data_Analysis_f0$ci.ub[1], All_Data_Analysis_f0$ci.ub[2], All_Data_Analysis_f0$ci.ub[3], All_Data_Analysis_f0$ci.ub[4], All_Data_Analysis_f0$ci.ub[5], All_Data_Analysis_f0$ci.ub[6])
)
```

```
plot_lnRR_overall_mods_f0_sex <- ggplot(Overall_effects_not_split_f0_sex, aes(x=ID, y=lnRR))+
  geom_errorbar(aes(ymin=ci.lb, ymax=ci.ub), width = 0, position = position_dodge(0.3)) +
  geom_point(aes(x = ID, y = lnRR), position = position_dodge(0.3))+
  geom_hline(yintercept = 0, lty = "dotted") +
  labs(x = "ID", y = "lnRR") +
  coord_flip()
```

```
plot_lnRR_overall_mods_f0_sex
```





### Meta-analysis with subsetting dataset (MG and OF exposure type)

## Meta-analysis overall results (lnCVR)

### 4. Calculating effect sizes (Done)

We calculated our effect sizes (lnCVR) for our complete data set (all traits).

### 5. Running meta-analysis for lnCVR

## Modelling traits with overall dataset

```
All_Traits_Analysis_traits_lnCVR <- rma.mv(yi, vi, mods= ~Trait-1, random = list(~1|Paper_ID,~1|Cohort_ID))
summary(All_Traits_Analysis_traits_lnCVR)
```

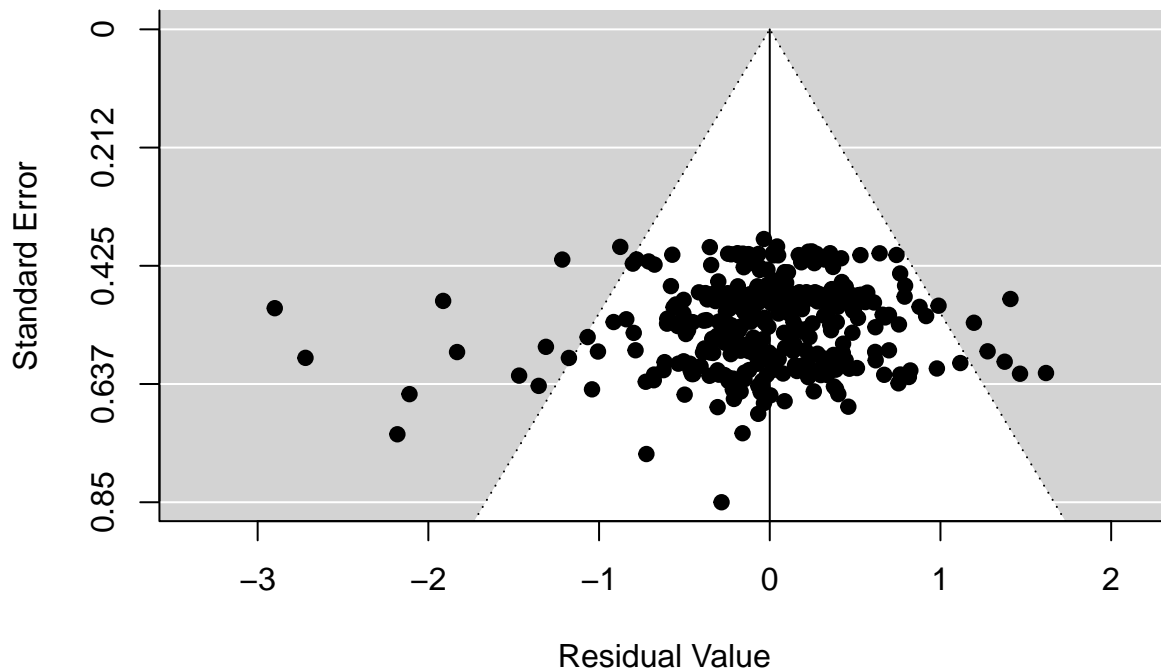
```
##
## Multivariate Meta-Analysis Model (k = 341; method: REML)
##
##      logLik   Deviance      AIC      BIC     AICc
## -257.8572   515.7144   537.7144   579.6040   538.5368
##
```

```

## Variance Components:
##
##      estim      sqrt  nlvls  fixed      factor
## sigma^2.1  0.0253  0.1590    25    no   Paper_ID
## sigma^2.2  0.0000  0.0000    74    no   Cohort_ID
## sigma^2.3  0.1095  0.3308   341    no    ES_ID
##
## Test for Residual Heterogeneity:
## QE(df = 333) = 762.1820, p-val < .0001
##
## Test of Moderators (coefficient(s) 1:8):
## QM(df = 8) = 20.0331, p-val = 0.0102
##
## Model Results:
##
##      estimate      se      zval      pval      ci.lb      ci.ub
## TraitAdiposity    -0.0610  0.0838  -0.7282  0.4665  -0.2254  0.1033
## TraitBody_Weight   0.0298  0.0540   0.5519  0.5810  -0.0760  0.1355
## TraitGlucose_FBG   -0.1652  0.1469  -1.1249  0.2606  -0.4531  0.1226
## TraitGlucose_TT     0.0992  0.1124   0.8830  0.3772  -0.1210  0.3195
## TraitInsulin_FI    -0.3983  0.1174  -3.3937  0.0007  -0.6284 -0.1683
## TraitInsulin_TT     0.2099  0.1417   1.4815  0.1385  -0.0678  0.4877
## TraitLeptin        -0.1094  0.1575  -0.6945  0.4874  -0.4180  0.1993
## TraitTriglycerides -0.1040  0.1046  -0.9940  0.3202  -0.3090  0.1011
##
## TraitAdiposity
## TraitBody_Weight
## TraitGlucose_FBG
## TraitGlucose_TT
## TraitInsulin_FI    ***
## TraitInsulin_TT
## TraitLeptin
## TraitTriglycerides
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

```

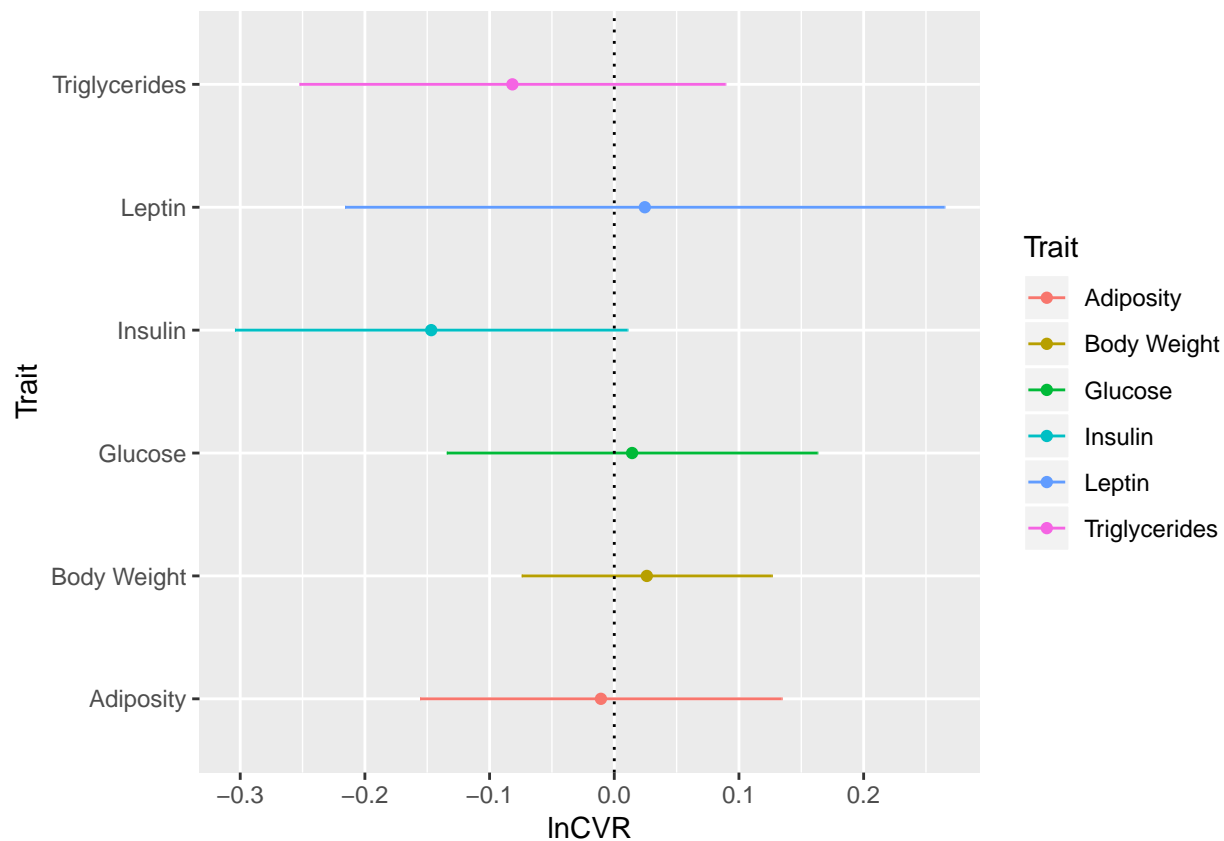
```
funnel(All_Traits_Analysis_traits_lnCVR)
```



