RQ 1.2: Subsequent pharmacological therapy for the management of type 2 diabetes.

October 2024

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Research Question

This analysis focused on subsequent therapies for management of type 2 diabetes. In this context, study participants would be receiving the trialled treatments against a background of initial management, which could include treatments included in the subsequent treatment set. Study populations varied in their existing treatments and in the use of rescue therapies.

Definition of the subpopulation with chronic kidney disease (CKD)

These analyses focus on people with type 2 diabetes mellitus (T2D) and chronic kidney disease (CKD). Studies in people who had CKD with or without T2D were not included in the evidence, including where a T2D subgroup was reported.

Following the addition of Perkovic 2024, a recently published trial comparing subcutaneous semaglutide against placebo in the population with type 2 diabetes and chronic kidney disease, the TSU reran the sensitivity analysis fitting an additive model to weight change data (such that estimated treatment effects are mean difference between treatments).

Methods

Transformation of data

Arm-level summaries reporting final values were converted to arm-level CFB summaries, assuming correlation between baseline and follow-up values of 0.5. One study, Pollock 2019, reporting change in weight as percent change, was excluded from analysis.

Network Meta-Analysis

Re-analysis of additive data took place in multinma (Phillippo 2024), following standard TSD code (Dias 2011) implemented in Stan. The network of evidence from studies reporting arm-level differences and the network of evidence from studies reporting contrasts between arms were combined in a single network for analysis. Network meta-analysis (NMA) models were based on TSD code TSD2-8 (Normal shared), which uses a Normal likelihood with an identity link function and thus assumes additivity of treatment effects.

Both the intercept terms and treatment effects were given Normal priors, with default scale values for intercepts (scale=10) and weakly informative priors for treatment effects (scale=15). Tau was given a half-Normal prior (scale=15).

Models were run on four chains, with burn-in of 1000 iterations per chain and sampling of 1000 iterations per chain. This was sufficient for R hat values of 1 for all parameters in all models. The adapt delta option was increased to 0.99 in RE NMA and UME models to improve sampling.

Model selection

The choice of whether to proceed with the NMA with fixed-effect (FE) or random-effects (RE) structure on the treatment differences was made by first considering the network structure, then by comparing model fit statistics between the two models, taking into account the size and precision of the between-study variation estimated under the RE model.

Where all edges in the network were informed only by a single study, only FE models were fitted because there was insufficient evidence from which to estimate the between-study variation. Where the randomised trial evidence formed star networks, there would be no indirect evidence (appearing as loops in the network) from which to estimate inconsistency. Therefore, inconsistency – or unrelated mean effect – models were not run on star networks.

Where DIC in the FE and RE models differed by >3 units, the model with the lower DIC was chosen. Where DIC values in FE and RE models were within 2 units, the FE model was selected provided that total residual deviance was similar to the number of data points and either the median of between-study SD was low or between-study SD was poorly estimated from the data (skewed distribution and a large uncertainty interval). There were no cases where differences in FE DIC and RE DIC were within 2 units and the between-study SD was both high and precisely estimated.

Assessing inconsistency with Unrelated Mean Effect models

NMA assumes that the included studies are similar in terms of factors that might interact with the intervention effects (effect modifiers). So, the relative effect of intervention B vs intervention A would be expected to be similar in all of the studies (if they had included A and B interventions). We can assess this assumption by measuring statistical heterogeneity, and also by checking if the direct and indirect estimates are in agreement when there are loops of evidence in the network. To determine if there is evidence of inconsistency, the selected consistency model (fixed or random effects) was compared to an “inconsistency”, or unrelated mean effects (UME), model (Dias 2013). The latter is equivalent to having separate, unrelated, meta-analyses for every pairwise contrast, with a common variance parameter assumed in the case of random effects models. We further explored inconsistency using dev-dev plots, which can highlight individual studies that are contributing to inconsistency. These study arms appear in the area shaded grey in the included dev-dev plots.

Results

The analysis of mean change in body weight, assuming additive treatment effects, included 18 studies of 13 treatments (Figure 1). NMA with fixed-effects structure on treatment effects was sufficient for modelling this outcome on the basis of model fit (Table 1).

