Supplementary material

Cerebrospinal fluid and venous biomarkers of shunt-responsive idiopathic normal pressure hydrocephalus: a systematic review and meta-analysis

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**Supplementary Figure 1:** In Fig. A, as part of the sensitivity analysis of the meta-analysis, a forest plot indicating and visualizing the effect size in standard mean difference (SMD) of Total-Tau (T-Tau) levels in lumbar (n=4) and ventricular (n=1, Tarnaris et al. (2011) [6]) samples of shunt responder (S-R) versus shunt non-responder (S-NR) iNPH patients is shown (n = 5 studies). This meta-analysis for T-Tau does not include the study by Tullberg et al. (2008) [7], which is the only study on T-Tau which scored “critical” level of risk of bias on the ROBINS-I tool [5] (Table 2). The size of the grey square of the SMD visual correlates to study sample size and the straight line indicated the confidence interval. The diamond at the bottom indicates the overall pooled effect. The red bar below it indicates the prediction interval. Heterogeneity is indicated by the chi-squared statistic ($I^2$) with associated p-value. The 95% confidence intervals (CI) are shown in squared bracket ([ ]). Furthermore, for every study the following are displayed: author, total number of S-R and their respective mean level and standard deviation (SD) of T-Tau lumbar CSF levels, as well as the respective values for S-NR, weighting of each study in percentage.
Supplementary Figure 2: In Fig. B, a bubble plot is shown which visualises the result of the meta-regression on the meta-analysis of T-Tau (n= 6 studies) of the treatment effect (standard mean difference) relative to the covariate “neuro”. This covariate implies the explicit inclusion of patients with neurological co-morbidities. The size of the bubbles correlates to the sample size. The two studies on the bottom right are Ågren-Wilsson et al. (2007) [1] and Migliorati et al. (2021) [3], which are the only two studies included in this subgroup analysis that explicitly included patients with neurological co-morbidities. The others, on the top left, are Hong et al. (2018) [2], Tarnaris et al. (2011) [6], Tullberg et al. (2008) [7] and Vanninen et al. (2021) [8]
Supplementary Figure 3: In Fig. C, as part of the sensitivity analysis of the meta-analysis, a forest plot indicating and visualizing the effect size in standard mean difference (SMD) of Total-Tau (T-Tau) levels in lumbar (n=5) and ventricular (n=1, Tarnaris et al. (2011) [6] ) samples of shunt responder (S-R) versus shunt non-responder (S-NR) iNPH patients is shown (n = 5 studies). This meta-analysis for T-Tau does not include Ågren-Wilsson et al. (2007) [1] and Migliorati et al. (2021) [3] , which are the only two studies included in this subgroup analysis that explicitly included patients with neurological co-morbidities and caused a significant result in the meta-regression of the Total-Tau meta-analysis [5] (Figure B, Supplementary Material and Table 4, main article). The size of the grey square of the SMD visual correlates to study sample size and the straight line indicated the confidence interval. The diamond at the bottom indicates the overall pooled effect. The red bar below it indicates the prediction interval. Heterogeneity is indicated by the chi-squared statistic ($I^2$) with associated p-value. The 95% confidence intervals (CI) are shown in squared bracket ([ ]). Furthermore, for every study the following are displayed: author, total number of S-R and their respective mean level and standard deviation (SD) of T-Tau lumbar CSF levels, as well as the respective values for S-NR, weighting of each study in percentage.
**Supplementary Table 1:** The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement comprises a 27-item checklist addressing the introduction, methods, results and discussion sections of this systematic review report [4].

