# Analysis report (Supporting information)

Effect of oral nutritional supplements with or without nutritional counselling on mortality, treatment tolerance, and quality of life in head and neck cancer patients receiving

(chemo)radiotherapy: a systematic review and meta-analysis

Mello et al. (2020)

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5.2.2       Quality of life subscales         5.2.2.1       Appetite loss         5.2.2.2       Constipation         5.2.2.3       Diarrhoea         5.2.2.4       Nausea         5.2.2.5       Pain         5.3       Body weight (end of treatment)         5.3.1       Forest plot         5.3.2       Proportion of information at each level of risk         5.3.3       Risk of bias assessments by study         6       Comparison 3         6.1       Mortality		70 71 73 74 75 76 76 77 77 78 78
<ul> <li>5.2.2 Quality of life subscales</li></ul>	of bias	70 71 73 74 75 76 76 77 77 78 78 78
<ul> <li>5.2.2 Quality of life subscales</li></ul>	of bias	70 70 71 73 74 75 76 77 76 77 77 78 78 78 78 78
<ul> <li>5.2.2 Quality of life subscales</li></ul>	of bias	70 70 71 73 74 75 76 77 76 77 77 78 78 78 78 78 79 79
<ul> <li>5.2.2 Quality of life subscales</li></ul>	of bias	70 70 71 73 74 75 76 76 77 77 78 78 78 78 79 79 80
<ul> <li>5.2.2 Quality of life subscales</li></ul>	of bias	70 70 71 73 74 75 76 77 76 77 77 78 78 78 78 79 79 80 80
<ul> <li>5.2.2 Quality of life subscales</li></ul>		70 70 71 73 74 75 76 77 76 77 77 78 78 78 79 79 80 80 81
<ul> <li>5.2.2 Quality of life subscales</li></ul>	i       i	70 70 71 73 74 75 76 77 76 77 77 78 78 78 78 79 79 80 80

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		6.3.2	Proportion of the summary at each level of risk of bias
		6.3.3	Risk of bias assessments by study
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		6.4.1	Forest plot
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		7.1.2	Proportion of information at each level of risk of bias
		7.1.3	Risk of bias assessments by study
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		7.2.1	Forest plot
		7.2.2	Proportion of the summary at each level of risk of bias
		7.2.3	Risk of bias assessments by study

# 1 Abbreviations

CCRT: concurrent chemo-radiotherapy
CI: confidence interval
CT: chemotherapy
MD: mean difference
MID: minimal important difference
NC: nutritional counselling
ONS: oral nutritional supplements
RR: risk ratio
RT: radiotherapy
SD: standard deviation
seTE: standard error
SMD: standardized mean difference
TE: estimated treatment effect
2 Packages

# library(meta)

```
## Loading 'meta' package (version 4.9-7).
## Type 'help(meta)' for a brief overview.
library(readr)
library(rmeta)
library(devtools)
```

```
## Loading required package: usethis
```

```
library(robvis)
library(patchwork)
library(ggplot2)
library(tidyr)
```

# 3 Standard configurations for the meta-analyses

```
settings.meta(hakn = TRUE) # Hartung-Knapp adjustment
Parsed with column specification:
cols(
  .default = col_double(),
 outclab = col_character(),
 D1 = col_character(),
 D2 = col_character(),
 D3 = col_character(),
 D4 = col_character(),
 D5 = col_character(),
 Overall = col_character(),
 bias = col_character(),
  site = col_character(),
 studlab = col_character(),
 X23 = col_logical()
)
```

See spec(...) for full column specifications.

# 4 Comparison 1

# 4.1 Mortality

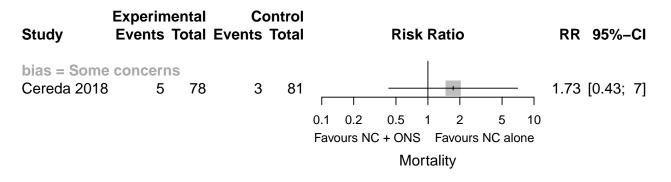
# 4.1.1 Main analysis

Including only results at most at some concerns of bias.

