# Identifying inconsistency in network meta-analysis: Is the net heat plot a reliable method? Supplementary material

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# A List of RCTs included in Lung Cancer network


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# B Statistical Details

This appendix provides further details on Section 4.2.

The network estimate of $c$ is equal to the weighted average of all the direct and indirect evidence combined; that is:

$$\hat{\theta}_c^{\text{net}} = \frac{1}{k+2}\left\{2\hat{\theta}_c^{\text{dir}} + \sum_{i=1}^{k}\hat{\theta}_c^{\text{ind}(i)}\right\}.$$

Assume that $d \neq c$ and let the effect size for design $d$ be $\hat{\theta}_c^{\text{ind}(d)}$. When design $d$ is detached the remaining network evidence on $c$ is:

$$\hat{\theta}_{c(d)}^{\text{net}} = \frac{1}{k+1}\left\{2\hat{\theta}_c^{\text{dir}} + \sum_{i,i\neq d}\hat{\theta}_c^{\text{ind}(i)}\right\}$$

If the direct comparison, $d = c$, is detached the network evidence remaining for design $c$ is:

$$\hat{\theta}_{c(c)}^{\text{net}} = \frac{1}{k}\sum_{i=1}^{k}\hat{\theta}_c^{\text{ind}(i)}$$

When $d \neq c$, $\hat{\theta}_c^{\text{net}}$ can be re-written in terms of $\hat{\theta}_c^{\text{ind}(i)}$ as follows:

$$\hat{\theta}_c^{\text{net}} = \frac{1}{k+2}\left\{2\hat{\theta}_c^{\text{dir}} + \hat{\theta}_c^{\text{ind}(d)} + \sum_{i,i\neq d}\hat{\theta}_c^{\text{ind}(i)}\right\}.$$

The inconsistency $Q$ statistics were defined in Section 4.1 as (3), (4) and (5). Expanding (5) and rearranging:

$$Q_{c,d}^{\text{diff}} = \frac{2}{s^2}\left(\hat{\theta}_{c(d)}^{\text{net}} - \hat{\theta}_c^{\text{net}}\right)\left[\hat{\theta}_c^{\text{dir}} - \frac{1}{2}\left(\hat{\theta}_{c(d)}^{\text{net}} + \hat{\theta}_c^{\text{net}}\right)\right]$$

Define $\hat{\theta}_{c(d/2)}^{\text{net}}$ as the average of all the network evidence for design $c$ and the network evidence that remains for design $c$ when design $d$ is excluded so that:

$$\hat{\theta}_{c(d/2)}^{\text{net}} = \frac{1}{2}\left(\hat{\theta}_{c(d)}^{\text{net}} + \hat{\theta}_c^{\text{net}}\right)$$

Then we can write:

$$Q_{c,d}^{\text{diff}} = \frac{2}{s^2}\left(\hat{\theta}_{c(d)}^{\text{net}} - \hat{\theta}_c^{\text{net}}\right)\left(\hat{\theta}_c^{\text{dir}} - \hat{\theta}_{c(d/2)}^{\text{net}}\right)$$

Write the difference between the network evidence on $c$ when $d$ is excluded and the network evidence on $c$ in terms of $\hat{\theta}_c^{\text{ind}(i)}$, as follows:

$$\hat{\theta}_{c(d)}^{\text{net}} - \hat{\theta}_c^{\text{net}} = \frac{1}{k+2}\left\{\frac{1}{k+1}\left(2\hat{\theta}_c^{\text{dir}} + \sum_{i,i\neq d}\hat{\theta}_c^{\text{ind}(i)}\right) - \hat{\theta}_c^{\text{ind}(d)}\right\}$$

and similarly

$$\hat{\theta}_{c(d/2)}^{\text{net}} = \frac{1}{2}\left(\hat{\theta}_{c(d)}^{\text{net}} + \hat{\theta}_c^{\text{net}}\right) = \frac{1}{2}\times\frac{1}{k+2}\left\{\frac{2k+3}{k+1}\left(2\hat{\theta}_c^{\text{dir}} + \sum_{i,i\neq d}\hat{\theta}_c^{\text{ind}(i)}\right) + \hat{\theta}_c^{\text{ind}(d)}\right\}$$