| Section and Topic               | Item # | Checklist item                                                                 | Location where item is reported |
|---------------------------------|--------|---------------------------------------------------------------------------------|---------------------------------|
| **TITLE**                       |        |                                                                                 |                                 |
| Title                           | 1      | Identify the report as a systematic review.                                    | Page 1.                         |
| **ABSTRACT**                    |        |                                                                                 |                                 |
| Abstract                        | 2      | See the PRISMA 2020 for Abstracts checklist.                                   | Page 2.                         |
| **INTRODUCTION**                |        |                                                                                 |                                 |
| Rationale                       | 3      | Describe the rationale for the review in the context of existing knowledge.     | Page 3-4.                       |
| Objectives                      | 4      | Provide an explicit statement of the objective(s) or question(s) the review addresses. | Page 4.                         |
| **METHODS**                     |        |                                                                                 |                                 |
| Eligibility criteria            | 5      | Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses. | Page 5.                         |
| Information sources             | 6      | Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted. | Page 5.                         |
| Search strategy                 | 7      | Present the full search strategies for all databases, registers and websites, including any filters and limits used. | Supplementary Material: Table B; Page 4. |
| Selection process               | 8      | Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process. | Page 5-6.                       |
| Data collection process         | 9      | Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process. | Page 6.                         |
| Data items                      | 10a    | List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect. | Page 6.                         |
|                                 | 10b    | List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information. | Page 6.                         |
| Study risk of bias assessment   | 11     | Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process. | Page 6.                         |
| Effect measures                 | 12     | Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results. | Page 6.                         |
| Synthesis methods               | 13a    | Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)). | Page 6.                         |
|                                 | 13b    | Describe any methods required to prepare the data for presentation or synthesis, such as handling of | Page 6.                         |
| Section and Topic       | Item # | Checklist item                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Location where item is reported |
|------------------------|--------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|
|                        |        | missing summary statistics, or data conversions.                                                                                                                                                                                                                                                                                                                                                                                                                                |                                  |
|                        | 13c    | Describe any methods used to tabulate or visually display results of individual studies and syntheses.                                                                                                                                                                                                                                                                                                                                                                      | Page 6.                         |
|                        | 13d    | Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.                                                                                                                                                                                                     | Page 6-7.                       |
|                        | 13e    | Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).                                                                                                                                                                                                                                                                                                                                                           | Page 7-8.                       |
|                        | 13f    | Describe any sensitivity analyses conducted to assess robustness of the synthesized results.                                                                                                                                                                                                                                                                                                                                                                                | Page 7-8.                       |
| Reporting bias assessment | 14    | Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).                                                                                                                                                                                                                                                                                                                                                   | Page 6.                         |
| Certainty assessment   | 15    | Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.                                                                                                                                                                                                                                                                                                                                                                      | Page 6.                         |
| **RESULTS**            |       |                                                                                                                                                                                                                                                                                                                                                                                                                  |                                  |
| Study selection        | 16a    | Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.                                                                                                                                                                                                 | Figure 1; page 35               |
|                        | 16b    | Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.                                                                                                                                                                                                                                                                                                                                                   | N/A                             |
| Study characteristics  | 17    | Cite each included study and present its characteristics.                                                                                                                                                                                                                                                                                                                                                       | Tables 1-3; Page 22-32.         |
| Risk of bias in studies | 18   | Present assessments of risk of bias for each included study.                                                                                                                                                                                                                                                                                                                                                      | Tables 1-3; Page 22-32. Figure 2; Page 36. |
| Results of individual studies | 19 | For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.                                                                                                                                                                                                                             | Tables 1-3; Page 22-32. Figure 4; page 38. Figure 5, page 39. Figure 6; page 40. Figure 7; page 41. |
| Results of syntheses   | 20a    | For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.                                                                                                                                                                                                                                                                                                                                                               | Page 13-14.                     |
|                        | 20b    | Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.                                                                                                                                                 | Page 12-14. Figure 4; page 38. Figure 5, page 39. Figure 6; page 40. Figure 7; page 41. |
|                        | 20c    | Present results of all investigations of possible causes of heterogeneity among study results.                                                                                                                                                                                                                                                                                                                                                                           | Figure 3; page 37.             |
|                        | 20d    | Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.                                                                                                                                                                                                                                                                                                                                                          | Pages 13-14. Tables 4-5; pages 33-34. |
| Section and Topic       | Item # | Checklist item                                                                 | Location where item is reported                                      |
|------------------------|--------|---------------------------------------------------------------------------------|-----------------------------------------------------------------------|
| Reporting biases       | 21     | Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed. | Risk of bias (ROBINS-1) Column, section E. Tables 1-3; Page 22-32.    |
| Certainty of evidence  | 22     | Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed. | Level of evidence (OECBM) column. Tables 1-3; Page 22-32.             |
| DISCUSSION             |        |                                                                                 |                                                                        |
| Discussion             | 23a    | Provide a general interpretation of the results in the context of other evidence. | Pages 16-20.                                                          |
|                        | 23b    | Discuss any limitations of the evidence included in the review.                 | Page 19-20.                                                          |
|                        | 23c    | Discuss any limitations of the review processes used.                            | Page 20.                                                             |
|                        | 23d    | Discuss implications of the results for practice, policy, and future research.    | Page 17, 18-19, 20.                                                  |
| OTHER INFORMATION      |        |                                                                                 |                                                                        |
| Registration and protocol | 24a  | Provide registration information for the review, including register name and registration number, or state that the review was not registered. | Page 5.                                                              |
|                        | 24b    | Indicate where the review protocol can be accessed, or state that a protocol was not prepared. | Page 5.                                                              |
|                        | 24c    | Describe and explain any amendments to information provided at registration or in the protocol. | N/A                                                                 |
| Support                | 25     | Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review. | Page 1.                                                              |
| Competing interests    | 26     | Declare any competing interests of review authors.                               | Page 1.                                                              |
| Availability of data, code and other materials | 27     | Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review. | Supplementary material; Appendix: A-D.                                  |
**Supplementary Table 2:** Search strategy performed on 1st November 2021 including the name of the database, search term(s)/search string used, as well as the publication dates chosen as limiting factors, and the results.

