Here we provide the code used for our project:

**Combined meta-analysis of preclinical cell therapy studies shows overlapping effect modifiers for multiple diseases**

Currently submitted to: BMJ Open Science.

For this analyses, we used R version 3.1.2. for the generation of figures and Stata (version 13.1) for the meta-regression analyses.

In R we used the additional packages metafor, lattice, rms and readxl.

Here, we will provide the analysis of one dataset (in the project we analyze 5). Through this code, one should be able to generate similar analyses for different datasets. We will provide the output for important steps **(in bold),** to show you how the output should look like.

If there are any questions, feel free to contact me at [P.P.M.Zwetsloot@umcutrecht.nl](mailto:P.P.M.Zwetsloot@umcutrecht.nl) .

As an example, we used the Large Animal MI Cardiac dataset.

**ANALYSIS IN R**

##########################

########## Dataset Cardiac cell therapy CSCs

###########################

# Load Files

setwd("XXXXX") ### Load your own working directory.

# Load Packages and Data

library(metafor)

library(lattice)

library(rms)

library(readxl)

read\_excel("2020ALL DATASETSPP new analyses.xls",sheet='MI\_largenewPP')->SanneEF

EFmaSanne<-rma(yi=lnROM,sei= ROM\_se,data=SanneEF)

EFmaSanne

forest(EFmaSanne,atransf=exp,xlim=c(-3, 3),slab=SanneEF$Author.ID,ilab=as.character(SanneEF $Animal),ilab.xpos=(c(-1.6)),cex=0.6,main="",at=c(log(0.5),0,log(2),log(4)))

pdf("LVEF\_forest.pdf",height=12,width=8)

forest(EFma,atransf=exp,xlim=c(-3, 3),slab=PPdat$AuthorYear,ilab=as.character(PPdat $Animal),ilab.xpos=(c(-1.6)),cex=0.6,main="",at=c(log(0.5),0,log(2),log(4)))

text(-3,111,"Author and Year",font=4,cex=0.8,pos=4)

text(-1.6,111,"Animal",font=4,cex=0.8)

text(-0,111,"LVEF Improvement",font=4,cex=0.8)

text(3,111,"ROM & 95% CI",font=4,cex=0.8,pos=2)

text(0,-5,"<-Deterioration Improvement->",cex=0.6)

dev.off()



#Simple Model

#Exhaustive Forest Plot

##################### Species model

> EFma2.1Sanne<-rma(yi=lnROM,sei=ROM\_se,mods=~(Animal),data=SanneEF)

> factor(SanneEF$Animal,levels=c("Dog","Sheep","Pig"))->SanneEF$Animal

> SanneEF$Animal

**[1] Dog Dog Dog Dog Dog Dog Dog Dog Pig Pig Pig Pig Pig Pig Pig Pig Pig**

**[18] Pig Pig Pig Pig Pig Pig Pig Pig Pig Pig Pig Pig Pig Pig Pig Pig Pig**

**[35] Pig Pig Pig Pig Pig Pig Pig Pig Pig Pig Pig Pig Pig Pig Pig Pig Pig**

**[52] Pig Pig Pig Pig Pig Pig Pig Pig Pig Pig Pig Pig Pig Pig Pig Pig Pig**

**[69] Pig Pig Pig Pig Pig Pig Pig Pig Pig Pig Pig Pig Pig Pig Pig Pig Pig**

**[86] Pig Pig Pig Pig Pig Pig Pig Pig Pig Pig Pig Pig Pig Pig Pig Pig Pig**

**[103] Pig Pig Pig Pig Pig Pig Sheep Sheep Sheep Sheep Sheep Sheep Sheep Sheep Sheep Sheep Sheep**

**[120] Sheep Sheep Sheep Sheep Sheep Sheep**

**Levels: Dog Sheep Pig**

> EFma2Sanne<-rma(yi=lnROM,sei=ROM\_se,mods=~(Animal-1),data=SanneEF)

>

> EFma2.1Sanne<-rma(yi=lnROM,sei=ROM\_se,mods=~(Animal),data=SanneEF)

