Meta-análises com SMD

Clarissa F. D. Carneiro

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## ── Attaching core tidyverse packages ──────────────────────── tidyverse 2.0.0 ──  
## ✔ dplyr 1.1.4 ✔ readr 2.1.5  
## ✔ forcats 1.0.0 ✔ stringr 1.5.1  
## ✔ ggplot2 3.5.1 ✔ tibble 3.2.1  
## ✔ lubridate 1.9.4 ✔ tidyr 1.3.1  
## ✔ purrr 1.0.4   
## ── Conflicts ────────────────────────────────────────── tidyverse\_conflicts() ──  
## ✖ dplyr::filter() masks stats::filter()  
## ✖ dplyr::lag() masks stats::lag()  
## ℹ Use the conflicted package (<http://conflicted.r-lib.org/>) to force all conflicts to become errors  
## Carregando pacotes exigidos: Matrix  
##   
##   
## Anexando pacote: 'Matrix'  
##   
##   
## Os seguintes objetos são mascarados por 'package:tidyr':  
##   
## expand, pack, unpack  
##   
##   
## Carregando pacotes exigidos: metadat  
##   
## Carregando pacotes exigidos: numDeriv  
##   
##   
## Loading the 'metafor' package (version 4.8-0). For an  
## introduction to the package please type: help(metafor)  
##   
##   
## Carregando pacotes exigidos: rJava  
##   
## Carregando pacotes exigidos: leaps

This script runs all analyses with Standardized Mean Difference (Hedge’s g) as the effect size measure. The original publications sometimes do not report any variation for the control group, we assumed they normalized each treated experimental unit by their own control. In these cases, we are using the S.D. of the control groups as zero for all following calculations, otherwise we take the values manually extracted.

# 2-level

##   
## Random-Effects Model (k = 1192; tau^2 estimator: REML)  
##   
## logLik deviance AIC BIC AICc   
## -3911.4472 7822.8945 7826.8945 7837.0596 7826.9046   
##   
## tau^2 (estimated amount of total heterogeneity): 17.7242 (SE = 0.8981)  
## tau (square root of estimated tau^2 value): 4.2100  
## I^2 (total heterogeneity / total variability): 93.77%  
## H^2 (total variability / sampling variability): 16.04  
##   
## Test for Heterogeneity:  
## Q(df = 1191) = 7860.2351, p-val < .0001  
##   
## Model Results:  
##   
## estimate se zval pval ci.lb ci.ub   
## -5.4660 0.1384 -39.4948 <.0001 -5.7372 -5.1947 \*\*\*   
##   
## ---  
## Signif. codes: 0 '\*\*\*' 0.001 '\*\*' 0.01 '\*' 0.05 '.' 0.1 ' ' 1

##   
## estimate ci.lb ci.ub   
## tau^2 17.7242 33.4876 44.2244   
## tau 4.2100 5.7868 6.6501   
## I^2(%) 93.7661 96.6008 97.4046   
## H^2 16.0414 29.4187 38.5303

Exact p value: 0 Exact Q test p value 0

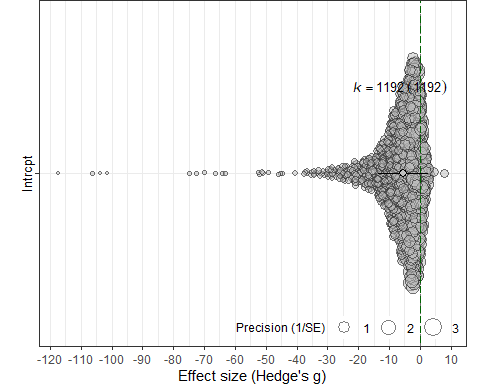
Effect (% of control): 0.0042281 CI.lb (%): 0.0032236 CI.ub (%): 0.0055457

Orchard Plot

## Warning: Group 'Comparison\_ID' is a numeric variable.

## Scale for colour is already present.  
## Adding another scale for colour, which will replace the existing scale.  
## Scale for fill is already present.  
## Adding another scale for fill, which will replace the existing scale.

## Warning: Using `size` aesthetic for lines was deprecated in ggplot2 3.4.0.  
## ℹ Please use `linewidth` instead.  
## This warning is displayed once every 8 hours.  
## Call `lifecycle::last\_lifecycle\_warnings()` to see where this warning was  
## generated.



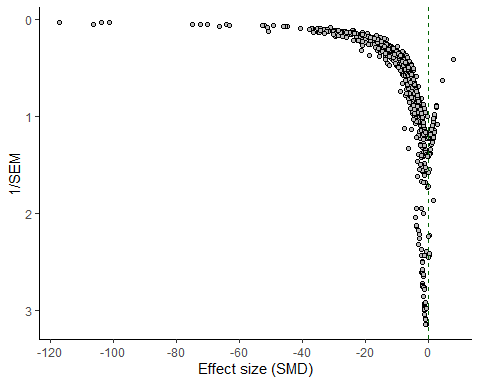
## Publication bias

Trim-and-fill

##   
## Estimated number of missing studies on the right side: 148 (SE = 17.2627)  
## Test of H0: no missing studies on the right side: p-val < .0001  
##   
## Random-Effects Model (k = 1340; tau^2 estimator: REML)  
##   
## tau^2 (estimated amount of total heterogeneity): 31.6343 (SE = 1.4803)  
## tau (square root of estimated tau^2 value): 5.6244  
## I^2 (total heterogeneity / total variability): 96.00%  
## H^2 (total variability / sampling variability): 24.97  
##   
## Test for Heterogeneity:  
## Q(df = 1339) = 9105.8288, p-val < .0001  
##   
## Model Results:  
##   
## estimate se zval pval ci.lb ci.ub   
## -4.7407 0.1726 -27.4729 <.0001 -5.0790 -4.4025 \*\*\*   
##   
## ---  
## Signif. codes: 0 '\*\*\*' 0.001 '\*\*' 0.01 '\*' 0.05 '.' 0.1 ' ' 1

##   
## Estimated number of missing studies on the right side: 364 (SE = 22.0171)  
##   
## Random-Effects Model (k = 1556; tau^2 estimator: REML)  
##   
## tau^2 (estimated amount of total heterogeneity): 51.2808 (SE = 2.1383)  
## tau (square root of estimated tau^2 value): 7.1611  
## I^2 (total heterogeneity / total variability): 97.16%  
## H^2 (total variability / sampling variability): 35.23  
##   
## Test for Heterogeneity:  
## Q(df = 1555) = 10727.1729, p-val < .0001  
##   
## Model Results:  
##   
## estimate se zval pval ci.lb ci.ub   
## -3.2553 0.1981 -16.4318 <.0001 -3.6436 -2.8671 \*\*\*   
##   
## ---  
## Signif. codes: 0 '\*\*\*' 0.001 '\*\*' 0.01 '\*' 0.05 '.' 0.1 ' ' 1

Funnel plot



## Saving 5 x 4 in image

Egger’s regression

##   
## Regression Test for Funnel Plot Asymmetry  
##   
## Model: mixed-effects meta-regression model  
## Predictor: inverse of the square root sample size  
##   
## Test for Funnel Plot Asymmetry: z = -2.1881, p = 0.0287  
## Limit Estimate (as ni -> inf): b = -3.8469 (CI: -5.3177, -2.3762)