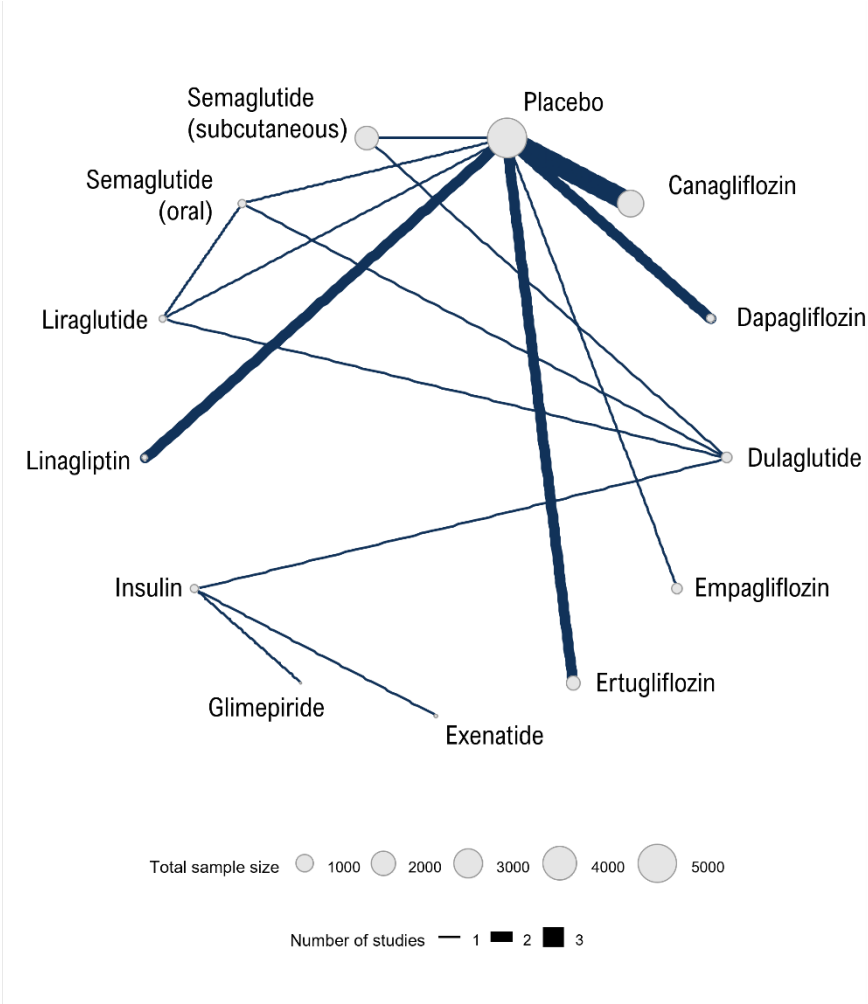

Figure 1. Network of evidence for additive change in weight in the subpopulation of people with diabetes and CKD.

For the treatments included in the base-case analysis (weight change as a proportional measure), the treatment effects are consistent in this sensitivity analysis (Figure 2), with evidence to support weight loss with use of the included SGLT-2 inhibitors (canagliflozin, dapagliflozin, empagliflozin and ertugliflozin), and support for weight-neutral effect (with a trend for weight reduction) for linagliptin relative to placebo (Figure 2).

Turning to those treatments where there was only evidence for weight change as an additive measure, there was strong evidence to support reduction in weight for those receiving liraglutide, dulaglutide and for those receiving semaglutide (both oral and subcutaneous delivery) relative to those on the placebo arm (Table 2). The evidence for exenatide was uncertain, with the possibility of weight-reducing, weight-neutral and weight-increasing effects within the wide credible intervals. The treatment effect of glimepiride was highly uncertain, with the 95% credible interval spanning from a reduction in weight of 7.4kg to an increase in weight

of 9.3kg. There was evidence of an increase in weight in those receiving insulin, relative to placebo. For full information on all active-active treatment comparisons, see Table 3.

Table 1. Model fit statistics for the outcome additive weight change in the population with CKD and T2DM, following the addition of Perkovic 2024. [1]Lower values of DIC and residual deviance are preferred.

