Meta-análises

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## ── Attaching core tidyverse packages ──────────────────────── tidyverse 2.0.0 ──  
## ✔ dplyr 1.1.2 ✔ readr 2.1.4  
## ✔ forcats 1.0.0 ✔ stringr 1.5.0  
## ✔ ggplot2 3.4.2 ✔ tibble 3.2.1  
## ✔ lubridate 1.9.2 ✔ tidyr 1.3.0  
## ✔ purrr 1.0.1   
## ── 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  
## Lade nötiges Paket: Matrix  
##   
##   
## Attache Paket: 'Matrix'  
##   
##   
## Die folgenden Objekte sind maskiert von 'package:tidyr':  
##   
## expand, pack, unpack  
##   
##   
## Lade nötiges Paket: metadat  
##   
## Lade nötiges Paket: numDeriv  
##   
##   
## Loading the 'metafor' package (version 4.2-0). For an  
## introduction to the package please type: help(metafor)  
##   
##   
## Lade nötiges Paket: rJava  
##   
## Lade nötiges Paket: leaps

Depois da limpeza, importamos dados de volta para análises.

Para análises, precisamos da média e n dos dois grupos e da variacao no tratado, seja SEM, SD ou Unclear. Excluímos todos os casos em que falta pelo menos um desses valores.

Para montar um fluxograma: Número de comparações extraídas = 1617 Número de comparações excluídas por falta de dados: por média/variacao: 227, por n ausente: 190.

Número de artigos extraídos: 426

Outras limpezas:

Como re-extraímos alguns valores durante a verificacao de outliers, precisamos usar esses valores corrigidos

Calculei SDs a partir de SEMs (se estava ‘unclear’, considerei SEM).

Para usar SMD, precisamos do SD dos dois grupos necessariamente - decidimos considerar sd do controle igual ao tratado (que vai ser igual ao pooled).

Filtrando outliers

Ns finais N comparacoes: 1200 N artigos: 364

Excluindo ES < -900: N comparacoes: 1199 N artigos: 363

Excluindo ES < -100: N comparacoes: 1198 N artigos: 363

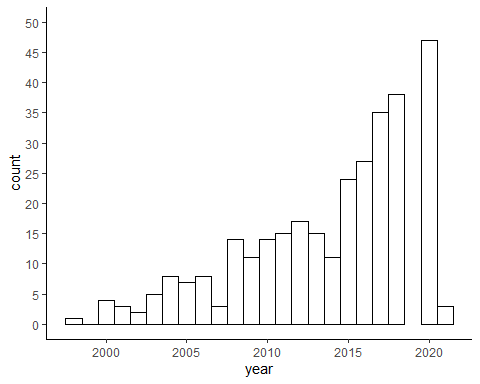
Excluindo ES < -50: N comparacoes: 1189 N artigos: 362

Excluindo ES < -20: N comparacoes: 1129 N artigos: 353

Excluindo ES < -10: N comparacoes: 955 N artigos: 311

# Sample description

## Warning: Removed 1 rows containing missing values (`geom\_bar()`).



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## Warning: Removed 1 rows containing missing values (`geom\_bar()`).

Os artigos foram publicados entre 1998 e 2021

Article-level info:

| Feature | Count | Percent |
| --- | --- | --- |
| Studies testing reversal | 254 | 69.8 |
| Provides sample size calculation | 0 | 0.0 |
| Includes conflict of interest statement | 185 | 50.8 |
| Has pre-registered | 10 | 2.7 |

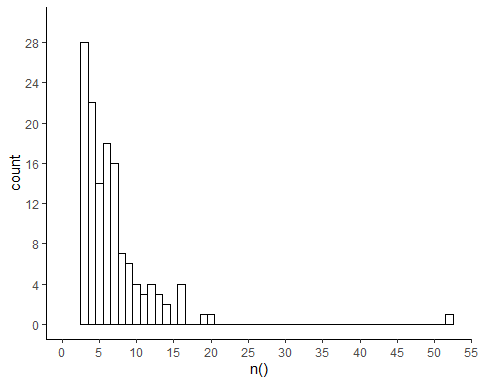
Número de comparacoes por artigo:

## [1] 1

## [1] 52

## [1] 2

## Warning: Removed 2 rows containing missing values (`geom\_bar()`).



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## Warning: Removed 2 rows containing missing values (`geom\_bar()`).

Experiment-level info

Assay

| Assay | n | Percent |
| --- | --- | --- |
| MTT | 1012 | 84.3 |
| WST | 81 | 6.8 |
| CCK-8 | 51 | 4.2 |
| MTS | 32 | 2.7 |
| XTT | 15 | 1.2 |
| Resazurin | 7 | 0.6 |
| EZ4U | 2 | 0.2 |

| Assay | n() | Percent |
| --- | --- | --- |
| MTT | 304 | 83.5 |
| WST | 23 | 6.3 |
| MTS | 17 | 4.7 |
| CCK-8 | 12 | 3.3 |
| XTT | 5 | 1.4 |
| EZ4U | 2 | 0.5 |
| Resazurin | 1 | 0.3 |

Cell line QC

| Cell\_source | n | Percent |
| --- | --- | --- |
| Cell bank | 648 | 54.0 |
| Donation | 82 | 6.8 |
| Unclear | 470 | 39.2 |

| Cell\_source | n() | Percent |
| --- | --- | --- |
| Cell bank | 183 | 50.3 |
| Donation | 17 | 4.7 |
| Unclear | 164 | 45.1 |

| Cell\_bank | n |
| --- | --- |
| American Type Culture Collection (ATCC) | 305 |
| Chinese Academy of Sciences | 43 |
| European Collection of Authenticated Cell Cultures (ECACC) | 192 |
| Institute of Biochemistry and Cell Biology | 7 |
| Invitrogen | 5 |
| Korean Cell Line Bank | 4 |
| LGC Promo-chem | 1 |
| Leibniz Institute DSMZ - German Collection of Microorganisms and Cell Cultures GmbH | 29 |
| National Centre for Cell Science (NCCS) | 15 |
| Pasteur Institute of Iran | 5 |
| Riken Cell Bank | 28 |
| Sigma-Aldrich | 8 |
| The Cell Resource Centre of Institute of Basic Medicine | 1 |
| cells were purchased from Zhong Qiao Xin Zhou Biotec Co., Ltd (Shanghai, China) | 2 |
| NA | 3 |

| Cell\_bank | n() | Percent |
| --- | --- | --- |
| American Type Culture Collection (ATCC) | 110 | 30.2 |
| Chinese Academy of Sciences | 15 | 4.1 |
| European Collection of Authenticated Cell Cultures (ECACC) | 30 | 8.2 |
| Institute of Biochemistry and Cell Biology | 1 | 0.3 |
| Invitrogen | 1 | 0.3 |
| Korean Cell Line Bank | 3 | 0.8 |
| LGC Promo-chem | 1 | 0.3 |
| Leibniz Institute DSMZ - German Collection of Microorganisms and Cell Cultures GmbH | 7 | 1.9 |
| National Centre for Cell Science (NCCS) | 5 | 1.4 |
| Pasteur Institute of Iran | 2 | 0.5 |
| Riken Cell Bank | 3 | 0.8 |
| Sigma-Aldrich | 2 | 0.5 |
| The Cell Resource Centre of Institute of Basic Medicine | 1 | 0.3 |
| cells were purchased from Zhong Qiao Xin Zhou Biotec Co., Ltd (Shanghai, China) | 1 | 0.3 |
| NA | 1 | 0.3 |

| Cell\_authentication | n |
| --- | --- |
| No | 1177 |
| Yes, no protocol | 17 |
| NA | 6 |

| Cell\_authentication | n() | Percent |
| --- | --- | --- |
| No | 362 | 99.5 |
| Yes, no protocol | 2 | 0.5 |
| NA | 1 | 0.3 |

| Cell\_mycoplasma | n | Percent |
| --- | --- | --- |
| No | 1182 | 98.5 |
| Yes, no protocol | 18 | 1.5 |

| Cell\_mycoplasma | n() | Percent |
| --- | --- | --- |
| No | 361 | 99.2 |
| Yes, no protocol | 3 | 0.8 |

Cell culture protocol

| Serum\_type | n | Percent |
| --- | --- | --- |
| FBS | 774 | 64.5 |
| FCS | 234 | 19.5 |
| Unclear | 183 | 15.2 |
| FBS and HS | 3 | 0.2 |
| CS | 2 | 0.2 |
| NO SERUM | 2 | 0.2 |
| FCS and FHS | 1 | 0.1 |
| FCS and HS | 1 | 0.1 |

| Serum\_concentration | n | Percent |
| --- | --- | --- |
| 0.1 | 768 | 64.0 |
| 0.15 | 205 | 17.1 |
| NA | 191 | 15.9 |
| 0.05 | 7 | 0.6 |
| 0.18 | 7 | 0.6 |
| 0.17 | 6 | 0.5 |
| 0.02 | 4 | 0.3 |
| 0.2 | 4 | 0.3 |
| 5% of each | 3 | 0.2 |
| 5% or 10 % | 2 | 0.2 |
| 0.12 | 1 | 0.1 |
| 10% and 5% | 1 | 0.1 |
| 5% and 10% | 1 | 0.1 |

| Serum\_type | Serum\_concentration | n |
| --- | --- | --- |
| FBS | 0.1 | 688 |
| Unclear | NA | 183 |
| FCS | 0.15 | 146 |
| FCS | 0.1 | 78 |
| FBS | 0.15 | 59 |
| FBS | 0.18 | 7 |
| FBS | 0.17 | 6 |
| FCS | 0.05 | 6 |
| FBS | NA | 5 |
| FBS | 0.02 | 3 |
| FBS and HS | 5% of each | 3 |
| CS | 0.1 | 2 |
| FBS | 0.2 | 2 |
| FBS | 5% or 10 % | 2 |
| FCS | 0.2 | 2 |
| NO SERUM | NA | 2 |
| FBS | 0.05 | 1 |
| FBS | 0.12 | 1 |
| FCS | 0.02 | 1 |
| FCS | NA | 1 |
| FCS and FHS | 10% and 5% | 1 |
| FCS and HS | 5% and 10% | 1 |

| Culture\_medium\_corrected | n | Percent |
| --- | --- | --- |
| DMEM\_F12 | 439 | 36.6 |
| DMEM | 376 | 31.3 |
| MEM\_F12 | 119 | 9.9 |
| NA | 103 | 8.6 |
| MEM | 60 | 5.0 |
| RPMI | 47 | 3.9 |
| F12 | 24 | 2.0 |
| EMEM\_F12 | 21 | 1.8 |
| EMEM | 8 | 0.7 |
| OptiMEM | 3 | 0.2 |

| Antibiotics | n | Percent |
| --- | --- | --- |
| yes | 863 | 71.9 |
| NA | 321 | 26.8 |
| no | 16 | 1.3 |

| Glutamine | n | Percent |
| --- | --- | --- |
| yes | 472 | 39.3 |
| no | 467 | 38.9 |
| NA | 261 | 21.8 |