# 3-level

##   
## Multivariate Meta-Analysis Model (k = 1192; method: REML)  
##   
## Variance Components:  
##   
## estim sqrt nlvls fixed factor   
## sigma^2.1 10.3942 3.2240 359 no rayyan.key   
## sigma^2.2 8.2045 2.8643 1192 no rayyan.key/Comparison\_ID   
##   
## Test for Heterogeneity:  
## Q(df = 1191) = 7860.2351, p-val < .0001  
##   
## Model Results:  
##   
## estimate se zval pval ci.lb ci.ub   
## -6.1321 0.2212 -27.7225 <.0001 -6.5657 -5.6986 \*\*\*   
##   
## ---  
## Signif. codes: 0 '\*\*\*' 0.001 '\*\*' 0.01 '\*' 0.05 '.' 0.1 ' ' 1

##   
## estimate ci.lb ci.ub   
## sigma^2.1 10.3942 7.9504 13.5359   
## sigma.1 3.2240 2.8196 3.6791   
##   
## estimate ci.lb ci.ub   
## sigma^2.2 8.2045 6.9802 9.6272   
## sigma.2 2.8643 2.6420 3.1028

Exact p value: 3.7391062^{-169} Exact Q test p value 0

Effect (% of control): 0.002172 CI.lb (%): 0.0014079 CI.ub (%): 0.0033507

## $results  
## % of total variance I2  
## Level 1 5.958217 ---  
## Level 2 (exp) 41.484833 41.48  
## Level 3 (art) 52.556949 52.56  
##   
## $totalI2  
## [1] 94.04178  
##   
## $plot

##   
## attr(,"class")  
## [1] "mlm.variance.distribution" "list"

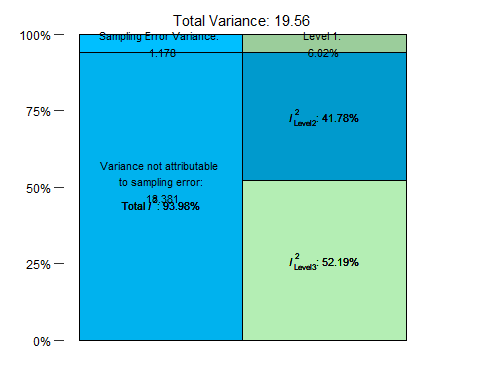
# Meta-regressions (3-level)

Differentiation

##   
## Multivariate Meta-Analysis Model (k = 1192; method: REML)  
##   
## Variance Components:  
##   
## estim sqrt nlvls fixed factor   
## sigma^2.1 10.2088 3.1951 359 no rayyan.key   
## sigma^2.2 8.1727 2.8588 1192 no rayyan.key/Comparison\_ID   
##   
## Test for Residual Heterogeneity:  
## QE(df = 1190) = 7813.1335, p-val < .0001  
##   
## Test of Moderators (coefficient 2):  
## QM(df = 1) = 2.3361, p-val = 0.1264  
##   
## Model Results:  
##   
## estimate   
## intrcpt -6.2745   
## relevel(factor(dados\_meta\_smd$Diferentiation\_method\_YN), ref = "No")Yes 0.7785   
## se   
## intrcpt 0.2413   
## relevel(factor(dados\_meta\_smd$Diferentiation\_method\_YN), ref = "No")Yes 0.5094   
## zval   
## intrcpt -26.0054   
## relevel(factor(dados\_meta\_smd$Diferentiation\_method\_YN), ref = "No")Yes 1.5284   
## pval   
## intrcpt <.0001   
## relevel(factor(dados\_meta\_smd$Diferentiation\_method\_YN), ref = "No")Yes 0.1264   
## ci.lb   
## intrcpt -6.7474   
## relevel(factor(dados\_meta\_smd$Diferentiation\_method\_YN), ref = "No")Yes -0.2198   
## ci.ub   
## intrcpt -5.8016   
## relevel(factor(dados\_meta\_smd$Diferentiation\_method\_YN), ref = "No")Yes 1.7769   
##   
## intrcpt \*\*\*   
## relevel(factor(dados\_meta\_smd$Diferentiation\_method\_YN), ref = "No")Yes   
##   
## ---  
## Signif. codes: 0 '\*\*\*' 0.001 '\*\*' 0.01 '\*' 0.05 '.' 0.1 ' ' 1

## $results  
## % of total variance I2  
## Level 1 6.024394 ---  
## Level 2 (exp) 41.782770 41.78  
## Level 3 (art) 52.192836 52.19  
##   
## $totalI2  
## [1] 93.97561  
##   
## $plot

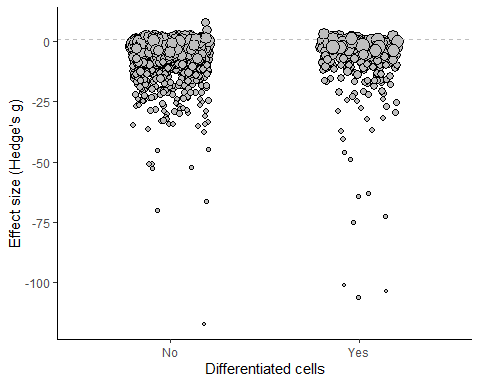
## Warning in is.na(x): is.na() aplicado a um objeto diferente de lista ou vetor  
## de tipo 'language'  
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## de tipo 'language'  
## Warning in is.na(x): is.na() aplicado a um objeto diferente de lista ou vetor  
## de tipo 'language'



##   
## attr(,"class")  
## [1] "mlm.variance.distribution" "list"

Exact p value: 4.3022431^{-149}, 0.1264056 Exact Q test p value 0

Differentiation bubble plot



Diff. duration

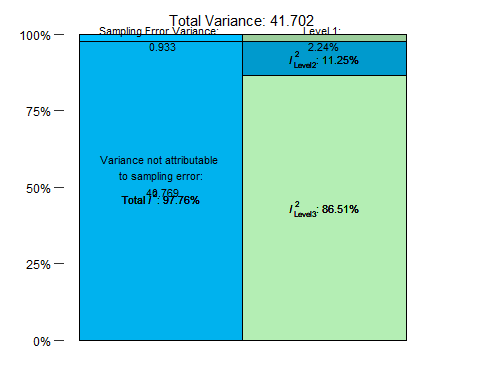
## Warning: 970 rows with NAs omitted from model fitting.