>

>

> EFma2Sanne

**Mixed-Effects Model (k = 125; tau^2 estimator: REML)**

**tau^2 (estimated amount of residual heterogeneity): 0.0172 (SE = 0.0033)**

**tau (square root of estimated tau^2 value): 0.1310**

**I^2 (residual heterogeneity / unaccounted variability): 77.82%**

**H^2 (unaccounted variability / sampling variability): 4.51**

**Test for Residual Heterogeneity:**

**QE(df = 122) = 517.4633, p-val < .0001**

**Test of Moderators (coefficients 1:3):**

**QM(df = 3) = 188.7030, p-val < .0001**

**Model Results:**

**estimate se zval pval ci.lb ci.ub**

**AnimalDog -0.2227 0.0621 -3.5860 0.0003 -0.3445 -0.1010 \*\*\***

**AnimalSheep -0.3072 0.0432 -7.1035 <.0001 -0.3920 -0.2224 \*\*\***

**AnimalPig -0.1817 0.0162 -11.1975 <.0001 -0.2135 -0.1499 \*\*\***

**---**

**Signif. codes: 0 ‘\*\*\*’ 0.001 ‘\*\*’ 0.01 ‘\*’ 0.05 ‘.’ 0.1 ‘ ’ 1**

> EFma2.1Sanne

**Mixed-Effects Model (k = 125; tau^2 estimator: REML)**

**tau^2 (estimated amount of residual heterogeneity): 0.0172 (SE = 0.0033)**

**tau (square root of estimated tau^2 value): 0.1310**

**I^2 (residual heterogeneity / unaccounted variability): 77.82%**

**H^2 (unaccounted variability / sampling variability): 4.51**

**R^2 (amount of heterogeneity accounted for): 3.63%**

**Test for Residual Heterogeneity:**

**QE(df = 122) = 517.4633, p-val < .0001**

**Test of Moderators (coefficients 2:3):**

**QM(df = 2) = 7.5379, p-val = 0.0231**

**Model Results:**

**estimate se zval pval ci.lb ci.ub**

**intrcpt -0.2227 0.0621 -3.5860 0.0003 -0.3445 -0.1010 \*\*\***

**AnimalSheep -0.0844 0.0757 -1.1157 0.2645 -0.2328 0.0639**

**AnimalPig 0.0410 0.0642 0.6390 0.5228 -0.0848 0.1669**

**---**

**Signif. codes: 0 ‘\*\*\*’ 0.001 ‘\*\*’ 0.01 ‘\*’ 0.05 ‘.’ 0.1 ‘ ’ 1**

> as.data.frame(table(SanneEF $Animal))->SpeciestableSanne

> signif(EFma2Sanne $pval,digits=2)-> EFpvalsSanne

> SpeciestableSanne

**Var1 Freq**

**1 Dog 8**

**2 Sheep 17**

**3 Pig 100**

> EFpvalsSanne

**[1] 3.4e-04 1.2e-12 4.2e-29**

pdf("LVEFlargespecies.pdf",width=9,height=4)

forest(EFma2Sanne $b,sei= EFma2Sanne $se,atransf=exp,slab=paste(SpeciestableSanne $Var1),ilab=cbind(SpeciestableSanne$Freq, EFpvalsSanne),ilab.xpos=c(-4,-3),at=(c(log(0.5), 0, log(1),log(2))),xlim=c(-6, 3),main="Effects of Species")

text(-6,5,"Species",pos=4,font=4)

text(-5,5,"# Studycohorts",pos=4,font=4)

text(-3.5,5,"P-value",pos=4,font=4)

text(-3.5,4.5,"(vs no-effect)",pos=4,font=1,cex=0.8)

text(-1,5,"LVEF Improvement",pos=4,font=4)

text(3,5,"ROM + 95% CI",font=4,pos=2)

text(1,1.9,paste(c("p = ",round(EFma2.1Sanne $QMp,3))),srt=-90,cex=0.8)

arrows(x0=0.8,x1=0.8,y0=1,y1=3,length=0.05,angle=90,code=3)

dev.off()



> EFmaImmSanne<-rma(yi=lnROM,sei=ROM\_se,mods=~(Immunisupp2-1),data=SanneEF)

> EFmaImm1Sanne<-rma(yi=lnROM,sei=ROM\_se,mods=~(Immunisupp2),data=SanneEF)

>

> EFmaImmSanne

**Mixed-Effects Model (k = 125; tau^2 estimator: REML)**

**tau^2 (estimated amount of residual heterogeneity): 0.0180 (SE = 0.0034)**

**tau (square root of estimated tau^2 value): 0.1343**

**I^2 (residual heterogeneity / unaccounted variability): 79.31%**

**H^2 (unaccounted variability / sampling variability): 4.83**

**Test for Residual Heterogeneity:**

**QE(df = 122) = 541.2325, p-val < .0001**

**Test of Moderators (coefficients 1:3):**

**QM(df = 3) = 175.8127, p-val < .0001**

**Model Results:**

**estimate se zval pval ci.lb ci.ub**

**Immunisupp2Cyclosporin A -0.1925 0.0663 -2.9025 0.0037 -0.3225 -0.0625 \*\***

**Immunisupp2Cyclosporin A + -0.2925 0.1145 -2.5540 0.0107 -0.5169 -0.0680 \***

**Immunisupp2None -0.1975 0.0156 -12.6833 <.0001 -0.2280 -0.1670 \*\*\***

**---**

**Signif. codes: 0 ‘\*\*\*’ 0.001 ‘\*\*’ 0.01 ‘\*’ 0.05 ‘.’ 0.1 ‘ ’ 1**

> EFmaImm1Sanne

**Mixed-Effects Model (k = 125; tau^2 estimator: REML)**

**tau^2 (estimated amount of residual heterogeneity): 0.0180 (SE = 0.0034)**

**tau (square root of estimated tau^2 value): 0.1343**

**I^2 (residual heterogeneity / unaccounted variability): 79.31%**

**H^2 (unaccounted variability / sampling variability): 4.83**

**R^2 (amount of heterogeneity accounted for): 0.00%**

**Test for Residual Heterogeneity:**

**QE(df = 122) = 541.2325, p-val < .0001**

**Test of Moderators (coefficients 2:3):**

**QM(df = 2) = 0.6855, p-val = 0.7098**

**Model Results:**

**estimate se zval pval ci.lb ci.ub**

**intrcpt -0.1925 0.0663 -2.9025 0.0037 -0.3225 -0.0625 \*\***

**Immunisupp2Cyclosporin A + -0.1000 0.1323 -0.7555 0.4499 -0.3594 0.1594**

**Immunisupp2None -0.0050 0.0681 -0.0730 0.9418 -0.1385 0.1285**

**---**

**Signif. codes: 0 ‘\*\*\*’ 0.001 ‘\*\*’ 0.01 ‘\*’ 0.05 ‘.’ 0.1 ‘ ’ 1**

>

> as.data.frame(table(SanneEF $Immunisupp2))->ImmunotableSanne

> signif(EFmaImmSanne $pval,digits=2)-> EFpvalsSanneimm

>

> pdf("LVEFlargeimmuno.pdf",width=9,height=4)

>

> forest(EFmaImmSanne $b,sei= EFmaImmSanne $se,atransf=exp,slab=paste(ImmunotableSanne $Var1),ilab=cbind(ImmunotableSanne$Freq, EFpvalsSanneimm),ilab.xpos=c(-4,-3),at=(c(log(0.5), 0, log(1),log(2))),xlim=c(-6, 3),main="Effects of Immunosuppression")

> text(-6,5,"Imm. supp.",pos=4,font=4)

> text(-5,5,"# Studycohorts",pos=4,font=4)

> text(-3,5,"P-value",pos=4,font=4)

> text(-3,4.5,"(vs no-effect)",pos=4,font=1,cex=0.8)

> text(-1,5,"LVEF Improvement",pos=4,font=4)

> text(3,5,"ROM + 95% CI",font=4,pos=2)