Treatment protocol

| Control\_description | n | Percent |
| --- | --- | --- |
| Unclear | 524 | 43.7 |
| Vehicle | 345 | 28.7 |
| Medium only | 290 | 24.2 |
| Other | 41 | 3.4 |

| Abeta\_sequence | n | Percent |
| --- | --- | --- |
| 1-42 | 963 | 80.2 |
| 1-40 | 217 | 18.1 |
| 1-43 | 10 | 0.8 |
| NA | 8 | 0.7 |
| 1-38 | 2 | 0.2 |

| Abeta\_origin | n | Percent |
| --- | --- | --- |
| Unclear | 624 | 52.0 |
| synthetic | 524 | 43.7 |
| recombinant | 52 | 4.3 |

| Abeta\_species | n | Percent |
| --- | --- | --- |
| Unclear | 963 | 80.2 |
| Human | 232 | 19.3 |
| Rat | 5 | 0.4 |

| Abeta\_aggregation | n | Percent |
| --- | --- | --- |
| Unclear | 539 | 44.9 |
| Oligomers | 462 | 38.5 |
| Fibers | 107 | 8.9 |
| Monomers | 92 | 7.7 |

| Single\_exposure | n | Percent |
| --- | --- | --- |
| Yes, single | 1199 | 99.9 |
| Unclear | 1 | 0.1 |

| Protocol\_variable | Estimate | Data |
| --- | --- | --- |
| Duration of exposure, in hours | n | 1188.00000 |
| Duration of exposure, in hours | mean | 33.13519 |
| Duration of exposure, in hours | sd | 16.82464 |
| Duration of exposure, in hours | median | 24.00000 |
| Duration of exposure, in hours | min | 0.00000 |
| Duration of exposure, in hours | max | 144.00000 |
| Concentration, in uM | n | 1183.00000 |
| Concentration, in uM | mean | 41.31051 |
| Concentration, in uM | sd | 872.44248 |
| Concentration, in uM | median | 8.00000 |
| Concentration, in uM | min | 0.00000 |
| Concentration, in uM | max | 30000.00000 |

Diferenciacao

| Diferentiation\_method | n |
| --- | --- |
| No differentiation | 928 |
| ATRA | 141 |
| ATRA plus | 80 |
| Unclear | 26 |
| Other | 25 |

| Differentiation\_serum\_type | n | Percent |
| --- | --- | --- |
| NA | 928 | 77.3 |
| Unclear | 129 | 10.8 |
| FBS | 121 | 10.1 |
| No serum | 15 | 1.2 |
| FCS | 7 | 0.6 |

| Differentiation\_serum\_concentration | n | Percent |
| --- | --- | --- |
| NA | 928 | 77.3 |
| Unclear | 129 | 10.8 |
| 10% | 42 | 3.5 |
| 1% | 29 | 2.4 |
| 2% | 18 | 1.5 |
| 0 | 15 | 1.2 |
| 5% | 9 | 0.8 |
| 3% | 8 | 0.7 |
| 0.1 | 7 | 0.6 |
| 2.5% | 6 | 0.5 |
| 0.5% | 5 | 0.4 |
| 0.01 | 3 | 0.2 |
| 0.02 | 1 | 0.1 |

| Differentiation\_serum\_type | Differentiation\_serum\_concentration | n |
| --- | --- | --- |
| NA | NA | 928 |
| Unclear | Unclear | 129 |
| FBS | 10% | 42 |
| FBS | 1% | 28 |
| FBS | 2% | 16 |
| No serum | 0 | 15 |
| FBS | 5% | 9 |
| FBS | 3% | 8 |
| FBS | 0.1 | 7 |
| FBS | 2.5% | 6 |
| FCS | 0.5% | 4 |
| FBS | 0.01 | 3 |
| FCS | 2% | 2 |
| FBS | 0.02 | 1 |
| FBS | 0.5% | 1 |
| FCS | 1% | 1 |

| Differentiation\_medium | n | Percent |
| --- | --- | --- |
| NA | 928 | 77.3 |
| DMEM\_F12 | 111 | 9.2 |
| Unclear | 96 | 8.0 |
| DMEM | 39 | 3.2 |
| MEM | 7 | 0.6 |
| MEM\_Neurobasal | 6 | 0.5 |
| N2 | 5 | 0.4 |
| Neurobasal | 4 | 0.3 |
| MEM\_F12 | 3 | 0.2 |
| RPMI | 1 | 0.1 |

| Differentiation\_antibiotics | n | Percent |
| --- | --- | --- |
| NA | 949 | 79.1 |
| Unclear | 185 | 15.4 |
| yes | 66 | 5.5 |

| Differentiation\_glutamine | n | Percent |
| --- | --- | --- |
| NA | 949 | 79.1 |
| Unclear | 192 | 16.0 |
| yes | 38 | 3.2 |
| no | 21 | 1.8 |

| Protocol\_variable | Estimate | Data |
| --- | --- | --- |
| Duration of differentiation, in days | n | 224.000000 |
| Duration of differentiation, in days | mean | 6.584821 |
| Duration of differentiation, in days | sd | 3.180933 |
| Duration of differentiation, in days | median | 6.000000 |
| Duration of differentiation, in days | min | 1.000000 |
| Duration of differentiation, in days | max | 14.000000 |
| Concentration of RA, in uM | n | 220.000000 |
| Concentration of RA, in uM | mean | 9.216591 |
| Concentration of RA, in uM | sd | 3.404967 |
| Concentration of RA, in uM | median | 10.000000 |
| Concentration of RA, in uM | min | 0.000000 |
| Concentration of RA, in uM | max | 20.000000 |

Reporting

| Feature | Count | Percent |
| --- | --- | --- |
| Describes cell source | 730 | 60.8 |
| Describes cell authentication | 17 | 1.4 |
| Describes mycoplasma testing | 18 | 1.5 |
| Control group is clear | 676 | 56.3 |
| Describes Abeta sequence | 1192 | 99.3 |
| Describes Abeta origin | 576 | 48.0 |
| Describes Abeta species | 237 | 19.8 |
| Describes Abeta aggregation | 661 | 55.1 |
| Has single exposure | 1199 | 99.9 |
| Describes duration of Abeta exposure | 1188 | 99.0 |
| Describes concentration of Abeta | 1183 | 98.6 |

# 2-level

Meta-análise (2-level SMD)

##   
## Random-Effects Model (k = 1200; tau^2 estimator: REML)  
##   
## logLik deviance AIC BIC AICc   
## -3729.9550 7459.9101 7463.9101 7474.0886 7463.9201   
##   
## tau^2 (estimated amount of total heterogeneity): 12.2008 (SE = 0.6270)  
## tau (square root of estimated tau^2 value): 3.4930  
## I^2 (total heterogeneity / total variability): 91.80%  
## H^2 (total variability / sampling variability): 12.19  
##   
## Test for Heterogeneity:  
## Q(df = 1199) = 7166.6124, p-val < .0001  
##   
## Model Results:  
##   
## estimate se zval pval ci.lb ci.ub   
## -4.6464 0.1155 -40.2188 <.0001 -4.8728 -4.4200 \*\*\*   
##   
## ---  
## Signif. codes: 0 '\*\*\*' 0.001 '\*\*' 0.01 '\*' 0.05 '.' 0.1 ' ' 1

##   
## estimate ci.lb ci.ub   
## tau^2 12.2008 23.3111 30.9308   
## tau 3.4930 4.8282 5.5615   
## I^2(%) 91.7980 95.5326 96.5956   
## H^2 12.1922 22.3842 29.3740

Exact p value: 0 Exact Q test p value 0 ————————————————————————

*OBS: Outliers e limpezas adicionais*

*Sobre o alerta “Ratio of largest to smallest sampling variance extremely large. May not be able to obtain stable results.”, ver essa discussao:* [*https://stat.ethz.ch/pipermail/r-sig-meta-analysis/2019-February/001426.html*](https://stat.ethz.ch/pipermail/r-sig-meta-analysis/2019-February/001426.html) *Ao observar esse erro, decidimos voltar e avaliar os outliers. Análises no script 3,5.*

Após as revisoes nao temos mais o erro, seguimos com todos os dados disponíveis e adicionamos uma análise removendo um outlier com tamanho de efeito ~ -900.