| Database    | Search terms                                                                                                                                                                                                 | Publications dates | Results (n) |
|-------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|-------------|
| MEDLINE     | normal pressure hydrocephalus.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, an, ui, sy] limit 1 to yr="1965 - 2021"                                                                         | 1965-2021          | n = 4133    |
| Embase      | normal pressure hydrocephalus.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, an, ui, sy] limit 1 to yr="1965 - 2021"                                                                         | 1965-2021          | n = 2891    |
| Scopus      | normal AND pressure AND hydrocephalus AND response OR responsiveness OR responder OR predict AND ( EXCLUDE ( PUBYEAR , 2021 ) OR EXCLUDE ( PUBYEAR , 2020 ) OR EXCLUDE ( PUBYEAR , 2019 ) OR EXCLUDE ( PUBYEAR , 2018 ) OR EXCLUDE ( PUBYEAR , 2022 ) ) | 1970-2021          | n = 4,456   |
| PubMed      | (normal pressure hydrocephalus) AND ((response) OR (responsiveness) OR (responder) OR (predict))                                                                                                             | 1971-2021          | n = 1,024   |
| Google Scholar | idiopathic normal pressure hydrocephalus shunt response predict marker                                                                                                                                    | 1965-2021          | n = 5,850   |
| JSTOR       | Normal pressure hydrocephalus                                                                                                                                                                               | 1965-2021          | n = 921     |
Supplementary Table 3: The R code utilised to program the meta-analysis and associated figures, ROB graphs, as well as the meta-regression.

```r
# Install relevant packages
install.packages(c("robumeta", "metafor", "dplyr"))
install.packages("meta")
install.packages("dmetar")
install.packages("readxl")
# Into library load
library("robumeta")
library("metafor")
library("dplyr")
library("mada")
library("meta")
library("dmetar")
library("readxl")

# Load TTAU dataset from dmetar (or download and open manually)
library(readxl)
iNPH_Biochem_TTau_Excel <- read_excel("~/Desktop/iNPH Biochem - T Tau.xlsx")
View(iNPH_Biochem_TTau_Excel)

# Use metcont to pool results.
meta_ttau <- metcont(n.e = iNPH_Biochem_TTau_Excel$n.SR,
mean.e = iNPH_Biochem_TTau_Excel$mean.SR,
sd.e = iNPH_Biochem_TTau_Excel$sd.SR,
n.c = iNPH_Biochem_TTau_Excel$n.SNR,
mean.c = iNPH_Biochem_TTau_Excel$mean.SNR,
sd.c = iNPH_Biochem_TTau_Excel$sd.SNR,
studlab = iNPH_Biochem_TTau_Excel$Author,
data = iNPH_Biochem_TTau_Excel,
sm = "SMD", method.smd = "Cohen",
```
fixed = FALSE,  
random = TRUE,  
method.tau = "REML",  
hakn = TRUE,  
title = "T-Tau levels in SR vs N-SR")

#numerical visualisation of meta_ttau (note that SR are the experimental group so reference group, so  
minus result means it is less in them)

print(meta_ttau)

#make the plot

forest.meta(meta_ttau,  
    sortvar = TE,  
    predict = TRUE,  
    print.tau2 = FALSE,  
    leftlabs = c("Author", "g", "SE"),  
    lab.e = "S-R",  
    lab.c = "S-NR",  
    JAMA.pval = FALSE,  
    test.overall.random = TRUE,  
    label.test.overall.random = "Overall statistical result of model: ")