> text(1,1.2,paste(c("p = ",round(EFmaImm1Sanne $QMp,2))),srt=-90,cex=0.8)

> arrows(x0=0.8,x1=0.8,y0=1,y1=2,length=0.05,angle=90,code=3)

> dev.off()

null device

1



######################### Cell Source

> EFmacellSanne<-rma(yi=lnROM,sei=ROM\_se,mods=~(SanneEF$`Cell Source3`-1),data=SanneEF)

> EFmacell1Sanne<-rma(yi=lnROM,sei=ROM\_se,mods=~(SanneEF$`Cell Source3`),data=SanneEF)

>

> EFmacellSanne

**Mixed-Effects Model (k = 125; tau^2 estimator: REML)**

**tau^2 (estimated amount of residual heterogeneity): 0.0181 (SE = 0.0034)**

**tau (square root of estimated tau^2 value): 0.1346**

**I^2 (residual heterogeneity / unaccounted variability): 79.17%**

**H^2 (unaccounted variability / sampling variability): 4.80**

**Test for Residual Heterogeneity:**

**QE(df = 122) = 537.5124, p-val < .0001**

**Test of Moderators (coefficients 1:3):**

**QM(df = 3) = 175.7913, p-val < .0001**

**Model Results:**

**estimate se zval pval ci.lb ci.ub**

**SanneEF$`Cell Source3`Allogeneic -0.2229 0.0334 -6.6668 <.0001 -0.2884 -0.1573 \*\*\***

**SanneEF$`Cell Source3`Autologous -0.1961 0.0177 -11.0666 <.0001 -0.2309 -0.1614 \*\*\***

**SanneEF$`Cell Source3`Xenogeneic -0.1613 0.0542 -2.9791 0.0029 -0.2675 -0.0552 \*\***

**---**

**Signif. codes: 0 ‘\*\*\*’ 0.001 ‘\*\*’ 0.01 ‘\*’ 0.05 ‘.’ 0.1 ‘ ’ 1**

> EFmacell1Sanne

**Mixed-Effects Model (k = 125; tau^2 estimator: REML)**

**tau^2 (estimated amount of residual heterogeneity): 0.0181 (SE = 0.0034)**

**tau (square root of estimated tau^2 value): 0.1346**

**I^2 (residual heterogeneity / unaccounted variability): 79.17%**

**H^2 (unaccounted variability / sampling variability): 4.80**

**R^2 (amount of heterogeneity accounted for): 0.00%**

**Test for Residual Heterogeneity:**

**QE(df = 122) = 537.5124, p-val < .0001**

**Test of Moderators (coefficients 2:3):**

**QM(df = 2) = 1.0187, p-val = 0.6009**

**Model Results:**

**estimate se zval pval ci.lb ci.ub**

**intrcpt -0.2229 0.0334 -6.6668 <.0001 -0.2884 -0.1573 \*\*\***

**SanneEF$`Cell Source3`Autologous 0.0267 0.0378 0.7062 0.4801 -0.0474 0.1009**

**SanneEF$`Cell Source3`Xenogeneic 0.0615 0.0636 0.9664 0.3338 -0.0632 0.1862**

**---**

**Signif. codes: 0 ‘\*\*\*’ 0.001 ‘\*\*’ 0.01 ‘\*’ 0.05 ‘.’ 0.1 ‘ ’ 1**

>

> as.data.frame(table(SanneEF $`Cell Source3`))->CelltableSanne

> signif(EFmacellSanne $pval,digits=2)-> EFpvalsSannecell

>

> pdf("LVEFlargecell.pdf",width=9,height=4)

>

> forest(EFmacellSanne $b,sei= EFmacellSanne $se,atransf=exp,slab=paste(CelltableSanne $Var1),ilab=cbind(CelltableSanne$Freq, EFpvalsSannecell),ilab.xpos=c(-4,-3),at=(c(log(0.5), 0, log(1),log(2),log(4))),xlim=c(-6, 3),main="Effects of Cell type")

> text(-6,5,"Cell",pos=4,font=4)

> text(-5,5,"# Studycohorts",pos=4,font=4)

> text(-3,5,"P-value",pos=4,font=4)

> text(-3,4.5,"(vs no-effect)",pos=4,font=1,cex=0.8)

> text(-1,5,"LVEF Improvement",pos=4,font=4)

> text(3,5,"ROM + 95% CI",font=4,pos=2)

> text(1,4.7,paste(c("p = ",round(EFmacell1Sanne $QMp,2))),srt=-90,cex=0.8)

> arrows(x0=0.8,x1=0.8,y0=0.8,y1=8.7,length=0.05,angle=90,code=3)

> dev.off()

null device

1



######################### Cell Type

> EFmatypeSanne<-rma(yi=lnROM,sei=ROM\_se,mods=~(SanneEF$`Cell Type2`-1),data=SanneEF)

> EFmatype1Sanne<-rma(yi=lnROM,sei=ROM\_se,mods=~(SanneEF$`Cell Type2`),data=SanneEF)