##   
## Random-Effects Model (k = 1199; tau^2 estimator: REML)  
##   
## logLik deviance AIC BIC AICc   
## -3717.5382 7435.0763 7439.0763 7449.2532 7439.0864   
##   
## tau^2 (estimated amount of total heterogeneity): 12.2002 (SE = 0.6270)  
## tau (square root of estimated tau^2 value): 3.4929  
## I^2 (total heterogeneity / total variability): 91.80%  
## H^2 (total variability / sampling variability): 12.20  
##   
## Test for Heterogeneity:  
## Q(df = 1198) = 7154.6659, p-val < .0001  
##   
## Model Results:  
##   
## estimate se zval pval ci.lb ci.ub   
## -4.6462 0.1155 -40.2177 <.0001 -4.8726 -4.4198 \*\*\*   
##   
## ---  
## Signif. codes: 0 '\*\*\*' 0.001 '\*\*' 0.01 '\*' 0.05 '.' 0.1 ' ' 1

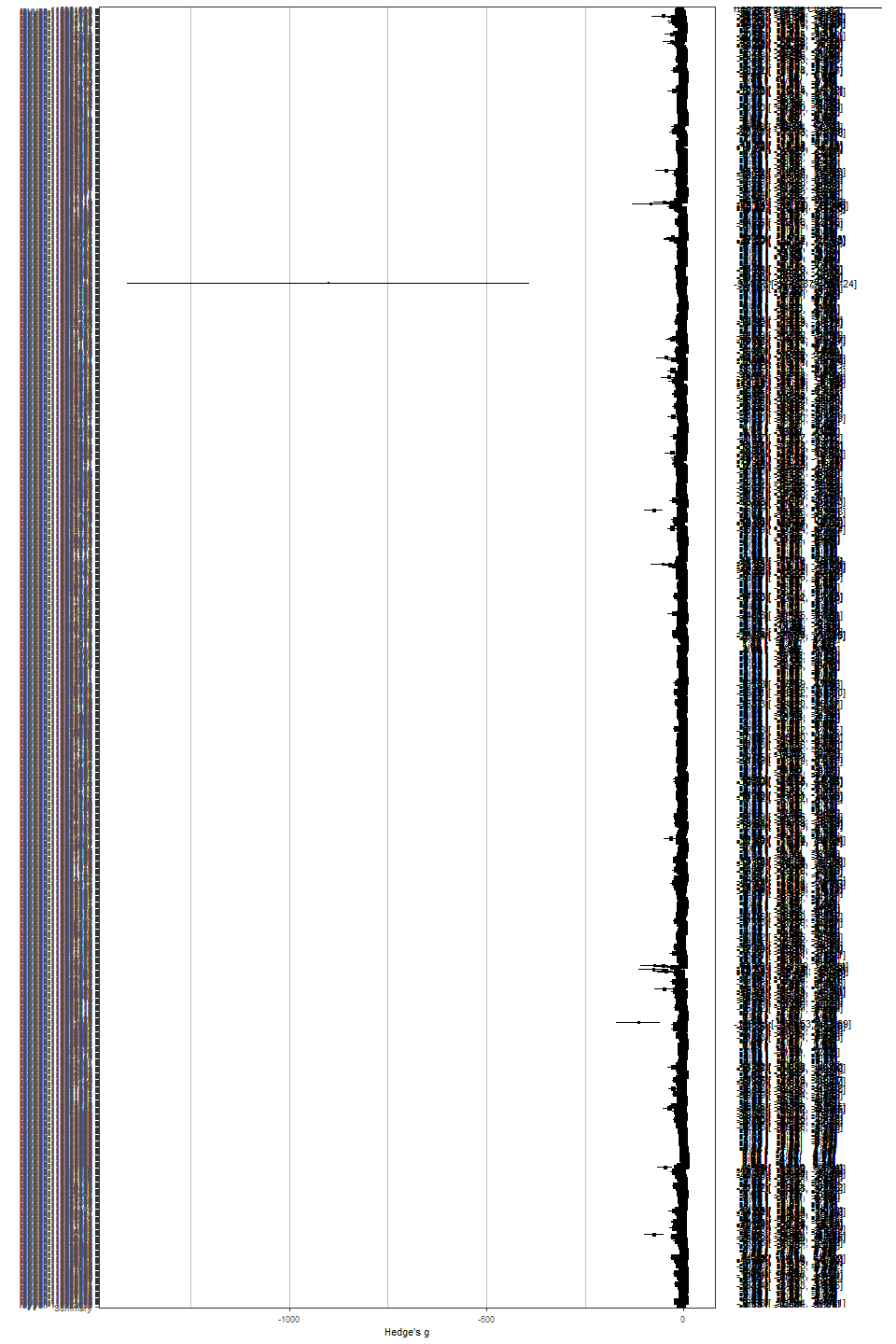
##   
## Random-Effects Model (k = 1198; tau^2 estimator: REML)  
##   
## logLik deviance AIC BIC AICc   
## -3705.9963 7411.9926 7415.9926 7426.1678 7416.0027   
##   
## tau^2 (estimated amount of total heterogeneity): 12.1897 (SE = 0.6265)  
## tau (square root of estimated tau^2 value): 3.4914  
## I^2 (total heterogeneity / total variability): 91.80%  
## H^2 (total variability / sampling variability): 12.20  
##   
## Test for Heterogeneity:  
## Q(df = 1197) = 7139.2280, p-val < .0001  
##   
## Model Results:  
##   
## estimate se zval pval ci.lb ci.ub   
## -4.6438 0.1155 -40.2111 <.0001 -4.8702 -4.4175 \*\*\*   
##   
## ---  
## Signif. codes: 0 '\*\*\*' 0.001 '\*\*' 0.01 '\*' 0.05 '.' 0.1 ' ' 1

##   
## Random-Effects Model (k = 1189; tau^2 estimator: REML)  
##   
## logLik deviance AIC BIC AICc   
## -3601.2092 7202.4183 7206.4183 7216.5784 7206.4284   
##   
## tau^2 (estimated amount of total heterogeneity): 11.8951 (SE = 0.6135)  
## tau (square root of estimated tau^2 value): 3.4489  
## I^2 (total heterogeneity / total variability): 91.68%  
## H^2 (total variability / sampling variability): 12.01  
##   
## Test for Heterogeneity:  
## Q(df = 1188) = 6973.9858, p-val < .0001  
##   
## Model Results:  
##   
## estimate se zval pval ci.lb ci.ub   
## -4.5955 0.1144 -40.1878 <.0001 -4.8196 -4.3714 \*\*\*   
##   
## ---  
## Signif. codes: 0 '\*\*\*' 0.001 '\*\*' 0.01 '\*' 0.05 '.' 0.1 ' ' 1

##   
## Random-Effects Model (k = 1129; tau^2 estimator: REML)  
##   
## logLik deviance AIC BIC AICc   
## -3173.8527 6347.7053 6351.7053 6361.7617 6351.7160   
##   
## tau^2 (estimated amount of total heterogeneity): 9.3863 (SE = 0.5023)  
## tau (square root of estimated tau^2 value): 3.0637  
## I^2 (total heterogeneity / total variability): 90.14%  
## H^2 (total variability / sampling variability): 10.14  
##   
## Test for Heterogeneity:  
## Q(df = 1128) = 6205.7012, p-val < .0001  
##   
## Model Results:  
##   
## estimate se zval pval ci.lb ci.ub   
## -4.1777 0.1044 -40.0061 <.0001 -4.3824 -3.9730 \*\*\*   
##   
## ---  
## Signif. codes: 0 '\*\*\*' 0.001 '\*\*' 0.01 '\*' 0.05 '.' 0.1 ' ' 1

##   
## Random-Effects Model (k = 955; tau^2 estimator: REML)  
##   
## logLik deviance AIC BIC AICc   
## -2326.4614 4652.9229 4656.9229 4666.6442 4656.9355   
##   
## tau^2 (estimated amount of total heterogeneity): 4.9751 (SE = 0.3030)  
## tau (square root of estimated tau^2 value): 2.2305  
## I^2 (total heterogeneity / total variability): 84.98%  
## H^2 (total variability / sampling variability): 6.66  
##   
## Test for Heterogeneity:  
## Q(df = 954) = 4428.6886, p-val < .0001  
##   
## Model Results:  
##   
## estimate se zval pval ci.lb ci.ub   
## -3.1591 0.0843 -37.4815 <.0001 -3.3243 -2.9939 \*\*\*   
##   
## ---  
## Signif. codes: 0 '\*\*\*' 0.001 '\*\*' 0.01 '\*' 0.05 '.' 0.1 ' ' 1

Forest plot (SMD)

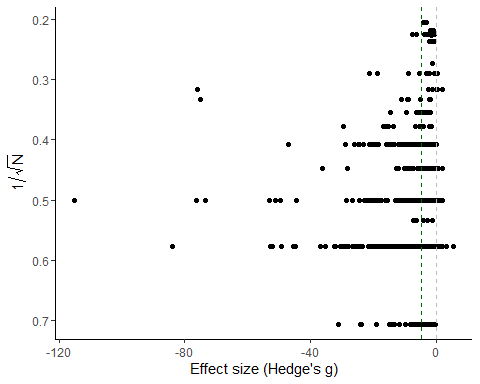


## Publication bias

Trim-and-fill (only for 2-level model)

OBS: Decidimos nao usar a análise de trim-and-fill por causa da questao biológica ser necessariamente assimétrica (impossível ter aumentos grandes de viabilidade celular com Abeta).