#meta-regression metareg: single ones (all)

metareg_ttau_females <- metareg(meta_ttau,  
    ~ females)

print(metareg_ttau_females)

metareg_ttau_age <- metareg(meta_ttau,  
    ~ age)

print(metareg_ttau_age)

metareg_ttau_sample <- metareg(meta_ttau,  
    ~ sample)
print(metareg_ttau_sample)

metareg_ttau_neuro <- metareg(meta_ttau, ~ neuro)
print(metareg_ttau_neuro)

metareg_ttau_dropout <- metareg(meta_ttau, ~ dropout)
print(metareg_ttau_dropout)

metareg_ttau_srm <- metareg(meta_ttau, ~ srm)
print(metareg_ttau_srm)

metareg_ttau_date <- metareg(meta_ttau, ~ date)
print(metareg_ttau_date)
# meta regression step 2: neuro plus others

metareg_ttau_neuroagefemales <- metareg(meta_ttau, ~ neuro + age + females)
print(metareg_ttau_neuroagefemales)

metareg_ttau_neurosamlpe + date)
print(metareg_ttau_neurosamlpe + date)

metareg_ttau_neurofemales + date)
print(metareg_ttau_neurofemales + date)

metareg_ttau_neuroagedate <- metareg(meta_ttau, ~ neuro + age + date)
print(metareg_ttau_neuroagedate)
metareg_ttau_neurosamlpefemales <- metareg(meta_ttau,
```r
print(metareg_ttau_neurosamplefemales)

#other models were tried, no significance

#plot the metaregression neuro

bubble(metareg_ttau_neuro, studlab = TRUE, scale = TRUE)

#meta-analysis without the study positive for "neuro" (explicitly included neuro patients)

iNPH_Biochem_TTau_Excel2 <- read_excel("~/Desktop/iNPH Biochem - TTau2.xlsx")
View(iNPH_Biochem_TTau_Excel2)

# Use metcont to pool results.
meta_ttau2 <- metcont(n.e = iNPH_Biochem_TTau_Excel2$n.SR,
                      mean.e = iNPH_Biochem_TTau_Excel2$mean.SR,
                      sd.e = iNPH_Biochem_TTau_Excel2$sd.SR,
                      n.c = iNPH_Biochem_TTau_Excel2$n.SNR,
                      mean.c = iNPH_Biochem_TTau_Excel2$mean.SNR,
                      sd.c = iNPH_Biochem_TTau_Excel2$sd.SNR,
                      studlab = iNPH_Biochem_TTau_Excel2$Author,
                      data = iNPH_Biochem_TTau_Excel2,
                      sm = "SMD",
                      method.smd = "Cohen",
                      fixed = FALSE,
                      random = TRUE,
                      method.tau = "REML",
                      hakn = TRUE,
                      title = "T-Tau levels in SR vs N-SR")

#numerical visualisation of meta_ttau (note that SR are the experimental group so reference group, so
minus result means it is less in them)

print(meta_ttau2)

#make the plot
```
forest.meta(meta_ttau2,
      sortvar = TE,
      predict = TRUE,
      print.tau2 = FALSE,
      leftlabs = c("Author", "g", "SE"),
      lab.e = "S-R",
      lab.c = "S-NR",
      JAMA.pval = FALSE,
      test.overall.random = TRUE,
      label.test.overall.random = "Overall statistical result of model: ")

# Load P-TAU dataset from dmetar (or download and open manually)
library(readxl)
iNPH_Biochem_PTau_Excel <- read_excel("~/Desktop/iNPH Biochem - P Tau.xlsx")
View(iNPH_Biochem_PTau_Excel)

# Use metcont to pool results.
meta_ptau <- metcont(n.e = iNPH_Biochem_PTau_Excel$n.SR,
                      mean.e = iNPH_Biochem_PTau_Excel$mean.SR,
                      sd.e = iNPH_Biochem_PTau_Excel$sd.SR,
                      n.c = iNPH_Biochem_PTau_Excel$n.SNR,
                      mean.c = iNPH_Biochem_PTau_Excel$mean.SNR,
                      sd.c = iNPH_Biochem_PTau_Excel$sd.SNR,
                      studlab = iNPH_Biochem_PTau_Excel$Author,
                      data = iNPH_Biochem_PTau_Excel,
                      sm = "SMD",
                      method.smd = "Cohen",
                      fixed = FALSE,
                      random = TRUE,
                      method.tau = "REML",
                      hakn = TRUE,
                      title = "P-Tau levels in SR vs N-SR")
# numerical visualisation of meta_ttau (note that SR are the experimental group so reference group, so minus result means it is less in them)

print(meta_ptau)

# make the plot

forest.meta(meta_ptau,
             sortvar = TE,
             predict = TRUE,
             print.tau2 = FALSE,
             leftlabs = c("Author", "g", "SE"),
             lab.e = "S-R",
             lab.c = "S-NR",
             JAMA.pval = FALSE,
             test.overall.random = TRUE,
             label.test.overall.random = "Overall statistical result of model: ")