>

> EFmatypeSanne

**Mixed-Effects Model (k = 125; tau^2 estimator: REML)**

**tau^2 (estimated amount of residual heterogeneity): 0.0171 (SE = 0.0034)**

**tau (square root of estimated tau^2 value): 0.1308**

**I^2 (residual heterogeneity / unaccounted variability): 77.85%**

**H^2 (unaccounted variability / sampling variability): 4.52**

**Test for Residual Heterogeneity:**

**QE(df = 117) = 490.0224, p-val < .0001**

**Test of Moderators (coefficients 1:8):**

**QM(df = 8) = 191.0821, p-val < .0001**

**Model Results:**

**estimate se zval pval ci.lb ci.ub**

**SanneEF$`Cell Type2`Blood -0.1452 0.0397 -3.6566 0.0003 -0.2230 -0.0674 \*\*\***

**SanneEF$`Cell Type2`BM -0.1999 0.0277 -7.2266 <.0001 -0.2542 -0.1457 \*\*\***

**SanneEF$`Cell Type2`MSC -0.1931 0.0230 -8.4076 <.0001 -0.2381 -0.1481 \*\*\***

**SanneEF$`Cell Type2`Other -0.4669 0.1396 -3.3447 0.0008 -0.7404 -0.1933 \*\*\***

**SanneEF$`Cell Type2`Pluripotent -0.0862 0.1565 -0.5503 0.5821 -0.3930 0.2207**

**SanneEF$`Cell Type2`Tissue-specific -0.2339 0.0403 -5.8075 <.0001 -0.3129 -0.1550 \*\*\***

**SanneEF$`Cell Type2`Tissue-specific + BM -0.4747 0.2041 -2.3262 0.0200 -0.8747 -0.0747 \***

**SanneEF$`Cell Type2`Tissue-specific + MSC -0.3784 0.1853 -2.0426 0.0411 -0.7416 -0.0153 \***

**---**

**Signif. codes: 0 ‘\*\*\*’ 0.001 ‘\*\*’ 0.01 ‘\*’ 0.05 ‘.’ 0.1 ‘ ’ 1**

> EFmatype1Sanne

**Mixed-Effects Model (k = 125; tau^2 estimator: REML)**

**tau^2 (estimated amount of residual heterogeneity): 0.0171 (SE = 0.0034)**

**tau (square root of estimated tau^2 value): 0.1308**

**I^2 (residual heterogeneity / unaccounted variability): 77.85%**

**H^2 (unaccounted variability / sampling variability): 4.52**

**R^2 (amount of heterogeneity accounted for): 3.86%**

**Test for Residual Heterogeneity:**

**QE(df = 117) = 490.0224, p-val < .0001**

**Test of Moderators (coefficients 2:8):**

**QM(df = 7) = 9.6217, p-val = 0.2110**

**Model Results:**

**estimate se zval pval ci.lb ci.ub**

**intrcpt -0.1452 0.0397 -3.6566 0.0003 -0.2230 -0.0674 \*\*\***

**SanneEF$`Cell Type2`BM -0.0548 0.0484 -1.1313 0.2579 -0.1496 0.0401**

**SanneEF$`Cell Type2`MSC -0.0479 0.0459 -1.0434 0.2968 -0.1378 0.0420**

**SanneEF$`Cell Type2`Other -0.3217 0.1451 -2.2165 0.0267 -0.6061 -0.0372 \***

**SanneEF$`Cell Type2`Pluripotent 0.0590 0.1615 0.3656 0.7147 -0.2575 0.3756**

**SanneEF$`Cell Type2`Tissue-specific -0.0887 0.0566 -1.5690 0.1166 -0.1996 0.0221**

**SanneEF$`Cell Type2`Tissue-specific + BM -0.3295 0.2079 -1.5850 0.1130 -0.7370 0.0780**

**SanneEF$`Cell Type2`Tissue-specific + MSC -0.2332 0.1895 -1.2309 0.2183 -0.6046 0.1381**

**---**

**Signif. codes: 0 ‘\*\*\*’ 0.001 ‘\*\*’ 0.01 ‘\*’ 0.05 ‘.’ 0.1 ‘ ’ 1**

>

> as.data.frame(table(SanneEF$`Cell Type2`))->typetableSanne

> signif(EFmatypeSanne $pval,digits=2)-> EFpvalsSannetype

>

> pdf("LVEFlargetype.pdf",width=9,height=4)

>

> forest(EFmatypeSanne $b,sei= EFmatypeSanne $se,atransf=exp,slab=paste(typetableSanne $Var1),ilab=cbind(typetableSanne$Freq, EFpvalsSannetype),ilab.xpos=c(-4,-3),at=(c(log(0.5), 0, log(1),log(2),log(4))),xlim=c(-6, 3),main="Effects of Cell Type")

> text(-6,10,"Cell Type",pos=4,font=4)

> text(-5,10,"# Studycohorts",pos=4,font=4)

> text(-3,10,"P-value",pos=4,font=4)

> text(-3,9.5,"(vs no-effect)",pos=4,font=1,cex=0.8)

> text(-1,10,"LVEF Improvement",pos=4,font=4)

> text(3,10,"ROM + 95% CI",font=4,pos=2)

> text(1,4.7,paste(c("p = ",round(EFmatype1Sanne $QMp,4))),srt=-90,cex=0.8)

> arrows(x0=0.8,x1=0.8,y0=0.8,y1=8.2,length=0.25,angle=90,code=3)

> dev.off()