# 4.1.1.1 Forest plot

```
mort_1_S <- metabin(</pre>
  HNC$event.e,
  HNC$n.e,
  HNC$event.c,
  HNC$n.c,
  sm = "RR",
  method = "MH",
  RR.cochrane = TRUE,
  MH.exact = FALSE,
  allstudies = FALSE,
  HNC$studlab,
  subset = HNC$outclab == "Mortality" & HNC$C == 1 & HNC$studlab == "Cereda 2018",
  exclude = HNC$studlab == "Jiang 2019",
  hakn = TRUE,
  byvar = HNC$bias
)
```

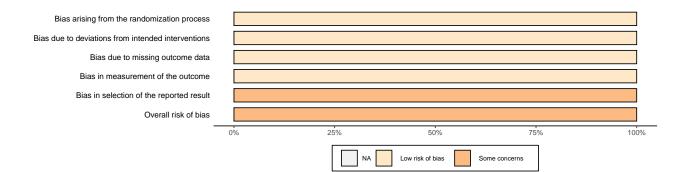
```
mort_1_Sd <- data.frame(mort_1_S)</pre>
rob_mort_1_S <- subset(rob_mort_1, studlab == "Cereda 2018")</pre>
rob_mort_1_S <- merge(rob_mort_1_S, mort_1_Sd[,c("w.random", "studlab")], by = "studlab", all = TRUE)</pre>
rob_mort_1_S <- rob_mort_1_S[1:3,]</pre>
forest(mort_1_S,
       xlab="Mortality",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 2,
       comb.fixed = FALSE,
       xlim = c(0.1, 10),
       #plotwidth = "2cm",
       subgroup = FALSE,
       hetstat = FALSE,
       overall.hetstat = TRUE,
       pooled.events = TRUE,
       resid.hetstat = FALSE,
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = C1,
       label.left = I1,
       fs.axis = 10,
       fs.lr = 10
)
```



# 4.1.1.2 Proportion of information at each level of risk of bias

Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result (when applicable)

rob\_summary(rob\_mort\_1\_S, tool = "ROB2", weighted = TRUE, overall = TRUE, colour = "colourblind")



# 4.1.2 Sensitivity analysis

Including all available results.

#### 4.1.2.1 Forest plot

```
mort_1 <- metabin(</pre>
  HNC$event.e,
  HNC$n.e,
  HNC$event.c,
  HNC$n.c,
  sm = "RR",
  method = "MH",
  RR.cochrane = TRUE,
  MH.exact = FALSE,
  allstudies = FALSE,
  HNC$studlab,
  subset = HNC$outclab == "Mortality" & HNC$C == 1,
  exclude = HNC$studlab == "Jiang 2019",
  hakn = TRUE,
  byvar = HNC$bias
)
## Warning in qt(1 - alpha/2, df = df): NaNs produzidos
## Warning in qt(1 - alpha/2, df = df): NaNs produzidos
mort_1d <- data.frame(mort_1)</pre>
rob_mort_1 <- merge(rob_mort_1, mort_1d[,c("w.random", "studlab")], by = "studlab", all = TRUE)</pre>
rob_mort_1 <- rob_mort_1[1:3,]</pre>
forest(mort_1,
       xlab="Mortality",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 2,
       comb.fixed = FALSE,
       xlim = c(0.01, 100),
       #plotwidth = "2cm",
       subgroup = FALSE,
       hetstat = FALSE,
       overall.hetstat = TRUE,
       pooled.events = TRUE,
```

```
resid.hetstat = FALSE,
colgap.forest = "0.5 cm",
just = "right",
label.right = C1,
label.left = I1,
fs.axis = 10,
fs.lr = 10
```

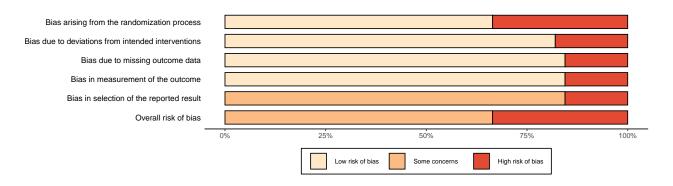
)

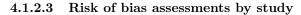
Study	Experimental Events Total E	Control Events Total	Risk Ratio	RR		95%-CI Weight
bias = High risk of bia Arnold 1989 Chitapanarux	s 3 23 0 20	0 27 1 20		→ 8.17 0.33	[0.44; [0.01;	150.30] 18.0% 7.72] 15.6%
bias = Some concerns Cereda 2018	5 78	3 81		1.73	[0.43;	7.00] 66.5%
bias = Unknown Jiang 2019	0 46	0 45				0.0%
<b>Random effects mode</b> Heterogeneity: $I^2 = 7\%$ , $\tau^2$		0.0	01 0.1 0.5 1 2 10 avours NC + ONS Favours NC al Mortality	1.77 100 lone	[0.11;	29.48] 100.0%