```
Traits_overall_lnCVR <- tibble(
  Trait = c("Adiposity", "Body Weight", "Glucose", "Insulin", "Leptin", "Triglycerides"),
  lnCVR = c(-0.0107, 0.0261, 0.0143, -0.1468, 0.0245, -0.0817),
  ci.lb = c(-0.1557, -0.0742, -0.1343, -0.3042, -0.2159, -0.2524),
  ci.ub = c(0.1343, 0.1264, 0.1629, 0.0106, 0.2648, 0.0891)
)
Traits_overall_lnCVR
```

```
## # A tibble: 6 x 4
##   Trait          lnCVR   ci.lb ci.ub
##   <chr>          <dbl>   <dbl> <dbl>
## 1 Adiposity    -0.0107 -0.156 0.134
## 2 Body Weight  0.0261 -0.0742 0.126
## 3 Glucose      0.0143 -0.134 0.163
## 4 Insulin     -0.147  -0.304 0.0106
## 5 Leptin       0.0245 -0.216 0.265
## 6 Triglycerides -0.0817 -0.252 0.0891
```

```
plot_lnRR_overall_traits_lnCVR <- ggplot(Traits_overall_lnCVR, aes(x=Trait, y=lnCVR, colour = Trait)) +
  geom_errorbar(aes(ymin=ci.lb, ymax=ci.ub), width = 0, position = position_dodge(0.3)) +
  geom_point(aes(x = Trait, y = lnCVR), position = position_dodge(0.3)) +
  geom_hline(yintercept = 0, lty = "dotted") +
  labs(x = "Trait", y = "lnCVR") +
  coord_flip()
plot_lnRR_overall_traits_lnCVR
```



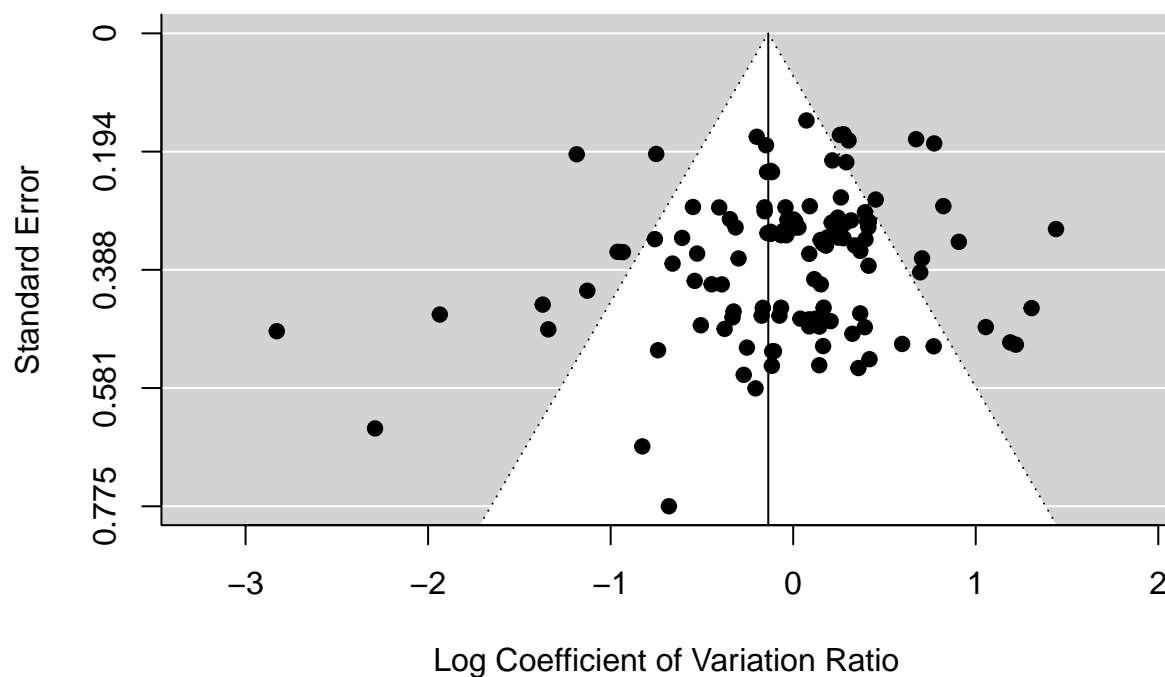
## Modelling MG and OF (no mods) (lnCVR)

```
All_Data_Analysis_Omods_MG_lnCVR <- rma.mv(yi, vi, random = list(~1|Trait, ~1|Paper_ID, ~1|Cohort_ID, ~1|
summary(All_Data_Analysis_Omods_MG_lnCVR)
```

