

Overall Results

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Meta-analysis overall results (lnRR)

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

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.

Overall Meta-analysis

Meta-analysis (Complete dataset)

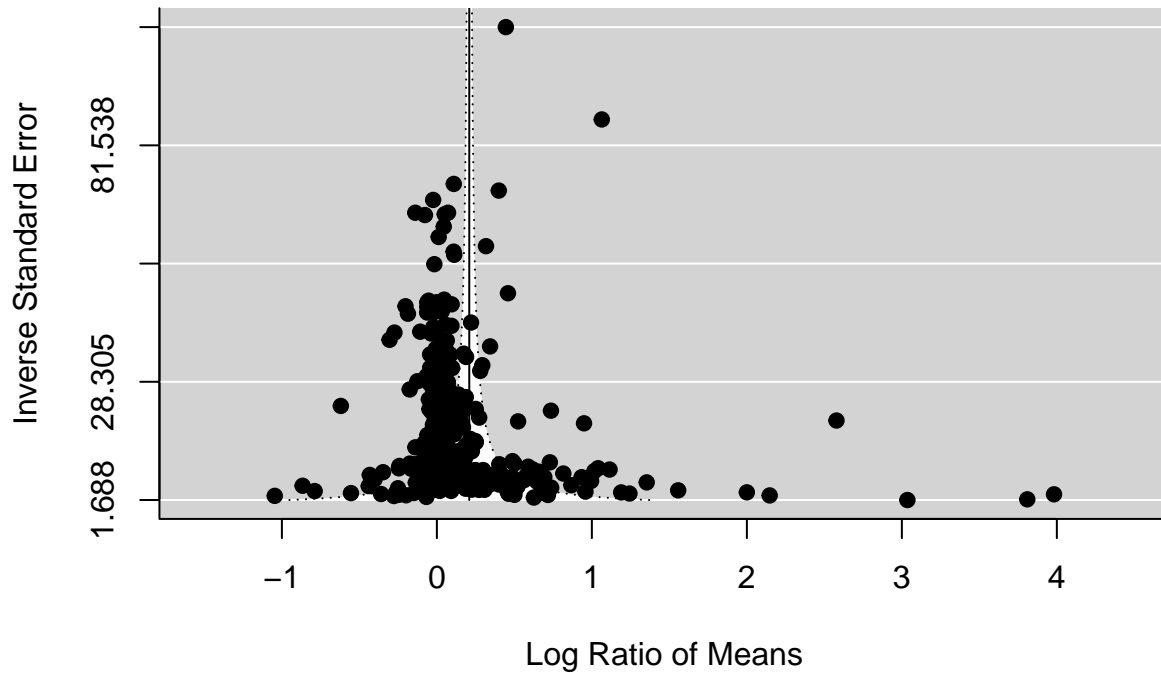
Data is not split, and there are no moderators

#ALL DATA

```
All_Traits_Analysis_0mods <- rma.mv(yi, vi, random = list(~1|Trait, ~1|Paper_ID, ~1|Cohort_ID, ~1|ES_ID),
summary(All_Traits_Analysis_0mods)
```

```
##
## Multivariate Meta-Analysis Model (k = 341; method: REML)
##
##   logLik  Deviance      AIC      BIC      AICc
## -73.0060  146.0120  156.0120  175.1567  156.1916
##
## Variance Components:
##
##           estim      sqrt  nlvls  fixed      factor
## sigma^2.1  0.0122  0.1105     8     no      Trait
## sigma^2.2  0.0890  0.2984    25     no    Paper_ID
## sigma^2.3  0.0092  0.0962    75     no    Cohort_ID
## sigma^2.4  0.0360  0.1897   341     no      ES_ID
##
## Test for Heterogeneity:
## Q(df = 340) = 16309.1328, p-val < .0001
##
## Model Results:
##
## estimate      se      zval      pval      ci.lb      ci.ub      **
##   0.2090  0.0758  2.7563  0.0058  0.0604  0.3576  **
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
funnel(All_Traits_Analysis_Omods,yaxis="seinv")
```



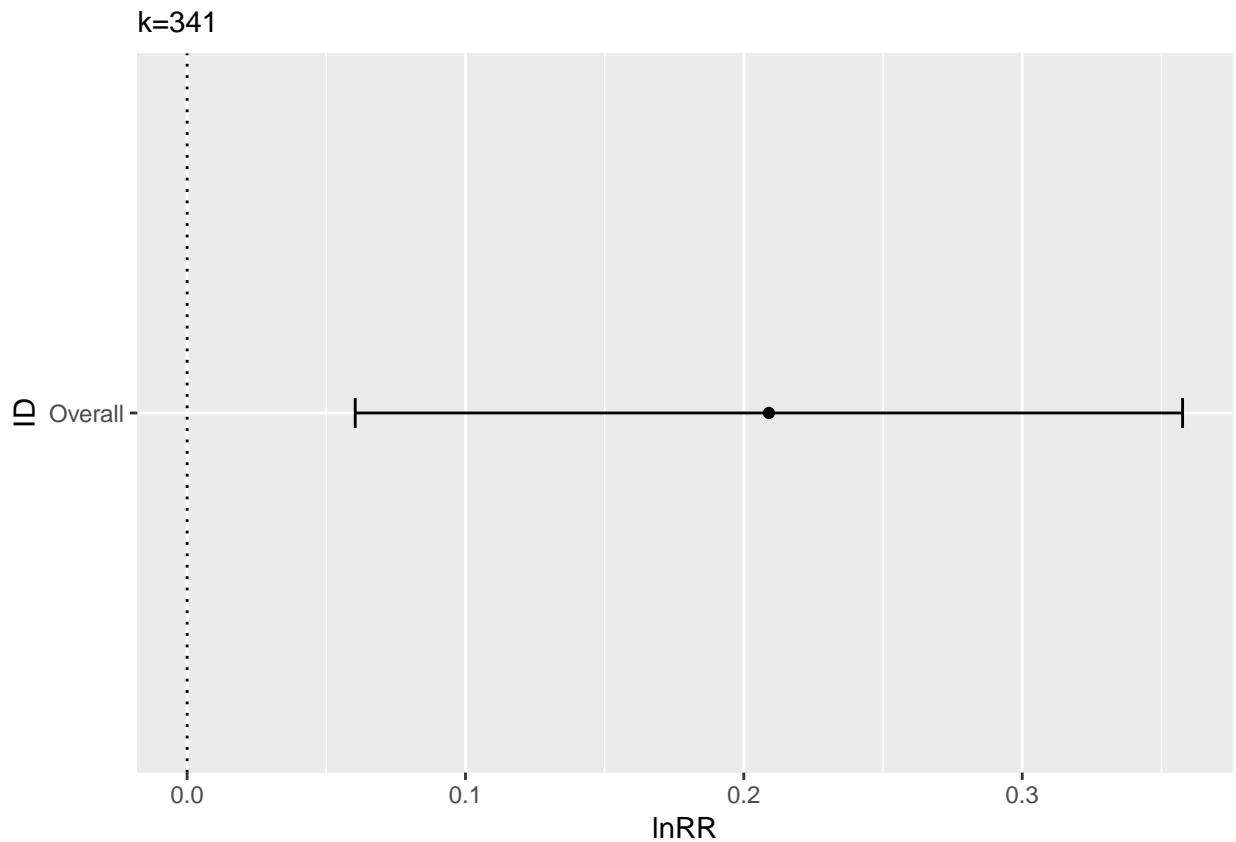
```
W <- diag(1/Effect_Size_All_Traits$vi)
X <- model.matrix(All_Traits_Analysis_Omods)
P <- W - W %*% X %*% solve(t(X) %*% W %*% X) %*% t(X) %*% W
I2_overall <- 100 * sum(All_Traits_Analysis_Omods$sigma2) / (sum(All_Traits_Analysis_Omods$sigma2) + (A
I2_overall
```

```
## [1] 98.80247
```

```
Overall_effect_size <- tibble(
  ID = "Overall",
  lnRR = c(All_Traits_Analysis_Omods$b[1]),
  ci.lb = c(All_Traits_Analysis_Omods$ci.lb),
  ci.ub = c(All_Traits_Analysis_Omods$ci.ub),
  k = 241
)
```

```
## Warning: `list_len()` is deprecated as of rlang 0.2.0.
## Please use `new_list()` instead.
## This warning is displayed once per session.
```

```
plot_lnRR_overall <- ggplot(Overall_effect_size, aes(x=ID, y=lnRR)) +
  geom_errorbar(aes(ymin=ci.lb, ymax=ci.ub), width = 0.05, 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", subtitle = "k=341") +
  coord_flip()
plot_lnRR_overall
```



Overall Meta-regression for Traits and Exposure Type

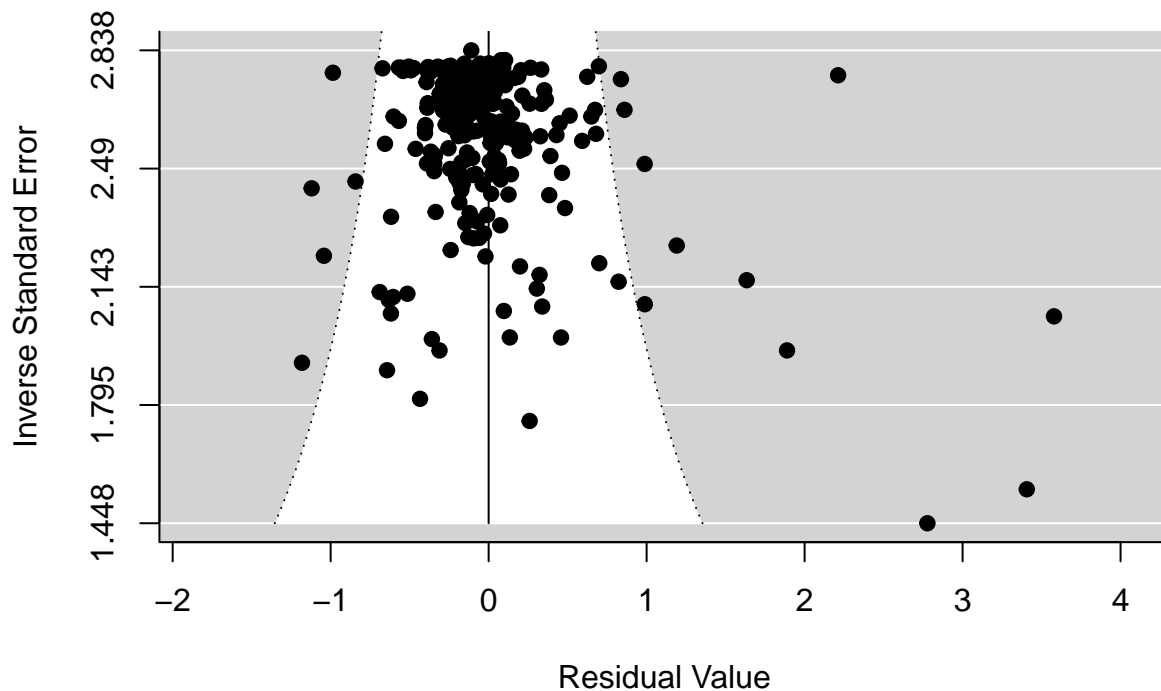
I ran univariate meta-regression, first using trait as a moderator, and then exposure type as a moderator.

```
#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
## -65.9365  131.8730  153.8730  195.7626  154.6954
##
## Variance Components:
##
##           estim      sqrt  nlvls  fixed      factor
```

```
## sigma^2.1 0.0875 0.2957 25 no Paper_ID
## sigma^2.2 0.0094 0.0971 75 no Cohort_ID
## sigma^2.3 0.0364 0.1908 341 no ES_ID
##
## Test for Residual Heterogeneity:
## QE(df = 333) = 15301.8255, p-val < .0001
##
## Test of Moderators (coefficient(s) 1:8):
## QM(df = 8) = 65.8081, p-val < .0001
##
## Model Results:
##
##               estimate      se    zval    pval    ci.lb    ci.ub
## TraitAdiposity      0.3662 0.0712  5.1452 <.0001  0.2267  0.5057 ***
## TraitBody_Weight     0.1119 0.0644  1.7384 0.0821 -0.0143  0.2381 .
## TraitGlucose_FBG     0.0388 0.0908  0.4271 0.6693 -0.1392  0.2167
## TraitGlucose_TT      0.1429 0.0760  1.8804 0.0601 -0.0060  0.2918 .
## TraitInsulin_FI      0.2585 0.0848  3.0494 0.0023  0.0923  0.4246 **
## TraitInsulin_TT      0.1354 0.0859  1.5766 0.1149 -0.0329  0.3038
## TraitLeptin          0.4030 0.1005  4.0098 <.0001  0.2060  0.5999 ***
## TraitTriglycerides   0.2541 0.0773  3.2853 0.0010  0.1025  0.4057 **
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
funnel(All_Traits_Analysis_traits,yaxis="seinv")
```



```
W <- diag(1/Effect_Size_All_Traits$vi)
X <- model.matrix(All_Traits_Analysis_traits)
P <- W - W %*% X %*% solve(t(X) %*% W %*% X) %*% t(X) %*% W
I2_Overall_Traits <- 100 * sum(All_Traits_Analysis_traits$sigma2) / (sum(All_Traits_Analysis_traits$sig
```

```
## [1] 98.67377
```

```
#Will not go into figure as of yet, just as a reference for how many effect sizes we see
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.
```

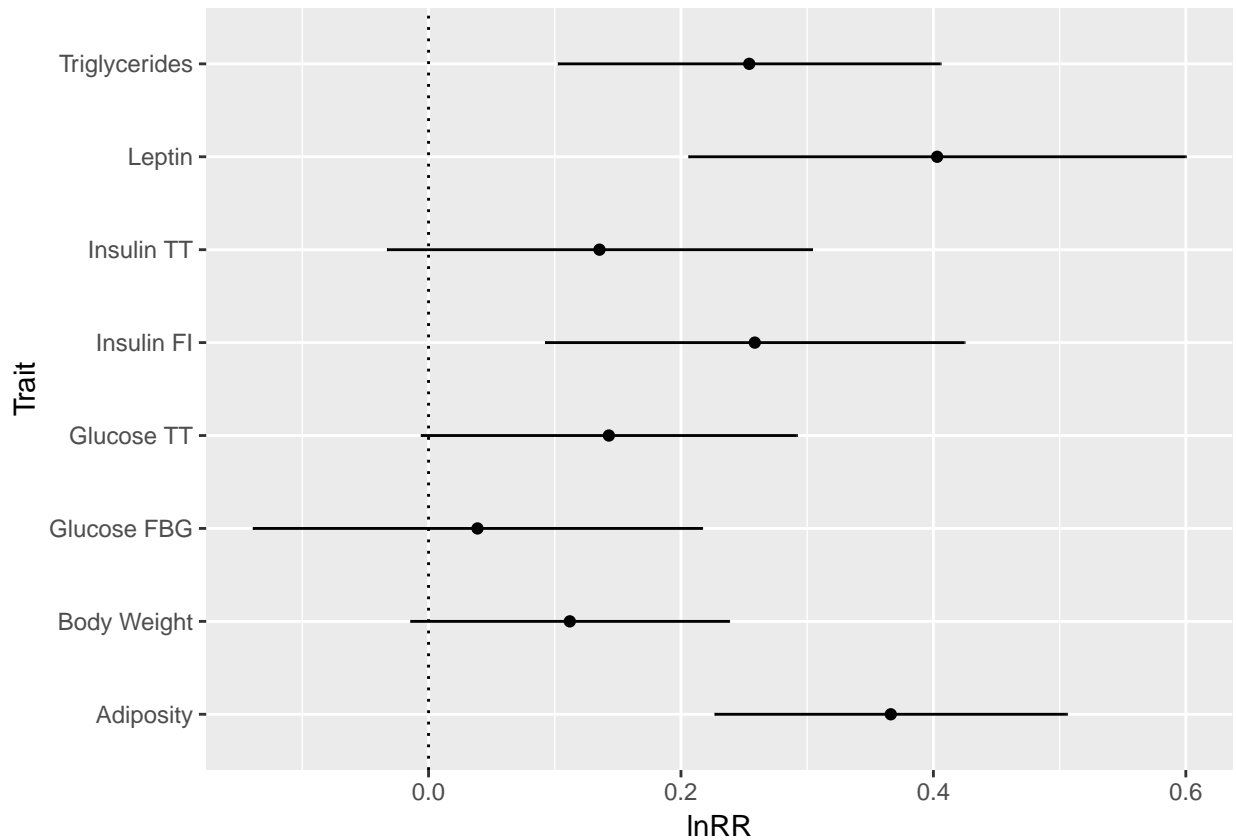
```
k_traits
```

```
## # 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(All_Traits_Analysis_traits$b[1], All_Traits_Analysis_traits$b[2], All_Traits_Analysis_traits$b[3],
  ci.lb = c(All_Traits_Analysis_traits$ci.lb[1], All_Traits_Analysis_traits$ci.lb[2], All_Traits_Analysis_traits$ci.lb[3],
  ci.ub = c(All_Traits_Analysis_traits$ci.ub[1], All_Traits_Analysis_traits$ci.ub[2], All_Traits_Analysis_traits$ci.ub[3],
  k = c(k_traits$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])
)
Traits_overall_lnRR
```

```
## # A tibble: 8 x 5
##   Trait      lnRR    ci.lb ci.ub    k
##   <chr>    <dbl>    <dbl> <dbl> <int>
## 1 Adiposity  0.366    0.227  0.506    65
## 2 Body Weight 0.112   -0.0143  0.238   146
## 3 Glucose FBG 0.0388  -0.139   0.217    12
## 4 Glucose TT  0.143   -0.00605 0.292    28
## 5 Insulin FI  0.258    0.0923  0.425    26
## 6 Insulin TT  0.135   -0.0329  0.304    19
## 7 Leptin     0.403    0.206   0.600    12
## 8 Triglycerides 0.254    0.102   0.406    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
```

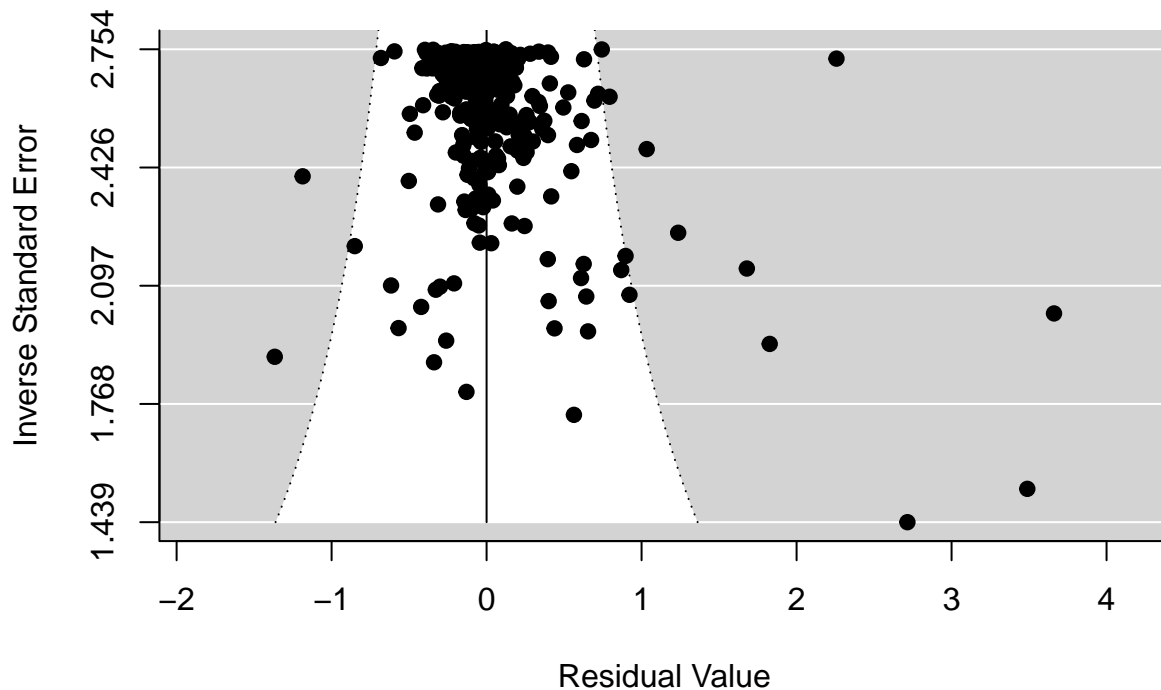


```
#Exposure type meta-regression
All_Traits_Analysis_Exp <- rma.mv(yi, vi, mods= ~Exposure_Type-1, random = list(~1|Paper_ID,~1|Cohort_ID))
summary(All_Traits_Analysis_Exp)
```

```
##
## Multivariate Meta-Analysis Model (k = 341; method: REML)
##
##   logLik  Deviance      AIC      BIC      AICc
## -82.6460  165.2920  175.2920  194.4221  175.4722
##
## Variance Components:
##
##      estim  sqrt  nlvls  fixed  factor
## sigma^2.1 0.0892 0.2987   25    no  Paper_ID
## sigma^2.2 0.0035 0.0590   75    no  Cohort_ID
## sigma^2.3 0.0441 0.2100  341    no    ES_ID
```

```
##
## Test for Residual Heterogeneity:
## QE(df = 339) = 13713.1650, p-val < .0001
##
## Test of Moderators (coefficient(s) 1:2):
## QM(df = 2) = 28.6740, p-val < .0001
##
## Model Results:
##
##               estimate      se   zval   pval   ci.lb
## Exposure_TypeMultigenerational    0.3207  0.0712  4.5067 <.0001  0.1812
## Exposure_TypeOne off              0.0621  0.0674  0.9205  0.3573 -0.0701
##               ci.ub
## Exposure_TypeMultigenerational 0.4602 ***
## Exposure_TypeOne off          0.1942
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
funnel(All_Traits_Analysis_Exp,yaxis="seinv")
```



```
W <- diag(1/Effect_Size_All_Traits$vi)
X <- model.matrix(All_Traits_Analysis_Exp)
P <- W - W %*% X %*% solve(t(X) %*% W %*% X) %*% t(X) %*% W
I2_Overall_Exposure <- 100 * sum(All_Traits_Analysis_Exp$sigma2) / (sum(All_Traits_Analysis_Exp$sigma2))
I2_Overall_Exposure
```

```
## [1] 98.69925
```