# meta-regression metareg: single ones (all)

metareg_ptau_females <- metareg(meta_ptau,
                                  ~ females)
print(metareg_ptau_females)

metareg_ptau_age <- metareg(meta_ptau,
                             ~ age)
print(metareg_ptau_age)

metareg_ptau_sample <- metareg(meta_ptau,
                                ~ sample)
print(metareg_ptau_sample)

metareg_ptau_neuro <- metareg(meta_ptau,
print(metareg_ptau_neuro)

metareg_ptau_dropout <- metareg(meta_ptau, ~ dropout)
print(metareg_ptau_dropout)

metareg_ptau_srm <- metareg(meta_ptau, ~ srm)
print(metareg_ptau_srm)

metareg_ptau_date <- metareg(meta_ptau, ~ date)
print(metareg_ptau_date)

# Load Abeta dataset from dmetar (or download and open manually)
library(readxl)
iNPH_Biochem_Abeta_Excel <- read_excel("~/Desktop/iNPH Biochem - Abeta.xlsx")
View(iNPH_Biochem_Abeta_Excel)

# Use metcont to pool results.
meta_Abeta <- metacont(n.e = iNPH_Biochem_Abeta_Excel$n.SR,
                      mean.e = iNPH_Biochem_Abeta_Excel$mean.SR,
                      sd.e = iNPH_Biochem_Abeta_Excel$sd.SR,
                      n.c = iNPH_Biochem_Abeta_Excel$n.SNR,
                      mean.c = iNPH_Biochem_Abeta_Excel$mean.SNR,
                      sd.c = iNPH_Biochem_Abeta_Excel$sd.SNR,
                      studlab = iNPH_Biochem_Abeta_Excel$Author,
                      data = iNPH_Biochem_Abeta_Excel,
                      sm = "SMD")
method.smd = "Cohen",
fixed = FALSE,
random = TRUE,
method.tau = "REML",
hakn = TRUE,
title = "Abeta levels in SR vs N-SR")

#numerical visualisation of meta_ttau (note that SR are the experimental group so reference group, so
minus result means it is less in them)

print(meta_Abeta)

#make the plot

forest.meta(meta_Abeta,
sortvar = TE,
predict = TRUE,
print.tau2 = FALSE,
leftlabs = c("Author", "g", "SE"),
lab.e = "S-R",
lab.c = "S-NR",
JAMA.pval = FALSE,
test.overall.random = TRUE,
label.test.overall.random = "Overall statistical result of model: ")

#meta-regression metareg: single ones (all)

metareg_Abeta_females <- metareg(meta_Abeta,
                                  ~ females)
print(metareg_Abeta_females)

metareg_Abeta_age <- metareg(meta_Abeta,
                              ~ age)
print(metareg_Abeta_age)

metareg_Abeta_sample <- metareg(meta_Abeta,
```
print(metareg_Abeta_sample)

metareg_Abeta_neuro <- metareg(meta_Abeta, 
~ neuro)
print(metareg_Abeta_neuro)

metareg_Abeta_dropout <- metareg(meta_Abeta, 
~ dropout)
print(metareg_Abeta_dropout)

metareg_Abeta_srm <- metareg(meta_Abeta, 
~ srm)
print(metareg_Abeta_srm)

metareg_Abeta_date <- metareg(meta_Abeta, 
~ date)
print(metareg_Abeta_date)

# meta regression step 2: neuro plus others
metareg_ttau_neuroagefemales <- metareg(meta_ttau, 
~ neuro + age + females)
print(metareg_ttau_neuroagefemales)

metareg_ttau_neurosampledate <- metareg(meta_ttau, 
~ neuro + sample + date)
print(metareg_ttau_neurosampledate)

# other models were tried, no significance
# plot the metaregression neuro
bubble(metareg_ttau_neuro, studlab = TRUE, scale = TRUE)

# meta-analysis without the study positive for "neuro" (explicitly included neuro patients)
```
iNPH_Biochem_TTau_Excel2 <- read_excel("~/Desktop/iNPH Biochem - TTau2.xlsx")
View(iNPH_Biochem_TTau_Excel2)