```
##
## Multivariate Meta-Analysis Model (k = 118; method: REML)
##
##      logLik   Deviance      AIC      BIC      AICc
## -101.4081   202.8163   212.8163   226.6272   213.3568
##
## Variance Components:
##
##      estim  sqrt  nlvls  fixed  factor
## sigma^2.1 0.0542 0.2328    8    no   Trait
## sigma^2.2 0.0000 0.0000   13    no  Paper_ID
## sigma^2.3 0.0000 0.0000   24    no  Cohort_ID
## sigma^2.4 0.1499 0.3871  118    no    ES_ID
##
## Test for Heterogeneity:
## Q(df = 117) = 330.3777, p-val < .0001
##
```

```
## Model Results:
##
## estimate      se      zval      pval      ci.lb      ci.ub
## -0.1366  0.1035  -1.3206  0.1866  -0.3394  0.0662
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
funnel(All_Data_Analysis_Omods_MG_lnCVR)
```

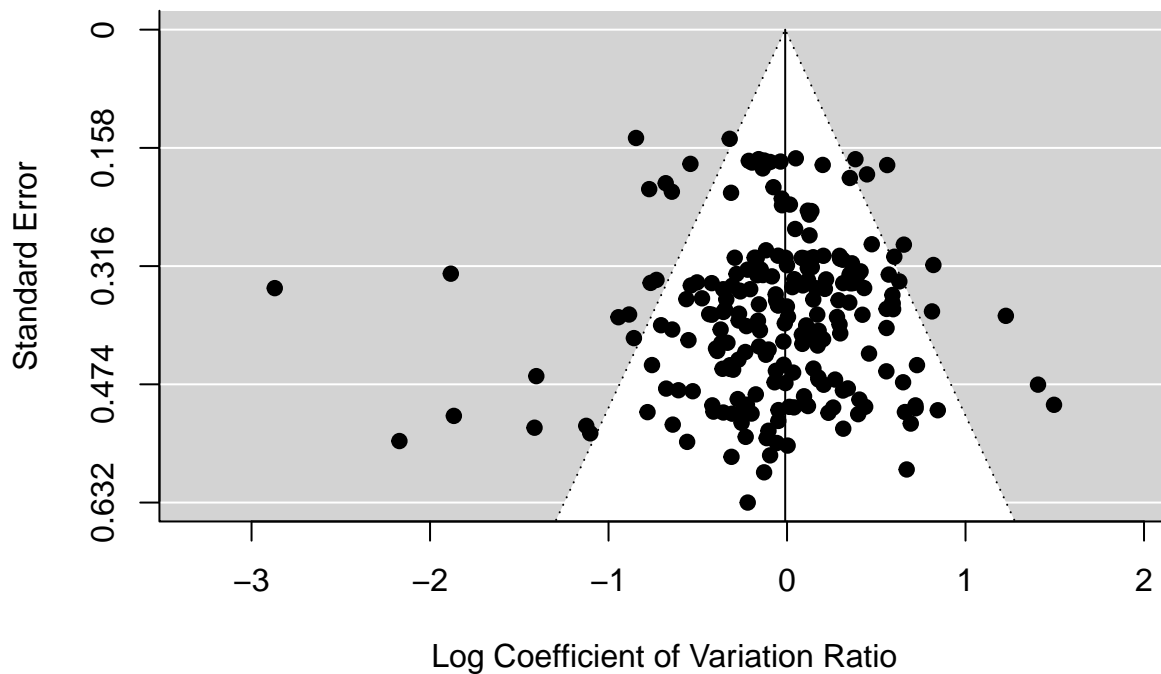


```
All_Data_Analysis_Omods_OF_lnCVR <- rma.mv(yi, vi, random = list(~1|Trait, ~1|Paper_ID, ~1|Cohort_ID, ~1|
summary(All_Data_Analysis_Omods_OF_lnCVR)
```

```
##
## Multivariate Meta-Analysis Model (k = 223; method: REML)
##
##      logLik    Deviance      AIC      BIC      AICc
## -161.0354    322.0708    332.0708    349.0842    332.3486
##
## Variance Components:
##
##      estim    sqrt  nlvls  fixed    factor
## sigma^2.1  0.0191  0.1381     8    no     Trait
## sigma^2.2  0.0320  0.1790    16    no  Paper_ID
```

```
## sigma^2.3  0.0013  0.0354    52    no Cohort_ID
## sigma^2.4  0.0785  0.2802   223    no    ES_ID
##
## Test for Heterogeneity:
## Q(df = 222) = 464.7551, p-val < .0001
##
## Model Results:
##
## estimate      se      zval    pval    ci.lb    ci.ub
## -0.0103  0.0840 -0.1226  0.9024 -0.1750  0.1544
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
funnel(All_Data_Analysis_0mods_OF_lnCVR)
```

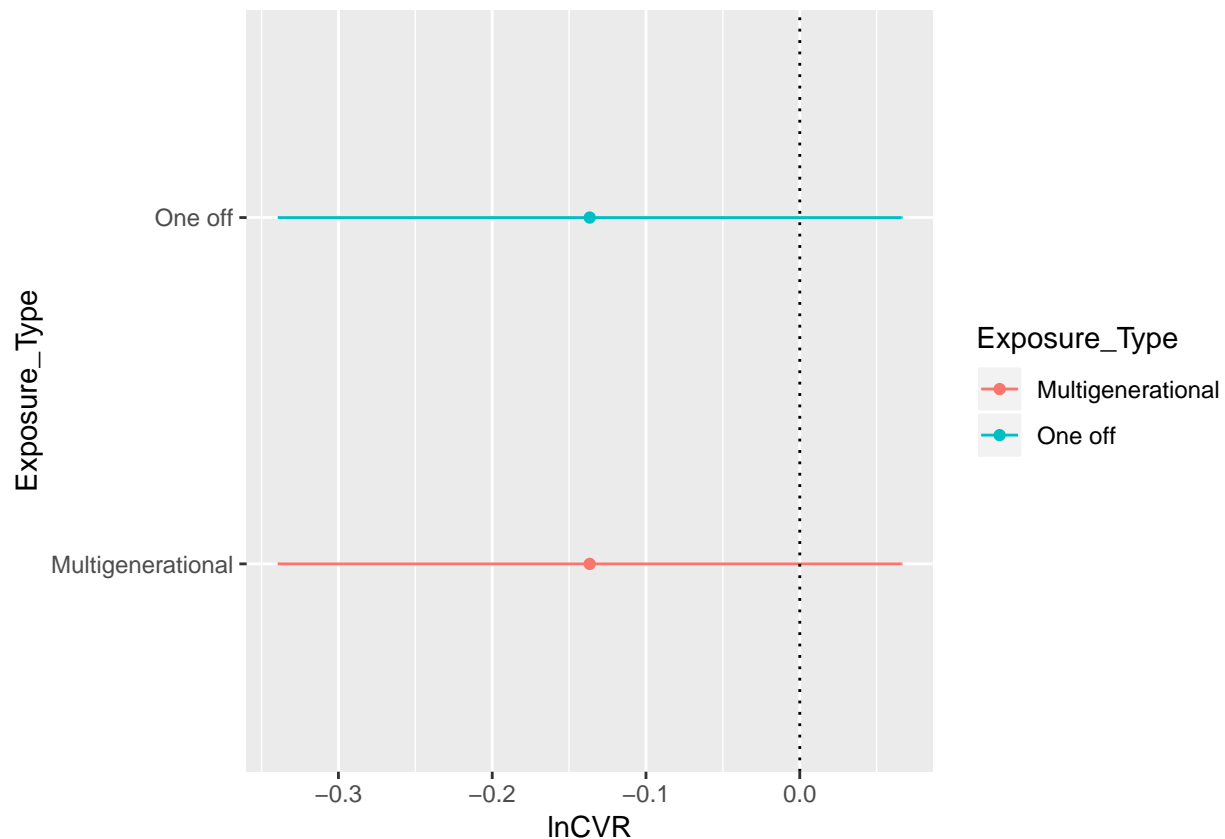