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 = -2.4804, p = 0.0131  
## Limit Estimate (as ni -> inf): b = -3.1179 (CI: -4.3433, -1.8926)

# 3-level

Meta-análise (3-level SMD)

##   
## Multivariate Meta-Analysis Model (k = 1200; method: REML)  
##   
## Variance Components:  
##   
## estim sqrt nlvls fixed factor   
## sigma^2.1 7.3213 2.7058 364 no rayyan.key   
## sigma^2.2 5.4303 2.3303 1200 no rayyan.key/Comparison\_ID   
##   
## Test for Heterogeneity:  
## Q(df = 1199) = 7166.6124, p-val < .0001  
##   
## Model Results:  
##   
## estimate se zval pval ci.lb ci.ub   
## -5.2829 0.1848 -28.5815 <.0001 -5.6452 -4.9206 \*\*\*   
##   
## ---  
## Signif. codes: 0 '\*\*\*' 0.001 '\*\*' 0.01 '\*' 0.05 '.' 0.1 ' ' 1

##   
## estimate ci.lb ci.ub   
## sigma^2.1 7.3213 5.6242 9.4938   
## sigma.1 2.7058 2.3715 3.0812   
##   
## estimate ci.lb ci.ub   
## sigma^2.2 5.4303 4.5957 6.4001   
## sigma.2 2.3303 2.1438 2.5298

##   
## Multivariate Meta-Analysis Model (k = 1199; method: REML)  
##   
## Variance Components:  
##   
## estim sqrt nlvls fixed factor   
## sigma^2.1 7.3205 2.7056 363 no rayyan.key   
## sigma^2.2 5.4301 2.3303 1199 no rayyan.key/Comparison\_ID   
##   
## Test for Heterogeneity:  
## Q(df = 1198) = 7154.6659, p-val < .0001  
##   
## Model Results:  
##   
## estimate se zval pval ci.lb ci.ub   
## -5.2824 0.1848 -28.5799 <.0001 -5.6447 -4.9201 \*\*\*   
##   
## ---  
## Signif. codes: 0 '\*\*\*' 0.001 '\*\*' 0.01 '\*' 0.05 '.' 0.1 ' ' 1

##   
## estimate ci.lb ci.ub   
## sigma^2.1 7.3205 5.6236 9.4928   
## sigma.1 2.7056 2.3714 3.0810   
##   
## estimate ci.lb ci.ub   
## sigma^2.2 5.4301 4.5956 6.3999   
## sigma.2 2.3303 2.1437 2.5298

##   
## Multivariate Meta-Analysis Model (k = 1198; method: REML)  
##   
## Variance Components:  
##   
## estim sqrt nlvls fixed factor   
## sigma^2.1 7.3088 2.7035 363 no rayyan.key   
## sigma^2.2 5.4213 2.3284 1198 no rayyan.key/Comparison\_ID   
##   
## Test for Heterogeneity:  
## Q(df = 1197) = 7139.2280, p-val < .0001  
##   
## Model Results:  
##   
## estimate se zval pval ci.lb ci.ub   
## -5.2803 0.1847 -28.5889 <.0001 -5.6423 -4.9183 \*\*\*   
##   
## ---  
## Signif. codes: 0 '\*\*\*' 0.001 '\*\*' 0.01 '\*' 0.05 '.' 0.1 ' ' 1

##   
## estimate ci.lb ci.ub   
## sigma^2.1 7.3088 5.6136 9.4788   
## sigma.1 2.7035 2.3693 3.0788   
##   
## estimate ci.lb ci.ub   
## sigma^2.2 5.4213 4.5879 6.3897   
## sigma.2 2.3284 2.1419 2.5278

##   
## Multivariate Meta-Analysis Model (k = 1189; method: REML)  
##   
## Variance Components:  
##   
## estim sqrt nlvls fixed factor   
## sigma^2.1 7.0217 2.6498 362 no rayyan.key   
## sigma^2.2 5.2824 2.2983 1189 no rayyan.key/Comparison\_ID   
##   
## Test for Heterogeneity:  
## Q(df = 1188) = 6973.9858, p-val < .0001  
##   
## Model Results:  
##   
## estimate se zval pval ci.lb ci.ub   
## -5.2239 0.1818 -28.7359 <.0001 -5.5802 -4.8676 \*\*\*   
##   
## ---  
## Signif. codes: 0 '\*\*\*' 0.001 '\*\*' 0.01 '\*' 0.05 '.' 0.1 ' ' 1

##   
## estimate ci.lb ci.ub   
## sigma^2.1 7.0217 5.3916 9.1037   
## sigma.1 2.6498 2.3220 3.0172   
##   
## estimate ci.lb ci.ub   
## sigma^2.2 5.2824 4.4701 6.2261   
## sigma.2 2.2983 2.1143 2.4952

##   
## Multivariate Meta-Analysis Model (k = 1129; method: REML)  
##   
## Variance Components:  
##   
## estim sqrt nlvls fixed factor   
## sigma^2.1 4.7821 2.1868 353 no rayyan.key   
## sigma^2.2 4.3770 2.0921 1129 no rayyan.key/Comparison\_ID   
##   
## Test for Heterogeneity:  
## Q(df = 1128) = 6205.7012, p-val < .0001  
##   
## Model Results:  
##   
## estimate se zval pval ci.lb ci.ub   
## -4.7405 0.1582 -29.9700 <.0001 -5.0506 -4.4305 \*\*\*   
##   
## ---  
## Signif. codes: 0 '\*\*\*' 0.001 '\*\*' 0.01 '\*' 0.05 '.' 0.1 ' ' 1

##   
## estimate ci.lb ci.ub   
## sigma^2.1 4.7821 3.6419 6.2331   
## sigma.1 2.1868 1.9084 2.4966   
##   
## estimate ci.lb ci.ub   
## sigma^2.2 4.3770 3.6954 5.1669   
## sigma.2 2.0921 1.9223 2.2731

##   
## Multivariate Meta-Analysis Model (k = 955; method: REML)  
##   
## Variance Components:  
##   
## estim sqrt nlvls fixed factor   
## sigma^2.1 2.3457 1.5316 311 no rayyan.key   
## sigma^2.2 2.4556 1.5670 955 no rayyan.key/Comparison\_ID   
##   
## Test for Heterogeneity:  
## Q(df = 954) = 4428.6886, p-val < .0001  
##   
## Model Results:  
##   
## estimate se zval pval ci.lb ci.ub   
## -3.6611 0.1229 -29.7895 <.0001 -3.9020 -3.4202 \*\*\*   
##   
## ---  
## Signif. codes: 0 '\*\*\*' 0.001 '\*\*' 0.01 '\*' 0.05 '.' 0.1 ' ' 1

##   
## estimate ci.lb ci.ub   
## sigma^2.1 2.3457 1.7319 3.1314   
## sigma.1 1.5316 1.3160 1.7696   
##   
## estimate ci.lb ci.ub   
## sigma^2.2 2.4556 2.0391 2.9402   
## sigma.2 1.5670 1.4280 1.7147

## $results  
## % of total variance I2  
## Level 1 7.875525 ---  
## Level 2 (exp) 39.231300 39.23  
## Level 3 (art) 52.893175 52.89  
##   
## $totalI2  
## [1] 92.12448  
##   
## $plot

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

## $results  
## % of total variance I2  
## Level 1 7.870064 ---  
## Level 2 (exp) 39.235195 39.24  
## Level 3 (art) 52.894740 52.89  
##   
## $totalI2  
## [1] 92.12994  
##   
## $plot

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

## $results  
## % of total variance I2  
## Level 1 7.875721 ---  
## Level 2 (exp) 39.232485 39.23  
## Level 3 (art) 52.891794 52.89  
##   
## $totalI2  
## [1] 92.12428  
##   
## $plot

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

## $results  
## % of total variance I2  
## Level 1 8.070367 ---  
## Level 2 (exp) 39.467231 39.47  
## Level 3 (art) 52.462402 52.46  
##   
## $totalI2  
## [1] 91.92963  
##   
## $plot

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

## $results  
## % of total variance I2  
## Level 1 10.08156 ---  
## Level 2 (exp) 42.97079 42.97  
## Level 3 (art) 46.94765 46.95  
##   
## $totalI2  
## [1] 89.91844  
##   
## $plot

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

## $results  
## % of total variance I2  
## Level 1 15.48345 ---  
## Level 2 (exp) 43.22543 43.23  
## Level 3 (art) 41.29112 41.29  
##   
## $totalI2  
## [1] 84.51655  
##   
## $plot

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

### excluindo n de replicatas ou outras unidades nao independentes

| n\_definition | n |
| --- | --- |
| assays | 20 |
| biological replicates | 5 |
| cell cultures | 2 |
| determinations | 8 |
| experiments | 108 |
| independent determinations | 13 |
| independent experimental measurements | 6 |
| independent experiments | 549 |
| independent repetitions | 2 |
| independent replicates | 2 |
| independent runs | 1 |
| independent sets of studies | 1 |
| observations | 1 |
| replicates | 217 |
| samples | 12 |
| wells | 24 |
| NA | 229 |

##   
## Multivariate Meta-Analysis Model (k = 574; method: REML)  
##   
## Variance Components:  
##   
## estim sqrt nlvls fixed factor   
## sigma^2.1 8.1325 2.8518 173 no rayyan.key   
## sigma^2.2 5.1584 2.2712 574 no rayyan.key/Comparison\_ID   
##   
## Test for Heterogeneity:  
## Q(df = 573) = 3037.2765, p-val < .0001  
##   
## Model Results:  
##   
## estimate se zval pval ci.lb ci.ub   
## -5.4952 0.2784 -19.7366 <.0001 -6.0409 -4.9494 \*\*\*   
##   
## ---  
## Signif. codes: 0 '\*\*\*' 0.001 '\*\*' 0.01 '\*' 0.05 '.' 0.1 ' ' 1