# Use metcont to pool results.
meta_ttau2 <- metcont(n.e = iNPH_Biochem_TTau_Excel2$n.SR,
mean.e = iNPH_Biochem_TTau_Excel2$mean.SR,
sd.e = iNPH_Biochem_TTau_Excel2$sd.SR,
n.c = iNPH_Biochem_TTau_Excel2$n.SNR,
mean.c = iNPH_Biochem_TTau_Excel2$mean.SNR,
sd.c = iNPH_Biochem_TTau_Excel2$sd.SNR,
studlab = iNPH_Biochem_TTau_Excel2$Author,
data = iNPH_Biochem_TTau_Excel2,
sm = "SMD",
method.smd = "Cohen",
fixed = FALSE,
random = TRUE,
method.tau = "REML",
hakn = TRUE,
title = "T-Tau levels in SR vs N-SR")

#numerical visualisation of meta_ttau (note that SR are the experimental group so reference group, so
minus result means it is less in them)
print(meta_ttau2)

#make the plot

forest.meta(meta_ttau2,
  sortvar = TE,
predict = TRUE,
  print.tau2 = FALSE,
leftlabs = c("Author", "g", "SE"),
lab.e = "S-R",
lab.c = "S-NR",
JAMA.pval = FALSE,
test.overall.random = TRUE,
label.test.overall.random = "Overall statistical result of model: ")
library(readxl)

iNPH_Biochem_NFL_Excel <- read_excel("~/Desktop/iNPH Biochem - NFL.xlsx")

View(iNPH_Biochem_NFL_Excel)

meta_NFL <- metacont(n.e = iNPH_Biochem_NFL_Excel$n.SR,
mean.e = iNPH_Biochem_NFL_Excel$mean.SR,
sd.e = iNPH_Biochem_NFL_Excel$sd.SR,
n.c = iNPH_Biochem_NFL_Excel$n.SNR,
mean.c = iNPH_Biochem_NFL_Excel$mean.SNR,
sd.c = iNPH_Biochem_NFL_Excel$sd.SNR,
studlab = iNPH_Biochem_NFL_Excel$Author,
data = iNPH_Biochem_NFL_Excel,
sm = "SMD",
method.smd = "Cohen",
fixed = FALSE,
random = TRUE,
method.tau = "REML",
hakn = TRUE,
title = "NFL levels in SR vs N-SR")

print(meta_NFL)

# numerical visualisation of meta_ttau (note that SR are the experimental group so reference group, so minus result means it is less in them)

forest.meta(meta_NFL,
    sortvar = TE,
    predict = TRUE,
print.tau2 = FALSE,
leftlabs = c("Author", "g", "SE"),
lab.e = "S-R",
lab.c = "S-NR",
JAMA.pval = FALSE,
test.overall.random = TRUE,
label.test.overall.random = "Overall statistical result of model: ")

######################################################################################################
##############
# Load Sulfatide dataset from dmetar (or download and open manually)
library(readxl)
iNPH_Biochem_Sulfatide_Excel <- read_excel("~/Desktop/iNPH Biochem - Sulfatide.xlsx")
View(iNPH_Biochem_Sulfatide_Excel)

# Use metcont to pool results.
meta_Sulfatide <- metacont(n.e = iNPH_Biochem_Sulfatide_Excel$n.SR,
mean.e = iNPH_Biochem_Sulfatide_Excel$mean.SR,
sd.e = iNPH_Biochem_Sulfatide_Excel$sd.SR,
n.c = iNPH_Biochem_Sulfatide_Excel$n.SNR,
mean.c = iNPH_Biochem_Sulfatide_Excel$mean.SNR,
sd.c = iNPH_Biochem_Sulfatide_Excel$sd.SNR,
studlab = iNPH_Biochem_Sulfatide_Excel$Author,
data = iNPH_Biochem_Sulfatide_Excel,
sm = "SMD",
method.smd = "Cohen",
fixed = FALSE,
random = TRUE,
method.tau = "REML",
hakn = TRUE,
title = "Sulfatide levels in SR vs N-SR")

#numerical visualisation of meta_ttau (note that SR are the experimental group so reference group, so
minus result means it is less in them)
print(meta_Sulfatide)

# make the plot

forest.meta(meta_Sulfatide, 
    sortvar = TE, 
    predict = TRUE, 
    print.tau2 = FALSE, 
    leftlabs = c("Author", "g", "SE"), 
    lab.e = "S-R", 
    lab.c = "S-NR", 
    JAMA.pval = FALSE, 
    test.overall.random = TRUE, 
    label.test.overall.random = "Overall statistical result of model: ")

# Load Total set dataset from dmetar (or download and open manually)

library(readxl)
iNPH_Biochem_Total_Excel <- read_excel("~/Desktop/iNPH Biochem - Total.xlsx")
View(iNPH_Biochem_Total_Excel)