Putting it all together we get (8):

$$Q_{c,d}^{\text{diff}} = \frac{1}{s^2}\times\frac{1}{k+2}\left\{\frac{1}{k+1}\left(2\hat{\theta}_c^{\text{dir}} + \sum_{i,i\neq d}\hat{\theta}_c^{\text{ind}(i)}\right) - \hat{\theta}_c^{\text{ind}(d)}\right\}$$
$$\times\left[2\hat{\theta}_c^{\text{dir}}\left(1 - \frac{2k+3}{(k+1)(k+2)}\right) - \frac{1}{k+2}\left(\frac{2k+3}{k+1}\sum_{i,i\neq d}\hat{\theta}_c^{\text{ind}(i)} + \hat{\theta}_c^{\text{ind}(d)}\right)\right]$$

Or, if the direct comparison is detached:

$$Q_{c,c}^{\text{diff}} = -\frac{1}{s^2}\times\frac{4(k+1)}{(k+2)^2}\left(\hat{\theta}_c^{\text{dir}} - \frac{1}{k}\sum_{i=1}^{k}\hat{\theta}_c^{\text{ind}(i)}\right)^2$$

Suppose $k$ is large so that $k+1 \approx k$ then we can approximate (8) by:

$$Q_{c,d}^{\text{diff}} \approx \frac{1}{s^2}\cdot\frac{1}{k}\left\{\frac{1}{k}\left(2\hat{\theta}_c^{\text{dir}} + \sum_{i,i\neq d}\hat{\theta}_c^{\text{ind}(i)}\right) - \hat{\theta}_c^{\text{ind}(d)}\right\}$$
$$\times\left[2\hat{\theta}_c^{\text{dir}}\left(1 - \frac{2}{k}\right) - \frac{1}{k}\left(2\sum_{i,i\neq d}\hat{\theta}_c^{\text{ind}(i)} + \hat{\theta}_c^{\text{ind}(d)}\right)\right].$$

Let $1 - \frac{2}{k} \approx 1$, then:

$$Q_{c,d}^{\text{diff}} \approx \frac{1}{s^2}\left\{\frac{1}{k}\left(2\hat{\theta}_c^{\text{dir}} + \sum_{i,i\neq d}\hat{\theta}_c^{\text{ind}(i)}\right) - \hat{\theta}_c^{\text{ind}(d)}\right\}$$
$$\times\left[\frac{1}{k}\left\{2\hat{\theta}_c^{\text{dir}} - \frac{2}{k}\sum_{i,i\neq d}\hat{\theta}_c^{\text{ind}(i)} - \frac{1}{k}\hat{\theta}_c^{\text{ind}(d)}\right\}\right]$$

Now $\hat{\theta}_c^{\text{ind}}$ is the average of all the indirect evidence across the whole network:

$$\hat{\theta}_c^{\text{ind}} = \frac{1}{k}\left(\sum_{i,i\neq d} \hat{\theta}_c^{\text{ind}(i)} + \hat{\theta}_c^{\text{ind}(d)}\right).$$

Then:

$$\begin{aligned}
Q_{c,d}^{\text{diff}} &\approx \frac{1}{s^2}\left\{\frac{1}{k}\left(2\hat{\theta}_c^{\text{dir}} + \sum_{i,i\neq d} \hat{\theta}_c^{\text{ind}(i)}\right) - \hat{\theta}_c^{\text{ind}(d)}\right\} \\
&\quad \times \left[\frac{1}{k}\left\{2\hat{\theta}_c^{\text{dir}} - \frac{1}{k}\sum_{i,i\neq d} \hat{\theta}_c^{\text{ind}(i)} - \hat{\theta}_c^{\text{ind}}\right\}\right] \\
&\approx \frac{1}{s^2}\left\{\frac{1}{k}\left(2\hat{\theta}_c^{\text{dir}} + \sum_{i,i\neq d} \hat{\theta}_c^{\text{ind}(i)}\right) - \hat{\theta}_c^{\text{ind}(d)}\right\} \\
&\quad \times \left[\frac{1}{k}\left\{\left(\hat{\theta}_c^{\text{dir}} - \hat{\theta}_c^{\text{ind}}\right) + \left(\hat{\theta}_c^{\text{dir}} - \frac{1}{k}\sum_{i,i\neq d} \hat{\theta}_c^{\text{ind}(i)}\right)\right\}\right]
\end{aligned}$$