```
Exp_overall_lnCVR <- tibble(
  Exposure_Type = c("Multigenerational", "One off"),
  lnCVR = c(-0.1366, -0.1366),
  ci.lb = c(-0.3394, -0.3394),
  ci.ub = c(0.0662, 0.0662)
)
Exp_overall_lnCVR
```

```
## # A tibble: 2 x 4
```

```
## Exposure_Type      lnCVR ci.lb ci.ub
## <chr>              <dbl> <dbl> <dbl>
## 1 Multigenerational -0.137 -0.339 0.0662
## 2 One off           -0.137 -0.339 0.0662
```

```
plot_lnRR_overall_exp_lnCVR <- ggplot(Exp_overall_lnCVR, aes(x=Exposure_Type, y=lnCVR, colour = Exposure_Type)) +
  geom_errorbar(aes(ymin=ci.lb, ymax=ci.ub), width = 0, position = position_dodge(0.3)) +
  geom_point(aes(x = Exposure_Type, y = lnCVR), position = position_dodge(0.3)) +
  geom_hline(yintercept = 0, lty = "dotted") +
  labs(x = "Exposure_Type", y = "lnCVR") +
  coord_flip()
plot_lnRR_overall_exp_lnCVR
```



## Modelling all traits split by MG and OF (lnCVR)

```
All_Traits_Analysis_MG_lnCVR <- rma.mv(yi, vi, mods= ~Trait-1, random = list(~1|Paper_ID, ~1|Cohort_ID, ~1|Exposure_Type))
summary(All_Traits_Analysis_MG_lnCVR)
```

```
##
## Multivariate Meta-Analysis Model (k = 118; method: REML)
##
```

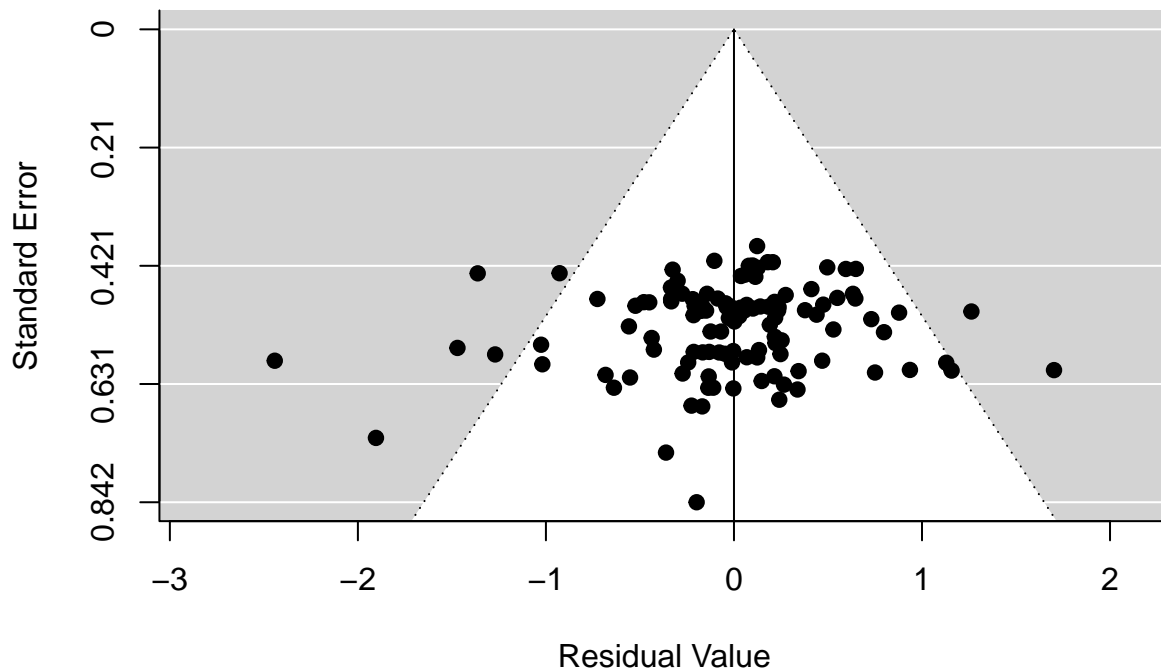
```

##    logLik  Deviance      AIC      BIC      AICc
## -91.8355  183.6709  205.6709  235.3762  208.3648
##
## Variance Components:
##
##          estim      sqrt  nlvls  fixed      factor
## sigma^2.1  0.0000  0.0000     13     no    Paper_ID
## sigma^2.2  0.0000  0.0000     24     no   Cohort_ID
## sigma^2.3  0.1541  0.3925    118     no      ES_ID
##
## Test for Residual Heterogeneity:
## QE(df = 110) = 280.3182, p-val < .0001
##
## Test of Moderators (coefficient(s) 1:8):
## QM(df = 8) = 24.9878, p-val = 0.0016
##
## Model Results:
##
##          estimate      se      zval      pval      ci.lb      ci.ub
## TraitAdiposity      -0.1021  0.1301  -0.7851  0.4324  -0.3570  0.1528
## TraitBody_Weight      0.1770  0.0688   2.5744  0.0100   0.0422  0.3118  *
## TraitGlucose_FBG     -0.3227  0.1844  -1.7505  0.0800  -0.6840  0.0386  .
## TraitGlucose_TT       0.0195  0.2099   0.0930  0.9259  -0.3920  0.4310
## TraitInsulin_FI      -0.4823  0.2156  -2.2369  0.0253  -0.9048 -0.0597  *
## TraitInsulin_TT       0.2532  0.2078   1.2185  0.2230  -0.1541  0.6604
## TraitLeptin          -0.3871  0.2111  -1.8338  0.0667  -0.8007  0.0266  .
## TraitTriglycerides   -0.4652  0.2119  -2.1953  0.0281  -0.8806 -0.0499  *
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

```