##   
## estimate ci.lb ci.ub   
## sigma^2.1 8.1325 5.4877 11.9438   
## sigma.1 2.8518 2.3426 3.4560   
##   
## estimate ci.lb ci.ub   
## sigma^2.2 5.1584 4.0437 6.5461   
## sigma.2 2.2712 2.0109 2.5585

## $results  
## % of total variance I2  
## Level 1 9.444531 ---  
## Level 2 (exp) 35.145806 35.15  
## Level 3 (art) 55.409663 55.41  
##   
## $totalI2  
## [1] 90.55547  
##   
## $plot

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

# Meta-regressions (3-level)

Differentiation

##   
## Multivariate Meta-Analysis Model (k = 1200; method: REML)  
##   
## Variance Components:  
##   
## estim sqrt nlvls fixed factor   
## sigma^2.1 7.5055 2.7396 364 no rayyan.key   
## sigma^2.2 5.3875 2.3211 1200 no rayyan.key/Comparison\_ID   
##   
## Test for Residual Heterogeneity:  
## QE(df = 1195) = 7119.6990, p-val < .0001  
##   
## Test of Moderators (coefficients 2:5):  
## QM(df = 4) = 6.6013, p-val = 0.1585  
##   
## Model Results:  
##   
## estimate   
## intrcpt -5.4216   
## relevel(factor(dados\_meta\_smd$Diferentiation\_method), ref = "No differentiation")ATRA 1.2733   
## relevel(factor(dados\_meta\_smd$Diferentiation\_method), ref = "No differentiation")ATRA plus -0.4416   
## relevel(factor(dados\_meta\_smd$Diferentiation\_method), ref = "No differentiation")Other 0.0529   
## relevel(factor(dados\_meta\_smd$Diferentiation\_method), ref = "No differentiation")Unclear 1.0373   
## se   
## intrcpt 0.2045   
## relevel(factor(dados\_meta\_smd$Diferentiation\_method), ref = "No differentiation")ATRA 0.5345   
## relevel(factor(dados\_meta\_smd$Diferentiation\_method), ref = "No differentiation")ATRA plus 0.7235   
## relevel(factor(dados\_meta\_smd$Diferentiation\_method), ref = "No differentiation")Other 1.3406   
## relevel(factor(dados\_meta\_smd$Diferentiation\_method), ref = "No differentiation")Unclear 1.7129   
## zval   
## intrcpt -26.5144   
## relevel(factor(dados\_meta\_smd$Diferentiation\_method), ref = "No differentiation")ATRA 2.3821   
## relevel(factor(dados\_meta\_smd$Diferentiation\_method), ref = "No differentiation")ATRA plus -0.6103   
## relevel(factor(dados\_meta\_smd$Diferentiation\_method), ref = "No differentiation")Other 0.0395   
## relevel(factor(dados\_meta\_smd$Diferentiation\_method), ref = "No differentiation")Unclear 0.6056   
## pval   
## intrcpt <.0001   
## relevel(factor(dados\_meta\_smd$Diferentiation\_method), ref = "No differentiation")ATRA 0.0172   
## relevel(factor(dados\_meta\_smd$Diferentiation\_method), ref = "No differentiation")ATRA plus 0.5417   
## relevel(factor(dados\_meta\_smd$Diferentiation\_method), ref = "No differentiation")Other 0.9685   
## relevel(factor(dados\_meta\_smd$Diferentiation\_method), ref = "No differentiation")Unclear 0.5448   
## ci.lb   
## intrcpt -5.8224   
## relevel(factor(dados\_meta\_smd$Diferentiation\_method), ref = "No differentiation")ATRA 0.2256   
## relevel(factor(dados\_meta\_smd$Diferentiation\_method), ref = "No differentiation")ATRA plus -1.8596   
## relevel(factor(dados\_meta\_smd$Diferentiation\_method), ref = "No differentiation")Other -2.5746   
## relevel(factor(dados\_meta\_smd$Diferentiation\_method), ref = "No differentiation")Unclear -2.3199   
## ci.ub   
## intrcpt -5.0208   
## relevel(factor(dados\_meta\_smd$Diferentiation\_method), ref = "No differentiation")ATRA 2.3209   
## relevel(factor(dados\_meta\_smd$Diferentiation\_method), ref = "No differentiation")ATRA plus 0.9765   
## relevel(factor(dados\_meta\_smd$Diferentiation\_method), ref = "No differentiation")Other 2.6805   
## relevel(factor(dados\_meta\_smd$Diferentiation\_method), ref = "No differentiation")Unclear 4.3945   
##   
## intrcpt \*\*\*   
## relevel(factor(dados\_meta\_smd$Diferentiation\_method), ref = "No differentiation")ATRA \*   
## relevel(factor(dados\_meta\_smd$Diferentiation\_method), ref = "No differentiation")ATRA plus   
## relevel(factor(dados\_meta\_smd$Diferentiation\_method), ref = "No differentiation")Other   
## relevel(factor(dados\_meta\_smd$Diferentiation\_method), ref = "No differentiation")Unclear   
##   
## ---  
## Signif. codes: 0 '\*\*\*' 0.001 '\*\*' 0.01 '\*' 0.05 '.' 0.1 ' ' 1

Differentiation bubble plot

## Warning in geom\_abline(yintercept = 0, slope = 0, linetype = "dashed", color =  
## "grey"): Ignoring unknown parameters: `yintercept`

Diff. duration

## Warning: 976 rows with NAs omitted from model fitting.

##   
## Multivariate Meta-Analysis Model (k = 224; method: REML)  
##   
## Variance Components:  
##   
## estim sqrt nlvls fixed factor   
## sigma^2.1 22.0908 4.7001 58 no rayyan.key   
## sigma^2.2 3.3630 1.8338 224 no rayyan.key/Comparison\_ID   
##   
## Test for Residual Heterogeneity:  
## QE(df = 222) = 1289.5325, p-val < .0001  
##   
## Test of Moderators (coefficient 2):  
## QM(df = 1) = 0.9531, p-val = 0.3289  
##   
## Model Results:  
##   
## estimate se   
## intrcpt -6.5678 1.5568   
## as.numeric(dados\_meta\_smd$Diferentiation\_duration\_days) 0.2180 0.2233   
## zval pval   
## intrcpt -4.2187 <.0001   
## as.numeric(dados\_meta\_smd$Diferentiation\_duration\_days) 0.9763 0.3289   
## ci.lb ci.ub   
## intrcpt -9.6191 -3.5165 \*\*\*   
## as.numeric(dados\_meta\_smd$Diferentiation\_duration\_days) -0.2197 0.6558   
##   
## ---  
## Signif. codes: 0 '\*\*\*' 0.001 '\*\*' 0.01 '\*' 0.05 '.' 0.1 ' ' 1

Diff. duration bubble plot

Aggregation

##   
## Multivariate Meta-Analysis Model (k = 1200; method: REML)  
##   
## Variance Components:  
##   
## estim sqrt nlvls fixed factor   
## sigma^2.1 7.3383 2.7089 364 no rayyan.key   
## sigma^2.2 5.2790 2.2976 1200 no rayyan.key/Comparison\_ID   
##   
## Test for Residual Heterogeneity:  
## QE(df = 1196) = 6918.3249, p-val < .0001  
##   
## Test of Moderators (coefficients 2:4):  
## QM(df = 3) = 18.2218, p-val = 0.0004  
##   
## Model Results:  
##   
## estimate   
## intrcpt -3.8423   
## relevel(factor(dados\_meta\_smd$Abeta\_aggregation), ref = "Monomers")Fibers -2.1916   
## relevel(factor(dados\_meta\_smd$Abeta\_aggregation), ref = "Monomers")Oligomers -0.9532   
## relevel(factor(dados\_meta\_smd$Abeta\_aggregation), ref = "Monomers")Unclear -1.7995   
## se   
## intrcpt 0.5296   
## relevel(factor(dados\_meta\_smd$Abeta\_aggregation), ref = "Monomers")Fibers 0.6254   
## relevel(factor(dados\_meta\_smd$Abeta\_aggregation), ref = "Monomers")Oligomers 0.5522   
## relevel(factor(dados\_meta\_smd$Abeta\_aggregation), ref = "Monomers")Unclear 0.5791   
## zval   
## intrcpt -7.2553   
## relevel(factor(dados\_meta\_smd$Abeta\_aggregation), ref = "Monomers")Fibers -3.5042   
## relevel(factor(dados\_meta\_smd$Abeta\_aggregation), ref = "Monomers")Oligomers -1.7262   
## relevel(factor(dados\_meta\_smd$Abeta\_aggregation), ref = "Monomers")Unclear -3.1075   
## pval   
## intrcpt <.0001   
## relevel(factor(dados\_meta\_smd$Abeta\_aggregation), ref = "Monomers")Fibers 0.0005   
## relevel(factor(dados\_meta\_smd$Abeta\_aggregation), ref = "Monomers")Oligomers 0.0843   
## relevel(factor(dados\_meta\_smd$Abeta\_aggregation), ref = "Monomers")Unclear 0.0019   
## ci.lb   
## intrcpt -4.8803   
## relevel(factor(dados\_meta\_smd$Abeta\_aggregation), ref = "Monomers")Fibers -3.4174   
## relevel(factor(dados\_meta\_smd$Abeta\_aggregation), ref = "Monomers")Oligomers -2.0354   
## relevel(factor(dados\_meta\_smd$Abeta\_aggregation), ref = "Monomers")Unclear -2.9345   
## ci.ub   
## intrcpt -2.8043   
## relevel(factor(dados\_meta\_smd$Abeta\_aggregation), ref = "Monomers")Fibers -0.9658   
## relevel(factor(dados\_meta\_smd$Abeta\_aggregation), ref = "Monomers")Oligomers 0.1291   
## relevel(factor(dados\_meta\_smd$Abeta\_aggregation), ref = "Monomers")Unclear -0.6645   
##   
## 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