Model	NMA effect structure	Number of data points	Model fit (total residual deviance[1])	pD (number of effective parameters)	DIC (penalised deviance[1])	Between-study SD median, (95% CrI)
NMA	Fixed	37	43.9	25.0	68.9	-
	Random	37	38.4	29.8	68.2	0.43 (0.03, 1.03)
UME	Fixed	37	41.7	27.0	68.7	-
	Random	37	38.7	30.5	69.2	0.41 (0.01, 1.15)

Table 2. Change in weight relative to placebo as an additive measure in the subpopulation of people with diabetes and CKD. Treatment effects are presented as mean differences (in kg) with the posterior median ranking with its range.

Class	Treatment	Mean change in body weight in kg (95% CrI)	Median rank (95% CrI)
Placebo	Placebo	*Reference*	11 (9, 12)
DPP-4i	Linagliptin	-1.43 (-3.73, 0.87)	6 (2, 12)
SGLT-2i	Canagliflozin	-0.90 (-1.38, -0.43)	9 (6, 11)
	Dapagliflozin	-1.59 (-2.33, -0.85)	5 (3, 9)
	Empagliflozin	-1.55 (-2.00, -1.10)	6 (4, 8)
	Ertugliflozin	-2.05 (-2.54, -1.57)	4 (3, 6)
GLP-1RA	Dulaglutide	-0.95 (-1.65, -0.29)	8 (5, 10)
	Liraglutide	-1.35 (-2.02, -0.67)	7 (4, 9)
	Semaglutide (oral)	-2.96 (-3.57, -2.34)	2 (2, 4)
	Semaglutide (subcutaneous)	-3.96 (-4.39, -3.54)	1 (1, 2)
	Exenatide	0.05 (-2.07, 2.16)	11 (4, 12)
Sulfonylurea	Glimepiride	0.75 (-7.40, 9.26)	12 (1, 13)
Insulin	Insulin	2.73 (1.55, 3.93)	13 (12, 13)

Inconsistency in network evidence

Model fit was similar between NMA and UME models, suggesting that there was no strong evidence of global inconsistency (Table 1). The estimated between-study heterogeneity estimated by RE models was similarly moderate between NMA and UME models, suggesting that inconsistency was not being modelled as heterogeneity within the NMA model.

Plotting residual deviance under the FE NMA and UME models did not reveal any substantial inconsistency (Figure 3). One arm of Takahashi 2023 showed relatively poor fit in the NMA model, which assumes consistency, suggesting that evidence from this study arm is in conflict with evidence from the network. However, Takahashi 2023 trialled oral semaglutide against liraglutide and dulaglutide, with two oral semaglutide arms trialling different dosages of semaglutide. Since the model constraints require both oral semaglutide arms to observe the same treatment effect on the same study-level baseline, the relatively high residual deviance for one of these arms is likely to be the result of the interaction between treatment effect and dose, where dose is not modelled.