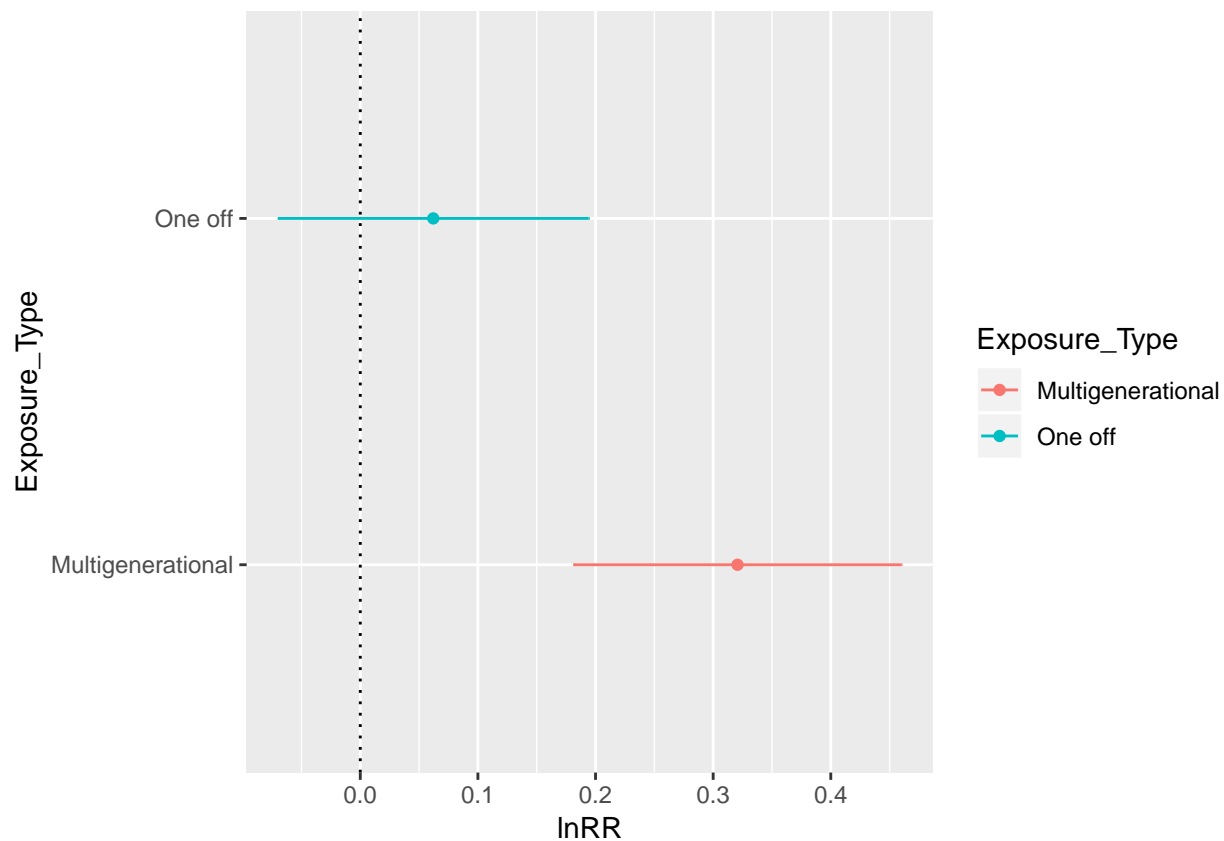
```
k_exp <- Effect_Size_All_Traits %>% group_by(Exposure_Type) %>% count()
k_exp
```

```
## # 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(All_Traits_Analysis_Exp$b[1], All_Traits_Analysis_Exp$b[2]),
  ci.lb = c(All_Traits_Analysis_Exp$ci.lb[1], All_Traits_Analysis_Exp$ci.lb[2]),
  ci.ub = c(All_Traits_Analysis_Exp$ci.ub[1], All_Traits_Analysis_Exp$ci.ub[2]),
  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 0.321   0.181  0.460   118
## 2 One off          0.0621 -0.0701 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

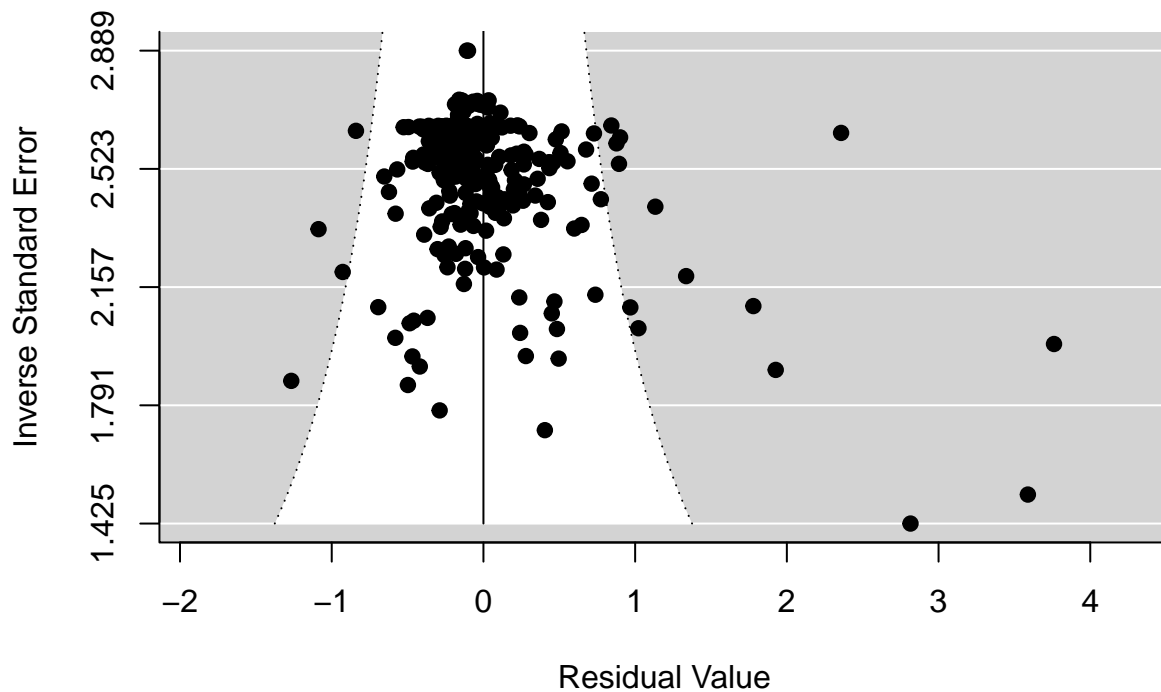
Univariate analysis

```
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
## -72.0231  144.0463  158.0463  184.8076  158.3857
##
## Variance Components:
##
##           estim      sqrt  nlvls  fixed    factor
## sigma^2.1  0.0122  0.1103     8     no     Trait
## sigma^2.2  0.0900  0.3000    25     no   Paper_ID
## sigma^2.3  0.0094  0.0969    75     no Cohort_ID
## sigma^2.4  0.0361  0.1899   341     no     ES_ID
##
## Test for Residual Heterogeneity:
## QE(df = 338) = 16239.8146, p-val < .0001
```

```
##
## Test of Moderators (coefficient(s) 1:3):
## QM(df = 3) = 8.6664, p-val = 0.0341
##
## Model Results:
##
##               estimate      se    zval    pval    ci.lb    ci.ub
## F0_Parent_ExposedBoth    0.2713  0.1728  1.5701  0.1164  -0.0674  0.6100
## F0_Parent_ExposedFemale    0.2207  0.0781  2.8260  0.0047   0.0676  0.3737
## F0_Parent_ExposedMale    0.1391  0.1215  1.1454  0.2520  -0.0989  0.3772
##
## F0_Parent_ExposedBoth
## F0_Parent_ExposedFemale **
## F0_Parent_ExposedMale
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
funnel(All_Data_Analysis_f0,yaxis="seinv")
```



```
W <- diag(1/Effect_Size_All_Traits$vi)
X <- model.matrix(All_Data_Analysis_f0)
P <- W - W %*% X %*% solve(t(X) %*% W %*% X) %*% t(X) %*% W
I2_Overall_F0 <- 100 * sum(All_Data_Analysis_f0$sigma2) / (sum(All_Data_Analysis_f0$sigma2) + (All_Data_Analysis_f0$N - 1) * sum(All_Data_Analysis_f0$vi))
I2_Overall_F0
```

```
## [1] 98.81046
```

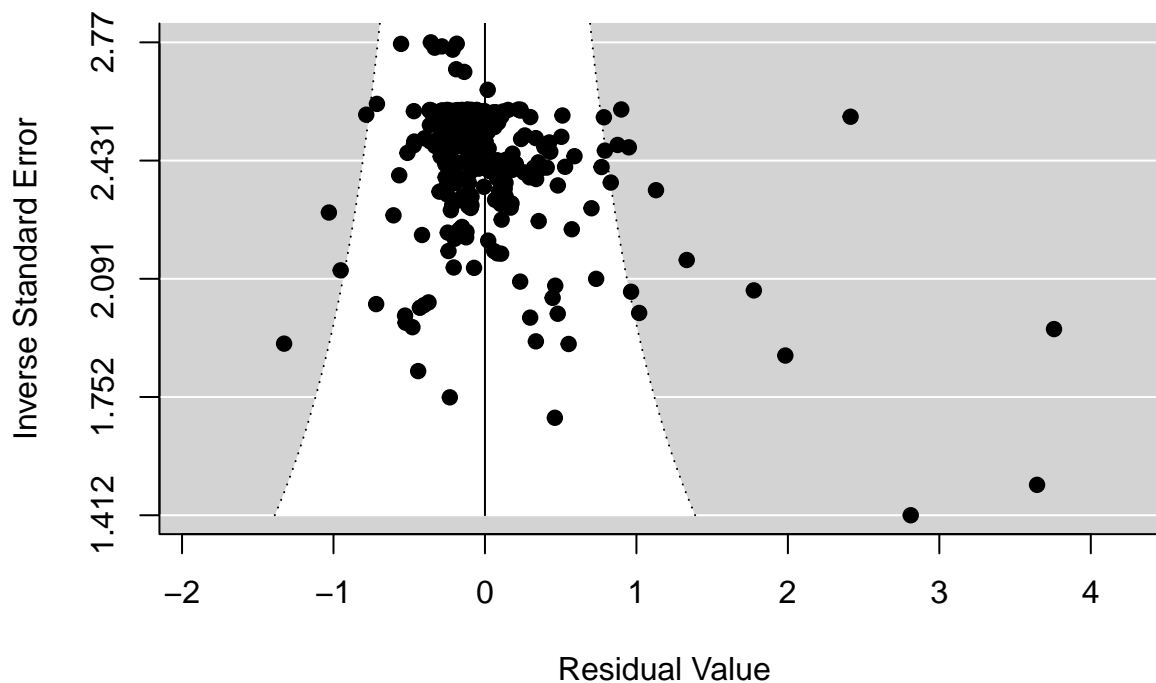
```
k_All_Data_Analysis_f0 <- Effect_Size_All_Traits %>% group_by(F0_Parent_Exposed) %>% count()
k_All_Data_Analysis_f0
```

```
## # 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
## -71.2312 142.4623 156.4623 183.2237 156.8017
##
## Variance Components:
##
##           estim      sqrt  nlvls  fixed      factor
## sigma^2.1  0.0117  0.1083     8     no      Trait
## sigma^2.2  0.1009  0.3177    25     no    Paper_ID
## sigma^2.3  0.0091  0.0955    75     no    Cohort_ID
## sigma^2.4  0.0357  0.1889   341     no      ES_ID
##
## Test for Residual Heterogeneity:
## QE(df = 338) = 15914.2219, p-val < .0001
##
## Test of Moderators (coefficient(s) 1:3):
## QM(df = 3) = 10.2411, p-val = 0.0166
##
## Model Results:
##
##           estimate      se    zval    pval    ci.lb    ci.ub
## SexBoth      0.2802  0.1655  1.6932  0.0904  -0.0441  0.6045
## SexFemale    0.1642  0.0841  1.9521  0.0509  -0.0007  0.3290
## SexMale      0.2246  0.0837  2.6832  0.0073   0.0605  0.3886 **
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
funnel(All_Data_Analysis_sex, yaxis="seinv")
```



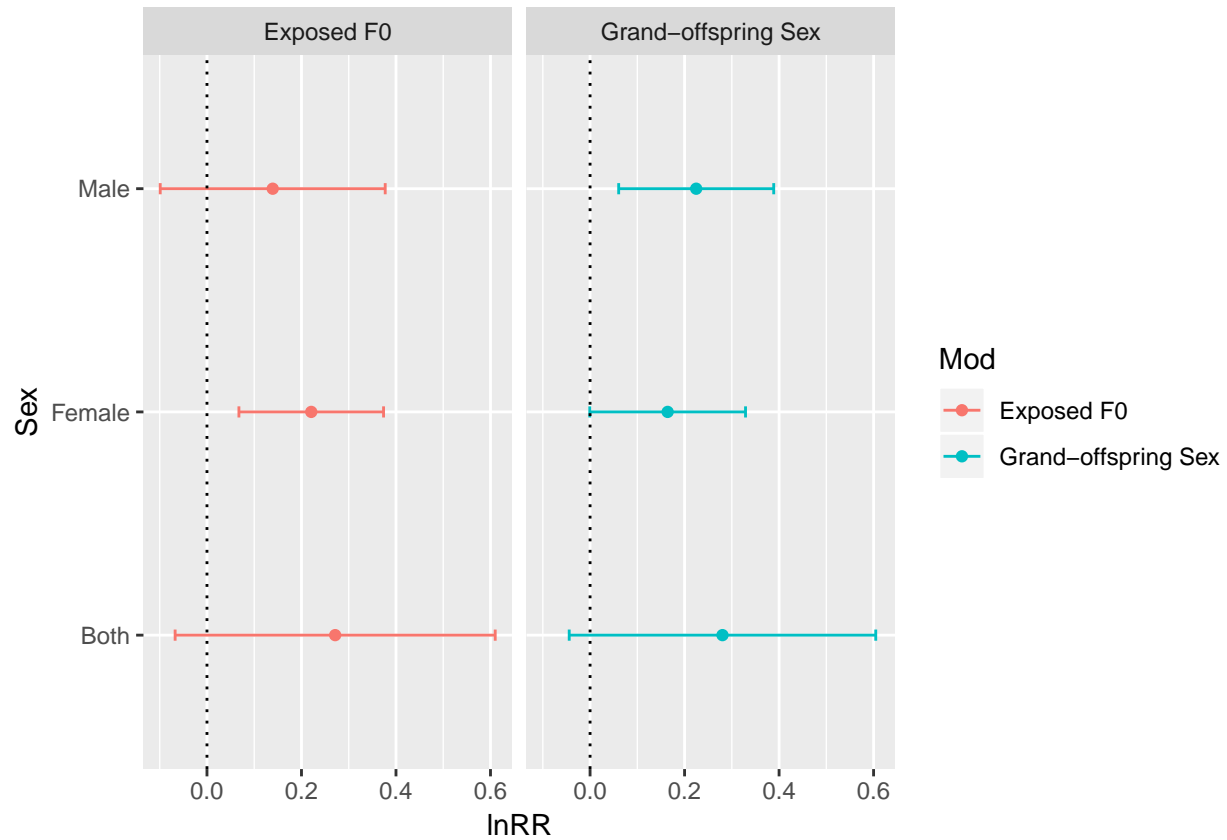
```
W <- diag(1/Effect_Size_All_Traits$vi)
X <- model.matrix(All_Data_Analysis_sex)
P <- W - W %*% X %*% solve(t(X) %*% W %*% X) %*% t(X) %*% W
I2_Overall_sex <- 100 * sum(All_Data_Analysis_sex$sigma2) / (sum(All_Data_Analysis_sex$sigma2) + (All_D
I2_Overall_sex
```

```
## [1] 98.85967
```

```
Overall_effects_not_split_f0_sex <- tibble(
  Sex = c("Both", "Female", "Male", "Both", "Female", "Male"),
  Mod = c("Exposed F0", "Exposed F0", "Exposed F0", "Grand-offspring Sex", "Grand-offspring Sex", "Grand-
  lnRR = c(All_Data_Analysis_f0$b[1], All_Data_Analysis_f0$b[2], All_Data_Analysis_f0$b[3], All_Data_Analy
  ci.lb = c(All_Data_Analysis_f0$ci.lb[1], All_Data_Analysis_f0$ci.lb[2], All_Data_Analysis_f0$ci.lb[3], A
  ci.ub = c(All_Data_Analysis_f0$ci.ub[1], All_Data_Analysis_f0$ci.ub[2], All_Data_Analysis_f0$ci.ub[3], A
)
```

```
plot_lnRR_overall_mods_f0_sex <- ggplot(Overall_effects_not_split_f0_sex, aes(x=Sex, y=lnRR, colour = M
  geom_errorbar(aes(ymin=ci.lb, ymax=ci.ub), width = 0.05, position = position_dodge(0.3)) +
  geom_point(aes(x = Sex, y = lnRR), position = position_dodge(0.3)) +
  geom_hline(yintercept = 0, lty = "dotted") +
  labs(x = "Sex", y = "lnRR") +
  coord_flip() +
  facet_grid(~Mod)
```

```
plot_lnRR_overall_mods_f0_sex
```



```
## Overall meta-analysis subset by exposure type
```

```
#Overall analysis split by exposure type
```

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

```
summary(All_Data_Analysis_MG)
```

```
##
```

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

```
##
```

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

```
## -70.9751 141.9502 151.9502 165.7610 152.4907
```

```
##
```

```
## Variance Components:
```

```
##
```

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

```
## sigma^2.1 0.0858 0.2929    8    no   Trait
```

```
## sigma^2.2 0.1605 0.4006   13    no Paper_ID
```

```
## sigma^2.3 0.0000 0.0000   24    no Cohort_ID
```

```
## sigma^2.4 0.0770 0.2776  118    no    ES_ID
```

```
##
```

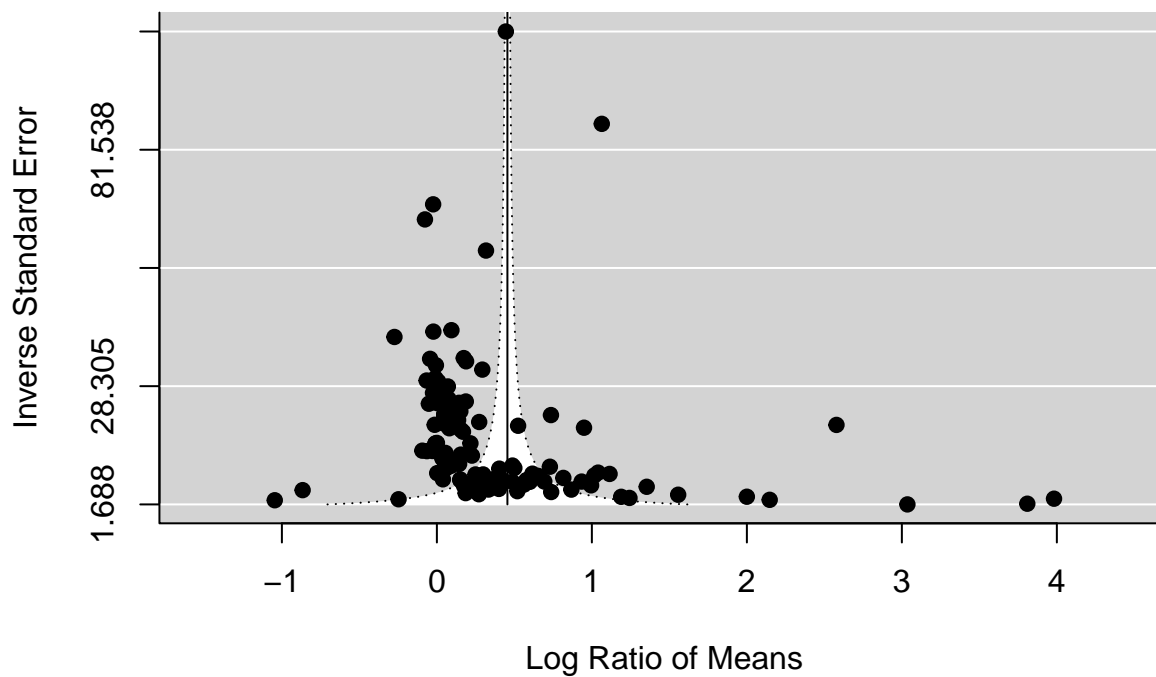
```
## Test for Heterogeneity:
```

```
## Q(df = 117) = 10974.0356, p-val < .0001
```

```
##
```

```
## Model Results:
##
## estimate      se      zval      pval      ci.lb      ci.ub
##    0.4551    0.1592    2.8586    0.0043    0.1431    0.7671    **
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
funnel(All_Data_Analysis_MG,yaxis="seinv")
```



```
W <- diag(1/MG_ALL$vi)
X <- model.matrix(All_Data_Analysis_MG)
P <- W - W %*% X %*% solve(t(X) %*% W %*% X) %*% t(X) %*% W
I2_Overall_MG <- 100 * sum(All_Data_Analysis_MG$sigma2) / (sum(All_Data_Analysis_MG$sigma2) + (All_Data_Analysis_MG$N - 1) * sum(P))
I2_Overall_MG
```

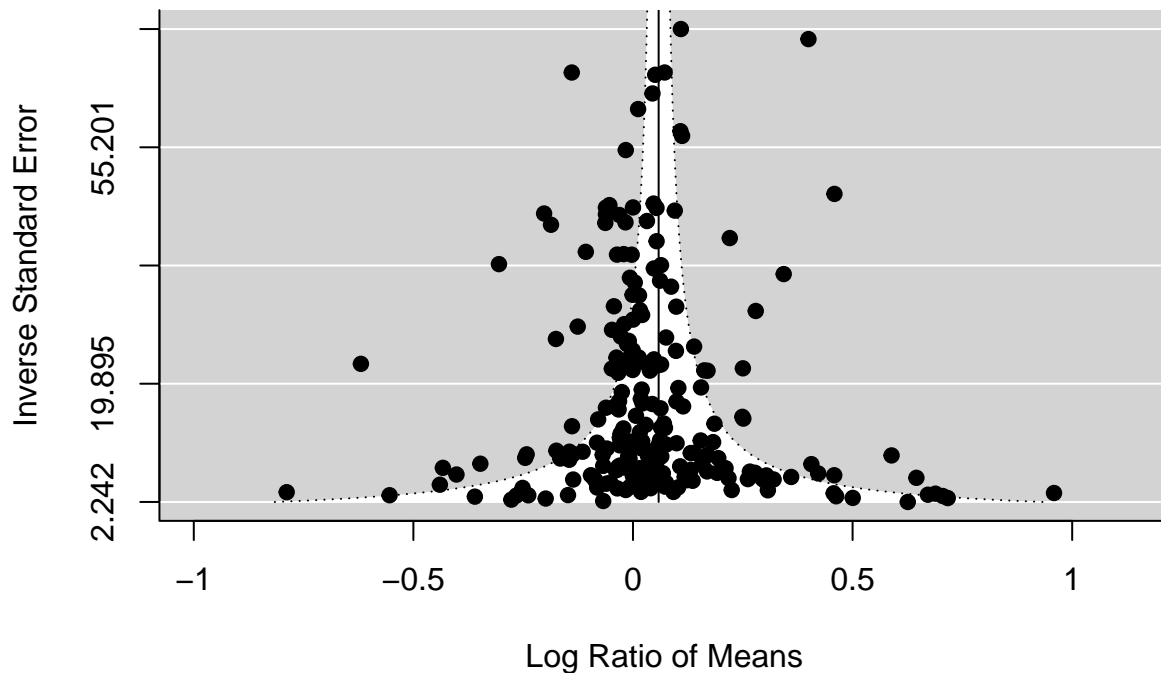
```
## [1] 99.41473
```

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