null device

1



###################### Dose

> rma(lnROM,sei=ROM\_se,data= SanneEF,mods=~allonetric)->dosemodlinLarge

>dosemodlinLarge

**Mixed-Effects Model (k = 121; tau^2 estimator: REML)**

**tau^2 (estimated amount of residual heterogeneity): 0.0186 (SE = 0.0036)**

**tau (square root of estimated tau^2 value): 0.1365**

**I^2 (residual heterogeneity / unaccounted variability): 79.03%**

**H^2 (unaccounted variability / sampling variability): 4.77**

**R^2 (amount of heterogeneity accounted for): 0.18%**

**Test for Residual Heterogeneity:**

**QE(df = 119) = 533.4923, p-val < .0001**

**Test of Moderators (coefficient 2):**

**QM(df = 1) = 1.6914, p-val = 0.1934**

**Model Results:**

**estimate se zval pval ci.lb ci.ub**

**intrcpt -0.1879 0.0174 -10.7797 <.0001 -0.2221 -0.1538 \*\*\***

**allonetric -0.0000 0.0000 -1.3006 0.1934 -0.0000 0.0000**

**---**

**Signif. codes: 0 ‘\*\*\*’ 0.001 ‘\*\*’ 0.01 ‘\*’ 0.05 ‘.’ 0.1 ‘ ’ 1**

> rma(lnROM,sei=ROM\_se,data= SanneEF,mods=~rcs(allonetric,3))->dosemodrcsLarge

>dosemodrcsLarge

**Mixed-Effects Model (k = 121; tau^2 estimator: REML)**

**tau^2 (estimated amount of residual heterogeneity): 0.0186 (SE = 0.0036)**

**tau (square root of estimated tau^2 value): 0.1365**

**I^2 (residual heterogeneity / unaccounted variability): 78.90%**

**H^2 (unaccounted variability / sampling variability): 4.74**

**R^2 (amount of heterogeneity accounted for): 0.21%**

**Test for Residual Heterogeneity:**

**QE(df = 118) = 524.1059, p-val < .0001**

**Test of Moderators (coefficients 2:3):**

**QM(df = 2) = 3.7169, p-val = 0.1559**

**Model Results:**

**estimate se zval pval ci.lb ci.ub**

**intrcpt -0.1651 0.0237 -6.9606 <.0001 -0.2115 -0.1186 \*\*\***

**rcs(allonetric, 3)allonetric -0.0000 0.0000 -1.6225 0.1047 -0.0000 0.0000**

**rcs(allonetric, 3)allonetric' 0.0000 0.0000 1.4231 0.1547 -0.0000 0.0000**

**---**

**Signif. codes: 0 ‘\*\*\*’ 0.001 ‘\*\*’ 0.01 ‘\*’ 0.05 ‘.’ 0.1 ‘ ’ 1**

> weights(dosemodrcsLarge)\*3->Largeweights

>

>

> plot(SanneEF $allonetric,exp(SanneEF $lnROM),pch=19,col=rgb(0,0,0,0.1),cex= Largeweights,ylab="Ratio of Means",xlab="Dose/Metabolic Weight",main="Myocardial Infaction Large Animals")

> predict(dosemodrcsLarge)->splinepreds

> data.frame(Dose= SanneEF $allonetric,Pred=splinepreds$pred,uci=splinepreds$ci.ub,lci=splinepreds$ci.lb)->splinepreds2

> splinepreds2[with(splinepreds2,order(Dose)),]->splinepreds2

> points(splinepreds2$Dose,exp(splinepreds2$Pred),type="l",lwd=2)

> points(splinepreds2$Dose,exp(splinepreds2$lci),type="l",lwd=1,lty=2)

> points(splinepreds2$Dose,exp(splinepreds2$uci),type="l",lwd=1,lty=2)



################ Timing

> EFmatimingSanne<-rma(yi=lnROM,sei=ROM\_se,mods=~(SanneEF$`Time of Admin`-1),data=SanneEF)

> EFmatiming1Sanne<-rma(yi=lnROM,sei=ROM\_se,mods=~(SanneEF$`Time of Admin`),data=SanneEF)

>

> EFmatimingSanne

**Mixed-Effects Model (k = 125; tau^2 estimator: REML)**

**tau^2 (estimated amount of residual heterogeneity): 0.0183 (SE = 0.0035)**

**tau (square root of estimated tau^2 value): 0.1354**

**I^2 (residual heterogeneity / unaccounted variability): 79.03%**

**H^2 (unaccounted variability / sampling variability): 4.77**

**Test for Residual Heterogeneity:**

**QE(df = 122) = 542.9185, p-val < .0001**

**Test of Moderators (coefficients 1:3):**

**QM(df = 3) = 173.8595, p-val < .0001**

**Model Results:**

**estimate se zval pval ci.lb ci.ub**

**SanneEF$`Time of Admin`acute -0.2079 0.0258 -8.0648 <.0001 -0.2584 -0.1573 \*\*\***

**SanneEF$`Time of Admin`chronic -0.1995 0.0206 -9.6924 <.0001 -0.2398 -0.1592 \*\*\***

**SanneEF$`Time of Admin`sub-acute -0.1700 0.0441 -3.8568 0.0001 -0.2564 -0.0836 \*\*\***

**---**

**Signif. codes: 0 ‘\*\*\*’ 0.001 ‘\*\*’ 0.01 ‘\*’ 0.05 ‘.’ 0.1 ‘ ’ 1**

> EFmatiming1Sanne

**Mixed-Effects Model (k = 125; tau^2 estimator: REML)**

**tau^2 (estimated amount of residual heterogeneity): 0.0183 (SE = 0.0035)**

**tau (square root of estimated tau^2 value): 0.1354**

**I^2 (residual heterogeneity / unaccounted variability): 79.03%**

**H^2 (unaccounted variability / sampling variability): 4.77**

**R^2 (amount of heterogeneity accounted for): 0.00%**

**Test for Residual Heterogeneity:**

**QE(df = 122) = 542.9185, p-val < .0001**

**Test of Moderators (coefficients 2:3):**

**QM(df = 2) = 0.5510, p-val = 0.7592**

**Model Results:**

**estimate se zval pval ci.lb ci.ub**

**intrcpt -0.2079 0.0258 -8.0648 <.0001 -0.2584 -0.1573 \*\*\***

**SanneEF$`Time of Admin`chronic 0.0084 0.0330 0.2539 0.7996 -0.0563 0.0730**

**SanneEF$`Time of Admin`sub-acute 0.0378 0.0511 0.7411 0.4586 -0.0622 0.1379**

**---**

**Signif. codes: 0 ‘\*\*\*’ 0.001 ‘\*\*’ 0.01 ‘\*’ 0.05 ‘.’ 0.1 ‘ ’ 1**

>

> as.data.frame(table(SanneEF$`Time of Admin`))->timingtableSanne

> signif(EFmatimingSanne $pval,digits=2)-> EFpvalsSannetiming

>

> pdf("LVEFlargetiming.pdf",width=9,height=4)

>

> forest(EFmatimingSanne $b,sei= EFmatimingSanne $se,atransf=exp,slab=paste(timingtableSanne $Var1),ilab=cbind(timingtableSanne$Freq, EFpvalsSannetiming),ilab.xpos=c(-4,-3),at=(c(log(0.5), 0, log(1),log(2),log(4))),xlim=c(-6, 3),main="Effects of Time of Administration")

> text(-6,5,"Timing",pos=4,font=4)

> text(-5,5,"# Studycohorts",pos=4,font=4)

> text(-3,5,"P-value",pos=4,font=4)

> text(-3,4.5,"(vs no-effect)",pos=4,font=1,cex=0.8)

> text(-1,5,"LVEF Improvement",pos=4,font=4)