##   
## Multivariate Meta-Analysis Model (k = 222; method: REML)  
##   
## Variance Components:  
##   
## estim sqrt nlvls fixed factor   
## sigma^2.1 36.0771 6.0064 56 no rayyan.key   
## sigma^2.2 4.6921 2.1661 222 no rayyan.key/Comparison\_ID   
##   
## Test for Residual Heterogeneity:  
## QE(df = 220) = 1385.1908, p-val < .0001  
##   
## Test of Moderators (coefficient 2):  
## QM(df = 1) = 1.1769, p-val = 0.2780  
##   
## Model Results:  
##   
## estimate se   
## intrcpt -8.0812 1.9730   
## as.numeric(dados\_meta\_smd$Diferentiation\_duration\_days) 0.3079 0.2838   
## zval pval   
## intrcpt -4.0959 <.0001   
## as.numeric(dados\_meta\_smd$Diferentiation\_duration\_days) 1.0849 0.2780   
## ci.lb ci.ub   
## intrcpt -11.9482 -4.2142 \*\*\*   
## as.numeric(dados\_meta\_smd$Diferentiation\_duration\_days) -0.2484 0.8642   
##   
## ---  
## Signif. codes: 0 '\*\*\*' 0.001 '\*\*' 0.01 '\*' 0.05 '.' 0.1 ' ' 1

## $results  
## % of total variance I2  
## Level 1 2.237695 ---  
## Level 2 (exp) 11.251375 11.25  
## Level 3 (art) 86.510930 86.51  
##   
## $totalI2  
## [1] 97.76231  
##   
## $plot

## Warning in is.na(x): is.na() aplicado a um objeto diferente de lista ou vetor  
## de tipo 'language'

## Warning in is.na(x): is.na() aplicado a um objeto diferente de lista ou vetor  
## de tipo 'language'  
## Warning in is.na(x): is.na() aplicado a um objeto diferente de lista ou vetor  
## de tipo 'language'

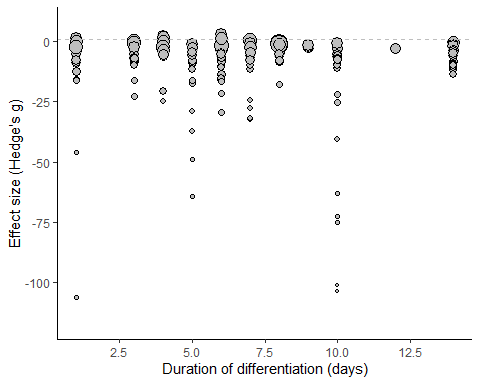


##   
## attr(,"class")  
## [1] "mlm.variance.distribution" "list"

Exact p value: 4.2046795^{-5}, 0.2779846 Exact Q test p value 5.4528253^{-168}

Diff. duration bubble plot

## Warning: Removed 970 rows containing missing values or values outside the scale range  
## (`geom\_point()`).



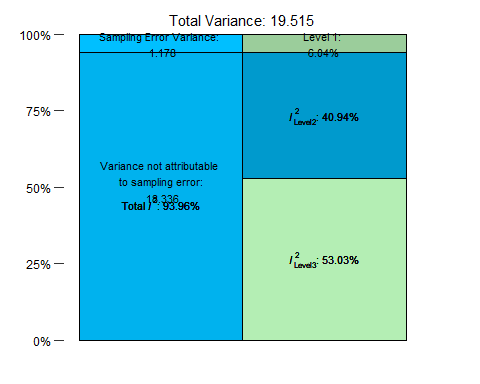
## Warning: Removed 970 rows containing missing values or values outside the scale range  
## (`geom\_point()`).

Aggregation

##   
## Multivariate Meta-Analysis Model (k = 1192; method: REML)  
##   
## Variance Components:  
##   
## estim sqrt nlvls fixed factor   
## sigma^2.1 10.3480 3.2168 359 no rayyan.key   
## sigma^2.2 7.9885 2.8264 1192 no rayyan.key/Comparison\_ID   
##   
## Test for Residual Heterogeneity:  
## QE(df = 1188) = 7584.0680, p-val < .0001  
##   
## Test of Moderators (coefficients 2:4):  
## QM(df = 3) = 20.4707, p-val = 0.0001  
##   
## Model Results:  
##   
## estimate   
## intrcpt -4.2622   
## relevel(factor(dados\_meta\_smd$Abeta\_aggregation), ref = "Monomers")Fibers -2.6631   
## relevel(factor(dados\_meta\_smd$Abeta\_aggregation), ref = "Monomers")Oligomers -1.2148   
## relevel(factor(dados\_meta\_smd$Abeta\_aggregation), ref = "Monomers")Unclear -2.3931   
## se   
## intrcpt 0.6357   
## relevel(factor(dados\_meta\_smd$Abeta\_aggregation), ref = "Monomers")Fibers 0.7542   
## relevel(factor(dados\_meta\_smd$Abeta\_aggregation), ref = "Monomers")Oligomers 0.6647   
## relevel(factor(dados\_meta\_smd$Abeta\_aggregation), ref = "Monomers")Unclear 0.6957   
## zval   
## intrcpt -6.7046   
## relevel(factor(dados\_meta\_smd$Abeta\_aggregation), ref = "Monomers")Fibers -3.5312   
## relevel(factor(dados\_meta\_smd$Abeta\_aggregation), ref = "Monomers")Oligomers -1.8276   
## relevel(factor(dados\_meta\_smd$Abeta\_aggregation), ref = "Monomers")Unclear -3.4399   
## pval   
## intrcpt <.0001   
## relevel(factor(dados\_meta\_smd$Abeta\_aggregation), ref = "Monomers")Fibers 0.0004   
## relevel(factor(dados\_meta\_smd$Abeta\_aggregation), ref = "Monomers")Oligomers 0.0676   
## relevel(factor(dados\_meta\_smd$Abeta\_aggregation), ref = "Monomers")Unclear 0.0006   
## ci.lb   
## intrcpt -5.5081   
## relevel(factor(dados\_meta\_smd$Abeta\_aggregation), ref = "Monomers")Fibers -4.1413   
## relevel(factor(dados\_meta\_smd$Abeta\_aggregation), ref = "Monomers")Oligomers -2.5176   
## relevel(factor(dados\_meta\_smd$Abeta\_aggregation), ref = "Monomers")Unclear -3.7566   
## ci.ub   
## intrcpt -3.0162   
## relevel(factor(dados\_meta\_smd$Abeta\_aggregation), ref = "Monomers")Fibers -1.1850   
## relevel(factor(dados\_meta\_smd$Abeta\_aggregation), ref = "Monomers")Oligomers 0.0880   
## relevel(factor(dados\_meta\_smd$Abeta\_aggregation), ref = "Monomers")Unclear -1.0296   
##   
## intrcpt \*\*\*   
## relevel(factor(dados\_meta\_smd$Abeta\_aggregation), ref = "Monomers")Fibers \*\*\*   
## relevel(factor(dados\_meta\_smd$Abeta\_aggregation), ref = "Monomers")Oligomers .   
## relevel(factor(dados\_meta\_smd$Abeta\_aggregation), ref = "Monomers")Unclear \*\*\*   
##   
## ---  
## Signif. codes: 0 '\*\*\*' 0.001 '\*\*' 0.01 '\*' 0.05 '.' 0.1 ' ' 1

## $results  
## % of total variance I2  
## Level 1 6.038285 ---  
## Level 2 (exp) 40.935350 40.94  
## Level 3 (art) 53.026365 53.03  
##   
## $totalI2  
## [1] 93.96172  
##   
## $plot