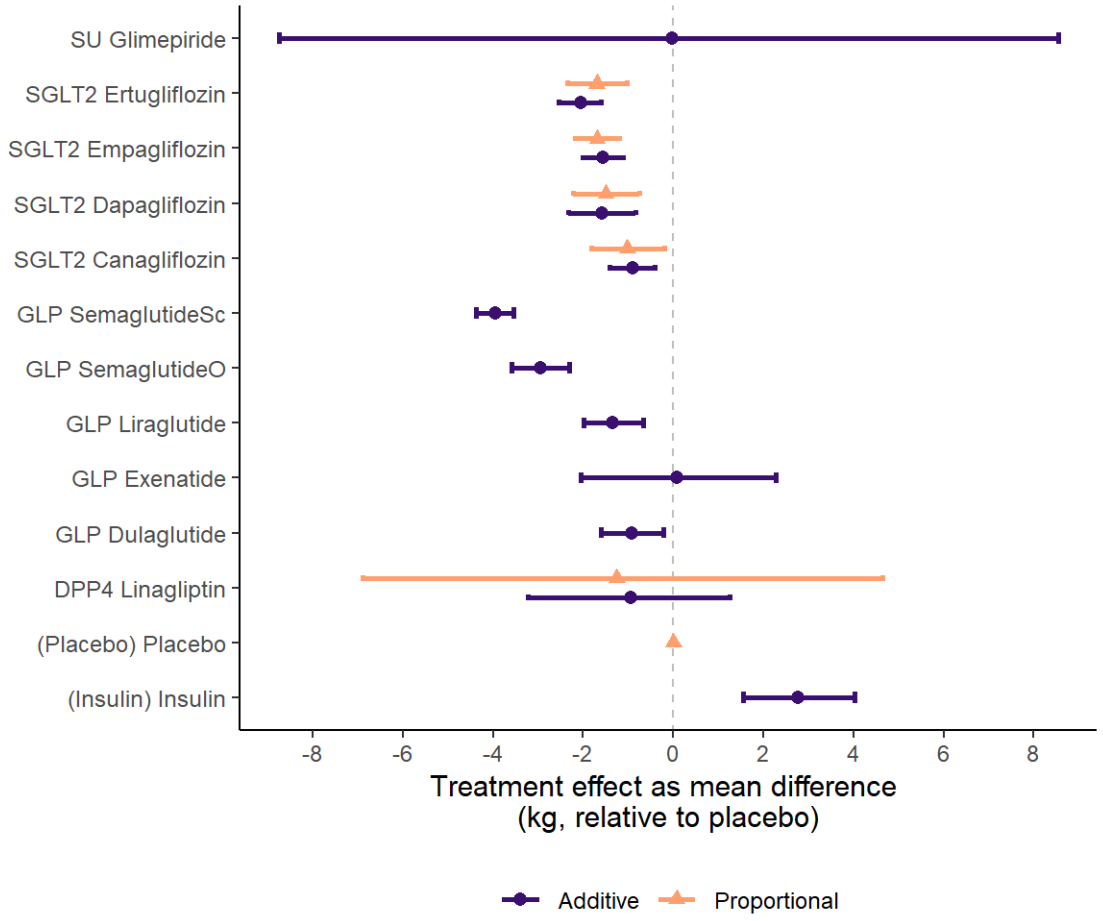

Figure 2. Mean difference in body weight (kg) on treatment, relative to placebo, in the subpopulation with diabetes and CKD. Mean treatment effects are shown as points, with the 95% credible interval. Treatment effects drawn from FE additive (purple circles) and FE proportional (orange triangles) NMA models. Note that only five active treatments were represented in the proportional model.