## variable  
## 1 Abeta aggregation  
## 2 Abeta aggregation  
## 3 Abeta aggregation  
## 4 Abeta aggregation  
## category  
## 1 intrcpt  
## 2 relevel(factor(dados\_meta\_smd$Abeta\_aggregation), ref = "Monomers")Fibers  
## 3 relevel(factor(dados\_meta\_smd$Abeta\_aggregation), ref = "Monomers")Oligomers  
## 4 relevel(factor(dados\_meta\_smd$Abeta\_aggregation), ref = "Monomers")Unclear  
## sample.size Effect.size..95..CI...Hedge.s.g.  
## 1 92 -3.84230682571111 [-4.88027610495202, -2.80433754647021]  
## 2 107 -2.19158968651866 [-3.41739081763433, -0.965788555402996]  
## 3 462 -0.953191922307572 [-2.03544180941495, 0.129057964799804]  
## 4 539 -1.79950427068351 [-2.93448003191575, -0.664528509451261]  
## p.value I2 p.value..QE. R2 p.value..QM.  
## 1 4.007598e-13 92.04725 0 1.05409 0.0003958585  
## 2 4.580030e-04 92.04725 0 1.05409 0.0003958585  
## 3 8.430445e-02 92.04725 0 1.05409 0.0003958585  
## 4 1.886621e-03 92.04725 0 1.05409 0.0003958585

Aggregation bubble plot

## Warning in geom\_abline(yintercept = 0, slope = 0, linetype = "dashed", color =  
## "grey"): Ignoring unknown parameters: `yintercept`

## mapping: intercept = ~intercept, slope = ~slope   
## geom\_abline: na.rm = FALSE  
## stat\_identity: na.rm = FALSE  
## position\_identity

Abeta concentration (só até 100 uM)

##   
## Multivariate Meta-Analysis Model (k = 1131; method: REML)  
##   
## Variance Components:  
##   
## estim sqrt nlvls fixed factor   
## sigma^2.1 7.0683 2.6586 350 no rayyan.key   
## sigma^2.2 4.4475 2.1089 1131 no rayyan.key/Comparison\_ID   
##   
## Test for Residual Heterogeneity:  
## QE(df = 1129) = 6502.4764, p-val < .0001  
##   
## Test of Moderators (coefficient 2):  
## QM(df = 1) = 119.9108, p-val < .0001  
##   
## Model Results:  
##   
## estimate se zval pval   
## intrcpt -4.0588 0.2078 -19.5290 <.0001   
## dados\_meta\_smd\_max100$Concentration\_uM -0.1096 0.0100 -10.9504 <.0001   
## ci.lb ci.ub   
## intrcpt -4.4661 -3.6514 \*\*\*   
## dados\_meta\_smd\_max100$Concentration\_uM -0.1293 -0.0900 \*\*\*   
##   
## ---  
## Signif. codes: 0 '\*\*\*' 0.001 '\*\*' 0.01 '\*' 0.05 '.' 0.1 ' ' 1

Abeta concentration bubble plot

Abeta duration of exposure

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

##   
## Multivariate Meta-Analysis Model (k = 1188; method: REML)  
##   
## Variance Components:  
##   
## estim sqrt nlvls fixed factor   
## sigma^2.1 7.5475 2.7473 357 no rayyan.key   
## sigma^2.2 5.2998 2.3021 1188 no rayyan.key/Comparison\_ID   
##   
## Test for Residual Heterogeneity:  
## QE(df = 1186) = 7106.0227, p-val < .0001  
##   
## Test of Moderators (coefficient 2):  
## QM(df = 1) = 16.3747, p-val < .0001  
##   
## Model Results:  
##   
## estimate se zval pval   
## intrcpt -4.2051 0.3308 -12.7113 <.0001   
## as.numeric(dados\_meta\_smd$Duration\_days) -0.8174 0.2020 -4.0466 <.0001   
## ci.lb ci.ub   
## intrcpt -4.8535 -3.5567 \*\*\*   
## as.numeric(dados\_meta\_smd$Duration\_days) -1.2133 -0.4215 \*\*\*   
##   
## ---  
## Signif. codes: 0 '\*\*\*' 0.001 '\*\*' 0.01 '\*' 0.05 '.' 0.1 ' ' 1

Abeta duration bubble plot

Assay

##   
## Multivariate Meta-Analysis Model (k = 1200; method: REML)  
##   
## Variance Components:  
##   
## estim sqrt nlvls fixed factor   
## sigma^2.1 7.3651 2.7139 364 no rayyan.key   
## sigma^2.2 5.4636 2.3374 1200 no rayyan.key/Comparison\_ID   
##   
## Test for Residual Heterogeneity:  
## QE(df = 1193) = 7087.3900, p-val < .0001  
##   
## Test of Moderators (coefficients 2:7):  
## QM(df = 6) = 5.4814, p-val = 0.4837  
##   
## Model Results:  
##   
## estimate se   
## intrcpt -5.4027 0.2037   
## relevel(factor(dados\_meta\_smd$Assay), ref = "MTT")CCK-8 0.0034 0.9621   
## relevel(factor(dados\_meta\_smd$Assay), ref = "MTT")EZ4U -0.2263 2.9696   
## relevel(factor(dados\_meta\_smd$Assay), ref = "MTT")MTS 0.1773 0.9209   
## relevel(factor(dados\_meta\_smd$Assay), ref = "MTT")Resazurin 4.9495 2.8801   
## relevel(factor(dados\_meta\_smd$Assay), ref = "MTT")WST 1.1701 0.7368   
## relevel(factor(dados\_meta\_smd$Assay), ref = "MTT")XTT 0.5449 1.5467   
## zval pval   
## intrcpt -26.5180 <.0001   
## relevel(factor(dados\_meta\_smd$Assay), ref = "MTT")CCK-8 0.0035 0.9972   
## relevel(factor(dados\_meta\_smd$Assay), ref = "MTT")EZ4U -0.0762 0.9393   
## relevel(factor(dados\_meta\_smd$Assay), ref = "MTT")MTS 0.1926 0.8473   
## relevel(factor(dados\_meta\_smd$Assay), ref = "MTT")Resazurin 1.7185 0.0857   
## relevel(factor(dados\_meta\_smd$Assay), ref = "MTT")WST 1.5880 0.1123   
## relevel(factor(dados\_meta\_smd$Assay), ref = "MTT")XTT 0.3523 0.7246   
## ci.lb ci.ub   
## intrcpt -5.8021 -5.0034   
## relevel(factor(dados\_meta\_smd$Assay), ref = "MTT")CCK-8 -1.8824 1.8892   
## relevel(factor(dados\_meta\_smd$Assay), ref = "MTT")EZ4U -6.0466 5.5941   
## relevel(factor(dados\_meta\_smd$Assay), ref = "MTT")MTS -1.6275 1.9822   
## relevel(factor(dados\_meta\_smd$Assay), ref = "MTT")Resazurin -0.6955 10.5944   
## relevel(factor(dados\_meta\_smd$Assay), ref = "MTT")WST -0.2741 2.6143   
## relevel(factor(dados\_meta\_smd$Assay), ref = "MTT")XTT -2.4866 3.5763   
##   
## 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

Assay bubble plot

## Warning in geom\_abline(yintercept = 0, slope = 0, linetype = "dashed", color =  
## "grey"): Ignoring unknown parameters: `yintercept`

Cell density

## Warning: 506 rows with NAs omitted from model fitting.

##   
## Multivariate Meta-Analysis Model (k = 694; method: REML)  
##   
## Variance Components:  
##   
## estim sqrt nlvls fixed factor   
## sigma^2.1 8.0453 2.8364 215 no rayyan.key   
## sigma^2.2 5.9893 2.4473 694 no rayyan.key/Comparison\_ID   
##   
## Test for Residual Heterogeneity:  
## QE(df = 692) = 4088.9027, p-val < .0001  
##   
## Test of Moderators (coefficient 2):  
## QM(df = 1) = 0.0040, p-val = 0.9497  
##   
## Model Results:  
##   
## estimate se zval pval   
## intrcpt -5.5997 0.2582 -21.6845 <.0001   
## as.numeric(dados\_meta\_smd$Cell\_density) 0.0000 0.0000 0.0631 0.9497   
## ci.lb ci.ub   
## intrcpt -6.1059 -5.0936 \*\*\*   
## as.numeric(dados\_meta\_smd$Cell\_density) -0.0000 0.0000   
##   
## ---  
## Signif. codes: 0 '\*\*\*' 0.001 '\*\*' 0.01 '\*' 0.05 '.' 0.1 ' ' 1