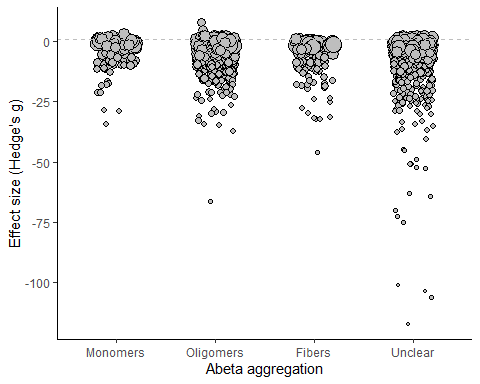
## Warning in is.na(x): is.na() aplicado a um objeto diferente de lista ou vetor  
## de tipo 'language'  
## Warning in is.na(x): is.na() aplicado a um objeto diferente de lista ou vetor  
## de tipo 'language'  
## Warning in is.na(x): is.na() aplicado a um objeto diferente de lista ou vetor  
## de tipo 'language'



##   
## attr(,"class")  
## [1] "mlm.variance.distribution" "list"

Exact p value: 2.0199784^{-11}, 4.1362829^{-4}, 0.0676126, 5.8185803^{-4} Exact Q test p value 0

Aggregation bubble plot

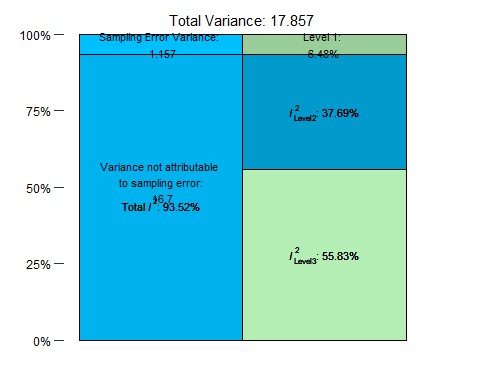


Abeta concentration (só até 100 uM)

##   
## Multivariate Meta-Analysis Model (k = 1123; method: REML)  
##   
## Variance Components:  
##   
## estim sqrt nlvls fixed factor   
## sigma^2.1 9.9693 3.1574 345 no rayyan.key   
## sigma^2.2 6.7308 2.5944 1123 no rayyan.key/Comparison\_ID   
##   
## Test for Residual Heterogeneity:  
## QE(df = 1121) = 7132.2605, p-val < .0001  
##   
## Test of Moderators (coefficient 2):  
## QM(df = 1) = 111.5951, p-val < .0001  
##   
## Model Results:  
##   
## estimate se zval pval   
## intrcpt -4.6949 0.2482 -18.9143 <.0001   
## dados\_meta\_smd\_max100$Concentration\_uM -0.1256 0.0119 -10.5639 <.0001   
## ci.lb ci.ub   
## intrcpt -5.1814 -4.2084 \*\*\*   
## dados\_meta\_smd\_max100$Concentration\_uM -0.1489 -0.1023 \*\*\*   
##   
## ---  
## Signif. codes: 0 '\*\*\*' 0.001 '\*\*' 0.01 '\*' 0.05 '.' 0.1 ' ' 1

## $results  
## % of total variance I2  
## Level 1 6.476903 ---  
## Level 2 (exp) 37.693622 37.69  
## Level 3 (art) 55.829474 55.83  
##   
## $totalI2  
## [1] 93.5231  
##   
## $plot

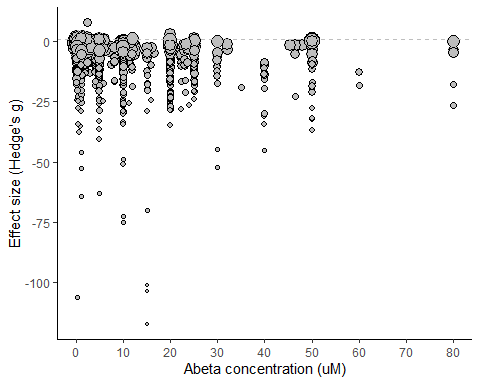
## Warning in is.na(x): is.na() aplicado a um objeto diferente de lista ou vetor  
## de tipo 'language'  
## Warning in is.na(x): is.na() aplicado a um objeto diferente de lista ou vetor  
## de tipo 'language'  
## Warning in is.na(x): is.na() aplicado a um objeto diferente de lista ou vetor  
## de tipo 'language'



##   
## attr(,"class")  
## [1] "mlm.variance.distribution" "list"

Exact p value: 8.6980766^{-80}, 4.3827756^{-26} Exact Q test p value 0

Abeta concentration bubble plot



Abeta duration of exposure

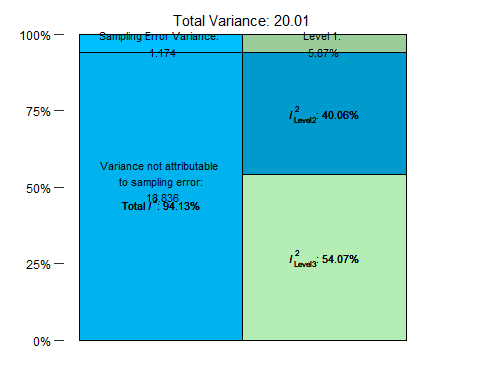
## Warning: 12 rows with NAs omitted from model fitting.

##   
## Multivariate Meta-Analysis Model (k = 1180; method: REML)  
##   
## Variance Components:  
##   
## estim sqrt nlvls fixed factor   
## sigma^2.1 10.8197 3.2893 352 no rayyan.key   
## sigma^2.2 8.0166 2.8314 1180 no rayyan.key/Comparison\_ID   
##   
## Test for Residual Heterogeneity:  
## QE(df = 1178) = 7793.5432, p-val < .0001  
##   
## Test of Moderators (coefficient 2):  
## QM(df = 1) = 13.9005, p-val = 0.0002  
##   
## Model Results:  
##   
## estimate se zval pval   
## intrcpt -4.9261 0.4015 -12.2682 <.0001   
## as.numeric(dados\_meta\_smd$Duration\_days) -0.9170 0.2460 -3.7283 0.0002   
## ci.lb ci.ub   
## intrcpt -5.7131 -4.1391 \*\*\*   
## as.numeric(dados\_meta\_smd$Duration\_days) -1.3991 -0.4350 \*\*\*   
##   
## ---  
## Signif. codes: 0 '\*\*\*' 0.001 '\*\*' 0.01 '\*' 0.05 '.' 0.1 ' ' 1

## $results  
## % of total variance I2  
## Level 1 5.86529 ---  
## Level 2 (exp) 40.06300 40.06  
## Level 3 (art) 54.07171 54.07  
##   
## $totalI2  
## [1] 94.13471  
##   
## $plot

## Warning in is.na(x): is.na() aplicado a um objeto diferente de lista ou vetor  
## de tipo 'language'

## Warning in is.na(x): is.na() aplicado a um objeto diferente de lista ou vetor  
## de tipo 'language'  
## Warning in is.na(x): is.na() aplicado a um objeto diferente de lista ou vetor  
## de tipo 'language'