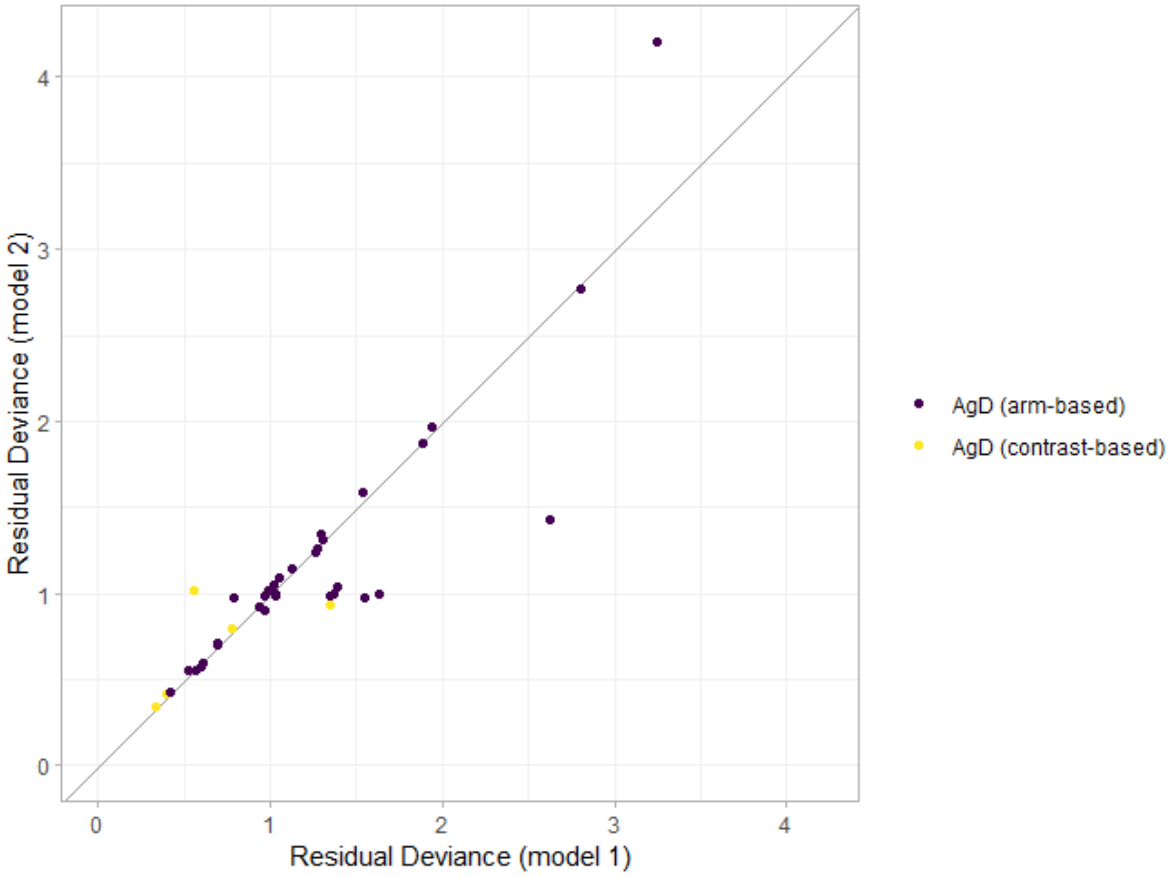

Figure 3. Dev-dev plot showing individual study arms' or contrasts' contribution to residual deviance under FE NMA (model 1, x axis) and FE UME (model 2, y axis) models. Studies where the treatment effect is poorly estimated by the model assuming consistency will appear in the lower right-hand corner of the plot.

Table 3. Mean difference in body weight (kg) on treatment in the subpopulation with diabetes and CKD. Treatment effect estimates are median and 95% credible intervals generated from a FE models assuming additive treatment effects. Treatment effects in the upper triangle are from meta-analysis without assuming consistency (UME models), treatment effect estimates in the lower triangle are from NMA. NA indicates comparisons without direct trial evidence.

Colour highlights intervention listed across top row is favoured in the results from the analysis	Colour highlights intervention listed down first column is favoured in the results from the analysis

	Placebo	**Cana.**	**Dapa.**	**Dula.**	**Empa.**	**Ertu.**	**Exen.**	**Glim.**	**Ins.**	**Lina.**	**Lira.**	**Sema. O**	**Sema. Sc**
Placebo		-0.9 (-1.39, -0.42)	-1.61 (-2.36, -0.84)	NA	-1.54 (-1.99, -1.11)	-2.05 (-2.52, -1.6)	NA	NA	NA	-1.37 (-3.67, 0.77)	-1.33 (-2.2, -0.4)	-2.5 (-3.34, -1.65)	-4.1 (-4.56, -3.64)
Canagliflozin	-0.9 (-1.38, -0.43)		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Dapagliflozin	-1.6 (-2.39, -0.82)	-0.7 (-1.59, 0.2)		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Dulaglutide	-0.94 (-1.65, -0.27)	-0.03 (-0.91, 0.8)	0.65 (-0.39, 1.69)		NA	NA	NA	NA	3.7 (2.72, 4.66)	NA	-0.7 (-1.61, 0.17)	-2.48 (-3.29, -1.65)	-2.5 (-3.38, -1.65)
Empagliflozin	-1.55 (-2.01, -1.1)	-0.64 (-1.3, -0.03)	0.05 (-0.84, 0.97)	-0.62 (-1.45, 0.24)		NA	NA	NA	NA	NA	NA	NA	NA
Ertugliflozin	-2.05 (-2.54, -1.56)	-1.15 (-1.8, -0.47)	-0.45 (-1.38, 0.46)	-1.11 (-1.94, -0.24)	-0.5 (-1.2, 0.15)		NA	NA	NA	NA	NA	NA	NA
Exenatide	0.1 (-2.14, 2.15)	1.02 (-1.33, 3.13)	1.7 (-0.65, 3.98)	1.04 (-1.07, 2.99)	1.66 (-0.62, 3.76)	2.16 (-0.17, 4.27)		NA	2.66 (0.96, 4.45)	NA	NA	NA	NA
Glimepiride	0.79 (-7.44, 9.15)	1.68 (-6.41, 10.03)	2.41 (-5.98, 10.7)	1.75 (-6.46, 10.09)	2.33 (-5.9, 10.73)	2.85 (-5.36, 11.1)	0.68 (-7.58, 9.19)		1.72 (-6.64, 10)	NA	NA	NA	NA