# 4.1.2.2 Proportion of information at each level of risk of bias

Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result (when applicable)

rob\_summary(rob\_mort\_1, tool = "ROB2", weighted = TRUE, overall = TRUE, colour = "colourblind")





rob\_traffic\_light(rob\_mort\_1, tool = "ROB2", colour = "colourblind", psize = 10)

				Risk of bia	s domains		
		D1	D2	D3	D4	D5	Overall
	Arnold 1989	×	×	+	+	-	×
Study	Cereda 2018	+	+	+	+	-	-
	Chitapanarux	×	+	×	×	×	×
		Domains:					Judgement
		D1: Bias due to randomis D2: Bias due to deviation	ation. s from intended interventio	n.			X High
		D3: Bias due to missing on D4: Bias due to outcome	lata.				<ul> <li>Some concerns</li> </ul>
		D4: Bias due to selection					+ Low

#forest(metainf(mort\_1,
# pooled = "random"))

#### 4.2 Treatment tolerance

# 4.2.1 RT Complete suspension

```
4.2.1.1 Forest plot
```

```
rt_susp <- metabin(</pre>
  HNC$event.e,
  HNC$n.e,
 HNC$event.c,
  HNC$n.c,
  sm = "RR",
  method = "MH",
  RR.cochrane = TRUE,
  MH.exact = TRUE,
  allstudies = FALSE,
  HNC$studlab,
  subset = HNC$outclab == "RT_Susp" & HNC$C == 1,
  byvar = HNC$bias,
  comb.fixed = FALSE,
  comb.random = TRUE,
)
```

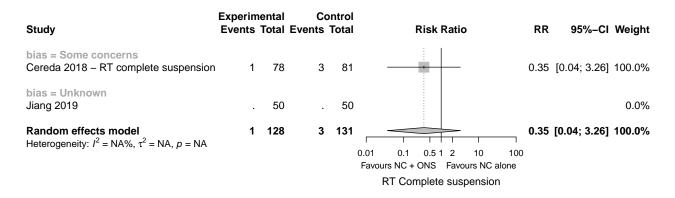
```
## Warning: For a single study, inverse variance method used instead of Mantel-
## Haenszel method.
```

```
rt_susp_d <- data.frame(rt_susp)</pre>
```

```
rob_rt_susp_1 <- merge(rob_rt_susp_1, rt_susp_d[,c("w.random", "studlab")], by = "studlab", all = TRUE)
rob_rt_susp_1_x <- subset(rob_rt_susp_1, studlab != "Jiang 2019")</pre>
```

```
overall.hetstat = TRUE,
xlim = c(0.01, 100),
#xlim = "s",
#plotwidth = "2cm",
colgap.forest = "0.5 cm",
just = "right",
label.right = C1,
label.left = I1,
fs.axis = 10,
fs.lr = 10
```

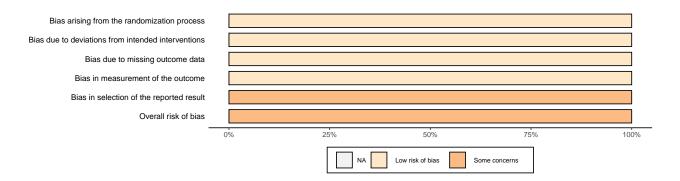
)



#### 4.2.1.2 Proportion of information at each level of risk of bias

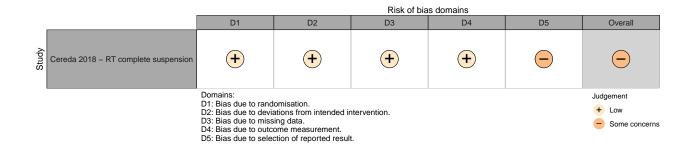
Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result (when applicable)

rob\_summary(rob\_rt\_susp\_1, tool = "ROB2", weighted = TRUE, overall = TRUE, colour = "colourblind")



4.2.1.3	Risk o	of bias	assessments	by	study
---------	--------	---------	-------------	----	-------

rob\_traffic\_light(rob\_rt\_susp\_1\_x, tool = "ROB2", colour = "colourblind", psize = 10)