Let

$$P_1 \approx \frac{1}{s^2}\left\{\frac{1}{k}\left(2\hat{\theta}_c^{\text{dir}} + \sum_{i,i\neq d} \hat{\theta}_c^{\text{ind}(i)}\right) - \hat{\theta}_c^{\text{ind}(d)}\right\}$$

$$P_2 \approx \frac{1}{k}\left\{\left(\hat{\theta}_c^{\text{dir}} - \hat{\theta}_c^{\text{ind}}\right) + \left(\hat{\theta}_c^{\text{dir}} - \frac{1}{k}\sum_{i,i\neq d} \hat{\theta}_c^{\text{ind}(i)}\right)\right\}.$$

We can simplify $P_1$ & $P_2$ further.

$$P_1 \approx \frac{1}{s^2}\left\{\frac{2}{k}\hat{\theta}_c^{\text{dir}} + \frac{1}{k}\sum_{i,i\neq d} \hat{\theta}_c^{\text{ind}(i)} - \hat{\theta}_c^{\text{ind}(d)}\right\}$$

$$P_2 \approx \frac{1}{k}\left\{2\hat{\theta}_c^{\text{dir}} - \hat{\theta}_c^{\text{ind}} - \frac{1}{k}\sum_{i,i\neq d} \hat{\theta}_c^{\text{ind}(i)}\right\}$$

Let $\hat{\theta}_c^{\text{ind}(-d)} = \text{average}\left(\sum_{i,i\neq d} \hat{\theta}_c^{\text{ind}(i)}\right)$ then if $k$ is large, $\frac{1}{k}$ is small and

$$P_1 \approx \frac{1}{s^2}\left\{\hat{\theta}_c^{\text{ind}(-d)} - \hat{\theta}_c^{\text{ind}(d)}\right\}$$

$$P_2 \approx \frac{2}{k}\left(\hat{\theta}_c^{\text{dir}} - \hat{\theta}_c^{\text{ind}}\right)$$

# C Additional Tables & Figures

## Table S1

Results for $Q^{\text{diff}}_{c,d}$, $Q^{\text{inc}}_{c}$ and $Q^{\text{inc}}_{c(d)}$ as the number of treatment loops in a network increases (Section 5).

| Loops | $Q^{\text{diff}}_{c,d}$ | $Q^{\text{inc}}_{c}$ | $Q^{\text{inc}}_{c(d)}$ |
|---|---|---|---|
| 1 | 42.325 | 42.325 | 0.000 |
| 2 | 26.868 | 26.869 | 0.001 |
| 3 | 18.430 | 18.431 | 0.0004 |
| 4 | 12.910 | 12.919 | 0.009 |
| 5 | 10.210 | 10.210 | 0.0001 |
| 6 | 8.498 | 8.507 | 0.009 |
| 7 | 7.004 | 7.018 | 0.014 |
| 8 | 5.874 | 5.891 | 0.017 |
| 9 | 4.838 | 4.846 | 0.008 |
| 10 | 4.634 | 4.691 | 0.057 |