	Placebo	Cana.	Dapa.	Dula.	Empa.	Ertu.	Exen.	Glim.	Ins.	Lina.	Lira.	Sema. O	Sema. Sc
Insulin	2.75 (1.51, 3.93)	3.65 (2.36, 4.96)	4.33 (2.92, 5.79)	3.69 (2.68, 4.7)	4.28 (3.02, 5.57)	4.79 (3.49, 6.07)	2.63 (0.85, 4.44)	1.98 (-6.48, 10.03)		NA	NA	NA	NA
Linagliptin	-1.44 (-3.7, 0.76)	-0.53 (-2.88, 1.75)	0.16 (-2.23, 2.52)	-0.51 (-2.9, 1.82)	0.11 (-2.22, 2.4)	0.63 (-1.7, 2.89)	-1.56 (-4.63, 1.55)	-2.28 (-10.91, 6.05)	-4.18 (-6.8, -1.68)		NA	NA	NA
Liraglutide	-1.36 (-2.05, -0.67)	-0.45 (-1.27, 0.36)	0.24 (-0.77, 1.27)	-0.41 (-1.17, 0.33)	0.19 (-0.63, 1.02)	0.69 (-0.15, 1.53)	-1.46 (-3.55, 0.78)	-2.15 (-10.44, 5.94)	-4.09 (-5.36, -2.84)	0.08 (-2.26, 2.42)		NA	NA
Sema. O	-2.96 (-3.6, -2.32)	-2.06 (-2.84, -1.25)	-1.36 (-2.37, -0.37)	-2.01 (-2.72, -1.31)	-1.4 (-2.18, -0.62)	-0.9 (-1.69, -0.12)	-3.07 (-5.1, -0.82)	-3.73 (-12.03, 4.47)	-5.69 (-6.93, -4.48)	-1.52 (-3.81, 0.83)	-1.6 (-2.32, -0.9)		NA
Sema. Sc	-3.96 (-4.38, -3.53)	-3.06 (-3.68, -2.44)	-2.35 (-3.25, -1.47)	-3.02 (-3.69, -2.34)	-2.41 (-3.04, -1.79)	-1.9 (-2.55, -1.26)	-4.07 (-6.14, -1.85)	-4.74 (-13.24, 3.43)	-6.7 (-7.87, -5.47)	-2.51 (-4.78, -0.25)	-2.6 (-3.37, -1.86)	-1 (-1.73, -0.3)	

References

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Daly C, Welton, S.J., Dias, S., Anwer,S., Ades, A.E. Meta-Analysis of Continuous Outcomes. Guideline Methodology Document 2: NICE Guidelines Technical Support Unit 2021.

Dias S, Welton N, Sutton A, Ades A. NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials, 2011, last updated September 2016, available from https://www.sheffield.ac.uk/nice-dsu/tsds

Dias S, Welton NJ, Sutton AJ, Caldwell DM, Lu G, Ades AE. Evidence Synthesis for Decision Making 4: Inconsistency in Networks of Evidence Based on Randomized Controlled Trials. Medical Decision Making 2013 33:641-656

Phillippo DM (2024). multinma: Bayesian Network Meta-Analysis of Individual and Aggregate Data. doi:10.5281/zenodo.3904454 <https://doi.org/10.5281/zenodo.3904454>, R package version 0.7.2, https://dmphillippo.github.io/multinma/