4.2.2 CT Complete suspension

```
4.2.2.1 Forest plot
```

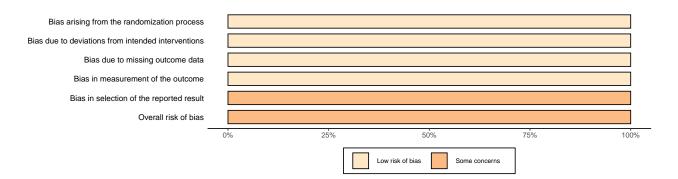
```
ct_susp <- metabin(</pre>
 HNC$event.e,
 HNC$n.e,
 HNC$event.c.
 HNC$n.c,
 sm = "RR",
 method = "MH",
 RR.cochrane = TRUE,
 MH.exact = TRUE,
  allstudies = TRUE,
 HNC$studlab,
  subset = HNC$outclab == "CT_Susp" & HNC$C == 1,
  byvar = HNC$bias,
  comb.fixed = FALSE,
  comb.random = TRUE,
)
ct_susp_d <- data.frame(ct_susp)</pre>
rob_ct_susp_1 <- merge(rob_ct_susp_1, ct_susp_d[,c("w.random", "studlab")], by = "studlab", all = TRUE)</pre>
forest(ct_susp,
       xlab="CT Complete suspension",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 2,
       digits.se = 1,
       comb.fixed = FALSE,
       pooled.events = TRUE,
       #overall = FALSE,
       subgroup = FALSE,
       hetstat = FALSE,
       overall.hetstat = TRUE,
       xlim = c(0.00001, 100000),
       #xlim
                = "s",
       #plotwidth = "2cm",
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = C1,
```

label.left = I1, fs.axis = 10,fs.lr = 10) Experimental Control **Risk Ratio** 95%-CI Weight Study **Events Total Events Total** RR bias = Some concerns Cereda 2018 - CT complete suspension 1 29 4 32 0.28 [0.03; 2.33] 23.8% Jiang 2019 – incomplete chemotherapy 10 11 50 50 1.10 [0.51; 2.36] 76.2% 0.79 [0.00; 1403.55] 100.0% Random effects model 79 12 14 82 Heterogeneity:  $l^2 = 32\%$ ,  $\tau^2 = 0.3170$ , p = 0.221e-05 0.001 0.1 1 10 1000 1e+05 Favours NC + ONS Favours NC alone CT Complete suspension

# 4.2.2.2 Proportion of information at each level of risk of bias

Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result (when applicable)

rob\_summary(rob\_ct\_susp\_1, tool = "ROB2", weighted = TRUE, overall = TRUE, colour = "colourblind")



# 4.2.2.3 Risk of bias assessments by study

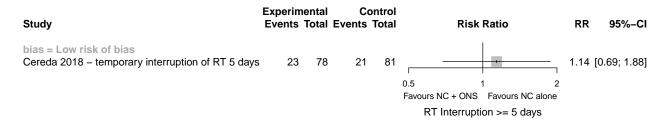
rob\_traffic\_light(rob\_ct\_susp\_1, tool = "ROB2", colour = "colourblind", psize = 10)

				Risk of bia	s domains		
		D1	D2	D3	D4	D5	Overall
Study	Cereda 2018 - CT complete suspension	+	+	+	+	-	-
Str	Jiang 2019 – incomplete chemotherapy	+	+	+	+	-	-
		D3: Bias due to miss D4: Bias due to outco	ations from intended ir ing data.				Judgement + Low - Some concerns

### 4.2.3 RT interruption >= 5 days

```
4.2.3.1 Forest plot
rt int5 <- metabin(</pre>
 HNC$event.e,
  HNC$n.e,
  HNC$event.c,
  HNC$n.c,
  sm = "RR",
  method = "MH",
  RR.cochrane = TRUE,
  MH.exact = TRUE,
  allstudies = TRUE,
  HNC$studlab.
  subset = HNC$outclab == "Interruption" & HNC$C == 1,
  byvar = HNC$bias,
  comb.fixed = FALSE,
  comb.random = TRUE,
)
rt_int5_d <- data.frame(rt_int5)</pre>
rob_rt_int5_1 <- merge(rob_rt_int5_1, rt_int5_d[,c("w.random", "studlab")], by = "studlab", all = TRUE)</pre>
forest(rt_int5,
       xlab="RT Interruption >= 5 days",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 2,
       digits.se = 1,
       comb.fixed = FALSE,
       pooled.events = TRUE,
       #overall = FALSE,
       subgroup = FALSE,
       hetstat = FALSE,
       overall.hetstat = TRUE,
       xlim = c(0.5, 2),
       #xlim = "s",
       #plotwidth = "2cm",
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = C1,
       label.left = I1,
       fs.axis = 10,
       fs.lr = 10
```