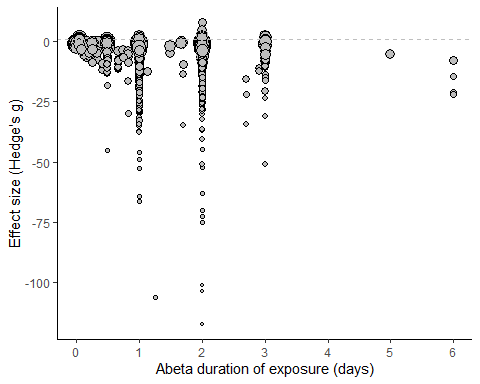


##   
## attr(,"class")  
## [1] "mlm.variance.distribution" "list"

Exact p value: 1.342729^{-34}, 1.9274499^{-4} Exact Q test p value 0

Abeta duration bubble plot

## Warning: Removed 12 rows containing missing values or values outside the scale range  
## (`geom\_point()`).



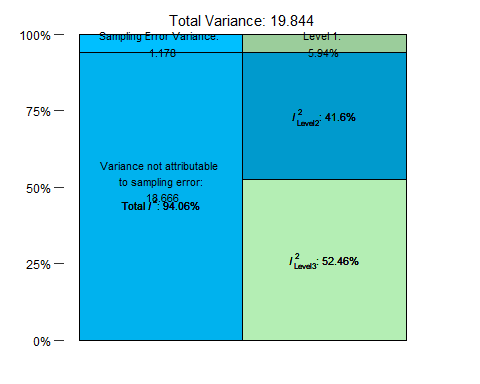
## Warning: Removed 12 rows containing missing values or values outside the scale range  
## (`geom\_point()`).

Assay

##   
## Multivariate Meta-Analysis Model (k = 1192; method: REML)  
##   
## Variance Components:  
##   
## estim sqrt nlvls fixed factor   
## sigma^2.1 10.4102 3.2265 359 no rayyan.key   
## sigma^2.2 8.2558 2.8733 1192 no rayyan.key/Comparison\_ID   
##   
## Test for Residual Heterogeneity:  
## QE(df = 1185) = 7763.9571, p-val < .0001  
##   
## Test of Moderators (coefficients 2:7):  
## QM(df = 6) = 7.0035, p-val = 0.3205  
##   
## Model Results:  
##   
## estimate se   
## intrcpt -6.3067 0.2439   
## relevel(factor(dados\_meta\_smd$Assay), ref = "MTT")CCK-8 -0.2098 1.1426   
## relevel(factor(dados\_meta\_smd$Assay), ref = "MTT")EZ4U -1.2180 3.6709   
## relevel(factor(dados\_meta\_smd$Assay), ref = "MTT")MTS 0.6358 1.0850   
## relevel(factor(dados\_meta\_smd$Assay), ref = "MTT")Resazurin 5.6731 3.4307   
## relevel(factor(dados\_meta\_smd$Assay), ref = "MTT")WST 1.6878 0.8726   
## relevel(factor(dados\_meta\_smd$Assay), ref = "MTT")XTT 0.9740 1.8345   
## zval pval   
## intrcpt -25.8527 <.0001   
## relevel(factor(dados\_meta\_smd$Assay), ref = "MTT")CCK-8 -0.1836 0.8543   
## relevel(factor(dados\_meta\_smd$Assay), ref = "MTT")EZ4U -0.3318 0.7400   
## relevel(factor(dados\_meta\_smd$Assay), ref = "MTT")MTS 0.5860 0.5578   
## relevel(factor(dados\_meta\_smd$Assay), ref = "MTT")Resazurin 1.6537 0.0982   
## relevel(factor(dados\_meta\_smd$Assay), ref = "MTT")WST 1.9344 0.0531   
## relevel(factor(dados\_meta\_smd$Assay), ref = "MTT")XTT 0.5309 0.5955   
## ci.lb ci.ub   
## intrcpt -6.7848 -5.8285   
## relevel(factor(dados\_meta\_smd$Assay), ref = "MTT")CCK-8 -2.4494 2.0297   
## relevel(factor(dados\_meta\_smd$Assay), ref = "MTT")EZ4U -8.4129 5.9769   
## relevel(factor(dados\_meta\_smd$Assay), ref = "MTT")MTS -1.4907 2.7624   
## relevel(factor(dados\_meta\_smd$Assay), ref = "MTT")Resazurin -1.0509 12.3971   
## relevel(factor(dados\_meta\_smd$Assay), ref = "MTT")WST -0.0223 3.3980   
## relevel(factor(dados\_meta\_smd$Assay), ref = "MTT")XTT -2.6216 4.5696   
##   
## intrcpt \*\*\*   
## relevel(factor(dados\_meta\_smd$Assay), ref = "MTT")CCK-8   
## relevel(factor(dados\_meta\_smd$Assay), ref = "MTT")EZ4U   
## relevel(factor(dados\_meta\_smd$Assay), ref = "MTT")MTS   
## relevel(factor(dados\_meta\_smd$Assay), ref = "MTT")Resazurin .   
## relevel(factor(dados\_meta\_smd$Assay), ref = "MTT")WST .   
## relevel(factor(dados\_meta\_smd$Assay), ref = "MTT")XTT   
##   
## ---  
## Signif. codes: 0 '\*\*\*' 0.001 '\*\*' 0.01 '\*' 0.05 '.' 0.1 ' ' 1

## $results  
## % of total variance I2  
## Level 1 5.937999 ---  
## Level 2 (exp) 41.602791 41.6  
## Level 3 (art) 52.459210 52.46  
##   
## $totalI2  
## [1] 94.062  
##   
## $plot

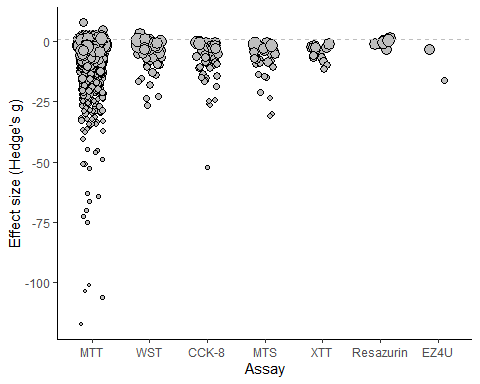
## Warning in is.na(x): is.na() aplicado a um objeto diferente de lista ou vetor  
## de tipo 'language'  
## Warning in is.na(x): is.na() aplicado a um objeto diferente de lista ou vetor  
## de tipo 'language'  
## Warning in is.na(x): is.na() aplicado a um objeto diferente de lista ou vetor  
## de tipo 'language'



##   
## attr(,"class")  
## [1] "mlm.variance.distribution" "list"

Exact p value: 2.2660986^{-147}, 0.8542904, 0.7400355, 0.5578456, 0.0981985, 0.0530677, 0.5954682 Exact Q test p value 0

Assay bubble plot



Cell density

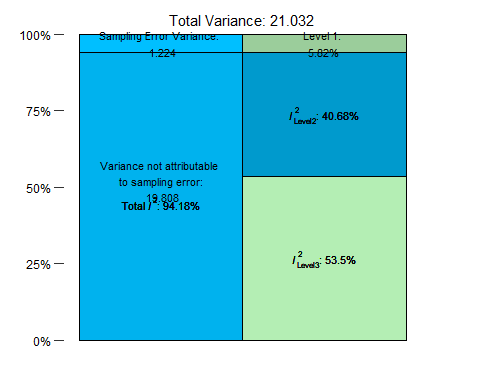
## Warning: 502 rows with NAs omitted from model fitting.