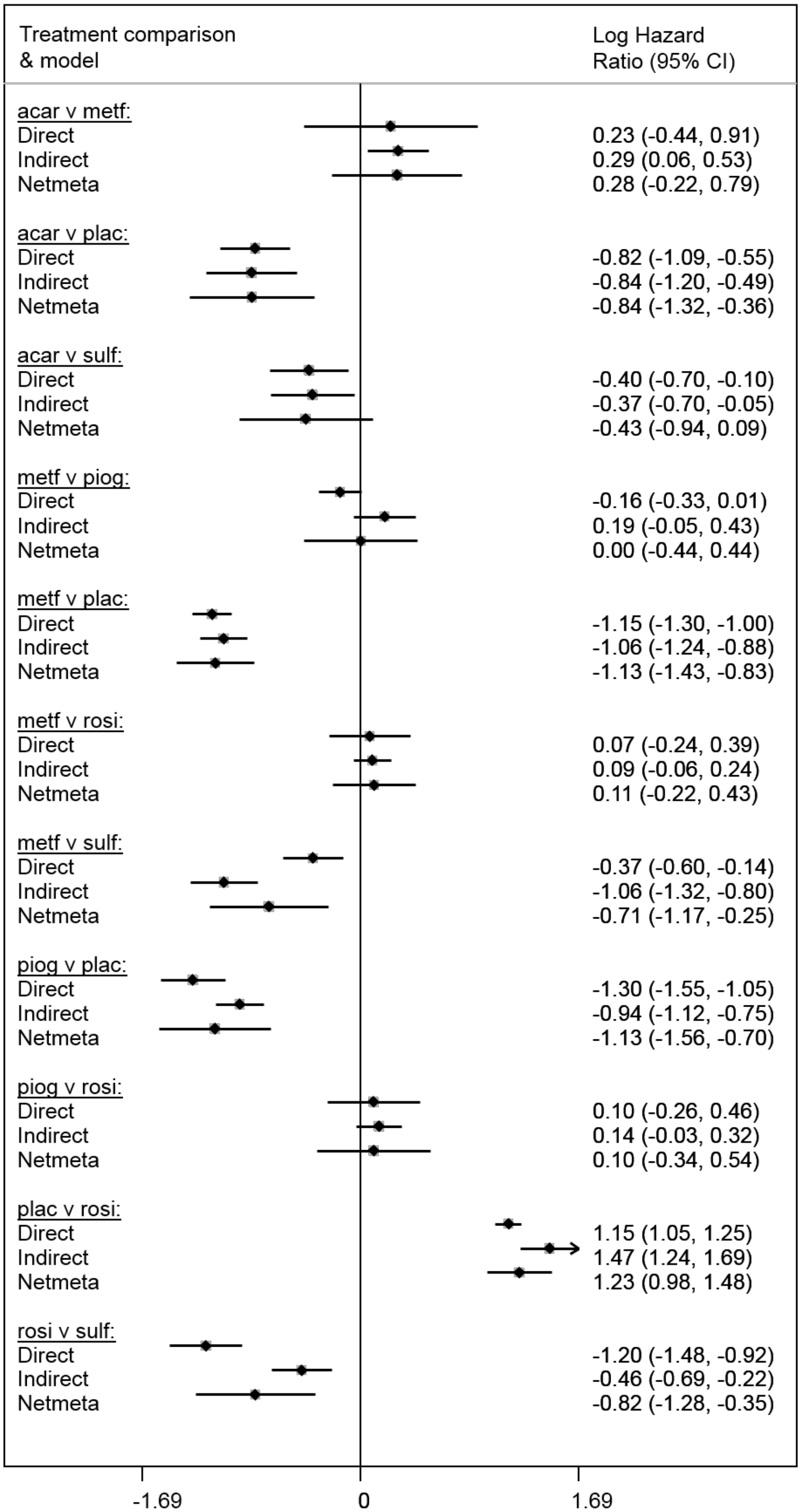
## Table S2

Node splitting results for the diabetes network. Coef = coefficient, Std.Err. = standard error.