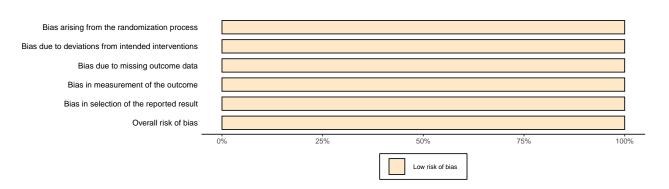
)



#### 4.2.3.2 Proportion of information at each level of risk of bias

Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result (when applicable)





# 4.2.3.3 Risk of bias assessments by study

rob\_traffic\_light(rob\_rt\_int5\_1, tool = "ROB2", colour = "colourblind", psize = 10)

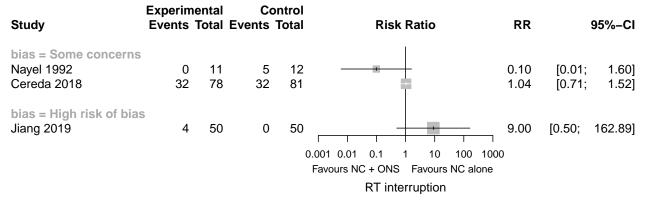
			Risk of bias domains						
		D1	D2	D3	D4	D5	Overall		
Study	Cereda 2018 – temporary interruption of RT 5 days	+	+	+	+	+	+		
_		D3: Bias due to mis D4: Bias due to out	viations from intende				Judgement + Low		

#### 4.2.4 RT interruption

#### 4.2.4.1 Forest plot

```
rt_int <- metabin(
    HNC$event.e,
    HNC$n.e,
    HNC$event.c,
    HNC$n.c,
    sm = "RR",
    method = "MH",
    RR.cochrane = TRUE,
    MH.exact = TRUE,</pre>
```

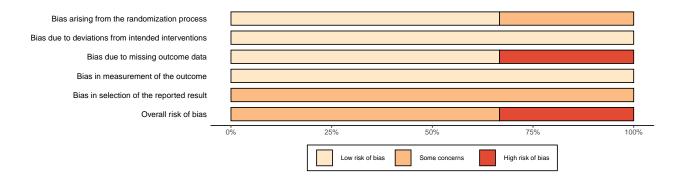
```
#allstudies = TRUE,
  HNC$studlab,
  subset = HNC$outclab == "RT Interruption" & HNC$C == 1,
  byvar = HNC$bias,
  comb.fixed = FALSE,
  comb.random = TRUE,
)
rt_int_d <- data.frame(rt_int)</pre>
rob_rt_int_1 <- merge(rob_rt_int_1, rt_int_d[,c("w.random", "studlab")], by = "studlab", all = TRUE)</pre>
forest(rt_int,
       xlab="RT interruption",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 2,
       digits.se = 1,
       comb.fixed = FALSE,
       pooled.events = TRUE,
       #overall = FALSE,
       subgroup = FALSE,
       hetstat = FALSE,
       overall.hetstat = FALSE,
       overall = FALSE,
       xlim = c(0.001, 1000),
       #xlim
                = "s",
       #plotwidth = "2cm",
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = C1,
       label.left = I1,
       fs.axis = 10,
       fs.lr = 10
)
```



#### 4.2.4.2 Proportion of information at each level of risk of bias

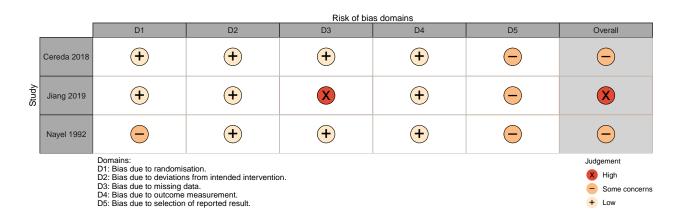
Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result (when applicable)