> text(3,5,"ROM + 95% CI",font=4,pos=2)

> text(1,1.7,paste(c("p = ",round(EFmatiming1Sanne $QMp,4))),srt=-90,cex=0.8)

> arrows(x0=0.8,x1=0.8,y0=0.8,y1=3.2,length=0.05,angle=90,code=3)

> dev.off()

RStudioGD

2



> rma(lnROM,sei=ROM\_se,data= SanneEF,mods=~SanneEF$Delivery...22-1)->delMod

> rma(lnROM,sei=ROM\_se,data= SanneEF,mods=~SanneEF$Delivery...22)->delMod2

>

>

> as.data.frame(table(SanneEF$Delivery...22))->deliverytable

> signif(delMod $pval,digits=2)-> deliverypvals

>

>

> pdf("MIlargeDelivery.pdf",height=6,width=10)

> forest(delMod $b,sei= delMod $se,atransf=exp,slab=paste(deliverytable $Var1),ilab=cbind(deliverytable$Freq, deliverypvals),ilab.xpos=c(-4,-3),at=(c(log(0.5), 0, log(1),log(2))),xlim=c(-6, 3),main="Effect of Cell Delivery Route on Ejection Fraction (large animals)")

> text(-6,5,"Delivery",pos=4,font=4)

> text(-5,5,"# Studycohorts",pos=4,font=4)

> text(-3.5,5,"P-value",pos=4,font=4)

> text(-1,5,"LVEF Improvement",pos=4,font=4)

> text(3,5,"ROM + 95% CI",font=4,pos=2)

>

> text(1,1.9,paste(c("P = ",round(delMod2 $QMp,3))),srt=-90,cex=0.8)

> arrows(x0=0.8,x1=0.8,y0=0.75,y1=3.25,length=0.05,angle=90,code=3)

> dev.off()

null device

1



**Analysis in Stata.**

NB. Analysis of ROMs is similar to analysis of original outcomes (RMD, SMD or NMD). Instead of lnROM and lnROM\_se, we used the RMD and RMD\_se in metaregression.

. import excel "/Users/peterpaulzw/Dropbox/CAMARADES joint stem cell in animal research proj

> ect/Datafiles/2020 revisions/2020ALL DATASETSPP new analyses.xls", sheet("MI\_largenewPP")

> firstrow clear

.

. encode TypeofDisease, generate (data)

.

. tabulate data, gen(data)

**Type of |**

**Disease | Freq. Percent Cum.**

**------------+-----------------------------------**

**MI Large | 125 100.00 100.00**

**------------+-----------------------------------**

**Total | 125 100.00**

.

. encode Animal2, generate (animal)

.

. tabulate animal, gen(animal)

**Animal2 | Freq. Percent Cum.**

**------------+-----------------------------------**

**Dog | 8 6.40 6.40**

**Pig | 100 80.00 86.40**

**Sheep | 17 13.60 100.00**

**------------+-----------------------------------**

**Total | 125 100.00**

.

. encode CellType2, generate (cell)

. tabulate cell, gen(cell)

**Cell Type2 | Freq. Percent Cum.**

**----------------------+-----------------------------------**

**BM | 31 24.80 24.80**

**Blood | 15 12.00 36.80**

**MSC | 55 44.00 80.80**

**Other | 1 0.80 81.60**

**Pluripotent | 1 0.80 82.40**

**Tissue-specific | 20 16.00 98.40**

**Tissue-specific + BM | 1 0.80 99.20**

**Tissue-specific + MSC | 1 0.80 100.00**

**----------------------+-----------------------------------**

**Total | 125 100.00**

.

. encode CellSource2, generate (origin)

.

. tabulate origin, gen(origin)

**Cell |**

**Source2 | Freq. Percent Cum.**

**------------+-----------------------------------**

**Allogeneic | 30 24.00 24.00**

**Autologous | 85 68.00 92.00**

**Xenogeneic | 10 8.00 100.00**

**------------+-----------------------------------**

**Total | 125 100.00**

.

.

. encode Immunisupp2, generate (immuno)

.

. tabulate immuno, gen(immuno)

**Immunisupp2 | Freq. Percent Cum.**

**----------------+-----------------------------------**

**Cyclosporin A | 6 4.80 4.80**

**Cyclosporin A + | 3 2.40 7.20**

**None | 116 92.80 100.00**

**----------------+-----------------------------------**

**Total | 125 100.00**

. encode Delivery, generate (deliver)

.

. tabulate deliver, gen(deliver)

**Delivery | Freq. Percent Cum.**

**--------------------+-----------------------------------**

**Direct Injection | 77 61.60 61.60**

**Local Infusion | 42 33.60 95.20**

**Peripheral Infusion | 6 4.80 100.00**

**--------------------+-----------------------------------**

**Total | 125 100.00**

**.**

. gen logallo = log(allonetric+1)

.

. encode TimeofAdmin, generate (timing)

.

. tabulate timing, gen(timing)

**Time of |**

**Admin | Freq. Percent Cum.**

**------------+-----------------------------------**

**acute | 41 32.80 32.80**

**chronic | 70 56.00 88.80**

**sub-acute | 14 11.20 100.00**

**------------+-----------------------------------**

**Total | 125 100.00**

**############### Species analysis.**

. metareg (lnROM) animal1 animal2, wsse (ROM\_se)

**Meta-regression Number of obs = 125**

**REML estimate of between-study variance tau2 = .01716**

**% residual variation due to heterogeneity I-squared\_res = 76.42%**

**Proportion of between-study variance explained Adj R-squared = 3.63%**

**Joint test for all covariates Model F(2,122) = 3.77**

**With Knapp-Hartung modification Prob > F = 0.0258**

**------------------------------------------------------------------------------**

**lnROM | Coef. Std. Err. t P>|t| [95% Conf. Interval]**

**-------------+----------------------------------------------------------------**

**animal1 | .0844476 .075687 1.12 0.267 -.0653824 .2342775**

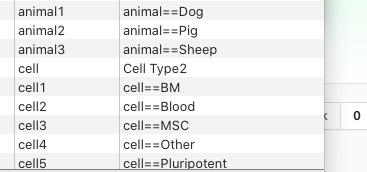
**animal2 | .1254694 .0461906 2.72 0.008 .0340305 .2169082**