```
funnel(All_Traits_Analysis_MG_lnCVR)
```



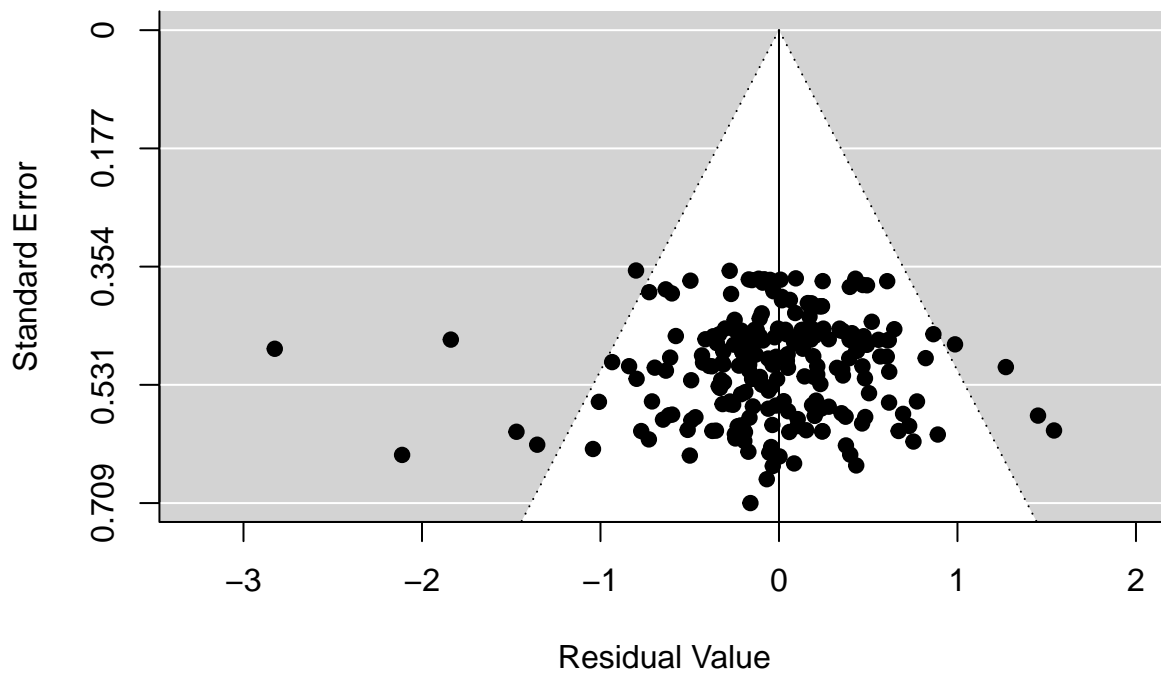


```
All_Traits_Analysis_OF_lnCVR <- rma.mv(yi, vi, mods= ~Trait-1, random = list(~1|Paper_ID,~1|Cohort_ID,~1|ES_ID))
summary(All_Traits_Analysis_OF_lnCVR)
```

```
##
## Multivariate Meta-Analysis Model (k = 223; method: REML)
##
##      logLik   Deviance      AIC      BIC      AICc
## -152.5433   305.0867   327.0867   364.1637   328.3871
##
## Variance Components:
##
##      estim      sqrt  nlvls  fixed    factor
## sigma^2.1  0.0346  0.1861    16     no   Paper_ID
## sigma^2.2  0.0015  0.0394    52     no   Cohort_ID
## sigma^2.3  0.0774  0.2783   223     no     ES_ID
##
## Test for Residual Heterogeneity:
## QE(df = 215) = 439.4961, p-val < .0001
##
## Test of Moderators (coefficient(s) 1:8):
## QM(df = 8) = 15.6057, p-val = 0.0484
##
## Model Results:
##
```

```
##               estimate      se      zval      pval      ci.lb      ci.ub
## TraitAdiposity    -0.0602  0.1023  -0.5890  0.5559  -0.2606  0.1402
## TraitBody_Weight  -0.0451  0.0699  -0.6458  0.5184  -0.1821  0.0919
## TraitGlucose_FBG   0.1298  0.2389   0.5434  0.5868  -0.3384  0.5981
## TraitGlucose_TT    0.1545  0.1281   1.2060  0.2278  -0.0966  0.4056
## TraitInsulin_FI    -0.3959  0.1328  -2.9816  0.0029  -0.6562 -0.1357
## TraitInsulin_TT    0.2375  0.1825   1.3011  0.1932  -0.1203  0.5953
## TraitLeptin        0.1847  0.2242   0.8237  0.4101  -0.2548  0.6242
## TraitTriglycerides -0.0098  0.1173  -0.0835  0.9335  -0.2398  0.2202
##
## TraitAdiposity
## TraitBody_Weight
## TraitGlucose_FBG
## TraitGlucose_TT
## TraitInsulin_FI    **
## TraitInsulin_TT
## TraitLeptin
## TraitTriglycerides
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