```
##
## Multivariate Meta-Analysis Model (k = 223; method: REML)
```

```
##
##      logLik   Deviance      AIC      BIC      AICc
##    87.8528  -175.7057  -165.7057  -148.6923  -165.4279
##
## Variance Components:
##
##      estim      sqrt  nlvls  fixed      factor
## sigma^2.1  0.0009  0.0298     8     no      Trait
## sigma^2.2  0.0033  0.0572    16     no    Paper_ID
## sigma^2.3  0.0039  0.0625    53     no   Cohort_ID
## sigma^2.4  0.0101  0.1004   223     no      ES_ID
##
## Test for Heterogeneity:
## Q(df = 222) = 2739.1294, p-val < .0001
##
## Model Results:
##
## estimate      se      zval      pval      ci.lb      ci.ub
##    0.0584  0.0250  2.3324  0.0197  0.0093  0.1075  *
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
funnel(All_Data_Analysis_OF,yaxis="seinv")
```



```

W <- diag(1/OF_ALL$vi)
X <- model.matrix(All_Data_Analysis_OF)
P <- W - W %*% X %*% solve(t(X) %*% W %*% X) %*% t(X) %*% W
I2_Overall_OF <- 100 * sum(All_Data_Analysis_OF$sigma2) / (sum(All_Data_Analysis_OF$sigma2) + (All_Data_Analysis_OF$ci.ub[1] - All_Data_Analysis_OF$ci.lb[1]))
I2_Overall_OF

```

```
## [1] 91.19124
```

```

Overall_Exp_lnRR <- tibble(
  Exposure_Type = c("Multigenerational", "One off"),
  lnRR = c(All_Data_Analysis_MG$b[1], All_Data_Analysis_OF$b[1]),
  ci.lb = c(All_Data_Analysis_MG$ci.lb[1], All_Data_Analysis_OF$ci.lb[1]),
  ci.ub = c(All_Data_Analysis_MG$ci.ub[1], All_Data_Analysis_OF$ci.ub[1]),
  k = c(118, 223)
)
Overall_Exp_lnRR

```

```

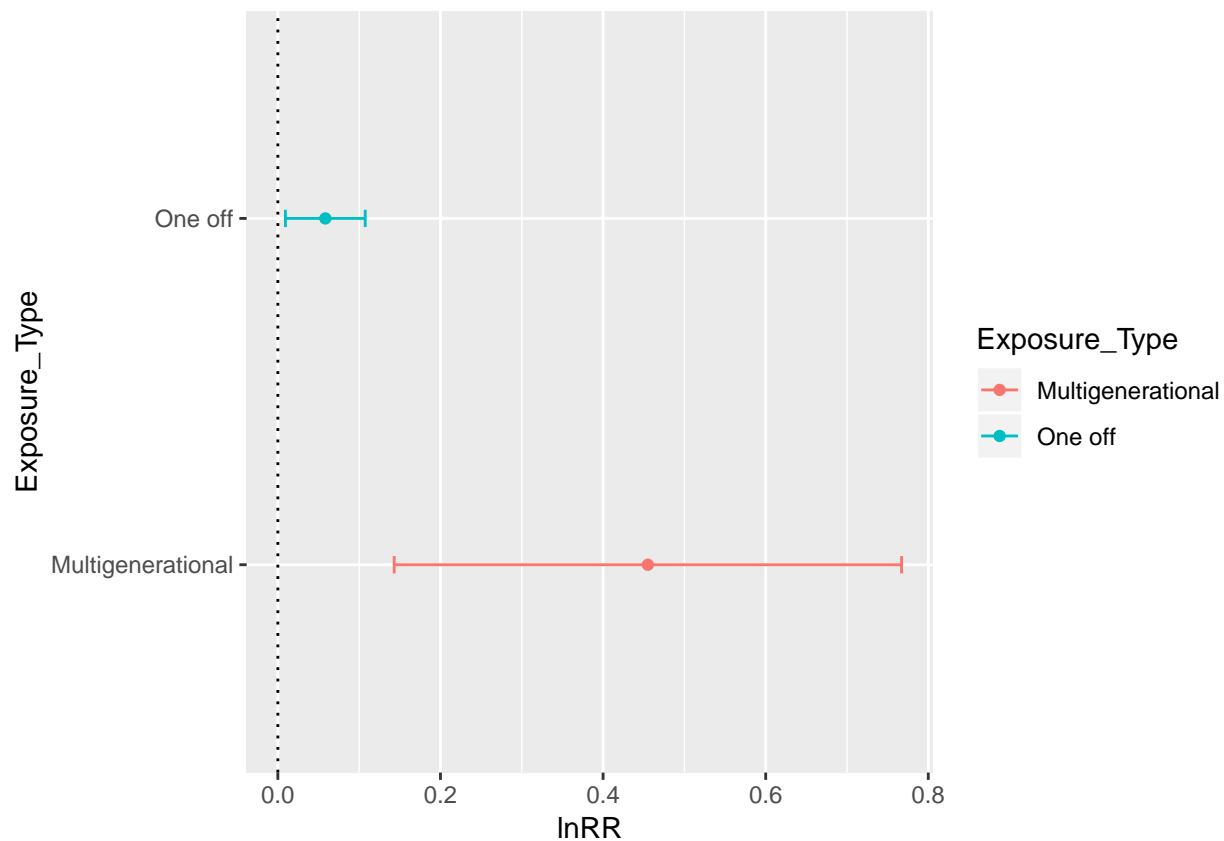
## # A tibble: 2 x 5
##   Exposure_Type      lnRR   ci.lb ci.ub    k
##   <chr>          <dbl>   <dbl> <dbl> <dbl>
## 1 Multigenerational 0.455  0.143  0.767  118
## 2 One off          0.0584 0.00932 0.107  223

```

```

plot_lnRR_overall_exp <- ggplot(Overall_Exp_lnRR, aes(x=Exposure_Type, y=lnRR, colour=Exposure_Type)) +
  geom_errorbar(aes(ymin=ci.lb, ymax=ci.ub), width = 0.05, 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_exp

```

Overall meta-analysis of traits (split by MG and OF datasets)

#Overall analysis with moderators (by exposure type)

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

```
summary(Traits_Analysis_MG)
```

##

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

##

	logLik	Deviance	AIC	BIC	AICc
##	-60.8735	121.7469	143.7469	173.4522	146.4408

##

Variance Components:

##

	estim	sqrt	nlvls	fixed	factor
## sigma^2.1	0.1549	0.3936	13	no	Paper_ID
## sigma^2.2	0.0000	0.0000	24	no	Cohort_ID
## sigma^2.3	0.0804	0.2836	118	no	ES_ID

##

Test for Residual Heterogeneity:

QE(df = 110) = 4000.4229, p-val < .0001

##

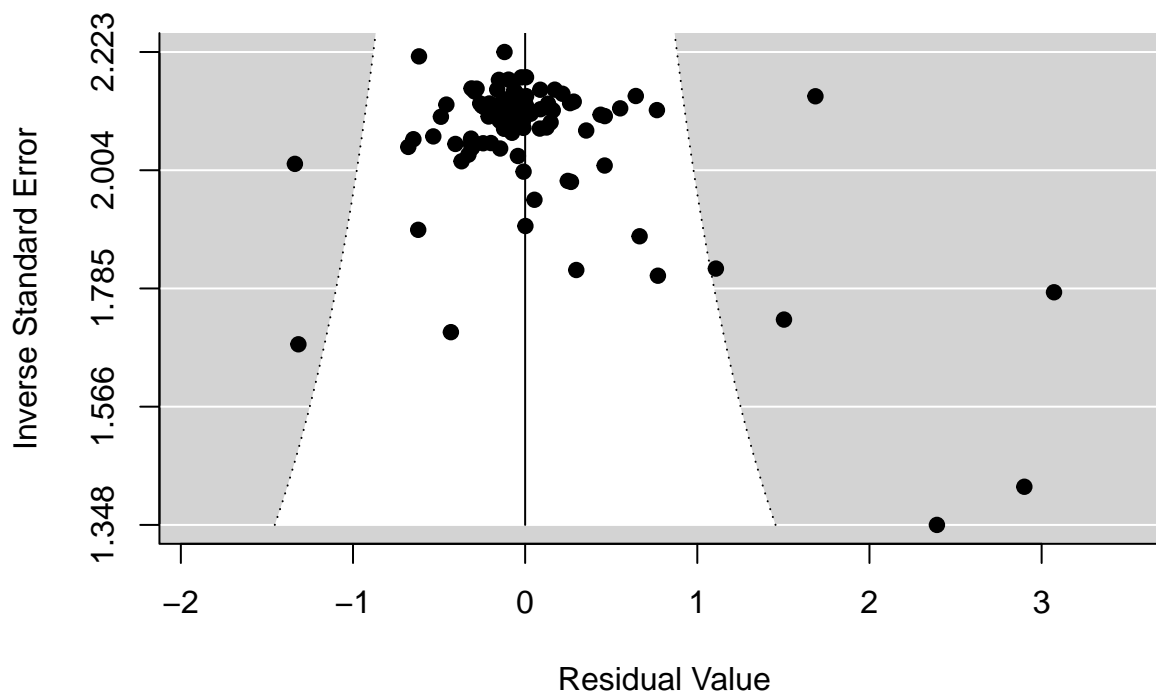
Test of Moderators (coefficient(s) 1:8):

QM(df = 8) = 82.1829, p-val < .0001

##

```
## Model Results:
##
##               estimate      se    zval    pval    ci.lb    ci.ub
## TraitAdiposity      0.8921  0.1405  6.3506 <.0001    0.6168  1.1674 ***
## TraitBody_Weight     0.1840  0.1208  1.5231  0.1277   -0.0528  0.4209
## TraitGlucose_FBG     0.1381  0.1606  0.8595  0.3900   -0.1767  0.4528
## TraitGlucose_TT      0.2176  0.1591  1.3671  0.1716   -0.0943  0.5295
## TraitInsulin_FI      0.6439  0.1886  3.4138  0.0006    0.2742  1.0136 ***
## TraitInsulin_TT      0.2712  0.1651  1.6428  0.1004   -0.0524  0.5948
## TraitLeptin          0.9097  0.1800  5.0528 <.0001    0.5568  1.2626 ***
## TraitTriglycerides   0.4714  0.1758  2.6808  0.0073    0.1268  0.8160 **
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
funnel(Traits_Analysis_MG,yaxis="seinv")
```



```
W <- diag(1/MG_ALL$vi)
X <- model.matrix(Traits_Analysis_MG)
P <- W - W %*% X %*% solve(t(X) %*% W %*% X) %*% t(X) %*% W
I2_Trait_MG <- 100 * sum(Traits_Analysis_MG$sigma2) / (sum(Traits_Analysis_MG$sigma2) + (Traits_Analysis_MG$sigma2))
I2_Trait_MG
```

```
## [1] 99.12503
```

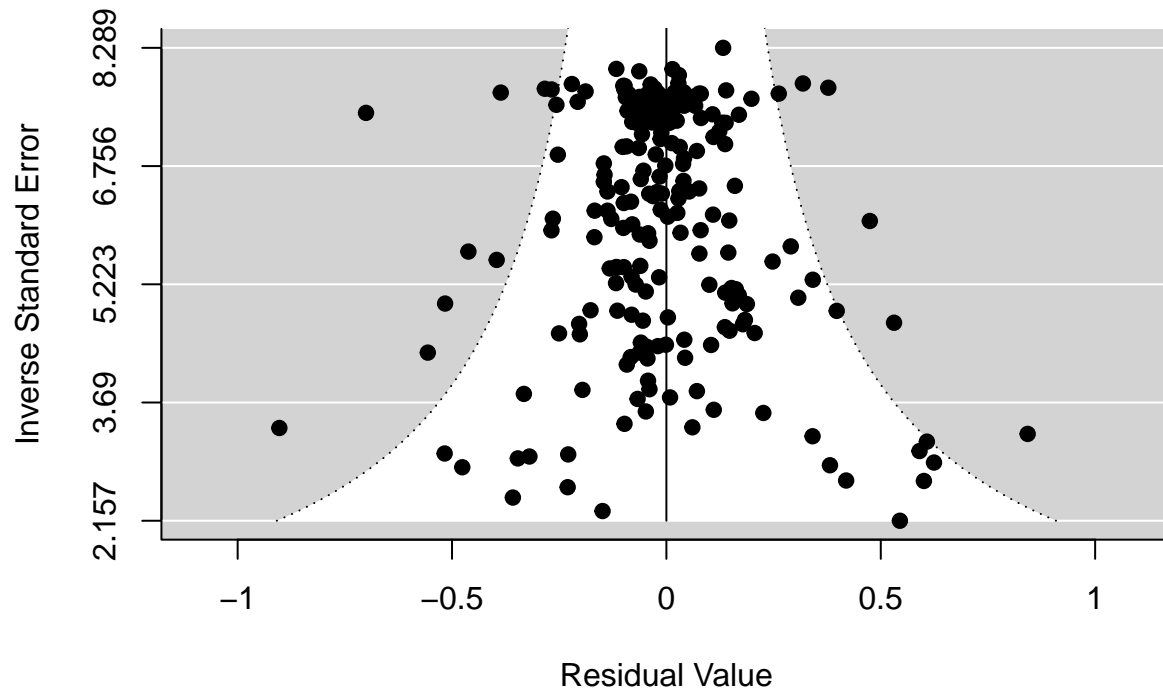
```
k_traits_MG <- MG_ALL %>% group_by(Trait) %>% count()
k_traits_MG
```

```
## # A tibble: 8 x 2
## # Groups:   Trait [8]
##   Trait      n
##   <fct>    <int>
## 1 Adiposity    19
## 2 Body_Weight   52
## 3 Glucose_FBG    8
## 4 Glucose_TT     9
## 5 Insulin_FI     7
## 6 Insulin_TT     9
## 7 Leptin        7
## 8 Triglycerides  7
```

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

```
##
## Multivariate Meta-Analysis Model (k = 223; method: REML)
##
##      logLik   Deviance      AIC      BIC      AICc
##    86.9899  -173.9797  -151.9797  -114.9027  -150.6793
##
## Variance Components:
##
##      estim      sqrt  nlvls  fixed      factor
## sigma^2.1  0.0031  0.0553    16     no  Paper_ID
## sigma^2.2  0.0038  0.0616    53     no  Cohort_ID
## sigma^2.3  0.0102  0.1011   223     no    ES_ID
##
## Test for Residual Heterogeneity:
## QE(df = 215) = 2681.8170, p-val < .0001
##
## Test of Moderators (coefficient(s) 1:8):
## QM(df = 8) = 18.2870, p-val = 0.0192
##
## Model Results:
##
##      estimate      se      zval      pval      ci.lb      ci.ub
## TraitAdiposity    0.0811  0.0307    2.6388  0.0083    0.0209    0.1413  **
## TraitBody_Weight   0.0315  0.0221    1.4286  0.1531   -0.0117    0.0748
## TraitGlucose_FBG   0.0850  0.0697    1.2192  0.2228   -0.0516    0.2216
## TraitGlucose_TT    0.0227  0.0375    0.6058  0.5446   -0.0507    0.0961
## TraitInsulin_FI    0.1160  0.0502    2.3125  0.0207    0.0177    0.2144  *
## TraitInsulin_TT   -0.0370  0.0555   -0.6679  0.5042   -0.1457    0.0716
## TraitLeptin        0.1168  0.0836    1.3971  0.1624   -0.0471    0.2806
## TraitTriglycerides  0.1143  0.0392    2.9172  0.0035    0.0375    0.1911  **
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
funnel(Traits_Analysis_OF,yaxis="seinv")
```



```
W <- diag(1/OF_ALL$vi)
X <- model.matrix(Traits_Analysis_OF)
P <- W - W %*% X %*% solve(t(X) %*% W %*% X) %*% t(X) %*% W
I2_Trait_OF <- 100 * sum(Traits_Analysis_OF$sigma2) / (sum(Traits_Analysis_OF$sigma2) + (Traits_Analysis_OF$seinv^2))
I2_Trait_OF
```

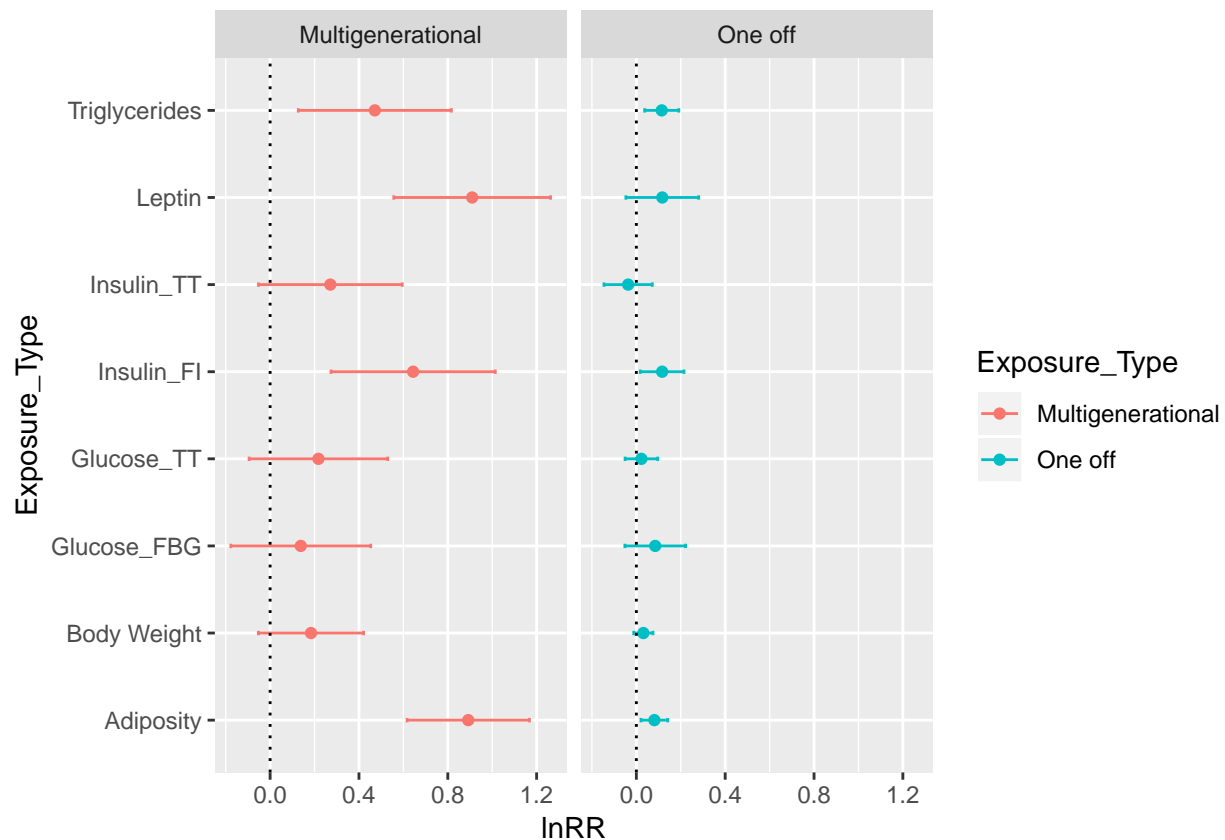
```
## [1] 90.66422
```

```
k_traits_OF <- OF_ALL %>% group_by(Trait) %>% count()
k_traits_OF
```

```
## # A tibble: 8 x 2
## # Groups:   Trait [8]
##   Trait      n
##   <fct>    <int>
## 1 Adiposity    46
## 2 Body_Weight   94
## 3 Glucose_FBG     4
## 4 Glucose_TT    19
## 5 Insulin_FI    19
## 6 Insulin_TT    10
## 7 Leptin         5
## 8 Triglycerides 26
```

```
Traits_analysis_Exp <- 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(Traits_Analysis_MG$b[1], Traits_Analysis_MG$b[2], Traits_Analysis_MG$b[3], Traits_Analysis_MG$b[4], Traits_Analysis_MG$b[5], Traits_Analysis_MG$b[6], Traits_Analysis_MG$b[7]),
  ci.lb = c(Traits_Analysis_MG$ci.lb[1], Traits_Analysis_MG$ci.lb[2], Traits_Analysis_MG$ci.lb[3], Traits_Analysis_MG$ci.lb[4], Traits_Analysis_MG$ci.lb[5], Traits_Analysis_MG$ci.lb[6], Traits_Analysis_MG$ci.lb[7]),
  ci.ub = c(Traits_Analysis_MG$ci.ub[1], Traits_Analysis_MG$ci.ub[2], Traits_Analysis_MG$ci.ub[3], Traits_Analysis_MG$ci.ub[4], Traits_Analysis_MG$ci.ub[5], Traits_Analysis_MG$ci.ub[6], Traits_Analysis_MG$ci.ub[7]),
  k = c(k_traits_MG$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 <- ggplot(Traits_analysis_Exp, aes(x=Trait, y=lnRR, colour=Exposure_Type)) +
  geom_errorbar(aes(ymin=ci.lb, ymax=ci.ub), width = 0.05, 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() +
  facet_grid(~Exposure_Type)
plot_lnRR_overall_trait_exp
```



Overall meta-analysis of moderators (split by MG and OF datasets)

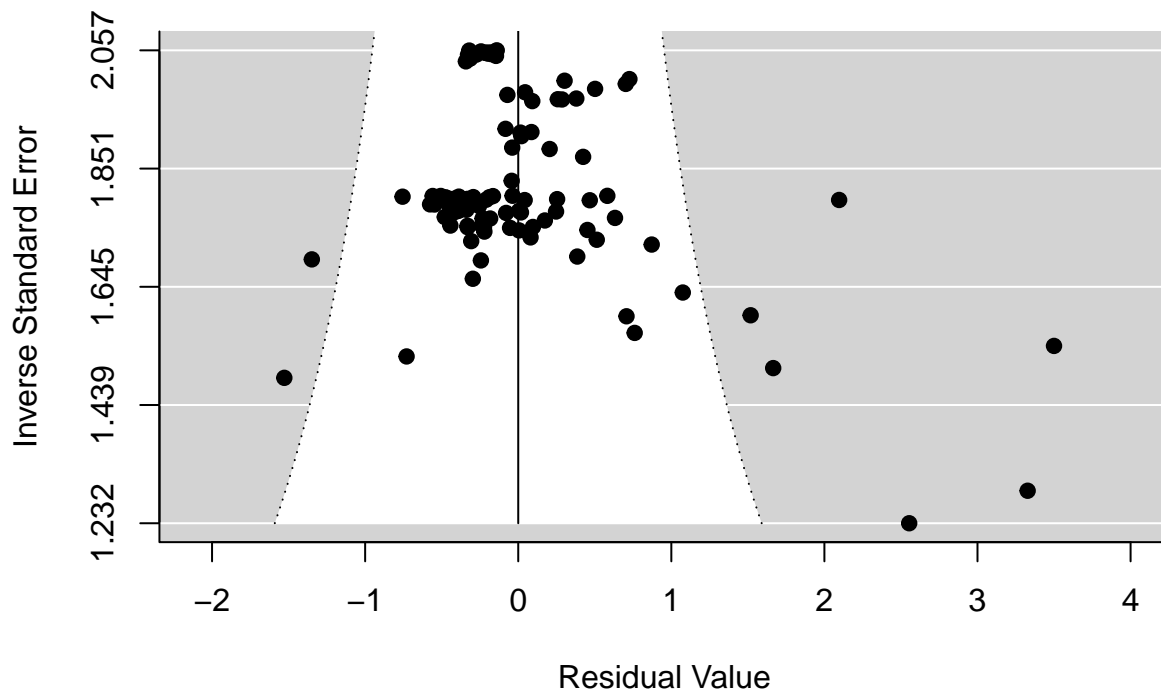
```
#F0 and offspring sex analysis
All Traits Analysis Omods MG f0 <- rma.mv(yi, vi, mods = ~F0 Parent Exposed-1, random = list(~1|Trait,
```

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