**\_cons | -.3071938 .0432457 -7.10 0.000 -.3928029 -.2215847**

**------------------------------------------------------------------------------**

**####** From these tables you can depict the total p-value for the comparison (top right) and the subgroup comparisons (animal 1 = animal 1 vs animal 3. Animal2 = animal2 vs animal3). The \_cons is the total ln(ROM) for animal3. The animal1 and animal2 numbers are the subgroup differences (ln(ROM)) compared to animal3

###### On the right side you see the ‘variables tab’ which tells you which number is which animal (see screenshot).



###### The values of the table above need to be log-transformed (both Coef. And 95% CI) to get the real back-transformed ROMs. For the other comparison, you switch to slightly different code, until you have seen/gotten all comparisons 🡪

. metareg (lnROM) animal1 animal3, wsse (ROM\_se)

**Meta-regression Number of obs = 125**

**REML estimate of between-study variance tau2 = .01716**

**% residual variation due to heterogeneity I-squared\_res = 76.42%**

**Proportion of between-study variance explained Adj R-squared = 3.63%**

**Joint test for all covariates Model F(2,122) = 3.77**

**With Knapp-Hartung modification Prob > F = 0.0258**

**------------------------------------------------------------------------------**

**lnROM | Coef. Std. Err. t P>|t| [95% Conf. Interval]**

**-------------+----------------------------------------------------------------**

**animal1 | -.0410218 .0642006 -0.64 0.524 -.1681132 .0860696**

**animal3 | -.1254694 .0461906 -2.72 0.008 -.2169082 -.0340305**

**\_cons | -.1817245 .016229 -11.20 0.000 -.2138514 -.1495976**

This comparison gives you the total ROM for animal2 (= \_cons) and the subgroup comparisons (lnROM), compared to animal2.

**#################### Cell-type**

. metareg (lnROM) cell1 cell2 cell3 cell4 cell5 cell6 cell7, wsse (ROM\_se)

**Meta-regression Number of obs = 125**

**REML estimate of between-study variance tau2 = .01712**

**% residual variation due to heterogeneity I-squared\_res = 76.12%**

**Proportion of between-study variance explained Adj R-squared = 3.86%**

**Joint test for all covariates Model F(7,117) = 1.37**

**With Knapp-Hartung modification Prob > F = 0.2225**

**------------------------------------------------------------------------------**

**lnROM | Coef. Std. Err. t P>|t| [95% Conf. Interval]**

**-------------+----------------------------------------------------------------**

**cell1 | .1784877 .1873287 0.95 0.343 -.1925069 .5494824**

**cell2 | .2332408 .1894815 1.23 0.221 -.1420173 .6084989**

**cell3 | .18538 .1866916 0.99 0.323 -.1843529 .5551129**

**cell4 | -.0884198 .2319685 -0.38 0.704 -.5478213 .3709817**

**cell5 | .2922823 .2425581 1.20 0.231 -.1880912 .7726559**

**cell6 | .144491 .1896028 0.76 0.448 -.2310074 .5199895**

**cell7 | -.0962799 .275631 -0.35 0.727 -.6421527 .4495929**

**\_cons | -.3784364 .1852741 -2.04 0.043 -.745362 -.0115109**

**#################### Origin**

. metareg (lnROM) origin1 origin2, wsse (ROM\_se)

**Meta-regression Number of obs = 125**

**REML estimate of between-study variance tau2 = .0181**

**% residual variation due to heterogeneity I-squared\_res = 77.30%**

**Proportion of between-study variance explained Adj R-squared = -1.68%**

**Joint test for all covariates Model F(2,122) = 0.51**

**With Knapp-Hartung modification Prob > F = 0.6022**

**------------------------------------------------------------------------------**

**lnROM | Coef. Std. Err. t P>|t| [95% Conf. Interval]**

**-------------+----------------------------------------------------------------**

**origin1 | -.0615078 .0636439 -0.97 0.336 -.1874972 .0644816**

**origin2 | -.034789 .0569849 -0.61 0.543 -.1475963 .0780183**

**\_cons | -.1613439 .0541588 -2.98 0.003 -.2685566 -.0541312**

**#################### Immuno**

. metareg (lnROM) immuno1 immuno2, wsse (ROM\_se)

**Meta-regression Number of obs = 125**

**REML estimate of between-study variance tau2 = .01805**

**% residual variation due to heterogeneity I-squared\_res = 77.46%**

**Proportion of between-study variance explained Adj R-squared = -1.37%**

**Joint test for all covariates Model F(2,122) = 0.34**

**With Knapp-Hartung modification Prob > F = 0.7105**

**------------------------------------------------------------------------------**

**lnROM | Coef. Std. Err. t P>|t| [95% Conf. Interval]**

**-------------+----------------------------------------------------------------**

**immuno1 | .00497 .0681235 0.07 0.942 -.1298872 .1398273**

**immuno2 | -.0950139 .1155746 -0.82 0.413 -.3238054 .1337776**

**\_cons | -.1974676 .0155692 -12.68 0.000 -.2282884 -.1666468**

**#################### Dose**

. metareg (lnROM) logallo, wsse (ROM\_se)

**Meta-regression Number of obs = 121**

**REML estimate of between-study variance tau2 = .01771**

**% residual variation due to heterogeneity I-squared\_res = 76.34%**

**Proportion of between-study variance explained Adj R-squared = 5.18%**

**With Knapp-Hartung modification**

**------------------------------------------------------------------------------**

**lnROM | Coef. Std. Err. t P>|t| [95% Conf. Interval]**

**-------------+----------------------------------------------------------------**

**logallo | -.0229527 .0088705 -2.59 0.011 -.0405171 -.0053882**

**\_cons | .0286903 .088936 0.32 0.748 -.1474118 .2047924**

**#################### Delivery**

. metareg (lnROM) deliver1 deliver2, wsse (ROM\_se)