##   
## Multivariate Meta-Analysis Model (k = 690; method: REML)  
##   
## Variance Components:  
##   
## estim sqrt nlvls fixed factor   
## sigma^2.1 11.2522 3.3544 211 no rayyan.key   
## sigma^2.2 8.5556 2.9250 690 no rayyan.key/Comparison\_ID   
##   
## Test for Residual Heterogeneity:  
## QE(df = 688) = 4417.8581, p-val < .0001  
##   
## Test of Moderators (coefficient 2):  
## QM(df = 1) = 0.0974, p-val = 0.7549  
##   
## Model Results:  
##   
## estimate se zval pval   
## intrcpt -6.4397 0.3058 -21.0617 <.0001   
## as.numeric(dados\_meta\_smd$Cell\_density) 0.0000 0.0000 0.3121 0.7549   
## ci.lb ci.ub   
## intrcpt -7.0389 -5.8404 \*\*\*   
## as.numeric(dados\_meta\_smd$Cell\_density) -0.0000 0.0000   
##   
## ---  
## Signif. codes: 0 '\*\*\*' 0.001 '\*\*' 0.01 '\*' 0.05 '.' 0.1 ' ' 1

## $results  
## % of total variance I2  
## Level 1 5.821664 ---  
## Level 2 (exp) 40.678477 40.68  
## Level 3 (art) 53.499859 53.5  
##   
## $totalI2  
## [1] 94.17834  
##   
## $plot

## Warning in is.na(x): is.na() aplicado a um objeto diferente de lista ou vetor  
## de tipo 'language'

## Warning in is.na(x): is.na() aplicado a um objeto diferente de lista ou vetor  
## de tipo 'language'  
## Warning in is.na(x): is.na() aplicado a um objeto diferente de lista ou vetor  
## de tipo 'language'

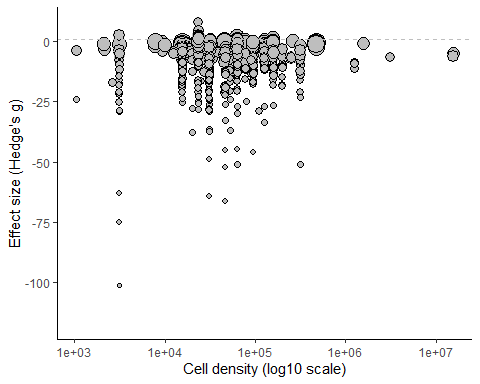


##   
## attr(,"class")  
## [1] "mlm.variance.distribution" "list"

Exact p value: 1.7847153^{-98}, 0.7549472 Exact Q test p value 0

Cell density bubble plot

## Warning: Removed 502 rows containing missing values or values outside the scale range  
## (`geom\_point()`).



## Warning: Removed 502 rows containing missing values or values outside the scale range  
## (`geom\_point()`).

# Multivariate Meta-regressions (3-level)

All combinations of variables from the selected list are tested in multivariable models, and the best models are ranked by corrected Akaike Information Criteria (AICc). For each best model selected, we decompose the R2 value for each moderator included. For this, we calculate the mean of the differences between R2 from models with and without the moderator in all possible orders of moderator inclusion. Additionally, we performed a Q test of moderators for each variable (including all dummy variables for each categorical moderator) to obtain p-values for individual variables.

Functions to decompose R2 (3-level)

For the multivariate analyses, we can only use the comparisons for which all variables of interest are reported.

Considering all pre-registered variables, we’d have 84 experiments available (i.e. 1108 exclusions due to missing data). As we have 7 variables, we should have at least 70 comparisons - so can use all of them now. There are 128 possible models.

## Initialization...  
## TASK: Exhaustive screening of candidate set.  
## Fitting...  
##   
## After 50 models:  
## Best model: yi~1+Concentration\_uM+Duration\_hours  
## Crit= 512.560961566997  
## Mean crit= 539.409119599157  
##   
## After 100 models:  
## Best model: yi~1+Concentration\_uM+Duration\_hours  
## Crit= 512.560961566997  
## Mean crit= 537.671497814322  
##   
## After 150 models:  
## Best model: yi~1+Concentration\_uM+Duration\_hours  
## Crit= 512.560961566997  
## Mean crit= 535.593981786102  
## Completed.

## glmulti.analysis  
## Method: h / Fitting: rma.mv.glmulti / IC used: aicc  
## Level: 1 / Marginality: FALSE  
## From 128 models:  
## Best IC: 512.560961566997  
## Best model:  
## [1] "yi ~ 1 + Concentration\_uM + Duration\_hours"  
## Evidence weight: 0.352316855659331  
## Worst IC: 557.625817903142  
## 2 models within 2 IC units.  
## 14 models to reach 95% of evidence weight.

Top models (within 2 IC units of best model)

## model aicc weights  
## 1 yi ~ 1 + Concentration\_uM + Duration\_hours 512.5610 0.3523169  
## 2 yi ~ 1 + Concentration\_uM + Duration\_hours + Cell\_density 514.2951 0.1480350

Decomposing R2 for the best model:

## [1] "Running models for Concentration\_uM"  
## [1] "Running models for Duration\_hours"

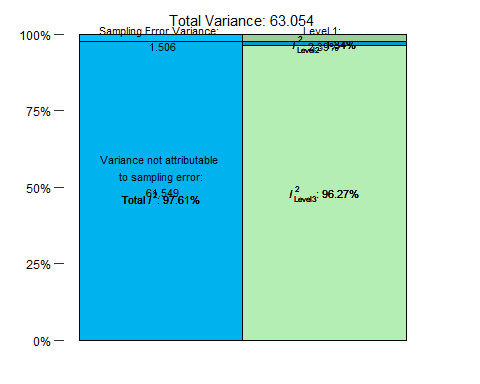
Resultados:

##   
## Multivariate Meta-Analysis Model (k = 84; method: ML)  
##   
## Variance Components:  
##   
## estim sqrt nlvls fixed factor   
## sigma^2.1 60.7019 7.7911 23 no rayyan.key   
## sigma^2.2 0.8467 0.9202 84 no rayyan.key/Comparison\_ID   
##   
## Test for Residual Heterogeneity:  
## QE(df = 81) = 376.7334, p-val < .0001  
##   
## Test of Moderators (coefficients 2:3):  
## QM(df = 2) = 45.5190, p-val < .0001  
##   
## Model Results:  
##   
## estimate se zval pval ci.lb ci.ub   
## intrcpt -0.3736 1.9266 -0.1939 0.8463 -4.1496 3.4024   
## Concentration\_uM -0.1320 0.0289 -4.5700 <.0001 -0.1886 -0.0754 \*\*\*   
## Duration\_hours -0.1287 0.0277 -4.6416 <.0001 -0.1830 -0.0743 \*\*\*   
##   
## ---  
## Signif. codes: 0 '\*\*\*' 0.001 '\*\*' 0.01 '\*' 0.05 '.' 0.1 ' ' 1

##   
## estimate ci.lb ci.ub   
## sigma^2.1 60.7019 28.2293 132.3398   
## sigma.1 7.7911 5.3131 11.5039   
##   
## estimate ci.lb ci.ub   
## sigma^2.2 0.8467 0.1134 2.3398   
## sigma.2 0.9202 0.3368 1.5296