# rob\_summary(rob\_rt\_int\_1, tool = "ROB2", weighted = FALSE, overall = TRUE, colour = "colourblind")



# 4.2.4.3 Risk of bias assessments by study

rob\_traffic\_light(rob\_rt\_int\_1, tool = "ROB2", colour = "colourblind", psize = 10)



# 4.2.5 Incomplete CCRT

#### 4.2.5.1 Forest plot

```
ccrt inc <- metabin(</pre>
  HNC$event.e,
  HNC$n.e,
  HNC$event.c,
  HNC$n.c,
  sm = "RR",
  method = "MH",
  RR.cochrane = TRUE,
  MH.exact = TRUE,
  #allstudies = TRUE,
  HNC$studlab,
  subset = HNC$outclab == "CCRT_Incomplete" & HNC$C == 1,
  byvar = HNC$bias,
  comb.fixed = FALSE,
  comb.random = TRUE,
)
```

<pre>ccrt_inc_d &lt;- data.frame(cc rob_ccrt_inc_1 &lt;- merge(rob</pre>	crt_inc) o_ccrt_inc_1, ccrt_inc_d[,c("	w.random", "studlab	")], by = "studlab"	, all = TH
<pre>forest(ccrt_inc, xlab="Incomplete CCR #ref = 10, #layout = "Revman5", layout = "meta", digits = 2, digits.se = 1, comb.fixed = FALSE, pooled.events = TRUE #overall = FALSE, subgroup = FALSE, hetstat = FALSE, overall.hetstat = TR xlim = c(0.1, 10), #xlim = "s", #plotwidth = "2cm", colgap.forest = "0.5 just = "right", label.right = C1, label.left = I1, fs.axis = 10, fs.lr = 10 )</pre>	z, RUE,			
Study	Experimental Control Events Total Events Total	Risk Ratio	RR 95%–Cl	
bias = High risk of bias Chitapanarux 2016 – incomplete CCF	RT 3 20 8 20 <u>—</u>		0.37 [0.12; 1.21]	

```
1
Favours NC + ONS Favours NC alone
       Incomplete CCRT
```

2

5 10

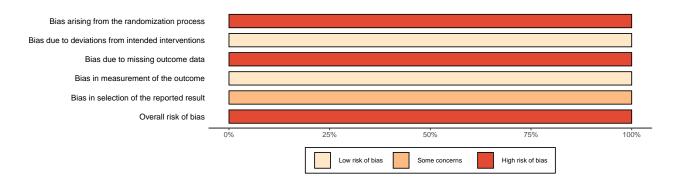
0.5

# 4.2.5.2 Proportion of information at each level of risk of bias

Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result (when applicable)



0.1 0.2



#### 4.2.5.3 Risk of bias assessments by study

```
rob_traffic_light(rob_ccrt_inc_1, tool = "ROB2", colour = "colourblind", psize = 10)
```

	Risk of bias domains					
	D1	D2	D3	D4	D5	Overall
Chitapanarux 2016 – incomplete CCRT	×	+	X	+	-	×
	D3: Bias due to missi D4: Bias due to outco	ations from intended in ing data.				Judgement High - Some concerns + Low

# 4.2.6 RT Dose reduction

```
4.2.6.1 Forest plot
```

```
rt_dose <- metabin(</pre>
 HNC$event.e,
  HNC$n.e,
  HNC$event.c,
 HNC$n.c,
  sm = "RR",
  method = "MH",
  RR.cochrane = TRUE,
 MH.exact = TRUE,
  #allstudies = TRUE,
 HNC$studlab,
  subset = HNC$outclab == "RT_Dose" & HNC$C == 1,
  byvar = HNC$bias,
  comb.fixed = FALSE,
  comb.random = TRUE,
)
rt_dose_d <- data.frame(rt_dose)</pre>
rob_rt_dose_1 <- merge(rob_rt_dose_1, rt_dose_d[,c("w.random", "studlab")], by = "studlab", all = TRUE)</pre>
forest(rt_dose,
       xlab="RT Dose reduction",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 2,
       digits.se = 1,
       comb.fixed = FALSE,
       pooled.events = TRUE,
       #overall = FALSE,
       subgroup = FALSE,
       hetstat = FALSE,
       overall.hetstat = TRUE,
       xlim = c(0.01, 100),
       #xlim = "s",
```