Cell density bubble plot

### Summary

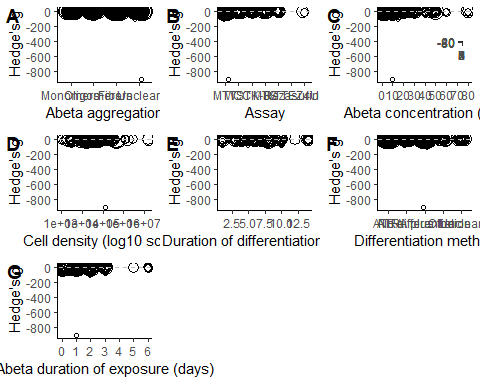
| variable | category | sample.size | Effect.size..95..CI…Hedge.s.g. | p.value | I2 | p.value..QE. | R2 | p.value..QM. |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Abeta aggregation | intrcpt | 92 | -3.84230682571111 [-4.88027610495202, -2.80433754647021] | 0.0000000 | 92.04725 | 0 | 1.054090 | 0.0003959 |
| Abeta aggregation | relevel(factor(dados\_meta\_smd$Abeta\_aggregation), ref = "Monomers")Fibers | 107|-2.19158968651866 [-3.41739081763433, -0.965788555402996] | 0.0004580| 92.04725| 0| 1.054090| 0.0003959| |Abeta aggregation |relevel(factor(dados\_meta\_smd$Abeta\_aggregation), ref = “Monomers”)Oligomers | 462 | -0.953191922307572 [-2.03544180941495, 0.129057964799804] | 0.0843044 | 92.04725 | 0 | 1.054090 | 0.0003959 |
| Abeta aggregation | relevel(factor(dados\_meta\_smd$Abeta\_aggregation), ref = "Monomers")Unclear | 539|-1.79950427068351 [-2.93448003191575, -0.664528509451261] | 0.0018866| 92.04725| 0| 1.054090| 0.0003959| |Assay |intrcpt | 1012|-5.40273602031708 [-5.80205669485501, -5.00341534577916] | 0.0000000| 92.16809| 0| 0.000000| 0.4837134| |Assay |relevel(factor(dados\_meta\_smd$Assay), ref = “MTT”)CCK-8 | 51 | 0.00340237012422128 [-1.88237146044428, 1.88917620069272] | 0.9971785 | 92.16809 | 0 | 0.000000 | 0.4837134 |
| Assay | relevel(factor(dados\_meta\_smd$Assay), ref = "MTT")EZ4U | 2|-0.226293444960693 [-6.04663793370032, 5.59405104377894] | 0.9392577| 92.16809| 0| 0.000000| 0.4837134| |Assay |relevel(factor(dados\_meta\_smd$Assay), ref = “MTT”)MTS | 32 | 0.177329412754682 [-1.62751392136273, 1.98217274687209] | 0.8472955 | 92.16809 | 0 | 0.000000 | 0.4837134 |
| Assay | relevel(factor(dados\_meta\_smd$Assay), ref = "MTT")Resazurin | 7|4.94946913046749 [-0.695460286776308, 10.5943985477113] | 0.0857064| 92.16809| 0| 0.000000| 0.4837134| |Assay |relevel(factor(dados\_meta\_smd$Assay), ref = “MTT”)WST | 81 | 1.17013140796572 [-0.274066363992736, 2.61432917992417] | 0.1122817 | 92.16809 | 0 | 0.000000 | 0.4837134 |
| Assay | relevel(factor(dados\_meta\_smd$Assay), ref = "MTT")XTT | 15|0.544872368292708 [-2.48660086286725, 2.61432917992417] | 0.7246276| 92.16809| 0| 0.000000| 0.4837134| |Abeta concentration |intercept | NA|-4.06 [-4.5, -3.7] | 0.0000000| 91.48335| 0| 9.691664| 0.0000000| |Abeta concentration |(uM) | 1131|-0.109646262383444 [-0.12927139895884, -0.0900211258080472] | 0.0000000| 91.48335| 0| 9.691664| 0.0000000| |cell density |intercept | NA|-5.59973561781115 [-6.10587107187424, -5.09360016374806] | 0.0000000| 92.49284| 0| 0.000000| 0.9496780| |cell density |(unit) | 694|1.29419513439506e-08 [-3.88979881409109e-07, 4.1486378409701e-07] | 0.9496780| 92.49284| 0| 0.000000| 0.9496780| |Duration of differentiation |intercept | NA|-6.57 [-9.6, -3.5] | 0.0000246| 96.64022| 0| 0.000000| 0.3289274| |Duration of differentiation |(unit) | 224|0.218032417253659 [-0.219687473762804, 0.655752308270122] | 0.3289274| 96.64022| 0| 0.000000| 0.3289274| |Method of differentiation |intrcpt | 928|-5.42160815626876 [-5.82237671851415, -5.02083959402337] | 0.0000000| 92.20409| 0| 0.000000| 0.1585162| |Method of differentiation |relevel(factor(dados\_meta\_smd$Diferentiation\_method), ref = “No differentiation”)ATRA | 141 | 1.27325723713694 [0.225634144941224, 2.32088032933265] | 0.0172144 | 92.20409 | 0 | 0.000000 | 0.1585162 |
| Method of differentiation | relevel(factor(dados\_meta\_smd$Diferentiation\_method), ref = "No differentiation")ATRA plus | 80|-0.441570613658081 [-1.85964049493356, 0.976499267617394] | 0.5416563| 92.20409| 0| 0.000000| 0.1585162| |Method of differentiation |relevel(factor(dados\_meta\_smd$Diferentiation\_method), ref = “No differentiation”)Other | 25 | 0.0529474379724324 [-2.57456762137249, 2.68046249731735] | 0.9684953 | 92.20409 | 0 | 0.000000 | 0.1585162 |
| Method of differentiation | relevel(factor(dados\_meta\_smd$Diferentiation\_method), ref = “No differentiation”)Unclear | 26 | 1.03731936614689 [-2.31990488138775, 4.39454361368153] | 0.5447856 | 92.20409 | 0 | 0.000000 | 0.1585162 |
| Abeta exposure duration | intercept | NA | -4.21 [-4.9, -3.6] | 0.0000000 | 92.20477 | 0 | 0.000000 | 0.0000520 |
| Abeta exposure duration | (days) | 1188 | -0.8174124154357 [-1.21332806455532, -0.421496766316077] | 0.0000520 | 92.20477 | 0 | 0.000000 | 0.0000520 |

## Warning: Removed 7 rows containing missing values (`geom\_point()`).

## Warning: Removed 506 rows containing missing values (`geom\_point()`).

## Warning: Removed 976 rows containing missing values (`geom\_point()`).

## Warning: Removed 12 rows containing missing values (`geom\_point()`).



# Meta-regressions (3-level) - sem outlier

Falta escolher qual, ou se queremos fazer todos também.

# Multivariate Meta-regressions (3-level)

“All combinations of variables from the selected list were tested in multivariable models, and the best models were ranked by corrected Akaike Information Criteria (AICc). For each best model selected (for complete, training and reactivation datasets with 2- and 3-level analyses), we decomposed the R2 value for each moderator included. For this, we calculated 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)

Como a gente só pode usar as comparacoes que tenham a descricao completa de todas as variáveis testadas, precisamos filtrar os dadose conferir se seguimos com N suficiente.

Considering all pre-registered variables, we’d have 86 experiments available (i.e. 1114 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= 503.657305181371  
## Mean crit= 528.746837757467  
##   
## After 100 models:  
## Best model: yi~1+Concentration\_uM+Duration\_hours  
## Crit= 503.657305181371  
## Mean crit= 526.90670098182  
##   
## After 150 models:  
## Best model: yi~1+Concentration\_uM+Duration\_hours  
## Crit= 503.657305181371  
## Mean crit= 525.455137183829  
## Completed.

## glmulti.analysis  
## Method: h / Fitting: rma.mv.glmulti / IC used: aicc  
## Level: 1 / Marginality: FALSE  
## From 128 models:  
## Best IC: 503.657305181371  
## Best model:  
## [1] "yi ~ 1 + Concentration\_uM + Duration\_hours"  
## Evidence weight: 0.364917782480779  
## Worst IC: 545.907434721382  
## 2 models within 2 IC units.  
## 13 models to reach 95% of evidence weight.

Decomposing R2 for the best model:

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

Resultados:

##   
## Multivariate Meta-Analysis Model (k = 86; method: ML)  
##   
## Variance Components:  
##   
## estim sqrt nlvls fixed factor   
## sigma^2.1 36.5063 6.0420 25 no rayyan.key   
## sigma^2.2 0.6958 0.8341 86 no rayyan.key/Comparison\_ID   
##   
## Test for Residual Heterogeneity:  
## QE(df = 83) = 367.2969, p-val < .0001  
##   
## Test of Moderators (coefficients 2:3):  
## QM(df = 2) = 42.3458, p-val < .0001  
##   
## Model Results:  
##   
## estimate se zval pval ci.lb ci.ub   
## intrcpt -0.1249 1.5296 -0.0817 0.9349 -3.1228 2.8730   
## Concentration\_uM -0.1300 0.0281 -4.6329 <.0001 -0.1850 -0.0750 \*\*\*   
## Duration\_hours -0.1043 0.0246 -4.2433 <.0001 -0.1524 -0.0561 \*\*\*   
##   
## ---  
## Signif. codes: 0 '\*\*\*' 0.001 '\*\*' 0.01 '\*' 0.05 '.' 0.1 ' ' 1

##   
## estimate ci.lb ci.ub   
## sigma^2.1 36.5063 17.1095 77.6561   
## sigma.1 6.0420 4.1364 8.8123   
##   
## estimate ci.lb ci.ub   
## sigma^2.2 0.6958 0.0396 2.0433   
## sigma.2 0.8341 0.1991 1.4294

# Controle de qualidade dos dados

Revisor como moderador

##   
## Created.By n   
## 1 Adriano Sebollela 37   
## 2 Ana Paula Sampaio 76   
## 3 Antônio Felix 133   
## 4 Clarissa Franca Dias Carneiro 43   
## 5 Giovanna Nogueira 143   
## 6 Giulia Scarcella Cancelliero 140   
## 7 Glaucia Maria Almeida 137   
## 8 Nathalia Fernandes 121   
## 9 Nathalia Pinheiro 218   
## 10 Samantha Martins 152