| | Direct | | Indirect | | Difference | | |
|---|---|---|---|---|---|---|---|
| Comparison | Coef. | Std. Err. | Coef. | Std. Err. | Coef. | Std. Err. | P-value |
| acar metf | 0.23 | 0.34 | 0.29 | 0.12 | -0.06 | 0.36 | 0.87 |
| acar plac | -0.82 | 0.14 | -0.84 | 0.18 | 0.03 | 0.23 | 0.90 |
| acar sulf | -0.40 | 0.15 | -0.37 | 0.17 | -0.03 | 0.23 | 0.91 |
| metf piog | -0.16 | 0.08 | 0.19 | 0.12 | -0.35 | 0.15 | 0.02 |
| metf plac | -1.15 | 0.08 | -1.06 | 0.09 | -0.09 | 0.12 | 0.47 |
| metf rosi | 0.07 | 0.16 | 0.09 | 0.07 | -0.02 | 0.18 | 0.92 |
| metf sulf | -0.37 | 0.12 | -1.06 | 0.13 | 0.69 | 0.18 | <0.001 |
| piog plac | -1.30 | 0.13 | -0.94 | 0.09 | -0.36 | 0.16 | 0.02 |
| piog rosi | 0.10 | 0.18 | 0.14 | 0.09 | -0.04 | 0.20 | 0.83 |
| plac rosi | 1.15 | 0.05 | 1.47 | 0.12 | -0.32 | 0.13 | 0.01 |
| rosi sulf | -1.20 | 0.14 | -0.46 | 0.12 | -0.74 | 0.19 | <0.001 |

## Figure S1

Forest plot of various analyses of the diabetes network. All models were fitted with fixed effects. Key to treatments: acar = acarbose, benf = benfluorex, metf = metformin, migl = miglitol, piog = pioglitazone, plac = placebo, rosi = rosiglitazone, sita = sitagliptin, sulf = sulfonylurea, vild = vildagliptin. CI = confidence interval.


Treatment comparison
& model
Log Hazard
Ratio (95% CI)
acar v metf:
Direct 0.23 (-0.44, 0.91)
Indirect 0.29 (0.06, 0.53)
Netmeta 0.28 (-0.22, 0.79)
acar v plac:
Direct -0.82 (-1.09, -0.55)
Indirect -0.84 (-1.20, -0.49)
Netmeta -0.84 (-1.32, -0.36)
acar v sulf:
Direct -0.40 (-0.70, -0.10)
Indirect -0.37 (-0.70, -0.05)
Netmeta -0.43 (-0.94, 0.09)
metf v piog:
Direct -0.16 (-0.33, 0.01)
Indirect 0.19 (-0.05, 0.43)
Netmeta 0.00 (-0.44, 0.44)
metf v plac:
Direct -1.15 (-1.30, -1.00)
Indirect -1.06 (-1.24, -0.88)
Netmeta -1.13 (-1.43, -0.83)
metf v rosi:
Direct 0.07 (-0.24, 0.39)
Indirect 0.09 (-0.06, 0.24)
Netmeta 0.11 (-0.22, 0.43)
metf v sulf:
Direct -0.37 (-0.60, -0.14)
Indirect -1.06 (-1.32, -0.80)
Netmeta -0.71 (-1.17, -0.25)
piog v plac:
Direct -1.30 (-1.55, -1.05)
Indirect -0.94 (-1.12, -0.75)
Netmeta -1.13 (-1.56, -0.70)
piog v rosi:
Direct 0.10 (-0.26, 0.46)
Indirect 0.14 (-0.03, 0.32)
Netmeta 0.10 (-0.34, 0.54)
plac v rosi:
Direct 1.15 (1.05, 1.25)
Indirect 1.47 (1.24, 1.69)
Netmeta 1.23 (0.98, 1.48)
rosi v sulf:
Direct -1.20 (-1.48, -0.92)
Indirect -0.46 (-0.69, -0.22)
Netmeta -0.82 (-1.28, -0.35)
-1.69
0
1.69