```
summary(All_Traits_Analysis_Omods_MG_f0)
```

```
##
## Multivariate Meta-Analysis Model (k = 118; method: REML)
##
##   logLik  Deviance      AIC      BIC      AICc
## -69.4667  138.9335  150.9335  167.4550  151.7041
##
## Variance Components:
##
##           estim      sqrt  nlvls  fixed      factor
## sigma^2.1  0.0859  0.2931     8     no      Trait
## sigma^2.2  0.1735  0.4166    13     no  Paper_ID
## sigma^2.3  0.0000  0.0000    24     no  Cohort_ID
## sigma^2.4  0.0774  0.2782   118     no     ES_ID
##
## Test for Residual Heterogeneity:
## QE(df = 116) = 10738.6028, p-val < .0001
##
## Test of Moderators (coefficient(s) 1:2):
## QM(df = 2) = 8.0690, p-val = 0.0177
##
## Model Results:
##
##              estimate      se    zval    pval    ci.lb    ci.ub
## F0_Parent_ExposedFemale    0.4819  0.1714  2.8111  0.0049   0.1459  0.8179
## F0_Parent_ExposedMale     0.3137  0.3182  0.9857  0.3243  -0.3100  0.9374
##
## F0_Parent_ExposedFemale **
## F0_Parent_ExposedMale
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
funnel(All_Traits_Analysis_Omods_MG_f0,yaxis="seinv")
```

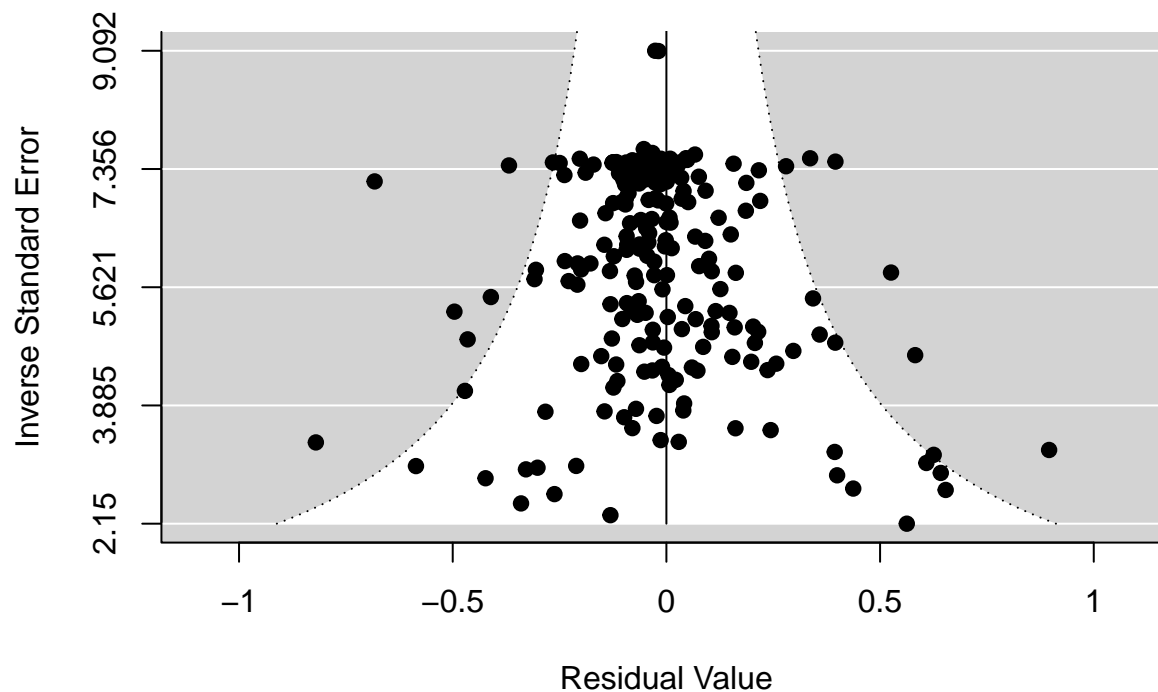


```
All_Traits_Analysis_0mods_OF_f0 <- rma.mv(yi, vi, mods = ~F0_Parent_Exposed-1, random = list(~1|Trait,
summary(All_Traits_Analysis_0mods_OF_f0)
```

```
##
## Multivariate Meta-Analysis Model (k = 223; method: REML)
##
##      logLik   Deviance      AIC      BIC      AICc
##    88.1433  -176.2866  -162.2866  -138.5312  -161.7583
##
## Variance Components:
##
##      estim      sqrt  nlvls  fixed    factor
## sigma^2.1  0.0009  0.0294     8    no      Trait
## sigma^2.2  0.0037  0.0609    16    no    Paper_ID
## sigma^2.3  0.0036  0.0603    53    no   Cohort_ID
## sigma^2.4  0.0101  0.1004   223    no      ES_ID
##
## Test for Residual Heterogeneity:
## QE(df = 220) = 2715.4930, p-val < .0001
##
## Test of Moderators (coefficient(s) 1:3):
## QM(df = 3) = 8.3408, p-val = 0.0395
##
## Model Results:
```

```
##
##               estimate      se    zval    pval    ci.lb    ci.ub
## F0_Parent_ExposedBoth    0.1884  0.0910  2.0701  0.0384    0.0100  0.3668
## F0_Parent_ExposedFemale    0.0632  0.0279  2.2675  0.0234    0.0086  0.1178
## F0_Parent_ExposedMale    0.0317  0.0430  0.7377  0.4607   -0.0526  0.1161
##
## F0_Parent_ExposedBoth      *
## F0_Parent_ExposedFemale    *
## F0_Parent_ExposedMale
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
funnel(All_Traits_Analysis_0mods_OF_f0,yaxis="seinv")
```



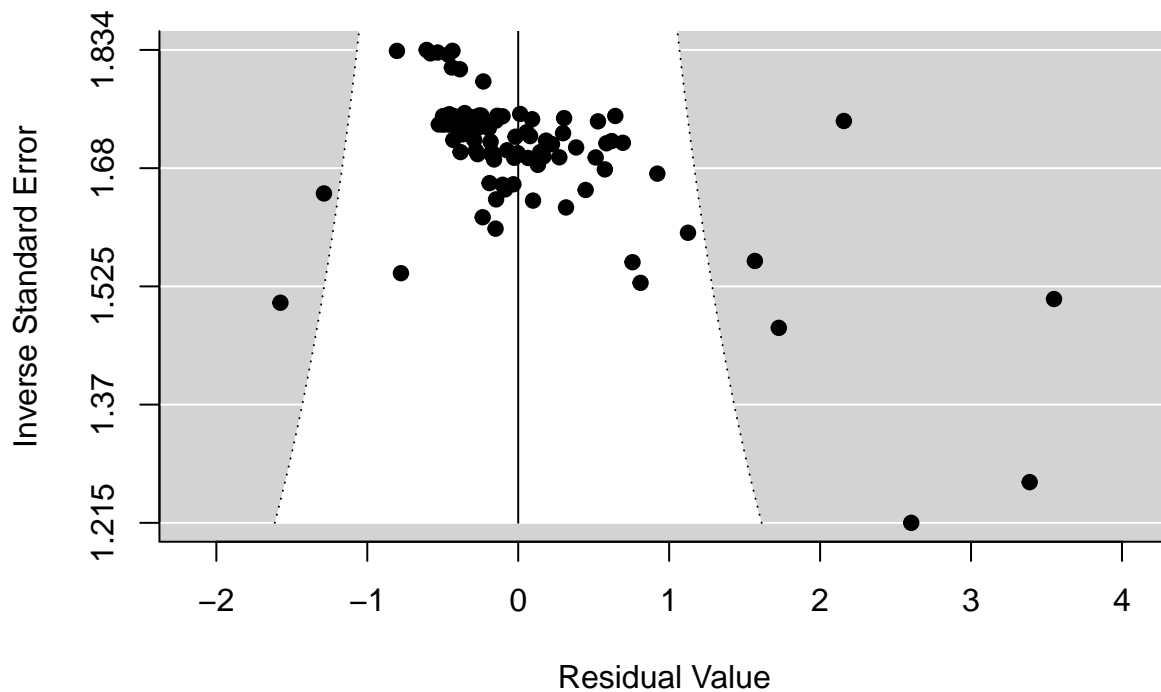
```
All_Traits_Analysis_0mods_MG_sex <- rma.mv(yi, vi, mods = ~Sex-1, random = list(~1|Trait, ~1|Paper_ID, ~1|Study))
summary(All_Traits_Analysis_0mods_MG_sex)
```

```
##
## Multivariate Meta-Analysis Model (k = 118; method: REML)
##
##   logLik  Deviance      AIC      BIC      AICc
## -70.3278  140.6556  154.6556  173.8701  155.7023
##
```



```
## Variance Components:
##
##      estim      sqrt  nlvls  fixed      factor
## sigma^2.1 0.0863  0.2938     8    no      Trait
## sigma^2.2 0.1961  0.4428    13    no    Paper_ID
## sigma^2.3 0.0000  0.0000    24    no   Cohort_ID
## sigma^2.4 0.0777  0.2787   118    no     ES_ID
##
## Test for Residual Heterogeneity:
## QE(df = 115) = 9001.0945, p-val < .0001
##
## Test of Moderators (coefficient(s) 1:3):
## QM(df = 3) = 7.4466, p-val = 0.0589
##
## Model Results:
##
##      estimate      se      zval      pval      ci.lb      ci.ub
## SexBoth      0.5296  0.2512  2.1082  0.0350  0.0372  1.0219 *
## SexFemale     0.4208  0.1813  2.3209  0.0203  0.0654  0.7762 *
## SexMale       0.4320  0.1839  2.3498  0.0188  0.0717  0.7923 *
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

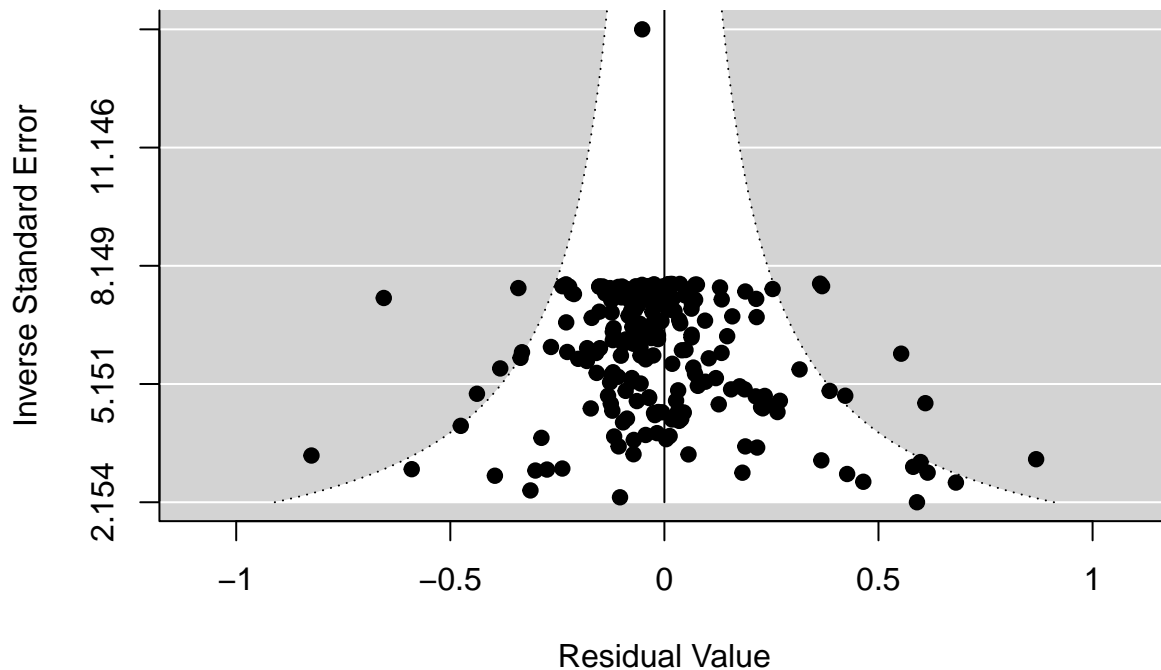
```
funnel(All_Traits_Analysis_0mods_MG_sex,yaxis="seinv")
```



```
All_Traits_Analysis_Omods_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_Omods_OF_sex)
```

```
##
## Multivariate Meta-Analysis Model (k = 223; method: REML)
##
##      logLik   Deviance      AIC      BIC      AICc
##    91.9105  -183.8211  -169.8211  -146.0657  -169.2928
##
## Variance Components:
##
##      estim      sqrt  nlvls  fixed      factor
## sigma^2.1  0.0006  0.0254     8     no      Trait
## sigma^2.2  0.0040  0.0632    16     no    Paper_ID
## sigma^2.3  0.0030  0.0547    53     no   Cohort_ID
## sigma^2.4  0.0099  0.0993   223     no      ES_ID
##
## Test for Residual Heterogeneity:
## QE(df = 220) = 2716.6868, p-val < .0001
##
## Test of Moderators (coefficient(s) 1:3):
## QM(df = 3) = 16.3914, p-val = 0.0009
##
## Model Results:
##
##      estimate      se      zval      pval      ci.lb      ci.ub
## SexBoth      -0.3810  0.1763  -2.1606  0.0307  -0.7266  -0.0354  *
## SexFemale      0.0358  0.0284   1.2611  0.2073  -0.0199   0.0915
## SexMale       0.0905  0.0275   3.2862  0.0010   0.0365   0.1445  **
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

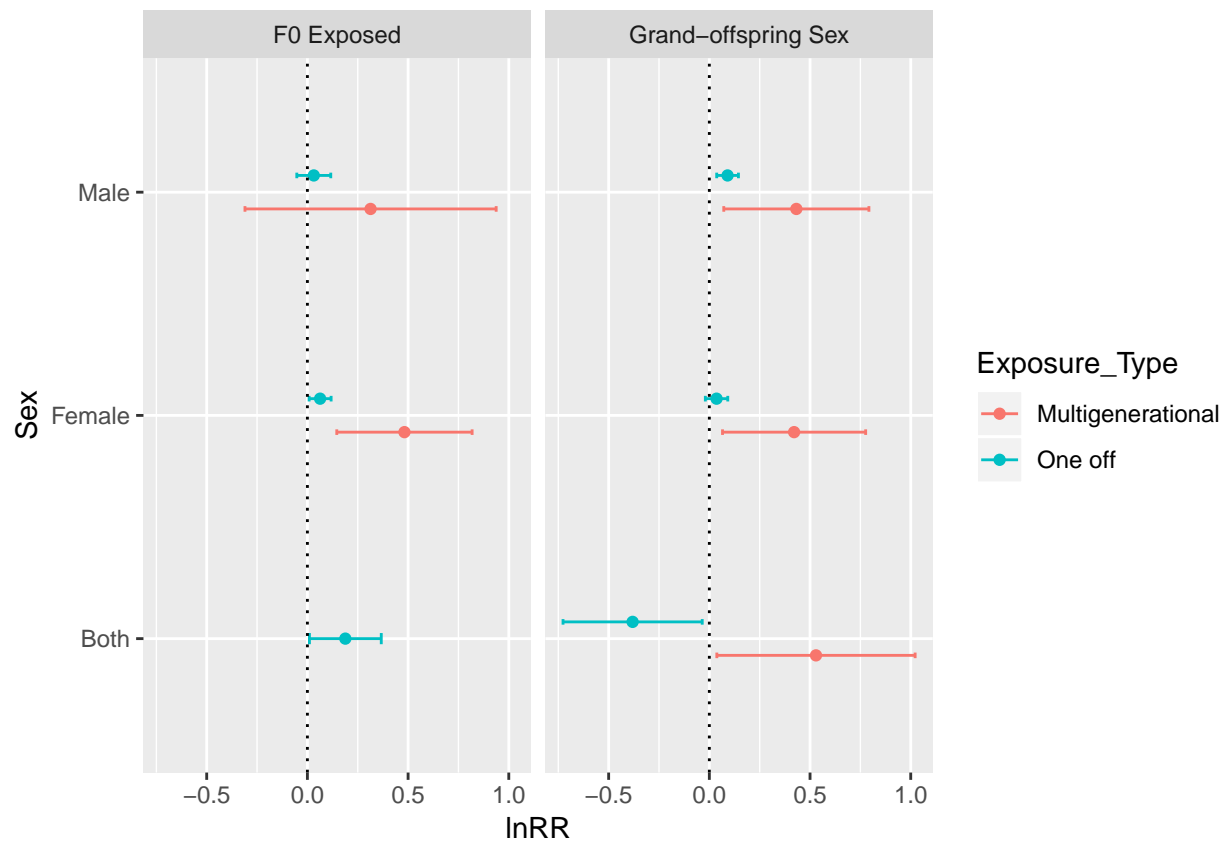
```
funnel(All_Traits_Analysis_Omods_OF_sex, yaxis="seinv")
```



```
Overall_Exp_mods_lnRR <- tibble(
  Exposure_Type = c("Multigenerational", "Multigenerational", "One off", "One off", "One off", "Multigen
  Sex = c("Female", "Male", "Both", "Female", "Male", "Both", "Female", "Male", "Both", "Female", "Male"),
  Mod = c("F0 Exposed", "F0 Exposed", "F0 Exposed", "F0 Exposed", "F0 Exposed", "Grand-offspring Sex", "Grand
  lnRR = c(All_Traits_Analysis_Omods_MG_f0$b[1], All_Traits_Analysis_Omods_MG_f0$b[2], All_Traits_Analysis
  ci.lb = c(All_Traits_Analysis_Omods_MG_f0$ci.lb[1], All_Traits_Analysis_Omods_MG_f0$ci.lb[2], All_Trai
  ci.ub = c(All_Traits_Analysis_Omods_MG_f0$ci.ub[1], All_Traits_Analysis_Omods_MG_f0$ci.ub[2], All_Trai
)

plot_lnRR_overall_mods_exp <- ggplot(Overall_Exp_mods_lnRR, aes(x=Sex, y=lnRR, colour=Exposure_Type))+
  geom_errorbar(aes(ymin=ci.lb, ymax=ci.ub), width = 0.05, position = position_dodge(0.3)) +
  geom_point(aes(x = Sex, y = lnRR), position = position_dodge(0.3))+
  geom_hline(yintercept = 0, lty = "dotted") +
  labs(x = "Sex", y = "lnRR") +
  coord_flip()+
  facet_grid(~Mod)

plot_lnRR_overall_mods_exp
```



Meta-analysis overall results (lnCVR)

Calculating effect sizes (Done)

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

Overall meta-analysis lnCVR (not split, no moderators)

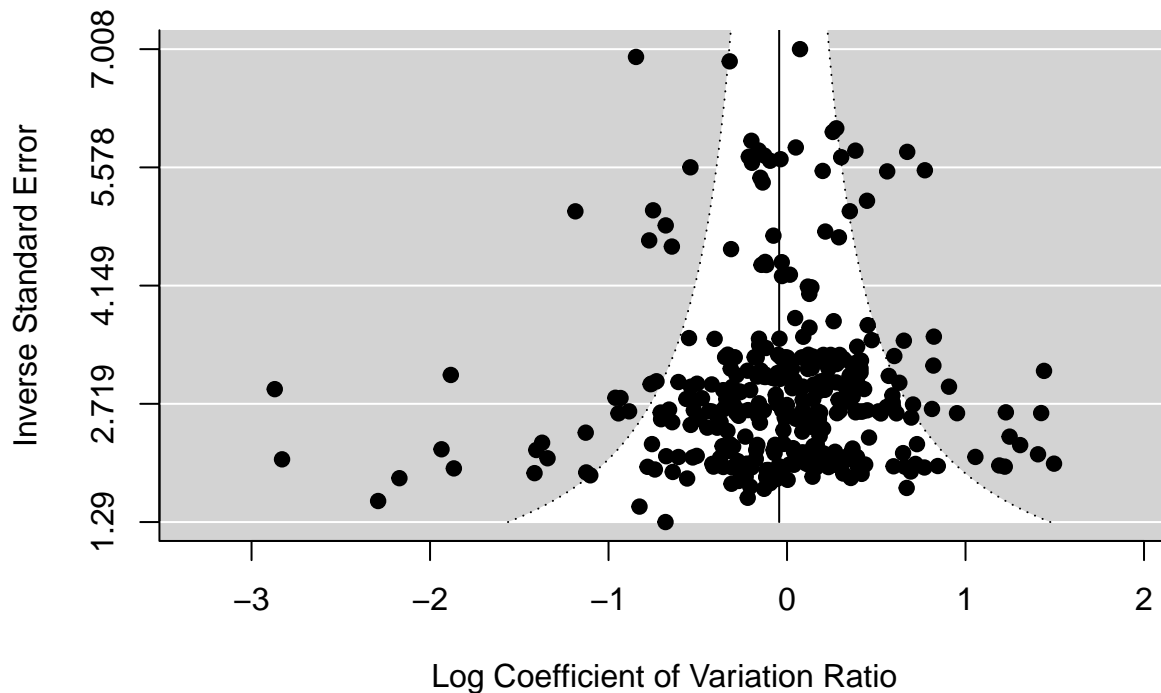
```
#ALL DATA
```