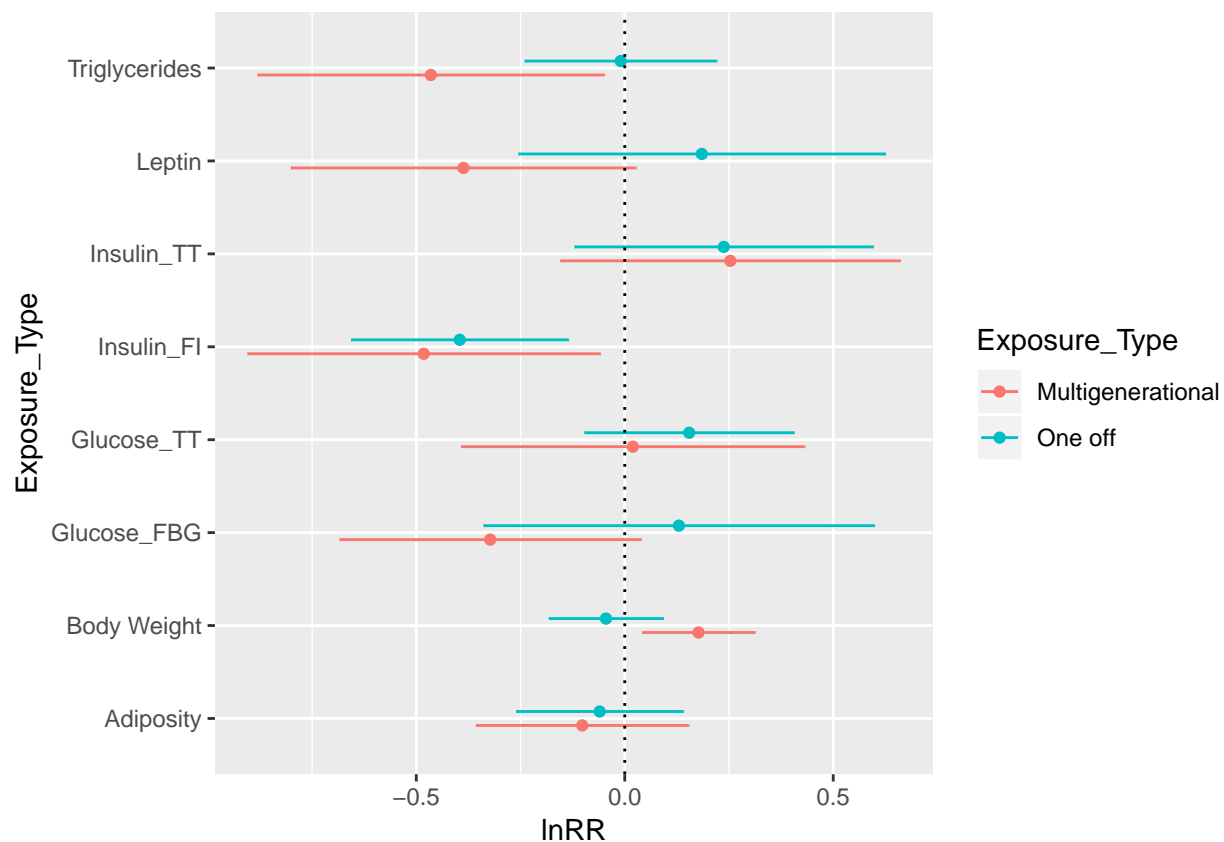
```
funnel(All_Traits_Analysis_OF_lnCVR)
```



```
Traits_analysis_Exp_lnCVR <- tibble(
  Exposure_Type = c("Multigenerational", "Multigenerational", "Multigenerational", "Multigenerational", "Multigenerational"),
  Trait = c("Adiposity", "Body Weight", "Glucose_FBG", "Glucose_TT", "Insulin_FI", "Insulin_TT", "Leptin"),
  lnRR = c(-0.1021, 0.1770, -0.3227, 0.0195, -0.4823, 0.2532, -0.387, -0.4652, -0.0602, -0.0451, 0.1298, 0.1545, -0.0195),
  ci.lb = c(-0.3570, 0.0422, -0.6840, -0.3920, -0.9048, -0.1541, -0.8007, -0.8806, -0.2606, -0.1821, -0.3384, -0.0384, -0.0384),
  ci.ub = c(0.1528, 0.3118, 0.0386, 0.4310, -0.0597, 0.6604, 0.0266, -0.0499, 0.1402, 0.0919, 0.5981, 0.4056, -0.1313),
  k = c(k_traits_MG$n[1], k_traits_MG$n[2], k_traits_MG$n[3], k_traits_MG$n[4], k_traits_MG$n[5], k_traits_MG$n[6], k_traits_MG$n[7])
)

plot_lnRR_overall_trait_exp_lnCVR <- ggplot(Traits_analysis_Exp_lnCVR, aes(x=Trait, y=lnRR, colour=Exposure_Type)) +
  geom_errorbar(aes(ymin=ci.lb, ymax=ci.ub), width = 0, position = position_dodge(0.3)) +
  geom_point(aes(x = Trait, y = lnRR), position = position_dodge(0.3)) +
  geom_hline(yintercept = 0, lty = "dotted") +
  labs(x = "Exposure_Type", y = "lnRR") +
  coord_flip()

plot_lnRR_overall_trait_exp_lnCVR
```



### Modelling all traits with moderators (split by exposure type)

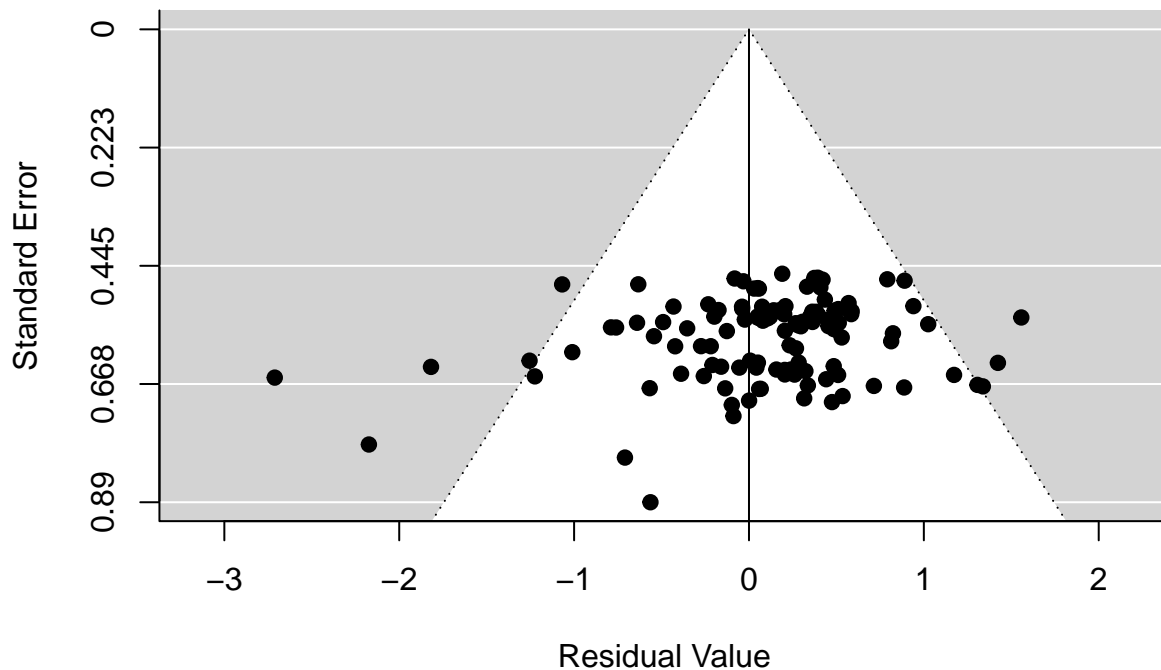
```
All_Traits_Analysis_lnCVR_MG_f0 <- rma.mv(yi, vi, mods = ~F0_Parent_Exposed-1, random = list(~1|Trait,

## Warning in rma.mv(yi, vi, mods = ~F0_Parent_Exposed - 1, random = list(~1
## | : Redundant predictors dropped from the model.
```

```
summary(All_Traits_Analysis_lnCVR_MG_f0)
```

```
##
## Multivariate Meta-Analysis Model (k = 118; method: REML)
##
##      logLik    Deviance      AIC      BIC      AICc
## -100.9803    201.9606    213.9606    230.4822    214.7313
##
## Variance Components:
##
##      estim    sqrt  nlvls  fixed    factor
## sigma^2.1  0.0498  0.2233     8     no     Trait
## sigma^2.2  0.0012  0.0352    13     no    Paper_ID
## sigma^2.3  0.0000  0.0001    24     no   Cohort_ID
## sigma^2.4  0.1518  0.3896   118     no     ES_ID
##
## Test for Residual Heterogeneity:
## QE(df = 116) = 324.9841, p-val < .0001
##
## Test of Moderators (coefficient(s) 1:2):
## QM(df = 2) = 1.9988, p-val = 0.3681
##
## Model Results:
##
##      estimate      se      zval      pval      ci.lb
## F0_Parent_ExposedFemale -0.1175  0.1081  -1.0866  0.2772  -0.3294
## F0_Parent_ExposedMale   -0.1728  0.1285  -1.3444  0.1788  -0.4247
##      ci.ub
## F0_Parent_ExposedFemale  0.0944
## F0_Parent_ExposedMale    0.0791
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
funnel(All_Traits_Analysis_lnCVR_MG_f0)
```