# D R code

R code for Section 5

```
# Load package
library(netmeta)

# 10 TREATMENT LOOPS

n.in.design<-6 # number of trials per design
n.design<-21 # number of designs

trialid <- seq(1, n.in.design*n.design, 1)

trt1 <- c(rep("A", n.in.design), rep("A", n.in.design), rep("B", n.in.design),
          rep("A",n.in.design),rep("B",n.in.design),
          rep("A",n.in.design),rep("B",n.in.design),
          rep("A",n.in.design),rep("B",n.in.design),
          rep("A",n.in.design),rep("B",n.in.design),
          rep("A",n.in.design),rep("B",n.in.design),
          rep("A",n.in.design),rep("B",n.in.design),
          rep("A",n.in.design),rep("B",n.in.design),
          rep("A",n.in.design),rep("B",n.in.design),
          rep("A",n.in.design),rep("B",n.in.design)
)


trt2 <- c(rep("B", n.in.design), rep("C", n.in.design), rep("C", n.in.design),
          rep("D",n.in.design), rep("D",n.in.design),
          rep("E",n.in.design), rep("E",n.in.design),
          rep("F",n.in.design), rep("F",n.in.design),
          rep("G",n.in.design), rep("G",n.in.design),
```

```
          rep("H",n.in.design), rep("H",n.in.design),
          rep("I",n.in.design), rep("I",n.in.design),
          rep("J",n.in.design), rep("J",n.in.design),
          rep("K",n.in.design), rep("K",n.in.design),
          rep("L",n.in.design), rep("L",n.in.design)
)

set.seed(10)
within.design.sd=0.2
te <- c(rnorm(n.in.design,mean=0,sd=within.design.sd),
        rnorm(n.in.design,mean=2,sd=within.design.sd),
        rnorm(n.in.design,mean=0,sd=within.design.sd),
        rnorm(n.in.design,mean=0,sd=within.design.sd),
        rnorm(n.in.design,mean=0,sd=within.design.sd),
        rnorm(n.in.design,mean=0,sd=within.design.sd),
        rnorm(n.in.design,mean=0,sd=within.design.sd),
        rnorm(n.in.design,mean=0,sd=within.design.sd),
        rnorm(n.in.design,mean=0,sd=within.design.sd),
        rnorm(n.in.design,mean=0,sd=within.design.sd),
        rnorm(n.in.design,mean=0,sd=within.design.sd),
        rnorm(n.in.design,mean=0,sd=within.design.sd),
        rnorm(n.in.design,mean=0,sd=within.design.sd),
        rnorm(n.in.design,mean=0,sd=within.design.sd),
        rnorm(n.in.design,mean=0,sd=within.design.sd),
        rnorm(n.in.design,mean=0,sd=within.design.sd),
        rnorm(n.in.design,mean=0,sd=within.design.sd),
        rnorm(n.in.design,mean=0,sd=within.design.sd),
        rnorm(n.in.design,mean=0,sd=within.design.sd),
        rnorm(n.in.design,mean=0,sd=within.design.sd),
        rnorm(n.in.design,mean=0,sd=within.design.sd),
        rnorm(n.in.design,mean=0,sd=within.design.sd)

)
```

```
set.seed(123)
sete <- dnorm(te)

data.nh <- data.frame(studlab=trialid, treat1=trt1, treat2=trt2, TE=te, seTE=sete)

# Conduct fixed and random effects NMA using A as reference group
nm <- netmeta(TE=TE, seTE=seTE, treat1=treat1, treat2=treat2, studlab=trialid,
data=data.nh, comb.fixed=TRUE,  reference.group="A", sm="MD")

# Check network diagram
netgraph(nm)

# Check results
summary(nm)

# net heat
netheat(nm)

# EXTRACT Qdiff

nmak <- netmeta:::nma.krahn(nm)
V <- nmak$V

# Decompose the nm model
# This gives us Qnet, Qhet and Qinc statistics
decomp <- decomp.design(nm)

# Next we create a matrix containing the residuals
residuals <- decomp$residuals.inc.detach

# Qinc statistics by design
```

```
Q.inc.design <- decomp$Q.inc.design

# Calculate Qinc(d'(d))
Q.inc.design.typ <- apply(residuals, 2, function(x) t(x) %*%
                            solve(V) * x)

# Matrix of Qinc(d') statistics
inc <- matrix(Q.inc.design, nrow = nrow(Q.inc.design.typ),
              ncol = ncol(Q.inc.design.typ))

#Calculate Qdiff(d',d)
diff <- inc - Q.inc.design.typ

# Vector of column names (i.e. the comparisons)
colnames(diff) <- colnames(Q.inc.design.typ)

# Vector of row names (i.e. the comparisons)
rownames(diff) <- rownames(residuals)

# Matrix of Qdiff(d',d)
diff

# Save Qdiff value for row=AB and column=AC
qdiff[10] <- diff[1,2]
qinc[10] <- inc[1,2]
qincdesign[10] <- Q.inc.design.typ[1, 2]
```