```
All_Traits_Analysis_0mods_lnCVR <- rma.mv(yi, vi, random = list(~1|Trait, ~1|Paper_ID, ~1|Cohort_ID, ~1|E
summary(All_Traits_Analysis_0mods_lnCVR)
```

```
##
## Multivariate Meta-Analysis Model (k = 341; method: REML)
##
##      logLik   Deviance      AIC      BIC      AICc
## -275.3576   550.7151   560.7151   579.8598   560.8948
##
## Variance Components:
##
##              estim      sqrt  nlvls  fixed      factor
```

```
## sigma^2.1 0.0171 0.1307      8      no      Trait
## sigma^2.2 0.0269 0.1639     25      no      Paper_ID
## sigma^2.3 0.0018 0.0420     75      no      Cohort_ID
## sigma^2.4 0.1194 0.3456    341      no      ES_ID
##
## Test for Heterogeneity:
## Q(df = 340) = 835.6920, p-val < .0001
##
## Model Results:
##
## estimate      se      zval      pval      ci.lb      ci.ub
## -0.0441  0.0713  -0.6182  0.5364  -0.1839  0.0957
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
funnel(All_Traits_Analysis_Omods_lnCVR,yaxis="seinv")
```



```
W <- diag(1/Effect_Size_All_Traits_lnCVR$vi)
X <- model.matrix(All_Traits_Analysis_Omods_lnCVR)
P <- W - W %*% X %*% solve(t(X) %*% W %*% X) %*% t(X) %*% W
I2_overall_lnCVR <- 100 * sum(All_Traits_Analysis_Omods_lnCVR$sigma2) / (sum(All_Traits_Analysis_Omods_
I2_overall_lnCVR
```

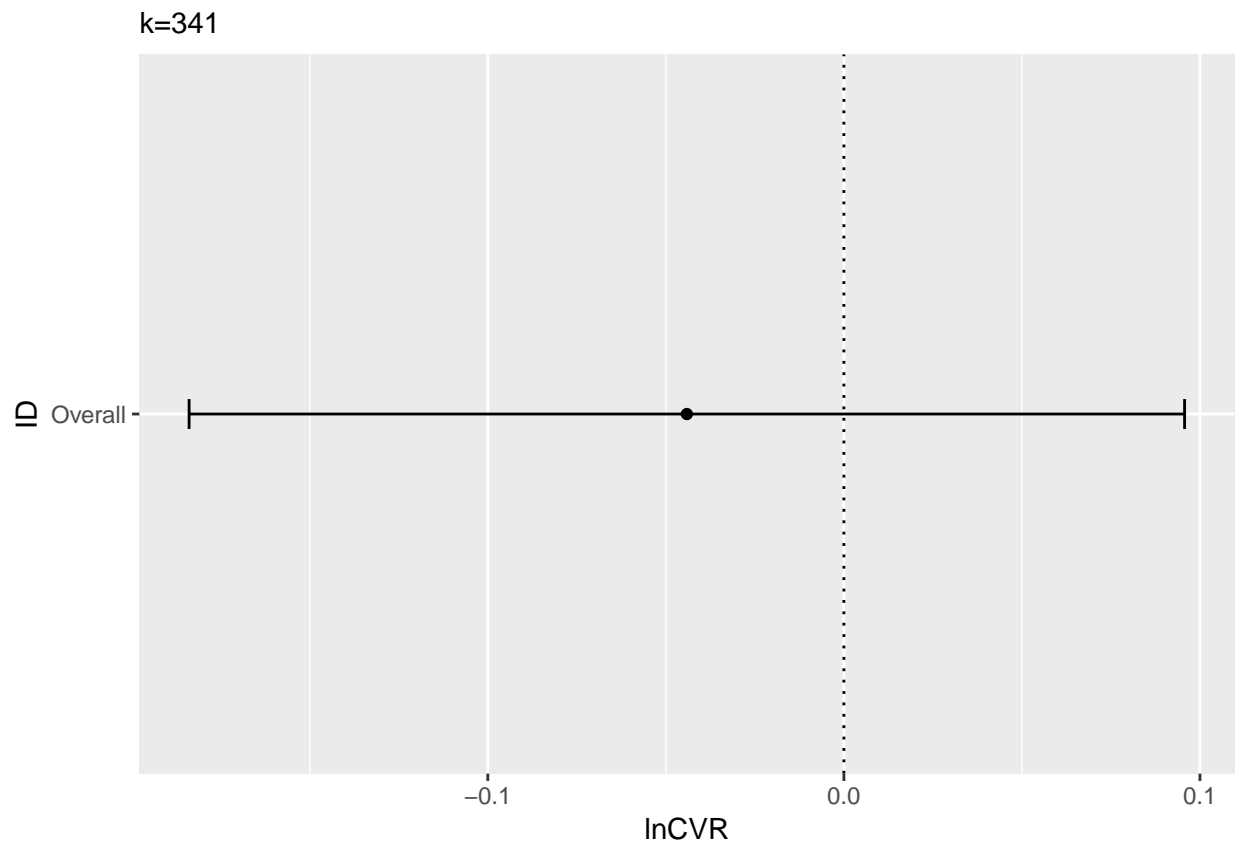
```
## [1] 61.03367
```

```

Overall_effect_size_lnCVR <- tibble(
  ID = "Overall",
  lnCVR = c(All_Traits_Analysis_Omods_lnCVR$b[1]),
  ci.lb = c(All_Traits_Analysis_Omods_lnCVR$ci.lb),
  ci.ub = c(All_Traits_Analysis_Omods_lnCVR$ci.ub),
  k = 241
)

plot_lnRR_overall_lnCVR <- ggplot(Overall_effect_size_lnCVR, aes(x=ID, y=lnCVR)) +
  geom_errorbar(aes(ymin=ci.lb, ymax=ci.ub), width = 0.05, position = position_dodge(0.3)) +
  geom_point(aes(x = ID, y = lnCVR), position = position_dodge(0.3)) +
  geom_hline(yintercept = 0, lty = "dotted") +
  labs(x = "ID", y = "lnCVR", subtitle = "k=341") +
  coord_flip()
plot_lnRR_overall_lnCVR

```



Meta Regression for Traits and Exposure Type lnCVR

```

#Traits meta-regression
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)

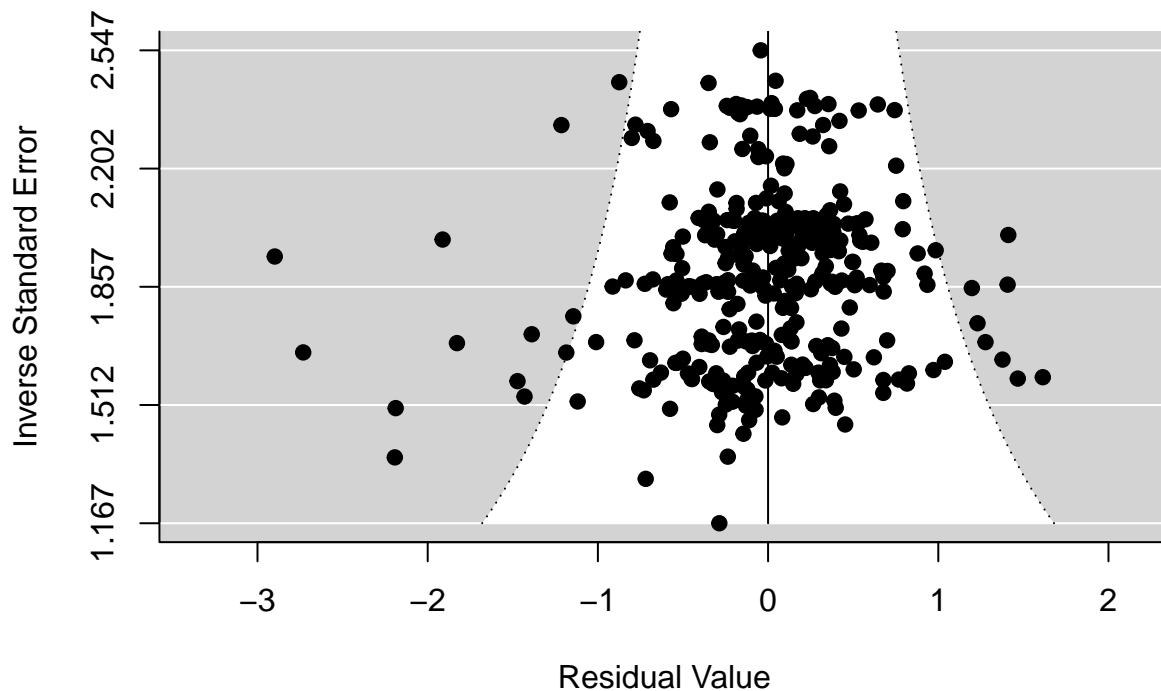
```

```

##
## Multivariate Meta-Analysis Model (k = 341; method: REML)
##
##      logLik    Deviance      AIC      BIC      AICc
## -265.7886    531.5772    553.5772    595.4668    554.3996
##
## Variance Components:
##
##      estim    sqrt  nlvls  fixed    factor
## sigma^2.1  0.0273  0.1653    25     no   Paper_ID
## sigma^2.2  0.0013  0.0361    75     no   Cohort_ID
## sigma^2.3  0.1196  0.3459   341     no     ES_ID
##
## Test for Residual Heterogeneity:
## QE(df = 333) = 798.6001, p-val < .0001
##
## Test of Moderators (coefficient(s) 1:8):
## QM(df = 8) = 18.4756, p-val = 0.0179
##
## Model Results:
##
##      estimate      se      zval      pval      ci.lb      ci.ub
## TraitAdiposity      0.0164  0.0849   0.1931  0.8469  -0.1499  0.1827
## TraitBody_Weight      0.0286  0.0558   0.5121  0.6086  -0.0808  0.1379
## TraitGlucose_FBG     -0.1562  0.1510  -1.0343  0.3010  -0.4522  0.1398
## TraitGlucose_TT       0.0925  0.1148   0.8054  0.4206  -0.1326  0.3176
## TraitInsulin_FI      -0.3943  0.1201  -3.2831  0.0010  -0.6297 -0.1589
## TraitInsulin_TT       0.2174  0.1444   1.5051  0.1323  -0.0657  0.5004
## TraitLeptin          -0.0978  0.1612  -0.6066  0.5441  -0.4136  0.2181
## TraitTriglycerides   -0.1077  0.1070  -1.0061  0.3143  -0.3175  0.1021
##
## 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,yaxis="seinv")
```



```
W <- diag(1/Effect_Size_All_Traits_lnCVR$vi)
X <- model.matrix(All_Traits_Analysis_traits_lnCVR)
P <- W - W %*% X %*% solve(t(X) %*% W %*% X) %*% t(X) %*% W
I2_Overall_Traits_lnCVR <- 100 * sum(All_Traits_Analysis_traits_lnCVR$sigma2) / (sum(All_Traits_Analysis_traits_lnCVR$sigma2) + sum(All_Traits_Analysis_traits_lnCVR$vi))
I2_Overall_Traits_lnCVR
```

```
## [1] 58.45726
```

```
#Will not go into figure as of yet, just as a reference for how many effect sizes we see
k_traits_lnCVR <- Effect_Size_All_Traits_lnCVR %>% group_by(Trait) %>% count()
k_traits_lnCVR
```

```
## # 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_lnCVR <- tibble(
  Trait = c("Adiposity", "Body Weight", "Glucose FBG", "Glucose TT", "Insulin FI", "Insulin TT", "Leptin", "Triglycerides"),
  lnCVR = c(All_Traits_Analysis_traits_lnCVR$b[1], All_Traits_Analysis_traits_lnCVR$b[2], All_Traits_Analysis_traits_lnCVR$b[3], All_Traits_Analysis_traits_lnCVR$b[4], All_Traits_Analysis_traits_lnCVR$b[5], All_Traits_Analysis_traits_lnCVR$b[6], All_Traits_Analysis_traits_lnCVR$b[7], All_Traits_Analysis_traits_lnCVR$b[8]),
  ci.lb = c(All_Traits_Analysis_traits_lnCVR$ci.lb[1], All_Traits_Analysis_traits_lnCVR$ci.lb[2], All_Traits_Analysis_traits_lnCVR$ci.lb[3], All_Traits_Analysis_traits_lnCVR$ci.lb[4], All_Traits_Analysis_traits_lnCVR$ci.lb[5], All_Traits_Analysis_traits_lnCVR$ci.lb[6], All_Traits_Analysis_traits_lnCVR$ci.lb[7], All_Traits_Analysis_traits_lnCVR$ci.lb[8]),
  ci.ub = c(All_Traits_Analysis_traits_lnCVR$ci.ub[1], All_Traits_Analysis_traits_lnCVR$ci.ub[2], All_Traits_Analysis_traits_lnCVR$ci.ub[3], All_Traits_Analysis_traits_lnCVR$ci.ub[4], All_Traits_Analysis_traits_lnCVR$ci.ub[5], All_Traits_Analysis_traits_lnCVR$ci.ub[6], All_Traits_Analysis_traits_lnCVR$ci.ub[7], All_Traits_Analysis_traits_lnCVR$ci.ub[8]),
  k = c(k_traits_lnCVR$n[1], k_traits_lnCVR$n[2], k_traits_lnCVR$n[3], k_traits_lnCVR$n[4], k_traits_lnCVR$n[5], k_traits_lnCVR$n[6], k_traits_lnCVR$n[7], k_traits_lnCVR$n[8])
)
Traits_overall_lnCVR

```

```

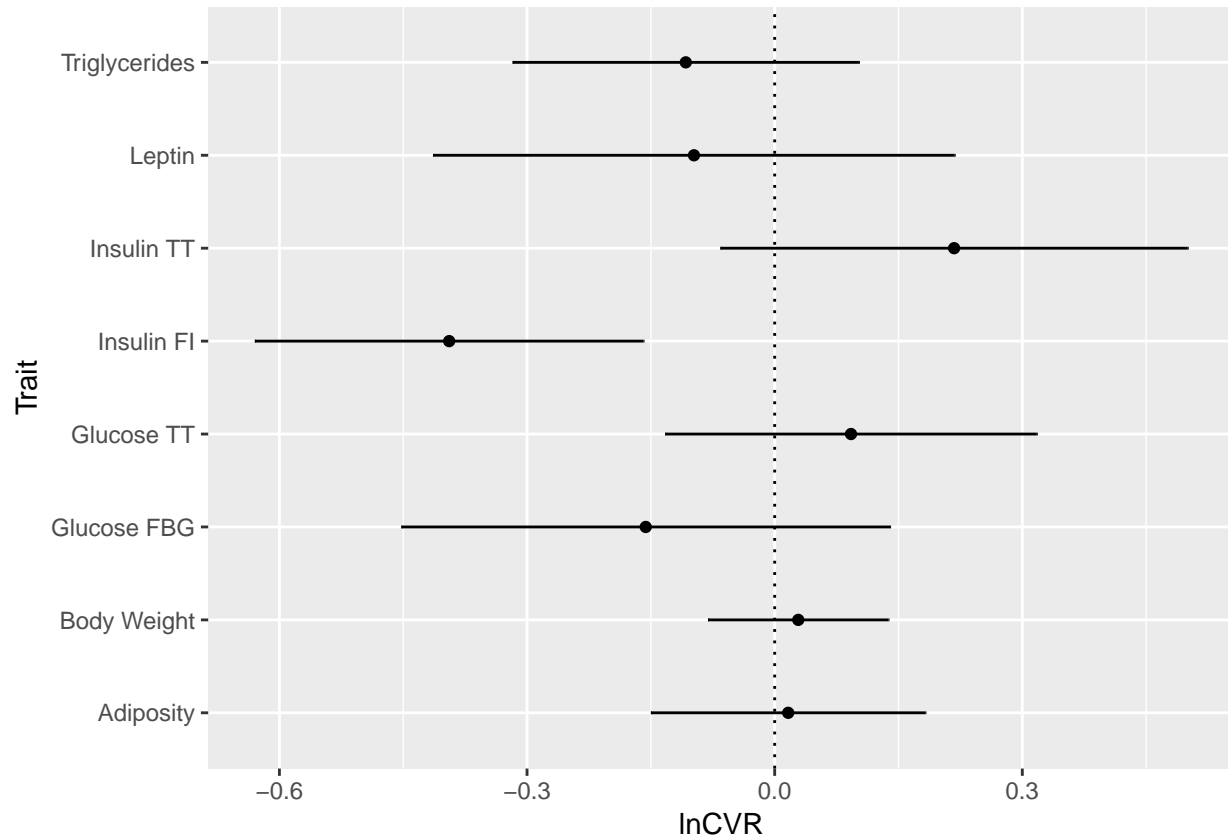
## # A tibble: 8 x 5
##   Trait          lnCVR   ci.lb   ci.ub     k
##   <chr>         <dbl>   <dbl>   <dbl> <int>
## 1 Adiposity     0.0164 -0.150  0.183    65
## 2 Body Weight   0.0286 -0.0808 0.138   146
## 3 Glucose FBG   -0.156  -0.452  0.140    12
## 4 Glucose TT    0.0925 -0.133  0.318    28
## 5 Insulin FI    -0.394  -0.630 -0.159    26
## 6 Insulin TT    0.217  -0.0657 0.500    19
## 7 Leptin        -0.0978 -0.414  0.218    12
## 8 Triglycerides -0.108  -0.317  0.102    33

```

```

plot_lnRR_overall_traits_lnCVR <- ggplot(Traits_overall_lnCVR, aes(x=Trait, y=lnCVR)) +
  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

```



```
#Exposure type meta-regression
```

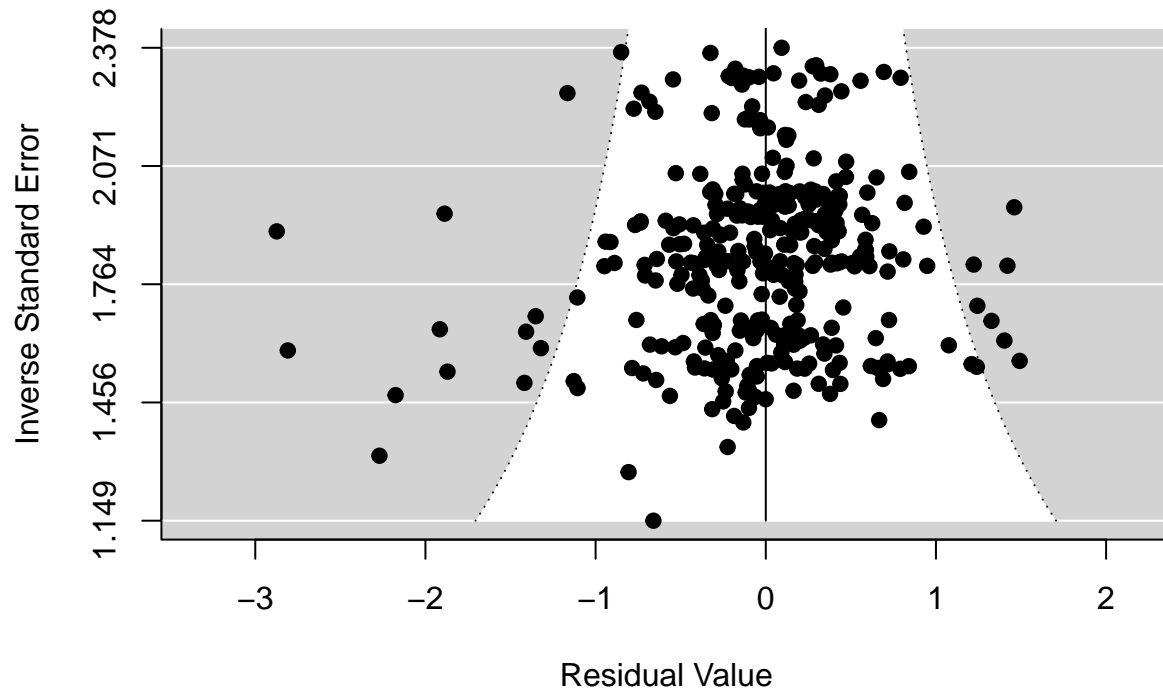
```
All_Traits_Analysis_Exp_lnCVR <- rma.mv(yi, vi, mods= ~Exposure_Type-1, random = list(~1|Paper_ID,~1|Cohort_ID))
```

```
summary(All_Traits_Analysis_Exp_lnCVR)
```

```
##
## Multivariate Meta-Analysis Model (k = 341; method: REML)
##
##      logLik   Deviance      AIC      BIC      AICc
## -276.6589   553.3177   563.3177   582.4477   563.4979
##
## Variance Components:
##
##      estim  sqrt  nlvls  fixed  factor
## sigma^2.1 0.0341 0.1848   25    no  Paper_ID
## sigma^2.2 0.0018 0.0424   75    no  Cohort_ID
## sigma^2.3 0.1255 0.3542  341    no    ES_ID
##
## Test for Residual Heterogeneity:
## QE(df = 339) = 832.0207, p-val < .0001
##
## Test of Moderators (coefficient(s) 1:2):
## QM(df = 2) = 0.1054, p-val = 0.9486
##
## Model Results:
##
```

```
##               estimate      se      zval      pval      ci.lb
## Exposure_TypeMultigenerational -0.0204 0.0703 -0.2905 0.7714 -0.1582
## Exposure_TypeOne off           0.0038 0.0618 0.0607 0.9516 -0.1174
##               ci.ub
## Exposure_TypeMultigenerational 0.1174
## Exposure_TypeOne off           0.1249
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
funnel(All_Traits_Analysis_Exp_lnCVR,yaxis="seinv")
```



```
W <- diag(1/Effect_Size_All_Traits_lnCVR$vi)
X <- model.matrix(All_Traits_Analysis_Exp_lnCVR)
P <- W - W %*% X %*% solve(t(X) %*% W %*% X) %*% t(X) %*% W
I2_Overall_Exposure_lnCVR <- 100 * sum(All_Traits_Analysis_Exp_lnCVR$sigma2) / (sum(All_Traits_Analysis_Exp_lnCVR$sigma2))
I2_Overall_Exposure_lnCVR
```