##   
## Multivariate Meta-Analysis Model (k = 1200; method: REML)  
##   
## Variance Components:  
##   
## estim sqrt nlvls fixed factor   
## sigma^2.1 7.4590 2.7311 364 no rayyan.key   
## sigma^2.2 5.4378 2.3319 1200 no rayyan.key/Comparison\_ID   
##   
## Test for Residual Heterogeneity:  
## QE(df = 1190) = 6957.7650, p-val < .0001  
##   
## Test of Moderators (coefficients 2:10):  
## QM(df = 9) = 12.6107, p-val = 0.1810  
##   
## Model Results:  
##   
## estimate   
## intrcpt -5.8444   
## relevel(factor(dados\_meta\_smd$Created.By), ref = "Adriano Sebollela")Ana Paula Sampaio 1.9762   
## relevel(factor(dados\_meta\_smd$Created.By), ref = "Adriano Sebollela")Antônio Felix 0.7275   
## relevel(factor(dados\_meta\_smd$Created.By), ref = "Adriano Sebollela")Clarissa Franca Dias Carneiro 0.2462   
## relevel(factor(dados\_meta\_smd$Created.By), ref = "Adriano Sebollela")Giovanna Nogueira 0.3433   
## relevel(factor(dados\_meta\_smd$Created.By), ref = "Adriano Sebollela")Giulia Scarcella Cancelliero -0.0714   
## relevel(factor(dados\_meta\_smd$Created.By), ref = "Adriano Sebollela")Glaucia Maria Almeida 0.9948   
## relevel(factor(dados\_meta\_smd$Created.By), ref = "Adriano Sebollela")Nathalia Fernandes 0.8151   
## relevel(factor(dados\_meta\_smd$Created.By), ref = "Adriano Sebollela")Nathalia Pinheiro 0.9923   
## relevel(factor(dados\_meta\_smd$Created.By), ref = "Adriano Sebollela")Samantha Martins -0.5280   
## se   
## intrcpt 0.8982   
## relevel(factor(dados\_meta\_smd$Created.By), ref = "Adriano Sebollela")Ana Paula Sampaio 1.1091   
## relevel(factor(dados\_meta\_smd$Created.By), ref = "Adriano Sebollela")Antônio Felix 1.0229   
## relevel(factor(dados\_meta\_smd$Created.By), ref = "Adriano Sebollela")Clarissa Franca Dias Carneiro 1.2201   
## relevel(factor(dados\_meta\_smd$Created.By), ref = "Adriano Sebollela")Giovanna Nogueira 1.0582   
## relevel(factor(dados\_meta\_smd$Created.By), ref = "Adriano Sebollela")Giulia Scarcella Cancelliero 1.0468   
## relevel(factor(dados\_meta\_smd$Created.By), ref = "Adriano Sebollela")Glaucia Maria Almeida 1.0455   
## relevel(factor(dados\_meta\_smd$Created.By), ref = "Adriano Sebollela")Nathalia Fernandes 1.1078   
## relevel(factor(dados\_meta\_smd$Created.By), ref = "Adriano Sebollela")Nathalia Pinheiro 1.0425   
## relevel(factor(dados\_meta\_smd$Created.By), ref = "Adriano Sebollela")Samantha Martins 1.0430   
## zval   
## intrcpt -6.5065   
## relevel(factor(dados\_meta\_smd$Created.By), ref = "Adriano Sebollela")Ana Paula Sampaio 1.7817   
## relevel(factor(dados\_meta\_smd$Created.By), ref = "Adriano Sebollela")Antônio Felix 0.7112   
## relevel(factor(dados\_meta\_smd$Created.By), ref = "Adriano Sebollela")Clarissa Franca Dias Carneiro 0.2018   
## relevel(factor(dados\_meta\_smd$Created.By), ref = "Adriano Sebollela")Giovanna Nogueira 0.3244   
## relevel(factor(dados\_meta\_smd$Created.By), ref = "Adriano Sebollela")Giulia Scarcella Cancelliero -0.0683   
## relevel(factor(dados\_meta\_smd$Created.By), ref = "Adriano Sebollela")Glaucia Maria Almeida 0.9516   
## relevel(factor(dados\_meta\_smd$Created.By), ref = "Adriano Sebollela")Nathalia Fernandes 0.7358   
## relevel(factor(dados\_meta\_smd$Created.By), ref = "Adriano Sebollela")Nathalia Pinheiro 0.9518   
## relevel(factor(dados\_meta\_smd$Created.By), ref = "Adriano Sebollela")Samantha Martins -0.5062   
## pval   
## intrcpt <.0001   
## relevel(factor(dados\_meta\_smd$Created.By), ref = "Adriano Sebollela")Ana Paula Sampaio 0.0748   
## relevel(factor(dados\_meta\_smd$Created.By), ref = "Adriano Sebollela")Antônio Felix 0.4770   
## relevel(factor(dados\_meta\_smd$Created.By), ref = "Adriano Sebollela")Clarissa Franca Dias Carneiro 0.8401   
## relevel(factor(dados\_meta\_smd$Created.By), ref = "Adriano Sebollela")Giovanna Nogueira 0.7457   
## relevel(factor(dados\_meta\_smd$Created.By), ref = "Adriano Sebollela")Giulia Scarcella Cancelliero 0.9456   
## relevel(factor(dados\_meta\_smd$Created.By), ref = "Adriano Sebollela")Glaucia Maria Almeida 0.3413   
## relevel(factor(dados\_meta\_smd$Created.By), ref = "Adriano Sebollela")Nathalia Fernandes 0.4619   
## relevel(factor(dados\_meta\_smd$Created.By), ref = "Adriano Sebollela")Nathalia Pinheiro 0.3412   
## relevel(factor(dados\_meta\_smd$Created.By), ref = "Adriano Sebollela")Samantha Martins 0.6127   
## ci.lb   
## intrcpt -7.6050   
## relevel(factor(dados\_meta\_smd$Created.By), ref = "Adriano Sebollela")Ana Paula Sampaio -0.1977   
## relevel(factor(dados\_meta\_smd$Created.By), ref = "Adriano Sebollela")Antônio Felix -1.2774   
## relevel(factor(dados\_meta\_smd$Created.By), ref = "Adriano Sebollela")Clarissa Franca Dias Carneiro -2.1451   
## relevel(factor(dados\_meta\_smd$Created.By), ref = "Adriano Sebollela")Giovanna Nogueira -1.7308   
## relevel(factor(dados\_meta\_smd$Created.By), ref = "Adriano Sebollela")Giulia Scarcella Cancelliero -2.1232   
## relevel(factor(dados\_meta\_smd$Created.By), ref = "Adriano Sebollela")Glaucia Maria Almeida -1.0543   
## relevel(factor(dados\_meta\_smd$Created.By), ref = "Adriano Sebollela")Nathalia Fernandes -1.3562   
## relevel(factor(dados\_meta\_smd$Created.By), ref = "Adriano Sebollela")Nathalia Pinheiro -1.0510   
## relevel(factor(dados\_meta\_smd$Created.By), ref = "Adriano Sebollela")Samantha Martins -2.5723   
## ci.ub   
## intrcpt -4.0839   
## relevel(factor(dados\_meta\_smd$Created.By), ref = "Adriano Sebollela")Ana Paula Sampaio 4.1501   
## relevel(factor(dados\_meta\_smd$Created.By), ref = "Adriano Sebollela")Antônio Felix 2.7324   
## relevel(factor(dados\_meta\_smd$Created.By), ref = "Adriano Sebollela")Clarissa Franca Dias Carneiro 2.6376   
## relevel(factor(dados\_meta\_smd$Created.By), ref = "Adriano Sebollela")Giovanna Nogueira 2.4173   
## relevel(factor(dados\_meta\_smd$Created.By), ref = "Adriano Sebollela")Giulia Scarcella Cancelliero 1.9803   
## relevel(factor(dados\_meta\_smd$Created.By), ref = "Adriano Sebollela")Glaucia Maria Almeida 3.0439   
## relevel(factor(dados\_meta\_smd$Created.By), ref = "Adriano Sebollela")Nathalia Fernandes 2.9864   
## relevel(factor(dados\_meta\_smd$Created.By), ref = "Adriano Sebollela")Nathalia Pinheiro 3.0355   
## relevel(factor(dados\_meta\_smd$Created.By), ref = "Adriano Sebollela")Samantha Martins 1.5163   
##   
## intrcpt \*\*\*   
## relevel(factor(dados\_meta\_smd$Created.By), ref = "Adriano Sebollela")Ana Paula Sampaio .   
## relevel(factor(dados\_meta\_smd$Created.By), ref = "Adriano Sebollela")Antônio Felix   
## relevel(factor(dados\_meta\_smd$Created.By), ref = "Adriano Sebollela")Clarissa Franca Dias Carneiro   
## relevel(factor(dados\_meta\_smd$Created.By), ref = "Adriano Sebollela")Giovanna Nogueira   
## relevel(factor(dados\_meta\_smd$Created.By), ref = "Adriano Sebollela")Giulia Scarcella Cancelliero   
## relevel(factor(dados\_meta\_smd$Created.By), ref = "Adriano Sebollela")Glaucia Maria Almeida   
## relevel(factor(dados\_meta\_smd$Created.By), ref = "Adriano Sebollela")Nathalia Fernandes   
## relevel(factor(dados\_meta\_smd$Created.By), ref = "Adriano Sebollela")Nathalia Pinheiro   
## relevel(factor(dados\_meta\_smd$Created.By), ref = "Adriano Sebollela")Samantha Martins   
##   
## ---  
## Signif. codes: 0 '\*\*\*' 0.001 '\*\*' 0.01 '\*' 0.05 '.' 0.1 ' ' 1

## Warning in geom\_abline(yintercept = 0, slope = 0, linetype = "dashed", color =  
## "grey"): Ignoring unknown parameters: `yintercept`