# Use metcont to pool results.
meta_Total <- metacont(n.e = iNPH_Biochem_Total_Excel$n.SR, 
                        mean.e = iNPH_Biochem_Total_Excel$mean.SR, 
                        sd.e = iNPH_Biochem_Total_Excel$sd.SR, 
                        n.c = iNPH_Biochem_Total_Excel$n.SNR, 
                        mean.c = iNPH_Biochem_Total_Excel$mean.SNR, 
                        sd.c = iNPH_Biochem_Total_Excel$sd.SNR, 
                        studlab = iNPH_Biochem_Total_Excel$Author, 
                        data = iNPH_Biochem_Total_Excel, 
                        sm = "SMD", 
                        )
method.smd = "Cohen",
fixed = FALSE,
random = TRUE,
method.tau = "REML",
hakn = TRUE,
title = "Total levels in SR vs N-SR"

#numerical visualisation of meta_ttau (note that SR are the experimental group so reference group, so minus result means it is less in them)

print(meta_Total)

#make the plot

forest.meta(meta_Total,
            sortvar = TE,
            predict = TRUE,
            print.tau2 = FALSE,
            leftlabs = c("Author", "g", "SE"),
            lab.e = "S-R",
            lab.c = "S-NR",
            JAMA.pval = FALSE,
            test.overall.random = TRUE,
            label.test.overall.random = "Overall statistical result of model: ")

#Eggers (Publication bias) calculation

eggersplot <- metabias(
                        meta_Total,
                        method.bias = meta_Total$method.bias,
                        plotit = FALSE,
                        correct = FALSE,
                        k.min = 10)

print(eggersplot,
      digits = gs("digits"),
      digits.stat = gs("digits.stat"),
digits.pval = max(gs("digits.pval"), 2),
digits.se = gs("digits.se"),
digits.tau2 = gs("digits.tau2"),
scientific.pval = gs("scientific.pval"),
big.mark = gs("big.mark"),
zero.pval = gs("zero.pval"),
JAMA.pval = gs("JAMA.pval"),
text.tau2 = gs("text.tau2")

# Eggers (Publication bias) plot

eggersplot <- metabias(
  meta_Total,
  method.bias = meta_Total$method.bias,
  plotit = TRUE,
  correct = FALSE,
  k.min = 14
)

funnel.meta(meta_Total,
  xlim = c(-2, 1),
  studlab = FALSE,
  method.bias = "linreg")
## Supplementary Table 4: The data spreadsheet that provided the basis for meta-analysis and meta-regression for Total-Tau

| Author         | mean.SR | sd.SR  | n. SR | mean.SNR | sd.SNR | n.SNR | age  | females | sample | date  | srm | neuro | dropout | SMD    | SE   |
|---------------|---------|--------|-------|----------|--------|-------|------|---------|--------|-------|-----|-------|---------|--------|------|
| Migliorati et al. | 161.1   | 185.6  | 15    | 245     | 137.975| 35    | 75.3 | 0.32    | 50     | 2021  | 1   | 0     | 0       | -0.55  | 0.313776 |
| Tarnaris et al.  | 550.97  | 551.65 | 17    | 1086    | 347.19 | 4     | 71.45| 0.32    | 21     | 2011  | 0   | 1     | 0       | -1.02  | 0.576531 |
| Ågren-Wilsson et al. | 164     | 115    | 33    | 269     | 93     | 22    | 72   | 0.37    | 55     | 2007  | 0   | 1     | 0       | -0.98  | 0.290816 |
| Hong et al.      | 141.9   | 40.8   | 17    | 177.2   | 126.7  | 14    | 78.7 | 0.35    | 31     | 2018  | 1   | 0     | 1       | -0.39  | 0.364796 |
| Vanninen et al.  | 190.4   | 86.8   | 91    | 211.3   | 75.9   | 27    | 75.4576 | 118    | 2021  | 1   | 0     | 0       | -0.25  | 0.219388 |
| Tullberg et al.  | 267     | 296    | 28    | 275     | 165    | 7     | 68   | 0.636   | 18     | 2008  | 0   | 0     | 0       | -0.03  | 0.423469 |