```
## [1] 60.4356
```

```
k_exp_lnCVR <- Effect_Size_All_Traits_lnCVR %>% group_by(Exposure_Type) %>% count()
k_exp_lnCVR
```

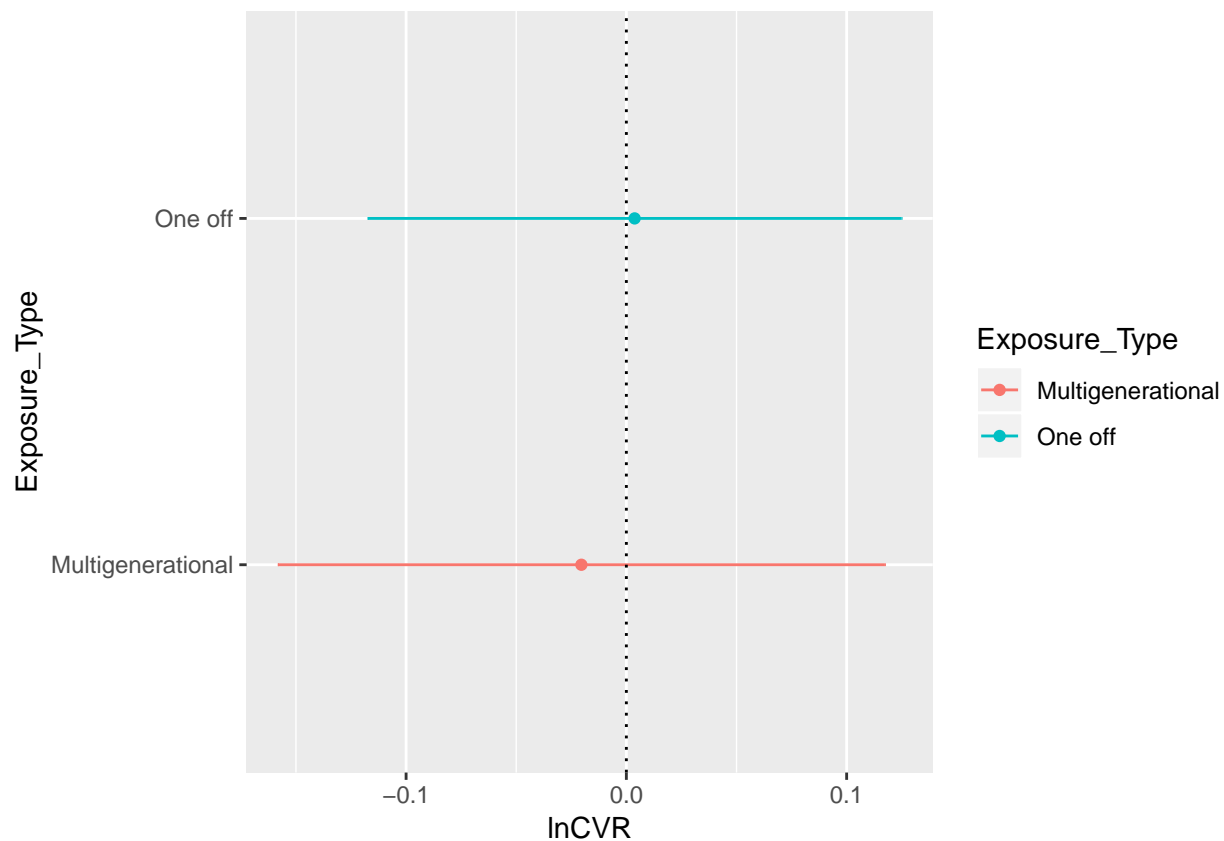
```
## # A tibble: 2 x 2
```

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

```
Overall_Exp_meta_lnCVR <- tibble(
  Exposure_Type = c("Multigenerational", "One off"),
  lnCVR = c(All_Traits_Analysis_Exp_lnCVR$b[1], All_Traits_Analysis_Exp_lnCVR$b[2]),
  ci.lb = c(All_Traits_Analysis_Exp_lnCVR$ci.lb[1], All_Traits_Analysis_Exp_lnCVR$ci.lb[2]),
  ci.ub = c(All_Traits_Analysis_Exp_lnCVR$ci.ub[1], All_Traits_Analysis_Exp_lnCVR$ci.ub[2]),
  k = c(k_exp_lnCVR$n[1], k_exp_lnCVR$n[2])
)
Overall_Exp_meta_lnCVR
```

```
## # A tibble: 2 x 5
##   Exposure_Type      lnCVR ci.lb ci.ub      k
##   <chr>          <dbl> <dbl> <dbl> <int>
## 1 Multigenerational -0.0204 -0.158 0.117   118
## 2 One off           0.00375 -0.117 0.125   223
```

```
plot_lnRR_overall_expmeta_lnCVR <- ggplot(Overall_Exp_meta_lnCVR, aes(x=Exposure_Type, y=lnCVR, colour=
  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_expmeta_lnCVR
```



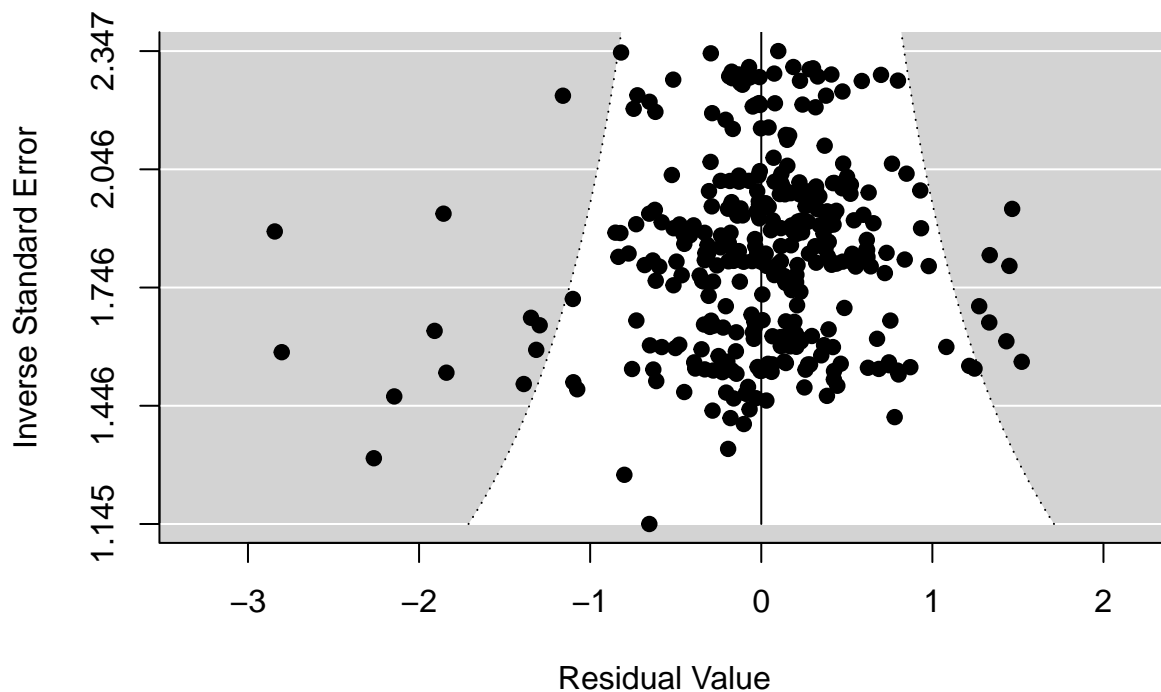
Meta-regression of overall dataset for F0 parent and offspring sex lnCVR

```
All_Data_Analysis_f0_lnCVR <- rma.mv(yi, vi, mods = ~F0_Parent_Exposed-1, random = list(~1|Trait, ~1|Paper_ID),
summary(All_Data_Analysis_f0_lnCVR)
```

```
##
## Multivariate Meta-Analysis Model (k = 341; method: REML)
##
##      logLik   Deviance      AIC      BIC      AICc
## -274.0750   548.1500   562.1500   588.9113   562.4894
##
## Variance Components:
##
##      estim      sqrt  nlvls  fixed      factor
## sigma^2.1  0.0162  0.1271     8    no      Trait
## sigma^2.2  0.0282  0.1679    25    no    Paper_ID
## sigma^2.3  0.0024  0.0486    75    no    Cohort_ID
## sigma^2.4  0.1201  0.3465   341    no      ES_ID
##
## Test for Residual Heterogeneity:
## QE(df = 338) = 832.8282, p-val < .0001
##
```

```
## Test of Moderators (coefficient(s) 1:3):
## QM(df = 3) = 0.8824, p-val = 0.8297
##
## Model Results:
##
##               estimate      se      zval      pval      ci.lb
## F0_Parent_ExposedBoth   -0.0985  0.2679  -0.3677  0.7131  -0.6236
## F0_Parent_ExposedFemale  -0.0266  0.0746  -0.3563  0.7216  -0.1728
## F0_Parent_ExposedMale   -0.1095  0.1171  -0.9347  0.3499  -0.3390
##               ci.ub
## F0_Parent_ExposedBoth    0.4266
## F0_Parent_ExposedFemale   0.1196
## F0_Parent_ExposedMale     0.1201
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
funnel(All_Data_Analysis_f0_lnCVR,yaxis="seinv")
```



```
W <- diag(1/Effect_Size_All_Traits_lnCVR$vi)
X <- model.matrix(All_Data_Analysis_f0_lnCVR)
P <- W - W %*% X %*% solve(t(X) %*% W %*% X) %*% t(X) %*% W
I2_Overall_F0_lnCVR <- 100 * sum(All_Data_Analysis_f0_lnCVR$sigma2) / (sum(All_Data_Analysis_f0_lnCVR$sigma2) + sum(All_Data_Analysis_f0_lnCVR$vi))
I2_Overall_F0_lnCVR
```

```
## [1] 61.25195
```

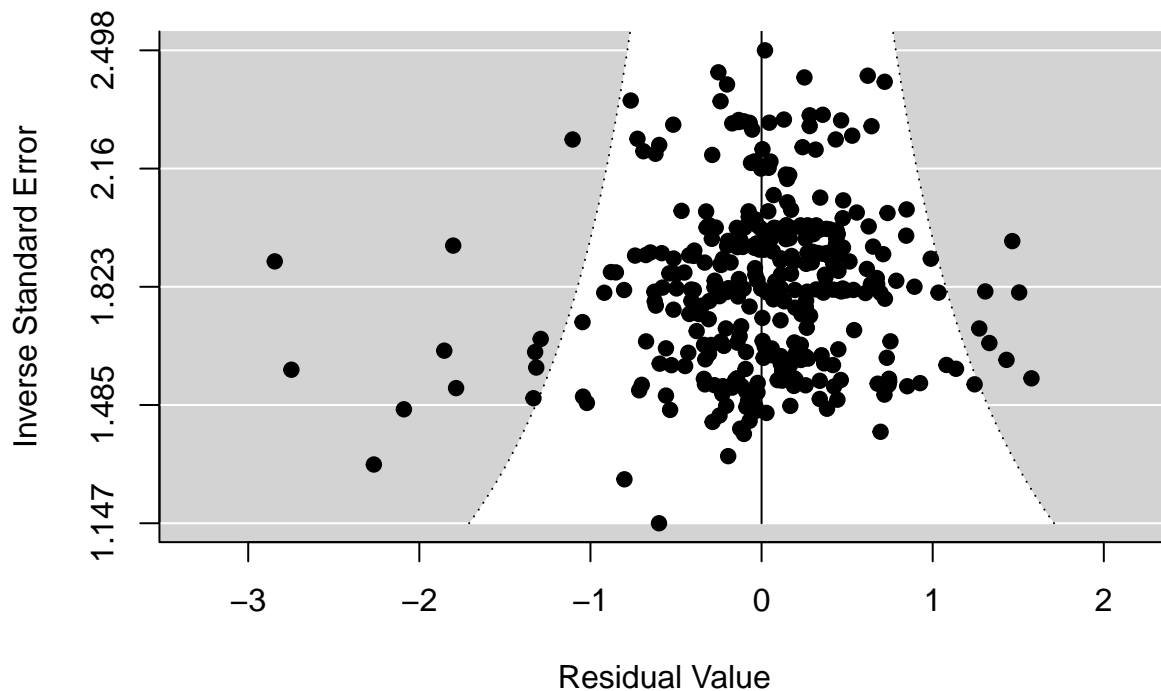
```
k_All_Data_Analysis_f0_lnCVR <- Effect_Size_All_Traits_lnCVR %>% group_by(F0_Parent_Exposed) %>% count()
k_All_Data_Analysis_f0_lnCVR
```

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

```
##
## Multivariate Meta-Analysis Model (k = 341; method: REML)
##
##      logLik   Deviance      AIC      BIC      AICc
## -273.9868   547.9737   561.9737   588.7350   562.3131
##
## Variance Components:
##
##      estim      sqrt  nlvls  fixed      factor
## sigma^2.1  0.0166  0.1289     8    no      Trait
## sigma^2.2  0.0262  0.1620    25    no    Paper_ID
## sigma^2.3  0.0032  0.0563    75    no    Cohort_ID
## sigma^2.4  0.1195  0.3457   341    no      ES_ID
##
## Test for Residual Heterogeneity:
## QE(df = 338) = 823.8554, p-val < .0001
##
## Test of Moderators (coefficient(s) 1:3):
## QM(df = 3) = 1.6943, p-val = 0.6382
##
## Model Results:
##
##      estimate      se      zval      pval      ci.lb      ci.ub
## SexBoth      0.0528  0.1602   0.3296  0.7417  -0.2612  0.3668
## SexFemale    -0.0251  0.0792  -0.3167  0.7515  -0.1803  0.1301
## SexMale     -0.0814  0.0782  -1.0411  0.2978  -0.2347  0.0719
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
funnel(All_Data_Analysis_sex_lnCVR, yaxis="seinv")
```



```
W <- diag(1/Effect_Size_All_Traits_lnCVR$vi)
X <- model.matrix(All_Data_Analysis_sex_lnCVR)
P <- W - W %*% X %*% solve(t(X) %*% W %*% X) %*% t(X) %*% W
I2_Overall_sex_lnCVR <- 100 * sum(All_Data_Analysis_sex_lnCVR$sigma2) / (sum(All_Data_Analysis_sex_lnCVR$
I2_Overall_sex_lnCVR
```

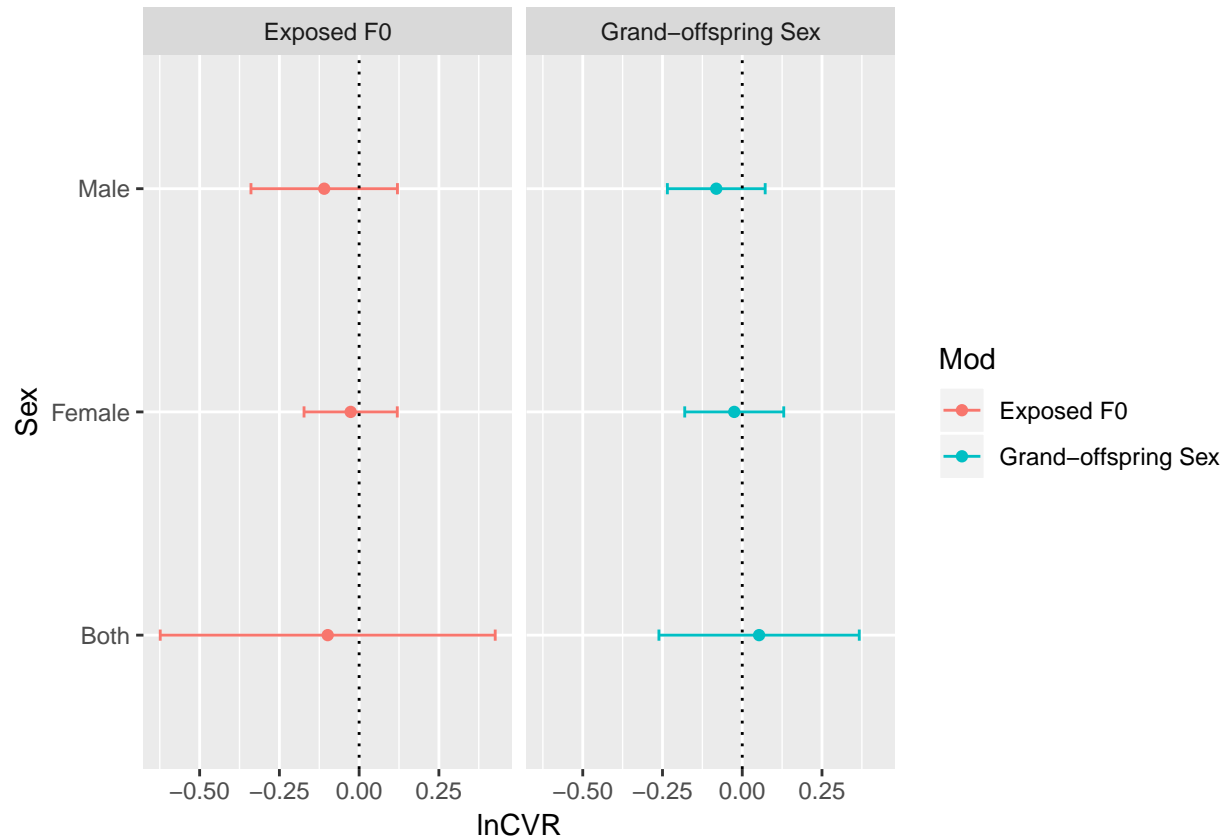
```
## [1] 60.89933
```

```
Overall_effects_not_split_f0_sex_lnCVR <- tibble(
  Sex = c("Both", "Female", "Male", "Both", "Female", "Male"),
  Mod = c("Exposed F0", "Exposed F0", "Exposed F0", "Grand-offspring Sex", "Grand-offspring Sex", "Grand-
  lnCVR = c(All_Data_Analysis_f0_lnCVR$b[1], All_Data_Analysis_f0_lnCVR$b[2], All_Data_Analysis_f0_lnCVR$b[3],
  ci.lb = c(All_Data_Analysis_f0_lnCVR$ci.lb[1], All_Data_Analysis_f0_lnCVR$ci.lb[2], All_Data_Analysis_f0_lnCVR$ci.lb[3],
  ci.ub = c(All_Data_Analysis_f0_lnCVR$ci.ub[1], All_Data_Analysis_f0_lnCVR$ci.ub[2], All_Data_Analysis_f0_lnCVR$ci.ub[3],
)

plot_lnCVR_overall_mods_f0_sex <- ggplot(Overall_effects_not_split_f0_sex_lnCVR, aes(x=Sex, y=lnCVR, col=Mod)) +
  geom_errorbar(aes(ymin=ci.lb, ymax=ci.ub), width = 0.05, position = position_dodge(0.3)) +
  geom_point(aes(x = Sex, y = lnCVR), position = position_dodge(0.3)) +
  geom_hline(yintercept = 0, lty = "dotted") +
  labs(x = "Sex", y = "lnCVR") +
  coord_flip() +
  facet_grid(~Mod)
```



```
plot_lnCVR_overall_mods_f0_sex
```



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

```
#Overall analysis split by exposure type
```

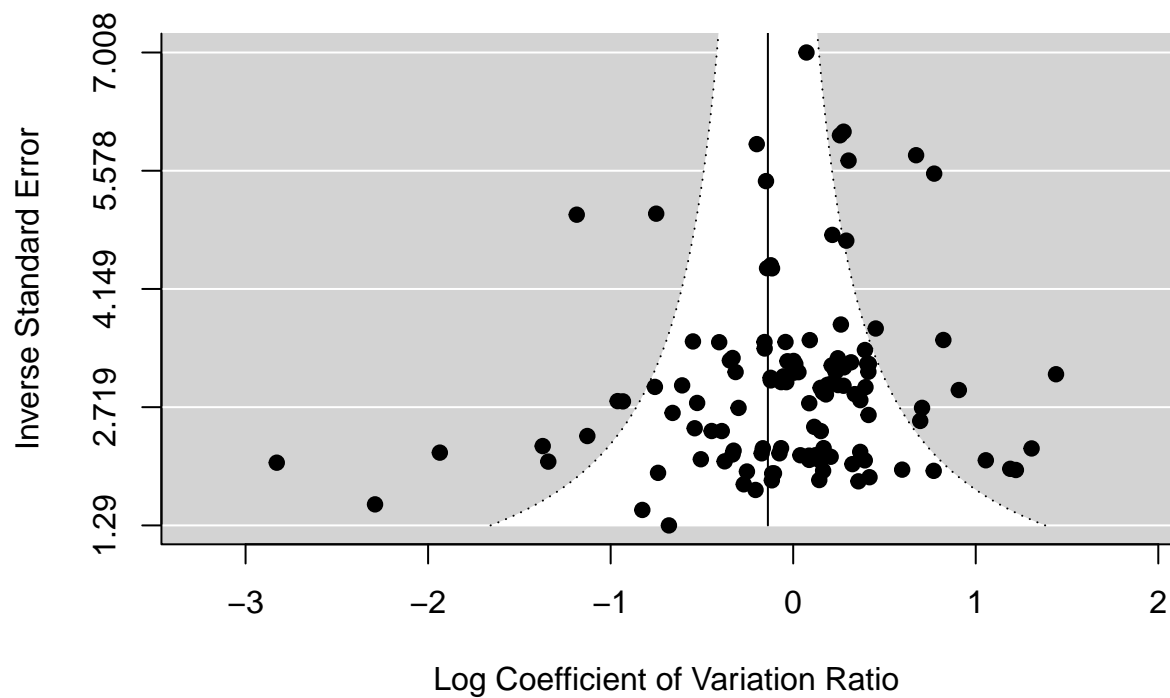
```
All_Data_Analysis_MG_lnCVR <- rma.mv(yi, vi, random = list(~1|Trait, ~1|Paper_ID, ~1|Cohort_ID, ~1|ES_ID))
```

```
summary(All_Data_Analysis_MG_lnCVR)
```

```
##
## Multivariate Meta-Analysis Model (k = 118; method: REML)
##
##      logLik   Deviance      AIC      BIC      AICc
## -101.4736   202.9472   212.9472   226.7581   213.4877
##
## 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  0.1503  0.3877   118    no     ES_ID
##
## Test for Heterogeneity:
## Q(df = 117) = 331.5313, p-val < .0001
##
```

```
## Model Results:
##
## estimate      se      zval    pval    ci.lb    ci.ub
## -0.1386  0.1035  -1.3399  0.1803  -0.3414  0.0642
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
funnel(All_Data_Analysis_MG_lnCVR,yaxis="seinv")
```