R script

```
##############################################

######## T2DM Analysis using multinma ##########

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# Author: George Wood - Amended by BCD

# Date: 2024/10/01


library(readxl) # For loading excel files

library(tidyverse) # For handling data frames and cleaning data

library(multinma) # For NMA

library(bayesplot) # For checking convergence for STAN models

library(ggplot2) # For plotting

options(mc.cores = parallel::detectCores()) # For running multiple cores while doing the NMA at the same time
```

```
#################################################################

########################## Weight ##############################

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


############## Data preparation ##############

options(tibble.width = Inf)

## Start from here with new data

long.df <- read.csv("CKD_1.2_kgdata_sep_additive_long.csv")

## Look at new study

long.df[long.df$parent_study_name=="Perkovic 2024",]


# Split data into studies reporting mds versus those reporting mean info only

md.study <- subset(long.df, !is.na(md))$parent_study_name # Names of studies reporting md

md.df <- subset(long.df, parent_study_name %in% md.study) # Subset of md studies only

y.df <- subset(long.df, !parent_study_name %in% md.study) # Subset of studies not reporting
md

dim(md.df)

dim(y.df)


############### Define treatment coding #################

md.df$trt <- md.df$drug

y.df$trt <- y.df$drug


## Calculate SE from arm SDs

y.df$seUse <- ifelse(is.na(y.df$SE),

                     y.df$SD/sqrt(y.df$n),

                     y.df$SE)


# CONTRAST DATA (mds)

md.net <- set_agd_contrast(md.df,

                           study=parent_study_name,
```

```
                trt=trt,
                y=md,
                se=SE,
                sample_size=n)

print(md.net)
plot(md.net, weight_nodes=TRUE, nudge=0.2) +
 ggplot2::theme(legend.position = "bottom",
          legend.box = "vertical")

# ARM DATA (y)
# set_agd_arm = set aggregate arm data
y.net <- set_agd_arm(y.df,
              study=parent_study_name,
              trt=trt,
              y=y,
              se=seUse,
              sample_size=n)

print(y.net)
plot(y.net, weight_nodes=TRUE, nudge=0.2) +
 ggplot2::theme(legend.position = "bottom",
          legend.box = "vertical")

# COMBINE CONTRAST AND ARM DATA
comb.net <- combine_network(md.net, y.net,
                trt_ref="Placebo")
print(comb.net)


######################## Run NMA ######################
```

```
## I have specified some priors:
## the defaults *should* be fine here but I have widened priors on both
## treatment effects and heterogeneity
nma.fe <- nma(comb.net, trt_effects="fixed",
        prior_trt = normal(location = 0, scale = 15)
        )
nma.fe
dic.fe <- dic(nma.fe)

nma.re <- nma(comb.net, trt_effects = "random",
        prior_trt = normal(location = 0, scale = 15),
        prior_het = half_normal(scale = 10),
        adapt_delta=0.99)
nma.re
plot(dic(nma.re))
dic.re <- dic(nma.re)

######################## Run UME ######################
nma.Ufe <- nma(comb.net,
        trt_effects="fixed",
        consistency="ume",
        prior_trt = normal(location = 0, scale = 15))
nma.Ufe
dic.Ufe <- dic(nma.Ufe)

nma.Ure <- nma(comb.net,
         trt_effects = "random",
         consistency = "ume",
         prior_trt = normal(location = 0, scale = 15),
         prior_het = half_normal(scale = 10),
         adapt_delta=0.99)  ## Worth the adapt delta being higher
```

```
nma.Ure

dic.Ure <- dic(nma.Ure)


## Compare fit

dic.fe

dic.re

dic.Ufe

dic.Ure


## Deviance relatively high for oral semaglutide arms of Takahashi 2023

## and placebo arm of Kohan 2014 - but only

## Takahashi 2023 oral semaglutide arm 1 drops noticeably in the UME model

plot(dic.fe)

plot(dic.fe, dic.Ufe, show_uncertainty = F)

plot(relative_effects(nma.fe))

relative_effects(nma.fe,probs =c(0.025, 0.975))

plot(posterior_rank_probs(nma.fe))

posterior_ranks(nma.fe,probs =c(0.5, 0.025, 0.975))
```