## $results  
## % of total variance I2  
## Level 1 2.387875 ---  
## Level 2 (exp) 1.342825 1.34  
## Level 3 (art) 96.269300 96.27  
##   
## $totalI2  
## [1] 97.61213  
##   
## $plot

## Warning in is.na(x): is.na() aplicado a um objeto diferente de lista ou vetor  
## de tipo 'language'  
## Warning in is.na(x): is.na() aplicado a um objeto diferente de lista ou vetor  
## de tipo 'language'  
## Warning in is.na(x): is.na() aplicado a um objeto diferente de lista ou vetor  
## de tipo 'language'



##   
## attr(,"class")  
## [1] "mlm.variance.distribution" "list"

## [1] -230.9289

## [1] "Running models for Concentration\_uM"  
## [1] "Running models for Duration\_hours"  
## [1] "Running models for Cell\_density"

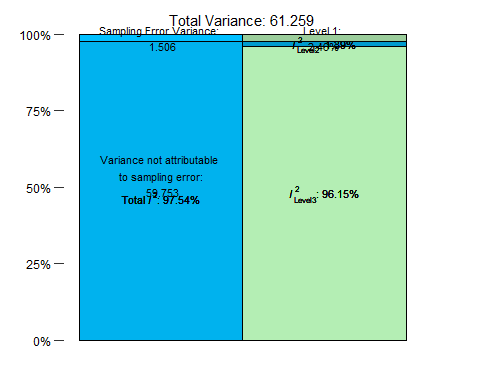
Resultados:

##   
## Multivariate Meta-Analysis Model (k = 84; method: ML)  
##   
## Variance Components:  
##   
## estim sqrt nlvls fixed factor   
## sigma^2.1 58.9015 7.6747 23 no rayyan.key   
## sigma^2.2 0.8516 0.9228 84 no rayyan.key/Comparison\_ID   
##   
## Test for Residual Heterogeneity:  
## QE(df = 80) = 372.8236, p-val < .0001  
##   
## Test of Moderators (coefficients 2:4):  
## QM(df = 3) = 45.9179, p-val < .0001  
##   
## Model Results:  
##   
## estimate se zval pval ci.lb ci.ub   
## intrcpt -0.8539 2.0083 -0.4252 0.6707 -4.7902 3.0823   
## Concentration\_uM -0.1318 0.0289 -4.5647 <.0001 -0.1884 -0.0752 \*\*\*   
## Duration\_hours -0.1281 0.0277 -4.6215 <.0001 -0.1824 -0.0738 \*\*\*   
## Cell\_density 0.0000 0.0000 0.7705 0.4410 -0.0000 0.0000   
##   
## ---  
## Signif. codes: 0 '\*\*\*' 0.001 '\*\*' 0.01 '\*' 0.05 '.' 0.1 ' ' 1

##   
## estimate ci.lb ci.ub   
## sigma^2.1 58.9015 27.2436 128.7308   
## sigma.1 7.6747 5.2195 11.3460   
##   
## estimate ci.lb ci.ub   
## sigma^2.2 0.8516 0.1158 2.3496   
## sigma.2 0.9228 0.3402 1.5328

## $results  
## % of total variance I2  
## Level 1 2.457865 ---  
## Level 2 (exp) 1.390147 1.39  
## Level 3 (art) 96.151988 96.15  
##   
## $totalI2  
## [1] 97.54214  
##   
## $plot

## Warning in is.na(x): is.na() aplicado a um objeto diferente de lista ou vetor  
## de tipo 'language'  
## Warning in is.na(x): is.na() aplicado a um objeto diferente de lista ou vetor  
## de tipo 'language'  
## Warning in is.na(x): is.na() aplicado a um objeto diferente de lista ou vetor  
## de tipo 'language'



##   
## attr(,"class")  
## [1] "mlm.variance.distribution" "list"

## [1] -221.2749

# Mudando diferenciação para sim/não, tirando Assay e duração da diferenciação

## Initialization...  
## TASK: Exhaustive screening of candidate set.  
## Fitting...  
##   
## After 50 models:  
## Best model: yi~1+Abeta\_aggregation+Concentration\_uM+Duration\_days  
## Crit= 3892.24614994386  
## Mean crit= 3944.506268313  
## Completed.

## glmulti.analysis  
## Method: h / Fitting: rma.mv.glmulti / IC used: aicc  
## Level: 1 / Marginality: FALSE  
## From 32 models:  
## Best IC: 3892.24614994386  
## Best model:  
## [1] "yi ~ 1 + Abeta\_aggregation + Concentration\_uM + Duration\_days"  
## Evidence weight: 0.448461610587176  
## Worst IC: 3995.1543575226  
## 3 models within 2 IC units.  
## 3 models to reach 95% of evidence weight.

Top models (within 2 IC units of best model)

## model  
## 1 yi ~ 1 + Abeta\_aggregation + Concentration\_uM + Duration\_days  
## 2 yi ~ 1 + Diferentiation\_method\_YN + Abeta\_aggregation + Concentration\_uM + Duration\_days  
## 3 yi ~ 1 + Abeta\_aggregation + Concentration\_uM + Duration\_days + Cell\_density  
## aicc weights  
## 1 3892.246 0.4484616  
## 2 3893.564 0.2320630  
## 3 3893.803 0.2058717

Decomposing R2 for the best model:

## [1] "Running models for Abeta\_aggregation"  
## [1] "Running models for Concentration\_uM"  
## [1] "Running models for Duration\_days"

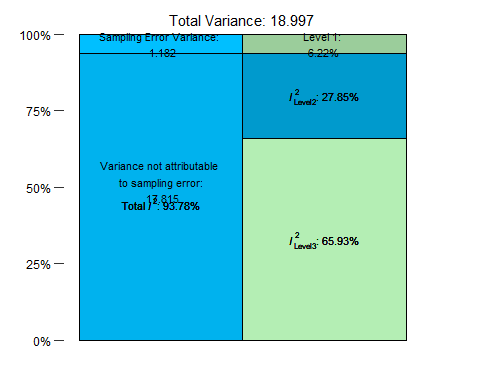
Resultados:

##   
## Multivariate Meta-Analysis Model (k = 641; method: ML)  
##   
## Variance Components:  
##   
## estim sqrt nlvls fixed factor   
## sigma^2.1 12.5249 3.5391 201 no rayyan.key   
## sigma^2.2 5.2901 2.3000 641 no rayyan.key/Comparison\_ID   
##   
## Test for Residual Heterogeneity:  
## QE(df = 635) = 3613.1164, p-val < .0001  
##   
## Test of Moderators (coefficients 2:6):  
## QM(df = 5) = 120.1605, p-val < .0001  
##   
## Model Results:  
##   
## estimate se zval pval ci.lb ci.ub   
## intrcpt -3.3043 0.7831 -4.2197 <.0001 -4.8391 -1.7695   
## Abeta\_aggregationMonomers 2.9768 0.7720 3.8560 0.0001 1.4637 4.4900   
## Abeta\_aggregationOligomers 0.8426 0.6279 1.3419 0.1796 -0.3881 2.0733   
## Abeta\_aggregationUnclear -0.9178 0.7282 -1.2604 0.2075 -2.3450 0.5094   
## Concentration\_uM -0.1182 0.0134 -8.8531 <.0001 -0.1444 -0.0921   
## Duration\_days -1.1601 0.3187 -3.6400 0.0003 -1.7847 -0.5354   
##   
## intrcpt \*\*\*   
## Abeta\_aggregationMonomers \*\*\*   
## Abeta\_aggregationOligomers   
## Abeta\_aggregationUnclear   
## Concentration\_uM \*\*\*   
## Duration\_days \*\*\*   
##   
## ---  
## Signif. codes: 0 '\*\*\*' 0.001 '\*\*' 0.01 '\*' 0.05 '.' 0.1 ' ' 1