```
W <- diag(1/MG_ALL_lnCVR$vi)
X <- model.matrix(All_Data_Analysis_MG_lnCVR)
P <- W - W %*% X %*% solve(t(X) %*% W %*% X) %*% t(X) %*% W
I2_Overall_MG_lnCVR <- 100 * sum(All_Data_Analysis_MG_lnCVR$sigma2) / (sum(All_Data_Analysis_MG_lnCVR$sigma2) + sum(All_Data_Analysis_MG_lnCVR$vi))
I2_Overall_MG_lnCVR
```

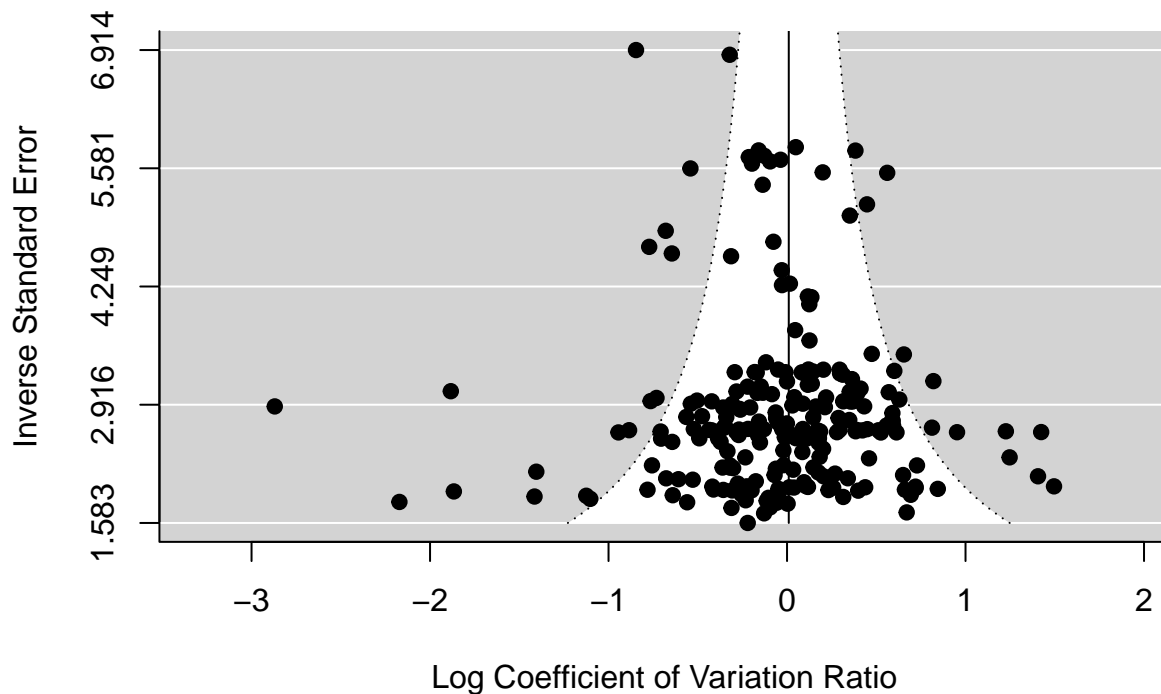
```
## [1] 66.89662
```

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

```
##
## Multivariate Meta-Analysis Model (k = 223; method: REML)
```

```
##
##      logLik    Deviance      AIC      BIC      AICc
## -169.0050   338.0100   348.0100   365.0233   348.2877
##
## Variance Components:
##
##      estim    sqrt  nlvls  fixed    factor
## sigma^2.1  0.0180  0.1342     8    no      Trait
## sigma^2.2  0.0333  0.1824    16    no    Paper_ID
## sigma^2.3  0.0069  0.0830    53    no   Cohort_ID
## sigma^2.4  0.0912  0.3020   223    no      ES_ID
##
## Test for Heterogeneity:
## Q(df = 222) = 500.4894, p-val < .0001
##
## Model Results:
##
## estimate      se    zval    pval    ci.lb    ci.ub
##  0.0097  0.0851  0.1143  0.9090  -0.1571  0.1765
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
funnel(All_Data_Analysis_OF_lnCVR,yaxis="seinv")
```



```

W <- diag(1/OF_ALL_lnCVR$vi)
X <- model.matrix(All_Data_Analysis_OF_lnCVR)
P <- W - W %*% X %*% solve(t(X) %*% W %*% X) %*% t(X) %*% W
I2_Overall_OF_lnCVR <- 100 * sum(All_Data_Analysis_OF_lnCVR$sigma2) / (sum(All_Data_Analysis_OF_lnCVR$s
I2_Overall_OF_lnCVR

```

```
## [1] 57.98863
```

```

Overall_Exp_lnCVR <- tibble(
  Exposure_Type = c("Multigenerational", "One off"),
  lnCVR = c(All_Data_Analysis_MG_lnCVR$b[1], All_Data_Analysis_OF_lnCVR$b[1]),
  ci.lb = c(All_Data_Analysis_MG_lnCVR$ci.lb[1], All_Data_Analysis_OF_lnCVR$ci.lb[1]),
  ci.ub = c(All_Data_Analysis_MG_lnCVR$ci.ub[1], All_Data_Analysis_OF_lnCVR$ci.ub[1]),
  k = c(118, 223)
)
Overall_Exp_lnCVR

```

```

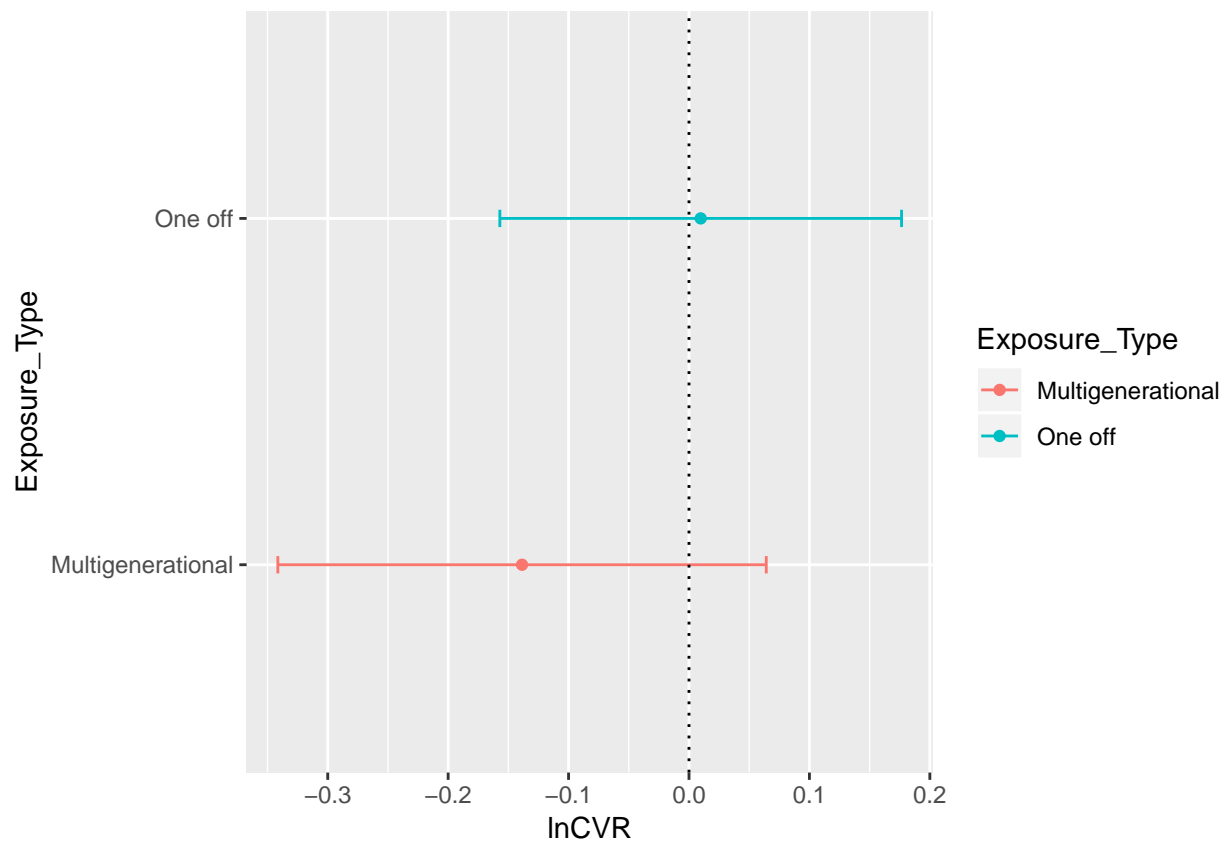
## # A tibble: 2 x 5
##   Exposure_Type      lnCVR ci.lb ci.ub    k
##   <chr>          <dbl> <dbl> <dbl> <dbl>
## 1 Multigenerational -0.139  -0.341 0.0642  118
## 2 One off          0.00973 -0.157 0.177   223

```

```

plot_lnCVR_overall_exp <- ggplot(Overall_Exp_lnCVR, aes(x=Exposure_Type, y=lnCVR, colour=Exposure_Type)) +
  geom_errorbar(aes(ymin=ci.lb, ymax=ci.ub), width = 0.05, 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_lnCVR_overall_exp

```



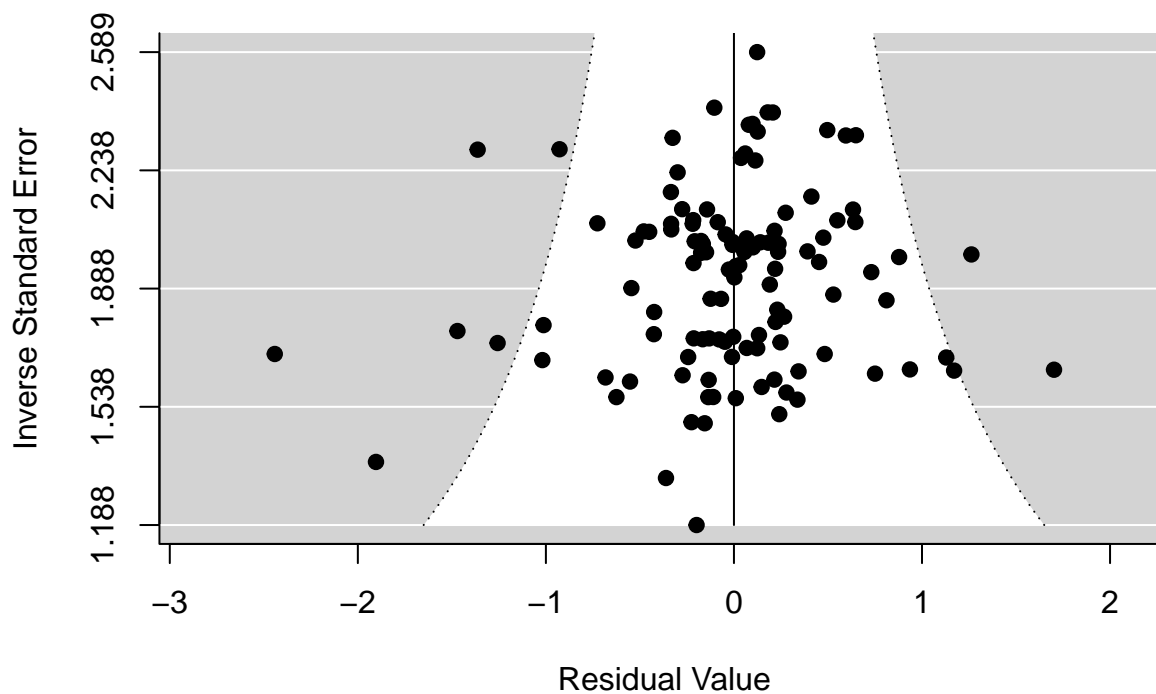
Overall analysis with moderators (by exposure type) lnCVR

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

```
##
## Multivariate Meta-Analysis Model (k = 118; method: REML)
##
##   logLik  Deviance      AIC      BIC     AICc
## -91.9055  183.8109  205.8109  235.5162  208.5048
##
## 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  0.1545  0.3931   118    no     ES_ID
##
## Test for Residual Heterogeneity:
## QE(df = 110) = 280.8877, p-val < .0001
##
## Test of Moderators (coefficient(s) 1:8):
## QM(df = 8) = 25.1293, p-val = 0.0015
##
## Model Results:
```

```
##
##               estimate      se      zval      pval      ci.lb      ci.ub
## TraitAdiposity    -0.1154  0.1299  -0.8886  0.3742  -0.3700  0.1391
## TraitBody_Weight   0.1770  0.0688   2.5722  0.0101   0.0421  0.3119 *
## TraitGlucose_FBG  -0.3228  0.1845  -1.7494  0.0802  -0.6845  0.0389 .
## TraitGlucose_TT    0.0196  0.2101   0.0931  0.9258  -0.3922  0.4313
## TraitInsulin_FI   -0.4822  0.2158  -2.2348  0.0254  -0.9051 -0.0593 *
## TraitInsulin_TT    0.2532  0.2079   1.2179  0.2233  -0.1543  0.6607
## TraitLeptin       -0.3874  0.2112  -1.8338  0.0667  -0.8014  0.0267 .
## TraitTriglycerides -0.4653  0.2121  -2.1940  0.0282  -0.8810 -0.0496 *
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
funnel(Traits_Analysis_MG_lnCVR,yaxis="seinv")
```



```
W <- diag(1/MG_ALL$vi)
X <- model.matrix(Traits_Analysis_MG_lnCVR)
P <- W - W %*% X %*% solve(t(X) %*% W %*% X) %*% t(X) %*% W
I2_Trait_MG_lnCVR <- 100 * sum(Traits_Analysis_MG_lnCVR$sigma2) / (sum(Traits_Analysis_MG_lnCVR$sigma2)
I2_Trait_MG_lnCVR
```

```
## [1] 98.67366
```

```
k_traits_MG_lnCVR <- MG_ALL_lnCVR %>% group_by(Trait) %>% count()
k_traits_MG_lnCVR
```

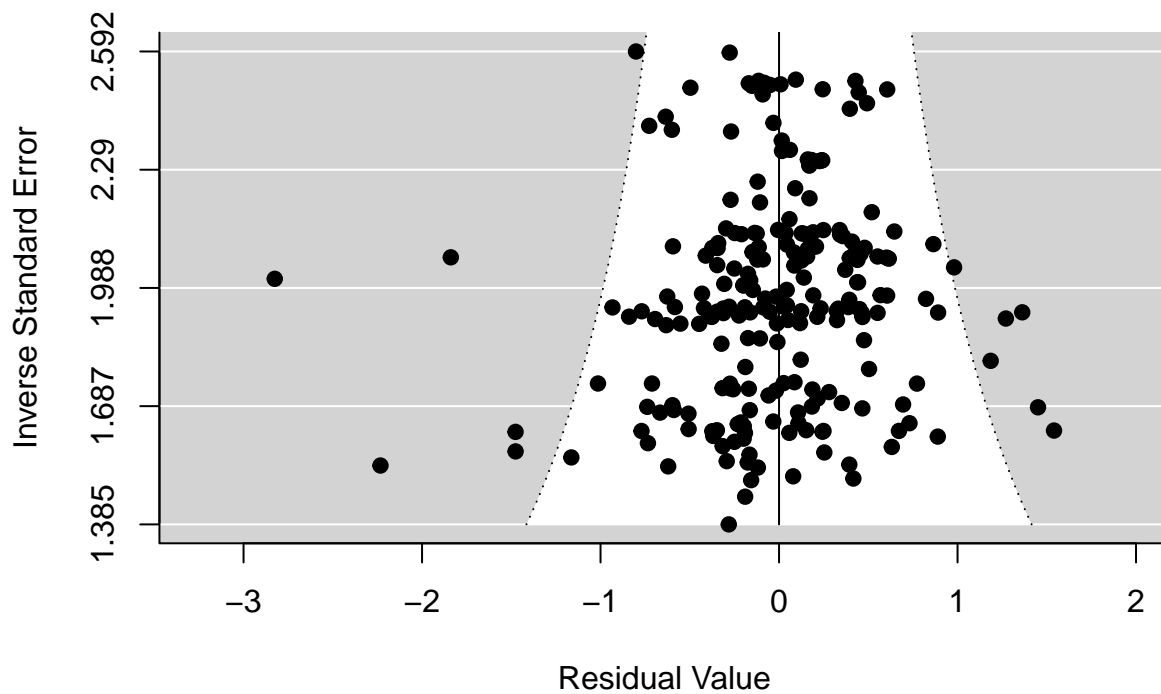
```
## # A tibble: 8 x 2
## # Groups:   Trait [8]
##   Trait      n
##   <fct>    <int>
## 1 Adiposity    19
## 2 Body_Weight   52
## 3 Glucose_FBG    8
## 4 Glucose_TT     9
## 5 Insulin_FI     7
## 6 Insulin_TT     9
## 7 Leptin        7
## 8 Triglycerides  7
```

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

```
##
## Multivariate Meta-Analysis Model (k = 223; method: REML)
##
##      logLik   Deviance      AIC      BIC      AICc
## -160.5081   321.0163   343.0163   380.0933   344.3168
##
## Variance Components:
##
##      estim      sqrt  nlvls  fixed      factor
## sigma^2.1  0.0366  0.1913    16     no   Paper_ID
## sigma^2.2  0.0068  0.0827    53     no   Cohort_ID
## sigma^2.3  0.0898  0.2997   223     no     ES_ID
##
## Test for Residual Heterogeneity:
## QE(df = 215) = 473.5074, p-val < .0001
##
## Test of Moderators (coefficient(s) 1:8):
## QM(df = 8) = 14.8914, p-val = 0.0613
##
## Model Results:
##
##      estimate      se      zval      pval      ci.lb      ci.ub
## TraitAdiposity      0.0613  0.1038    0.5905  0.5549   -0.1422    0.2649
## TraitBody_Weight    -0.0448  0.0728   -0.6158  0.5380   -0.1874    0.0978
## TraitGlucose_FBG     0.1290  0.2469    0.5223  0.6014   -0.3550    0.6130
## TraitGlucose_TT      0.1495  0.1324    1.1296  0.2586   -0.1099    0.4089
## TraitInsulin_FI     -0.3903  0.1370   -2.8493  0.0044   -0.6589   -0.1218
## TraitInsulin_TT      0.2540  0.1871    1.3574  0.1746   -0.1127    0.6207
## TraitLeptin          0.2079  0.2325    0.8943  0.3712   -0.2478    0.6636
## TraitTriglycerides  -0.0112  0.1211   -0.0928  0.9261   -0.2486    0.2261
##
## 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(Traits_Analysis_OF_lnCVR,yaxis="seinv")
```



```
W <- diag(1/OF_ALL_lnCVR$vi)
X <- model.matrix(Traits_Analysis_OF_lnCVR)
P <- W - W %*% X %*% solve(t(X) %*% W %*% X) %*% t(X) %*% W
I2_Trait_OF_lnCVR <- 100 * sum(Traits_Analysis_OF_lnCVR$sigma2) / (sum(Traits_Analysis_OF_lnCVR$sigma2)
I2_Trait_OF_lnCVR
```

```
## [1] 55.29582
```

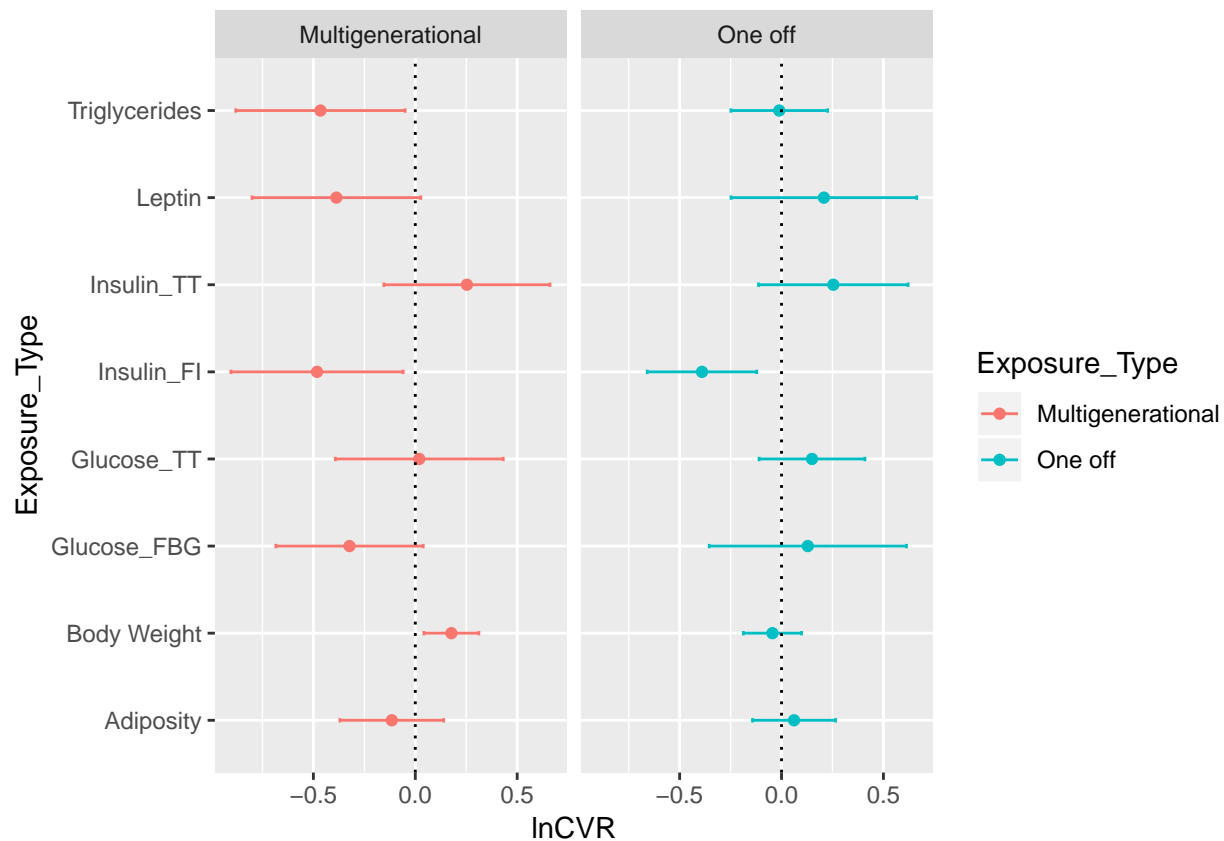
```
k_traits_OF_lnCVR <- OF_ALL_lnCVR %>% group_by(Trait) %>% count()
k_traits_OF_lnCVR
```



```
## # A tibble: 8 x 2
## # Groups:   Trait [8]
##   Trait      n
##   <fct>    <int>
## 1 Adiposity    46
## 2 Body_Weight   94
## 3 Glucose_FBG    4
## 4 Glucose_TT    19
## 5 Insulin_FI    19
## 6 Insulin_TT    10
## 7 Leptin        5
## 8 Triglycerides 26
```