## Supplementary Table 5: The data spreadsheet that provided the basis for meta-analysis and meta-regression for Total-Tau

| Author         | mean.SR | sd.SR  | n. SR | mean.SNR | sd.SNR | n.SNR | age  | females | sample | date  | srm | neuro | dropout | SMD    | SE   |
|---------------|---------|--------|-------|----------|--------|-------|------|---------|--------|-------|-----|-------|---------|--------|------|
| Migliorati et al. | 26.6    | 13.75  | 15    | 39.6     | 14.325 | 35    | 75.3 | 0.32    | 50     | 2021  | 1   | 0     | 0       | -0.92  | 0.321429 |
| Ågren-Wilsson et al. | 32      | 10     | 33    | 12       | 22     | 72   | 0.37 | 55     | 2007  | 0     | 1   | 0     | 1       | -0.85  | 0.278061 |
| Hong et al.      | 29.8    | 12.9   | 17    | 47.6     | 27.8   | 14    | 78.7 | 0.35    | 31     | 2018  | 1   | 0     | 1       | -0.46  | 0.377551 |
| Vanninen et al.  | 34.7    | 14.8   | 91    | 38.3     | 12.2   | 27    | 75.4576 | 118    | 2021  | 1   | 0     | 0       | -0.25  | 0.219388 |

## Supplementary Table 6: The data spreadsheet that provided the basis for meta-analysis and meta-regression for Amyloid-beta 1-12

| Author         | mean.SR | sd.SR  | n. SR | mean.SNR | sd.SNR | n.SNR | age  | females | sample | date  | srm | neuro | dropout | SMD    | SE   |
|---------------|---------|--------|-------|----------|--------|-------|------|---------|--------|-------|-----|-------|---------|--------|------|
| Migliorati et al. | 513.3   | 254.95 | 15    | 793      | 299.925| 35    | 75.3 | 0.32    | 50     | 2021  | 1   | 0     | 0       | -0.97  | 0.32398 |
| Ågren-Wilsson et al. | 515     | 107    | 33    | 492      | 98     | 22    | 72   | 0.37    | 55     | 2007  | 0   | 1     | 0       | 0.22   | 0.27551 |
| Hong et al.      | 581     | 173.9  | 17    | 594.3    | 274.3  | 14    | 78.7 | 0.35    | 31     | 2018  | 1   | 0     | 1       | -0.06  | 0.362245 |
| Vanninen et al.  | 673.9   | 192.2  | 91    | 617.5    | 172.7  | 27    | 75.4576 | 118    | 2021  | 1   | 0     | 0       | -0.1   | 0.471939 |
References

1. Ågren-Wilsson A, Lekman A, Sjöberg W, Rosengren L, Blennow K, Bergenheim AT, Malm J (2007) CSF biomarkers in the evaluation of idiopathic normal pressure hydrocephalus. Acta Neurol Scand 116(5):333-9
2. Hong YJ, Kim MJ, Jeong E, Kim JE, Hwang J, Lee JI, Lee JH, Na DL (2018) Preoperative biomarkers in patients with idiopathic normal pressure hydrocephalus showing a favorable shunt surgery outcome. J Neurol Sci 387:21-26
3. Migliorati K, Panciari PP, Pertichetti M, Borroni B, Archetti S, Rizzini L, Padovani A, Terzi L, Bruscella S, Fontanella MM (2021) P-Tau as prognostic marker in long term follow up for patients with shunted iNPH. Neurol Res 43(1):78-85
4. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, Moher D (2021) The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 372:n71
5. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, Henry D, Altman DG, Ansari MT, Boutron I, Carpenter JR, Chan AW, Churchill R, Deeks JJ, Hróbjartsson A, Kirkham J, Jüni P, Loke YK, Pigott TD, Ramsay CR, Regidor D, Rothstein HR, Sandhu L, Santaguida PL, Schünemann HJ, Shea B, Shrier I, Tugwell P, Turner L, Valentine JC, Waddington H, Waters E, Wells GA, Whiting PF, Higgins JP (2016) ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 355:i4919
6. Tarnaris A, Toma AK, Chapman MD, Keir G, Kitchen ND, Watkins LD (2011) Use of cerebrospinal fluid amyloid-β and total tau protein to predict favorable surgical outcomes in patients with idiopathic normal pressure hydrocephalus. J Neurosurg 115(1):145-50
7. Tullberg M, Blennow K, Månsson JE, Fredman P, Tisell M, Wikkelso C (2008) Cerebrospinal fluid markers before and after shunting in patients with secondary and idiopathic normal pressure hydrocephalus. Cerebrospinal Fluid Res 5:9
8. Vanninen A, Nakajima M, Miyajima M, Rauramaa T, Kokki M, Musialowicz T, Mäkinen PM, Herukka SK, Koivisto AM, Jääskeläinen JE, Hiltunen M, Leinonen V (2021) Elevated CSF LRG and Decreased Alzheimer’s Disease Biomarkers in Idiopathic Normal Pressure Hydrocephalus J Clin Med 10(5):1105