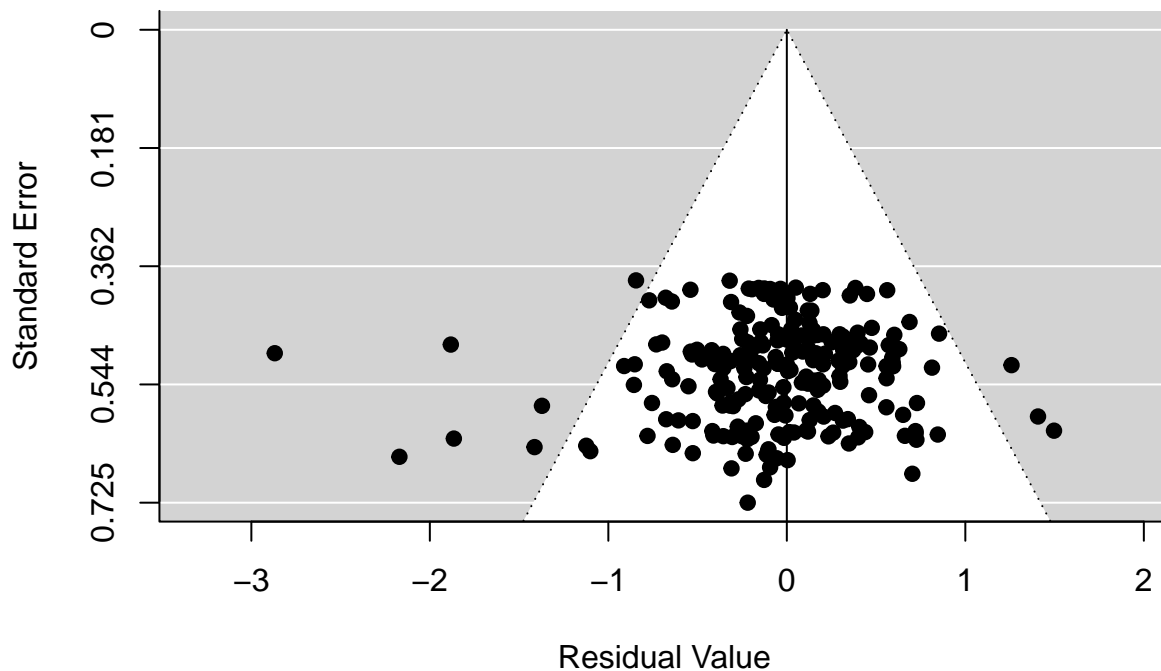


```
All_Traits_Analysis_lnCVR_OF_f0 <- rma.mv(yi, vi, mods = ~F0_Parent_Exposed-1, random = list(~1|Trait,
summary(All_Traits_Analysis_lnCVR_OF_f0)
```

```
##
## Multivariate Meta-Analysis Model (k = 223; method: REML)
##
##      logLik    Deviance      AIC      BIC      AICc
## -160.1924    320.3849    334.3849    358.1403    334.9132
##
## Variance Components:
##
##      estim    sqrt  nlvls  fixed    factor
## sigma^2.1  0.0187  0.1367     8    no      Trait
## sigma^2.2  0.0349  0.1869    16    no    Paper_ID
## sigma^2.3  0.0017  0.0416    52    no   Cohort_ID
## sigma^2.4  0.0797  0.2824   223    no      ES_ID
##
## Test for Residual Heterogeneity:
## QE(df = 220) = 464.4483, p-val < .0001
##
## Test of Moderators (coefficient(s) 1:3):
## QM(df = 3) = 0.0798, p-val = 0.9941
##
## Model Results:
```

```
##
##               estimate      se      zval      pval      ci.lb
## F0_Parent_ExposedBoth   -0.0418  0.2533  -0.1650  0.8689  -0.5383
## F0_Parent_ExposedFemale  -0.0011  0.0916  -0.0121  0.9903  -0.1806
## F0_Parent_ExposedMale   -0.0329  0.1298  -0.2533  0.8000  -0.2872
##               ci.ub
## F0_Parent_ExposedBoth    0.4547
## F0_Parent_ExposedFemale   0.1784
## F0_Parent_ExposedMale    0.2215
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
funnel(All_Traits_Analysis_lnCVR_OF_f0)
```



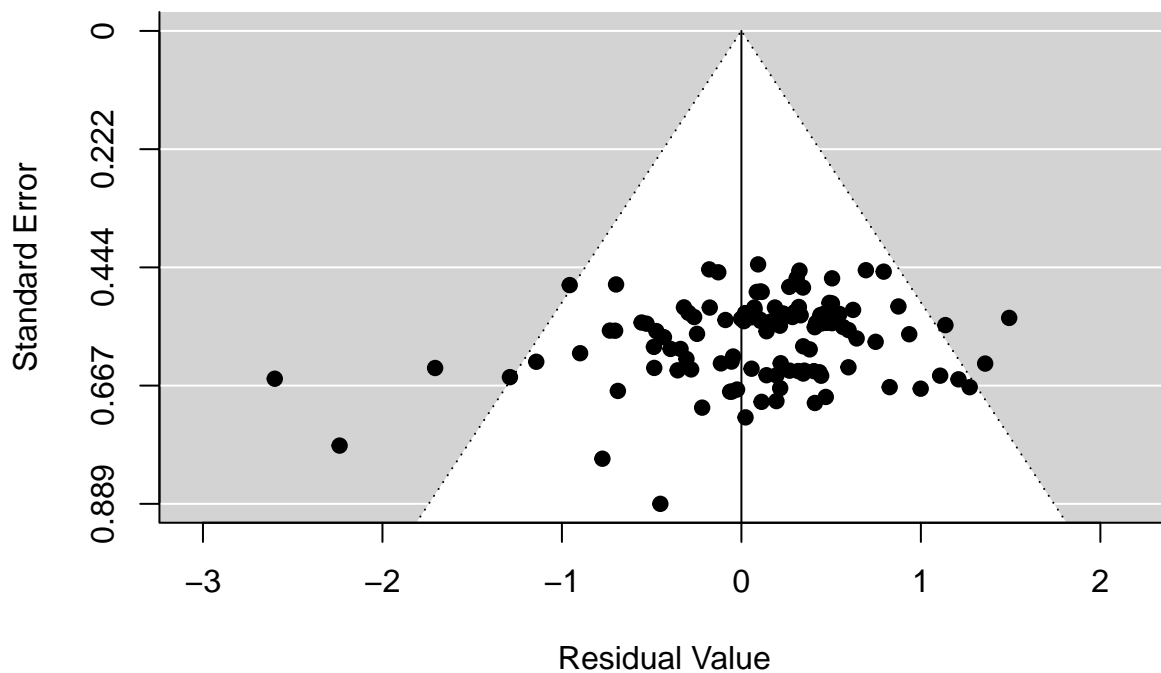
```
All_Traits_Analysis_lnCVR_MG_sex <- rma.mv(yi, vi, mods = ~Sex-1, random = list(~1|Trait, ~1|Paper_ID, ~1|Sex-1))
summary(All_Traits_Analysis_lnCVR_MG_sex)
```

```
##
## Multivariate Meta-Analysis Model (k = 118; method: REML)
##
##   logLik  Deviance      AIC      BIC      AICc
## -99.1372  198.2744  212.2744  231.4889  213.3211
##
```

```
## Variance Components:
##
##      estim      sqrt  nlvls  fixed      factor
## sigma^2.1  0.0565  0.2378     8     no      Trait
## sigma^2.2  0.0000  0.0000    13     no    Paper_ID
## sigma^2.3  0.0000  0.0000    24     no   Cohort_ID
## sigma^2.4  0.1458  0.3818   118     no     ES_ID
##
## Test for Residual Heterogeneity:
## QE(df = 115) = 312.6741, p-val < .0001
##
## Test of Moderators (coefficient(s) 1:3):
## QM(df = 3) = 5.1533, p-val = 0.1609
##
## Model Results:
##
##      estimate      se      zval      pval      ci.lb      ci.ub
## SexBoth      -0.0204  0.1739  -0.1171  0.9068  -0.3612  0.3205
## SexFemale     -0.0522  0.1201  -0.4346  0.6638  -0.2875  0.1832
## SexMale       -0.2292  0.1161  -1.9746  0.0483  -0.4567 -0.0017 *
```

```
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
funnel(All_Traits_Analysis_lnCVR_MG_sex)
```