**Meta-regression Number of obs = 125**

**REML estimate of between-study variance tau2 = .01729**

**% residual variation due to heterogeneity I-squared\_res = 77.44%**

**Proportion of between-study variance explained Adj R-squared = 2.87%**

**Joint test for all covariates Model F(2,122) = 3.77**

**With Knapp-Hartung modification Prob > F = 0.0257**

**------------------------------------------------------------------------------**

**lnROM | Coef. Std. Err. t P>|t| [95% Conf. Interval]**

**-------------+----------------------------------------------------------------**

**deliver1 | -.0279323 .0699239 -0.40 0.690 -.1663537 .110489**

**deliver2 | .0573117 .0713613 0.80 0.423 -.0839551 .1985785**

**\_cons | -.2041146 .0671495 -3.04 0.003 -.3370437 -.0711854**

**#################### Timing**

**. metareg (lnROM) timing1 timing2, wsse (ROM\_se)**

**Meta-regression Number of obs = 125**

**REML estimate of between-study variance tau2 = .01833**

**% residual variation due to heterogeneity I-squared\_res = 77.53%**

**Proportion of between-study variance explained Adj R-squared = -2.95%**

**Joint test for all covariates Model F(2,122) = 0.28**

**With Knapp-Hartung modification Prob > F = 0.7597**

**------------------------------------------------------------------------------**

**lnROM | Coef. Std. Err. t P>|t| [95% Conf. Interval]**

**-------------+----------------------------------------------------------------**

**timing1 | -.0378443 .0510659 -0.74 0.460 -.1389343 .0632457**

**timing2 | -.0294705 .0486522 -0.61 0.546 -.1257823 .0668414**

**\_cons | -.1700216 .0440841 -3.86 0.000 -.2572905 -.0827528**

**MULTIVARIABLE ANALYSES**

Similar to the univariable analyses, you fill in all subgroups but one, per group. Now you add multiple variables to the equation like below. The p-value in the top-right is the p-value of the total metaregression. To get the total p-value per variable, we use the post-hoc wald test (using the command ‘test’). The p-values for subgroup differences again are given in the table. Again, we log-transformed all variables to get the real values (which we put in the tables).

Again, to reach all subgroup differences, you need to adjust the formula for the specific subgroup, to get the differences from Stata.

. metareg (lnROM) animal1 animal2 cell1 cell2 cell3 cell4 cell5 cell6 cell7 origin1 origin2 immuno1 immuno2 logallo deliver1 deliver2 timing1 timing2, wsse (ROM\_se)

**Meta-regression Number of obs = 121**

**REML estimate of between-study variance tau2 = .01814**

**% residual variation due to heterogeneity I-squared\_res = 76.25%**

**Proportion of between-study variance explained Adj R-squared = 2.90%**

**Joint test for all covariates Model F(18,102)= 1.34**

**With Knapp-Hartung modification Prob > F = 0.1788**

**------------------------------------------------------------------------------**

**lnROM | Coef. Std. Err. t P>|t| [95% Conf. Interval]**

**-------------+----------------------------------------------------------------**

**animal1 | .0982217 .0847701 1.16 0.249 -.0699193 .2663628**

**animal2 | .0746532 .0653207 1.14 0.256 -.0549101 .2042166**

**cell1 | .093792 .2425365 0.39 0.700 -.3872779 .574862**

**cell2 | .1364933 .2459763 0.55 0.580 -.3513995 .6243861**

**cell3 | .0796344 .2412965 0.33 0.742 -.398976 .5582448**

**cell4 | -.0599421 .2844469 -0.21 0.834 -.6241412 .5042571**

**cell5 | .3113103 .3082523 1.01 0.315 -.3001066 .9227273**

**cell6 | .1167676 .2406973 0.49 0.629 -.3606542 .5941895**

**cell7 | -.167892 .3231282 -0.52 0.604 -.8088154 .4730313**

**origin1 | -.1851971 .1271746 -1.46 0.148 -.4374472 .0670531**

**origin2 | -.1957739 .1287345 -1.52 0.131 -.4511182 .0595703**

**immuno1 | -.2003727 .1295328 -1.55 0.125 -.4573004 .056555**

**immuno2 | -.2460432 .195247 -1.26 0.210 -.6333147 .1412283**

**logallo | -.0143234 .0108653 -1.32 0.190 -.0358746 .0072278**

**deliver1 | -.0588423 .0757113 -0.78 0.439 -.2090152 .0913307**

**deliver2 | .0171772 .0786079 0.22 0.827 -.1387411 .1730956**

**timing1 | -.0231983 .0553401 -0.42 0.676 -.132965 .0865685**

**timing2 | -.0066352 .0529692 -0.13 0.901 -.1116993 .0984289**

**\_cons | .0140871 .335786 0.04 0.967 -.6519429 .680117**

. test animal1 animal2

**( 1) animal1 = 0**

**( 2) animal2 = 0**

**F( 2, 102) = 0.89**

**Prob > F = 0.4147**

. test cell1 cell2 cell3 cell4 cell5 cell6 cell7

**( 1) cell1 = 0**

**( 2) cell2 = 0**

**( 3) cell3 = 0**

**( 4) cell4 = 0**

**( 5) cell5 = 0**

**( 6) cell6 = 0**

**( 7) cell7 = 0**

**F( 7, 102) = 0.74**

**Prob > F = 0.6358**

. test origin1 origin2

**( 1) origin1 = 0**

**( 2) origin2 = 0**

**F( 2, 102) = 1.16**

**Prob > F = 0.3168**

. test immuno1 immuno2

**( 1) immuno1 = 0**

**( 2) immuno2 = 0**

**F( 2, 102) = 1.35**

**Prob > F = 0.2634**

. test deliver1 deliver2

**( 1) deliver1 = 0**

**( 2) deliver2 = 0**

**F( 2, 102) = 2.32**

**Prob > F = 0.1031**

. test timing1 timing2

**( 1) timing1 = 0**

**( 2) timing2 = 0**

**F( 2, 102) = 0.12**

**Prob > F = 0.8886**