##   
## estimate ci.lb ci.ub   
## sigma^2.1 12.5249 8.4480 18.2424   
## sigma.1 3.5391 2.9065 4.2711   
##   
## estimate ci.lb ci.ub   
## sigma^2.2 5.2901 4.1182 6.7521   
## sigma.2 2.3000 2.0293 2.5985

## $results  
## % of total variance I2  
## Level 1 6.221772 ---  
## Level 2 (exp) 27.847170 27.85  
## Level 3 (art) 65.931058 65.93  
##   
## $totalI2  
## [1] 93.77823  
##   
## $plot

## Warning in is.na(x): is.na() aplicado a um objeto diferente de lista ou vetor  
## de tipo 'language'  
## Warning in is.na(x): is.na() aplicado a um objeto diferente de lista ou vetor  
## de tipo 'language'  
## Warning in is.na(x): is.na() aplicado a um objeto diferente de lista ou vetor  
## de tipo 'language'



##   
## attr(,"class")  
## [1] "mlm.variance.distribution" "list"

## [1] 4.213799

# Mudando diferenciação para sim/não, tirando Assay; duração da diferenciação igual a zero para não diferenciados

## Initialization...  
## TASK: Exhaustive screening of candidate set.  
## Fitting...  
##   
## After 50 models:  
## Best model: yi~1+Abeta\_aggregation+Concentration\_uM+Duration\_days  
## Crit= 3724.51100274034  
## Mean crit= 3775.37494973547  
## Completed.

## glmulti.analysis  
## Method: h / Fitting: rma.mv.glmulti / IC used: aicc  
## Level: 1 / Marginality: FALSE  
## From 64 models:  
## Best IC: 3724.51100274034  
## Best model:  
## [1] "yi ~ 1 + Abeta\_aggregation + Concentration\_uM + Duration\_days"  
## Evidence weight: 0.239333224062122  
## Worst IC: 3821.13504202841  
## 5 models within 2 IC units.  
## 6 models to reach 95% of evidence weight.

Top models (within 2 IC units of best model)

## model  
## 1 yi ~ 1 + Abeta\_aggregation + Concentration\_uM + Duration\_days  
## 2 yi ~ 1 + differentiation\_duration\_adjust + Abeta\_aggregation + Concentration\_uM + Duration\_days  
## 3 yi ~ 1 + Diferentiation\_method\_YN + Abeta\_aggregation + Concentration\_uM + Duration\_days  
## 4 yi ~ 1 + Abeta\_aggregation + Concentration\_uM + Duration\_days + Cell\_density  
## 5 yi ~ 1 + differentiation\_duration\_adjust + Abeta\_aggregation + Concentration\_uM + Duration\_days + Cell\_density  
## aicc weights  
## 1 3724.511 0.23933322  
## 2 3724.802 0.20689812  
## 3 3725.175 0.17175539  
## 4 3726.177 0.10406642  
## 5 3726.423 0.09201184

Decomposing R2 for the best model:

## [1] "Running models for Abeta\_aggregation"  
## [1] "Running models for Concentration\_uM"  
## [1] "Running models for Duration\_days"

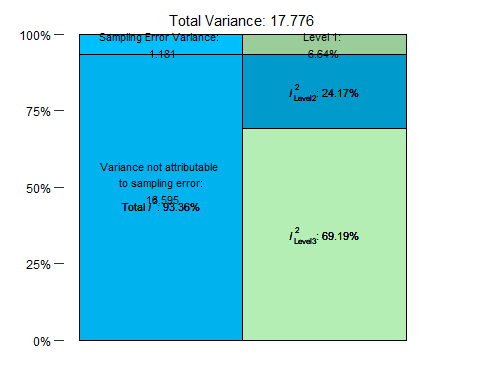
Resultados:

##   
## Multivariate Meta-Analysis Model (k = 621; method: ML)  
##   
## Variance Components:  
##   
## estim sqrt nlvls fixed factor   
## sigma^2.1 12.2994 3.5071 197 no rayyan.key   
## sigma^2.2 4.2958 2.0726 621 no rayyan.key/Comparison\_ID   
##   
## Test for Residual Heterogeneity:  
## QE(df = 615) = 3275.6593, p-val < .0001  
##   
## Test of Moderators (coefficients 2:6):  
## QM(df = 5) = 111.7183, p-val < .0001  
##   
## Model Results:  
##   
## estimate se zval pval ci.lb ci.ub   
## intrcpt -3.1988 0.7558 -4.2322 <.0001 -4.6802 -1.7174   
## Abeta\_aggregationMonomers 2.0829 0.7577 2.7492 0.0060 0.5980 3.5679   
## Abeta\_aggregationOligomers 0.8876 0.6027 1.4727 0.1408 -0.2937 2.0690   
## Abeta\_aggregationUnclear -0.8611 0.7070 -1.2180 0.2232 -2.2468 0.5246   
## Concentration\_uM -0.1111 0.0128 -8.6933 <.0001 -0.1362 -0.0861   
## Duration\_days -1.2071 0.3066 -3.9375 <.0001 -1.8079 -0.6062   
##   
## intrcpt \*\*\*   
## Abeta\_aggregationMonomers \*\*   
## Abeta\_aggregationOligomers   
## Abeta\_aggregationUnclear   
## Concentration\_uM \*\*\*   
## Duration\_days \*\*\*   
##   
## ---  
## Signif. codes: 0 '\*\*\*' 0.001 '\*\*' 0.01 '\*' 0.05 '.' 0.1 ' ' 1

##   
## estimate ci.lb ci.ub   
## sigma^2.1 12.2994 8.3038 17.9293   
## sigma.1 3.5071 2.8816 4.2343   
##   
## estimate ci.lb ci.ub   
## sigma^2.2 4.2958 3.2826 5.5739   
## sigma.2 2.0726 1.8118 2.3609

## $results  
## % of total variance I2  
## Level 1 6.642582 ---  
## Level 2 (exp) 24.166169 24.17  
## Level 3 (art) 69.191248 69.19  
##   
## $totalI2  
## [1] 93.35742  
##   
## $plot

## Warning in is.na(x): is.na() aplicado a um objeto diferente de lista ou vetor  
## de tipo 'language'  
## Warning in is.na(x): is.na() aplicado a um objeto diferente de lista ou vetor  
## de tipo 'language'  
## Warning in is.na(x): is.na() aplicado a um objeto diferente de lista ou vetor  
## de tipo 'language'



##   
## attr(,"class")  
## [1] "mlm.variance.distribution" "list"

## [1] 10.77261