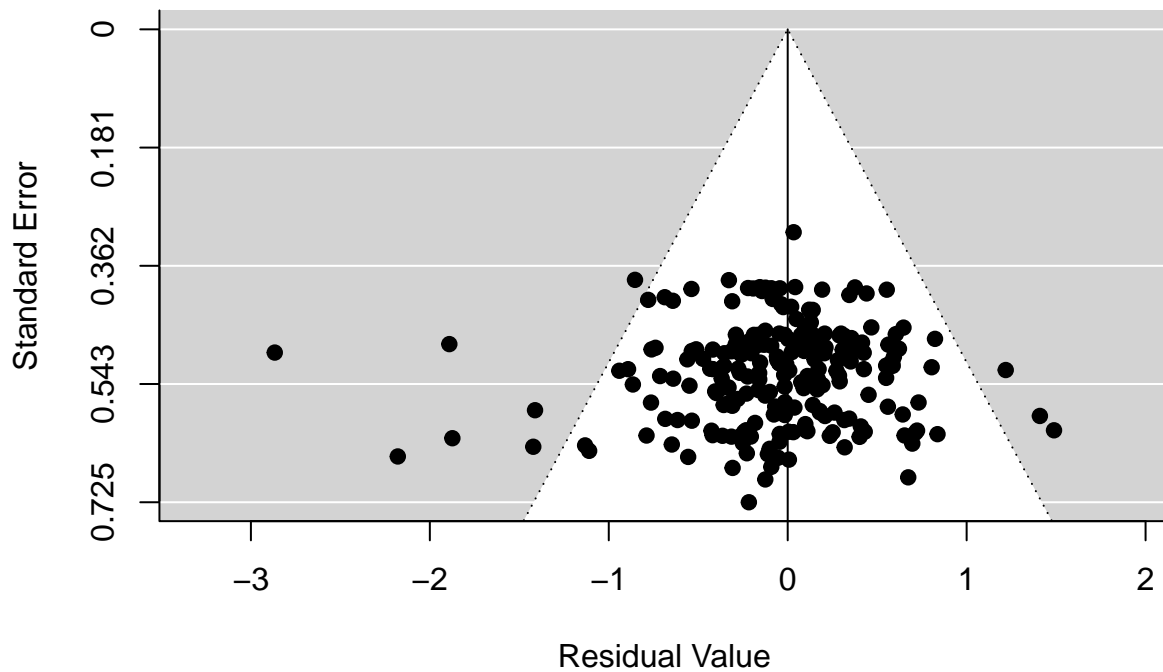


```
All_Traits_Analysis_lnCVR_OF_sex <- rma.mv(yi, vi, mods = ~Sex-1, random = list(~1|Trait, ~1|Paper_ID, ~1|Cohort_ID, ~1|ES_ID))
summary(All_Traits_Analysis_lnCVR_OF_sex)
```

```
##
## Multivariate Meta-Analysis Model (k = 223; method: REML)
##
##      logLik   Deviance      AIC      BIC      AICc
## -160.0393   320.0785   334.0785   357.8339   334.6068
##
## Variance Components:
##
##      estim      sqrt  nlvls  fixed      factor
## sigma^2.1  0.0217  0.1472     8     no      Trait
## sigma^2.2  0.0328  0.1811    16     no    Paper_ID
## sigma^2.3  0.0020  0.0443    52     no   Cohort_ID
## sigma^2.4  0.0785  0.2802   223     no      ES_ID
##
## Test for Residual Heterogeneity:
## QE(df = 220) = 463.6009, p-val < .0001
##
## Test of Moderators (coefficient(s) 1:3):
## QM(df = 3) = 0.8681, p-val = 0.8331
##
## Model Results:
##
##      estimate      se      zval      pval      ci.lb      ci.ub
## SexBoth      -0.3737  0.4100  -0.9115  0.3620  -1.1772  0.4298
## SexFemale     -0.0034  0.0942  -0.0359  0.9714  -0.1879  0.1812
## SexMale       0.0073  0.0926   0.0793  0.9368  -0.1742  0.1889
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
funnel(All_Traits_Analysis_lnCVR_OF_sex)
```





```
Overall_Exp_mods_lnCVR <- tibble(
  Exposure_Type = c("Multigenerational", "Multigenerational", "One off", "One off", "One off", "Multigen",
  mod = c("F0 Female", "F0 Male", "F0 Both", "F0 Female", "F0 Male", "Both Offspring Sex", "Female Offspring",
  lnCVR = c(-0.1175, -0.1728, -0.0418, -0.0011, -0.0329, -0.0204, -0.0522, -0.2292, -0.3737, -0.0034, 0.0073),
  ci.lb = c(-0.3294, -0.4247, -0.5383, -0.1806, -0.2872, -0.3612, -0.2875, -0.4567, -1.1772, -0.1879, -0.1742),
  ci.ub = c(0.0944, 0.0791, 0.4547, 0.1784, 0.2215, 0.3205, 0.1832, -0.0017, 0.4298, 0.1812, 0.1889)
)

plot_lnCVR_overall_mods_exp <- ggplot(Overall_Exp_mods_lnCVR, aes(x=mod, y=lnCVR, colour=Exposure_Type)) +
  geom_errorbar(aes(ymin=ci.lb, ymax=ci.ub), width = 0, position = position_dodge(0.3)) +
  geom_point(aes(x = mod, y = lnCVR), position = position_dodge(0.3)) +
  geom_hline(yintercept = 0, lty = "dotted") +
  labs(x = "mod", y = "lnCVR") +
  coord_flip()

plot_lnCVR_overall_mods_exp
```