```
Traits_analysis_Exp_lnCVR <- tibble(
  Exposure_Type = c("Multigenerational", "Multigenerational", "Multigenerational", "Multigenerational", "Multigenerational", "Multigenerational", "Multigenerational", "Multigenerational"),
  Trait = c("Adiposity", "Body Weight", "Glucose_FBG", "Glucose_TT", "Insulin_FI", "Insulin_TT", "Leptin", "Triglycerides"),
  lnCVR = c(Traits_Analysis_MG_lnCVR$b[1], Traits_Analysis_MG_lnCVR$b[2], Traits_Analysis_MG_lnCVR$b[3], Traits_Analysis_MG_lnCVR$b[4], Traits_Analysis_MG_lnCVR$b[5], Traits_Analysis_MG_lnCVR$b[6], Traits_Analysis_MG_lnCVR$b[7], Traits_Analysis_MG_lnCVR$b[8]),
  ci.lb = c(Traits_Analysis_MG_lnCVR$ci.lb[1], Traits_Analysis_MG_lnCVR$ci.lb[2], Traits_Analysis_MG_lnCVR$ci.lb[3], Traits_Analysis_MG_lnCVR$ci.lb[4], Traits_Analysis_MG_lnCVR$ci.lb[5], Traits_Analysis_MG_lnCVR$ci.lb[6], Traits_Analysis_MG_lnCVR$ci.lb[7], Traits_Analysis_MG_lnCVR$ci.lb[8]),
  ci.ub = c(Traits_Analysis_MG_lnCVR$ci.ub[1], Traits_Analysis_MG_lnCVR$ci.ub[2], Traits_Analysis_MG_lnCVR$ci.ub[3], Traits_Analysis_MG_lnCVR$ci.ub[4], Traits_Analysis_MG_lnCVR$ci.ub[5], Traits_Analysis_MG_lnCVR$ci.ub[6], Traits_Analysis_MG_lnCVR$ci.ub[7], Traits_Analysis_MG_lnCVR$ci.ub[8]),
  k = c(k_traits_MG_lnCVR$n[1], k_traits_MG_lnCVR$n[2], k_traits_MG_lnCVR$n[3], k_traits_MG_lnCVR$n[4], k_traits_MG_lnCVR$n[5], k_traits_MG_lnCVR$n[6], k_traits_MG_lnCVR$n[7], k_traits_MG_lnCVR$n[8])
)

plot_lnCVR_overall_trait_exp <- ggplot(Traits_analysis_Exp_lnCVR, aes(x=Trait, y=lnCVR, colour=Exposure_Type)) +
  geom_errorbar(aes(ymin=ci.lb, ymax=ci.ub), width = 0.05, 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 = "Exposure_Type", y = "lnCVR") +
  coord_flip() +
  facet_grid(~Exposure_Type)
plot_lnCVR_overall_trait_exp
```



#F0 and offspring sex analysis

```
All_Traits_Analysis_0mods_MG_f0_lnCVR <- rma.mv(yi, vi, mods = ~F0_Parent_Exposed-1, random = list(~1|T
```

```
## Warning in rma.mv(yi, vi, mods = ~F0_Parent_Exposed - 1, random = list(~1
```

```
## | : Redundant predictors dropped from the model.
```

```
summary(All_Traits_Analysis_0mods_MG_f0_lnCVR)
```

```
##
```

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

```
##
```

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

```
## -101.0644  202.1288   214.1288  230.6503  214.8994
```

```
##
```

```
## Variance Components:
```

```
##
```

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

```
## sigma^2.1  0.0510  0.2257     8    no      Trait
```

```
## sigma^2.2  0.0000  0.0010    13    no  Paper_ID
```

```
## sigma^2.3  0.0000  0.0004    24    no  Cohort_ID
```

```
## sigma^2.4  0.1530  0.3911   118    no     ES_ID
```

```
##
```

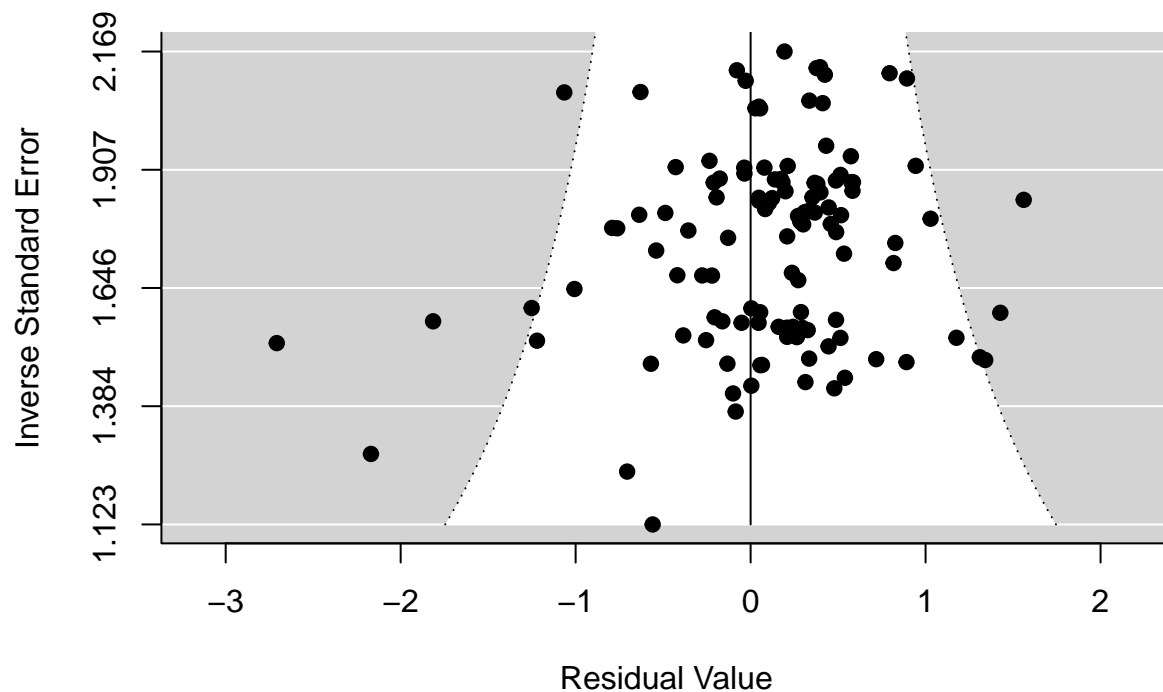
```
## Test for Residual Heterogeneity:
```

```
## QE(df = 116) = 326.3272, p-val < .0001
```

```
##
```

```
## Test of Moderators (coefficient(s) 1:2):
## QM(df = 2) = 2.0195, p-val = 0.3643
##
## Model Results:
##
##               estimate      se      zval      pval      ci.lb
## F0_Parent_ExposedFemale -0.1210  0.1080  -1.1204  0.2625  -0.3328
## F0_Parent_ExposedMale   -0.1705  0.1266  -1.3467  0.1781  -0.4187
##               ci.ub
## F0_Parent_ExposedFemale  0.0907
## F0_Parent_ExposedMale    0.0777
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
funnel(All_Traits_Analysis_Omods_MG_f0_lnCVR,yaxis="seinv")
```

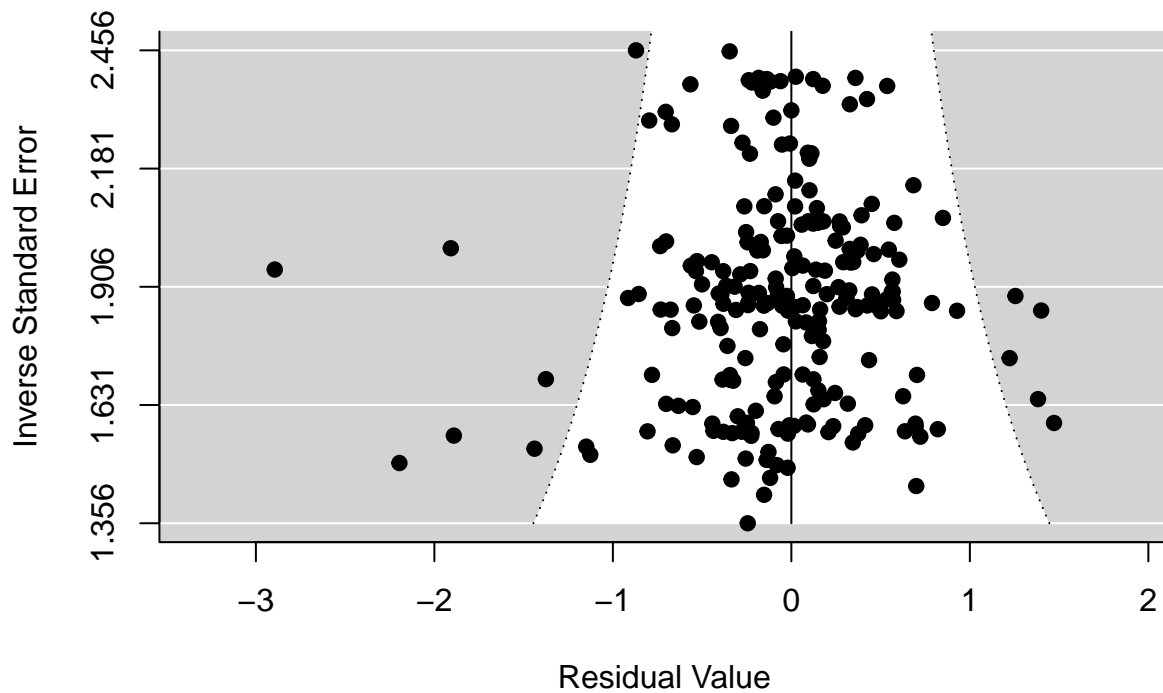


```
All_Traits_Analysis_Omods_OF_f0_lnCVR <- rma.mv(yi, vi, mods = ~F0_Parent_Exposed-1, random = list(~1|T:
summary(All_Traits_Analysis_Omods_OF_f0_lnCVR)
```

```
##
## Multivariate Meta-Analysis Model (k = 223; method: REML)
##
##      logLik   Deviance      AIC      BIC      AICc
```

```
## -168.0072   336.0144   350.0144   373.7698   350.5427
##
## Variance Components:
##
##          estim    sqrt  nlvls  fixed    factor
## sigma^2.1  0.0173  0.1315     8    no      Trait
## sigma^2.2  0.0360  0.1898    16    no    Paper_ID
## sigma^2.3  0.0076  0.0871    53    no   Cohort_ID
## sigma^2.4  0.0926  0.3043   223    no      ES_ID
##
## Test for Residual Heterogeneity:
## QE(df = 220) = 500.0038, p-val < .0001
##
## Test of Moderators (coefficient(s) 1:3):
## QM(df = 3) = 0.1775, p-val = 0.9811
##
## Model Results:
##
##              estimate      se    zval    pval    ci.lb
## F0_Parent_ExposedBoth   -0.0330  0.2670  -0.1235  0.9017  -0.5562
## F0_Parent_ExposedFemale    0.0243  0.0927   0.2619  0.7934  -0.1574
## F0_Parent_ExposedMale   -0.0294  0.1342  -0.2191  0.8266  -0.2924
##              ci.ub
## F0_Parent_ExposedBoth    0.4903
## F0_Parent_ExposedFemale  0.2060
## F0_Parent_ExposedMale    0.2336
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
funnel(All_Traits_Analysis_0mods_OF_f0_lnCVR,yaxis="seinv")
```

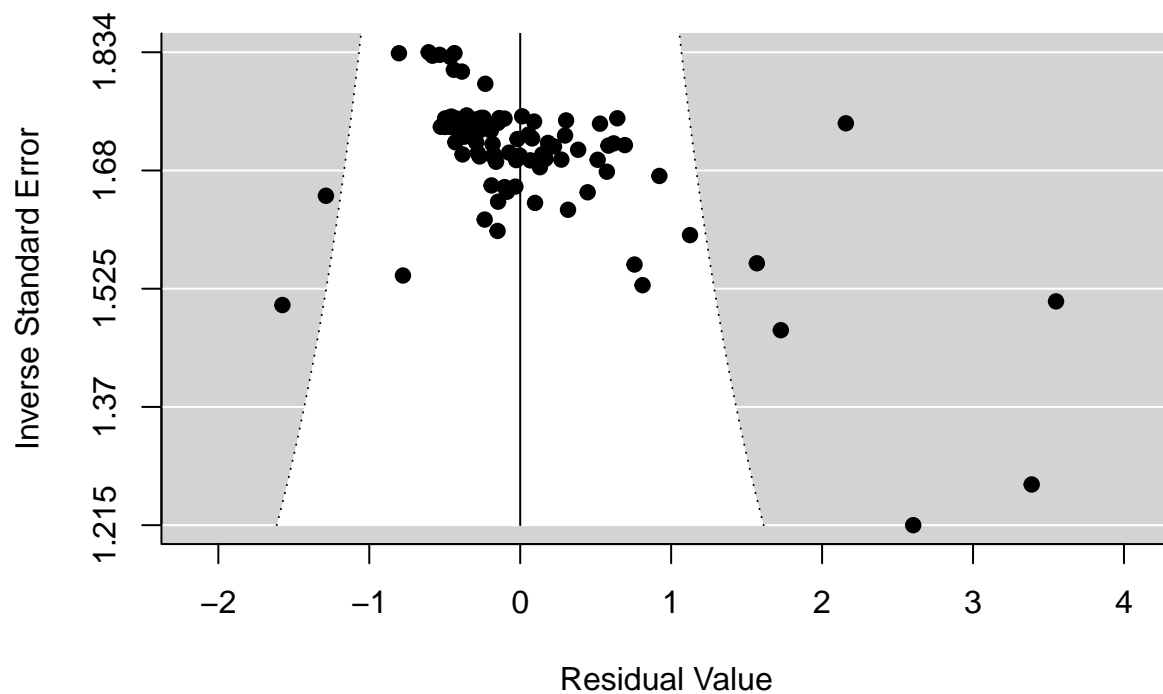


```
All_Traits_Analysis_0mods_MG_sex_lnCVR <- rma.mv(yi, vi, mods = ~Sex-1, random = list(~1|Trait, ~1|Paper_ID))
summary(All_Traits_Analysis_0mods_MG_sex_lnCVR)
```

```
##
## Multivariate Meta-Analysis Model (k = 118; method: REML)
##
##   logLik  Deviance      AIC      BIC     AICc
## -70.3278  140.6556  154.6556  173.8701  155.7023
##
## Variance Components:
##
##      estim    sqrt  nlvls  fixed    factor
## sigma^2.1  0.0863  0.2938     8    no     Trait
## sigma^2.2  0.1961  0.4428    13    no   Paper_ID
## sigma^2.3  0.0000  0.0000    24    no   Cohort_ID
## sigma^2.4  0.0777  0.2787   118    no     ES_ID
##
## Test for Residual Heterogeneity:
## QE(df = 115) = 9001.0945, p-val < .0001
##
## Test of Moderators (coefficient(s) 1:3):
## QM(df = 3) = 7.4466, p-val = 0.0589
##
## Model Results:
```

```
##
##           estimate      se    zval    pval    ci.lb    ci.ub
## SexBoth      0.5296  0.2512  2.1082  0.0350  0.0372  1.0219 *
## SexFemale    0.4208  0.1813  2.3209  0.0203  0.0654  0.7762 *
## SexMale      0.4320  0.1839  2.3498  0.0188  0.0717  0.7923 *
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
funnel(All_Traits_Analysis_0mods_MG_sex,yaxis="seinv")
```

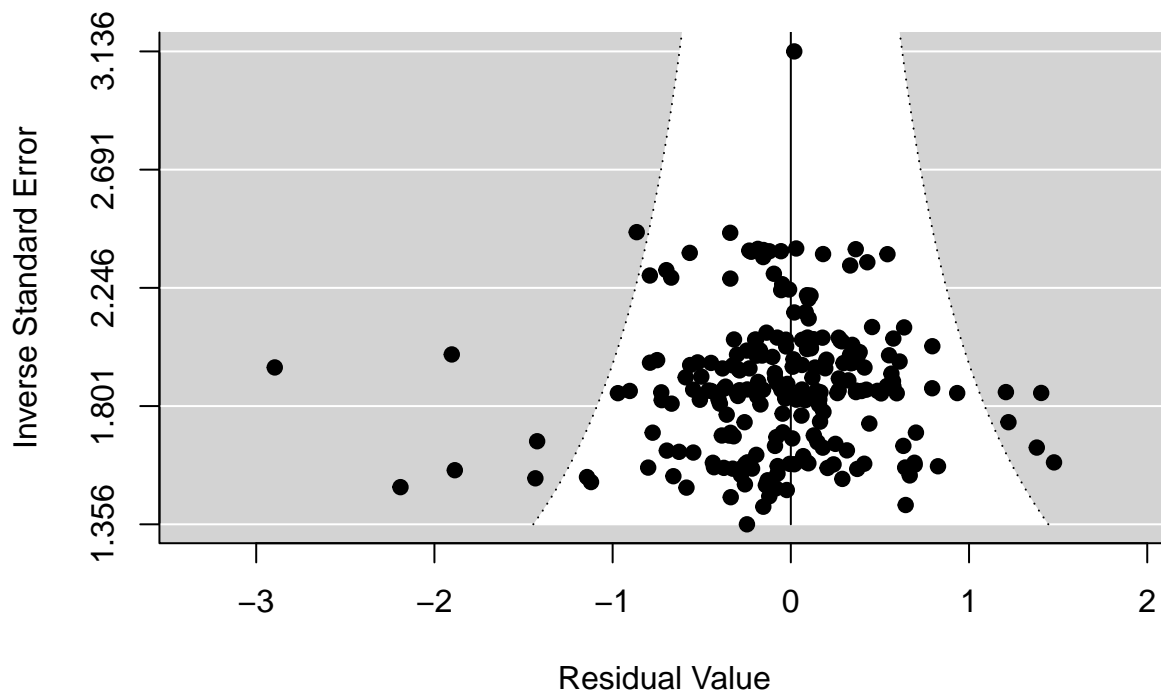


```
All_Traits_Analysis_0mods_OF_sex_lnCVR <- rma.mv(yi, vi, mods = ~Sex-1, random = list(~1|Trait, ~1|Paper))
summary(All_Traits_Analysis_0mods_OF_sex_lnCVR)
```

```
##
## Multivariate Meta-Analysis Model (k = 223; method: REML)
##
##      logLik   Deviance      AIC      BIC      AICc
## -167.9104   335.8207   349.8207   373.5761   350.3490
##
## Variance Components:
##
##      estim    sqrt  nlvls  fixed    factor
## sigma^2.1  0.0203  0.1426     8    no      Trait
```

```
## sigma^2.2  0.0342  0.1848    16    no  Paper_ID
## sigma^2.3  0.0081  0.0900    53    no  Cohort_ID
## sigma^2.4  0.0913  0.3022   223    no    ES_ID
##
## Test for Residual Heterogeneity:
## QE(df = 220) = 499.3108, p-val < .0001
##
## Test of Moderators (coefficient(s) 1:3):
## QM(df = 3) = 0.8189, p-val = 0.8449
##
## Model Results:
##
##           estimate      se    zval    pval    ci.lb    ci.ub
## SexBoth      -0.3595  0.4266  -0.8429  0.3993  -1.1955  0.4765
## SexFemale     0.0259  0.0959   0.2705  0.7868  -0.1620  0.2138
## SexMale       0.0189  0.0950   0.1990  0.8423  -0.1673  0.2052
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
funnel(All_Traits_Analysis_0mods_OF_sex_lnCVR,yaxis="seinv")
```



```
Overall_Exp_mods_lnCVR <- tibble(
  Exposure_Type = c("Multigenerational","Multigenerational", "One off", "One off", "One off", "Multigen
  Sex = c("Female","Male", "Both", "Female", "Male","Both","Female", "Male", "Both","Female", "Male"),
```

```

Mod = c("F0 Exposed", "F0 Exposed", "F0 Exposed", "F0 Exposed", "F0 Exposed", "Grand-offspring Sex", "Grand-offspring Sex")
lnCVR = c(All_Traits_Analysis_Omods_MG_f0_lnCVR$b[1], All_Traits_Analysis_Omods_MG_f0_lnCVR$b[2], All_Traits_Analysis_Omods_MG_f0_lnCVR$b[3], All_Traits_Analysis_Omods_MG_f0_lnCVR$b[4], All_Traits_Analysis_Omods_MG_f0_lnCVR$b[5], All_Traits_Analysis_Omods_MG_f0_lnCVR$b[6], All_Traits_Analysis_Omods_MG_f0_lnCVR$b[7])
ci.lb = c(All_Traits_Analysis_Omods_MG_f0_lnCVR$ci.lb[1], All_Traits_Analysis_Omods_MG_f0_lnCVR$ci.lb[2], All_Traits_Analysis_Omods_MG_f0_lnCVR$ci.lb[3], All_Traits_Analysis_Omods_MG_f0_lnCVR$ci.lb[4], All_Traits_Analysis_Omods_MG_f0_lnCVR$ci.lb[5], All_Traits_Analysis_Omods_MG_f0_lnCVR$ci.lb[6], All_Traits_Analysis_Omods_MG_f0_lnCVR$ci.lb[7])
ci.ub = c(All_Traits_Analysis_Omods_MG_f0_lnCVR$ci.ub[1], All_Traits_Analysis_Omods_MG_f0_lnCVR$ci.ub[2], All_Traits_Analysis_Omods_MG_f0_lnCVR$ci.ub[3], All_Traits_Analysis_Omods_MG_f0_lnCVR$ci.ub[4], All_Traits_Analysis_Omods_MG_f0_lnCVR$ci.ub[5], All_Traits_Analysis_Omods_MG_f0_lnCVR$ci.ub[6], All_Traits_Analysis_Omods_MG_f0_lnCVR$ci.ub[7])
)

```

```
Overall_Exp_mods_lnCVR
```

```

## # A tibble: 11 x 6
##   Exposure_Type Sex Mod lnCVR ci.lb ci.ub
##   <chr> <chr> <chr> <dbl> <dbl> <dbl>
## 1 Multigenerational Female F0 Exposed -0.121 -0.333 0.0907
## 2 Multigenerational Male F0 Exposed -0.171 -0.419 0.0777
## 3 One off Both F0 Exposed -0.0330 -0.556 0.490
## 4 One off Female F0 Exposed 0.0243 -0.157 0.206
## 5 One off Male F0 Exposed -0.0294 -0.292 0.234
## 6 Multigenerational Both Grand-offspring Sex 0.530 0.0372 1.02
## 7 Multigenerational Female Grand-offspring Sex 0.421 0.0654 0.776
## 8 Multigenerational Male Grand-offspring Sex 0.432 0.0717 0.792
## 9 One off Both Grand-offspring Sex -0.360 -1.20 0.476
## 10 One off Female Grand-offspring Sex 0.0259 -0.162 0.214
## 11 One off Male Grand-offspring Sex 0.0189 -0.167 0.205

```

```

plot_lnCVR_overall_mods_exp <- ggplot(Overall_Exp_mods_lnCVR, aes(x=Sex, y=lnCVR, colour=Exposure_Type)) +
  geom_errorbar(aes(ymin=ci.lb, ymax=ci.ub), width = 0.05, position = position_dodge(0.3)) +
  geom_point(aes(x = Sex, y = lnCVR), position = position_dodge(0.3)) +
  geom_hline(yintercept = 0, lty = "dotted") +
  labs(x = "Sex", y = "lnCVR") +
  coord_flip() +
  facet_grid(~Mod)

```

```
plot_lnCVR_overall_mods_exp
```