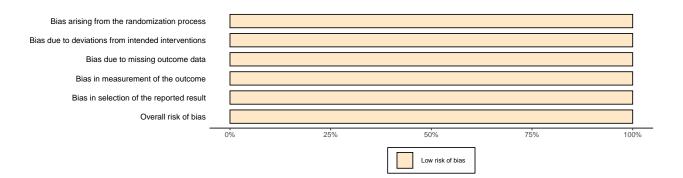
```
#plotwidth = "2cm",
        colgap.forest = "0.5 cm",
        just = "right",
        label.right = C1,
        label.left = I1,
        fs.axis = 10,
        fs.lr = 10
)
                              Experimental
                                                 Control
Study
                               Events Total Events Total
                                                                    Risk Ratio
                                                                                                95%-CI
                                                                                           RR
bias = Low risk of bias
                                                                                          0.17 [0.02; 1.4]
Cereda 2018 - RT dose reduction
                                     1
                                         78
                                                  6
                                                      81
                                                         0.01
                                                                 0.1
                                                                      0.512
                                                                               10
                                                                                      100
                                                          Favours NC + ONS Favours NC alone
```

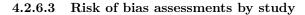
#### 4.2.6.2 Proportion of information at each level of risk of bias

Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result (when applicable)

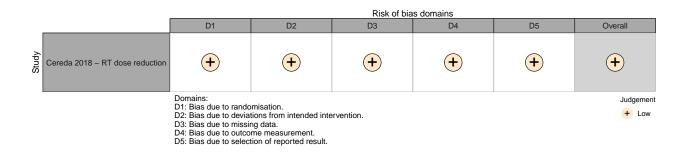
rob\_summary(rob\_rt\_dose\_1, tool = "ROB2", weighted = TRUE, overall = TRUE, colour = "colourblind")

**RT** Dose reduction





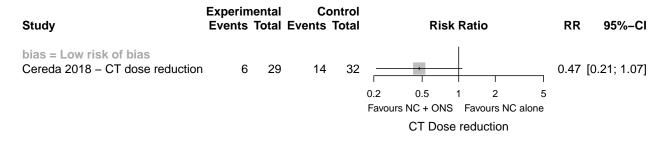
```
rob_traffic_light(rob_rt_dose_1, tool = "ROB2", colour = "colourblind", psize = 10)
```



#### 4.2.7 CT Dose reduction

```
4.2.7.1 Forest plot
ct_dose <- metabin(</pre>
 HNC$event.e,
  HNC$n.e,
  HNC$event.c,
  HNC$n.c,
  sm = "RR",
  method = "MH",
  RR.cochrane = TRUE,
 MH.exact = TRUE,
  #allstudies = TRUE,
  HNC$studlab.
  subset = HNC$outclab == "CT_Dose" & HNC$C == 1,
  byvar = HNC$bias,
  comb.fixed = FALSE,
  comb.random = TRUE,
)
ct_dose_d <- data.frame(ct_dose)</pre>
rob_ct_dose_1 <- merge(rob_ct_dose_1, ct_dose_d[,c("w.random", "studlab")], by = "studlab", all = TRUE)</pre>
forest(ct_dose,
       xlab="CT Dose reduction",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 2,
       digits.se = 1,
       comb.fixed = FALSE,
       pooled.events = TRUE,
       #overall = FALSE,
       subgroup = FALSE,
       hetstat = FALSE,
       overall.hetstat = TRUE,
       xlim = c(0.2, 5),
       #xlim = "s",
       #plotwidth = "2cm",
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = C1,
       label.left = I1,
       fs.axis = 10,
       fs.lr = 10
```

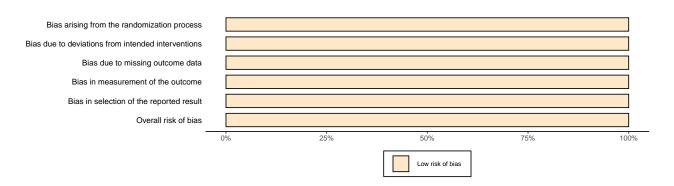
)



# 4.2.7.2 Proportion of information at each level of risk of bias

Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result (when applicable)

# rob\_summary(rob\_ct\_dose\_1, tool = "ROB2", weighted = TRUE, overall = TRUE, colour = "colourblind")



# 4.2.7.3 Risk of bias assessments by study

```
rob_traffic_light(rob_ct_dose_1, tool = "ROB2", colour = "colourblind", psize = 10)
```

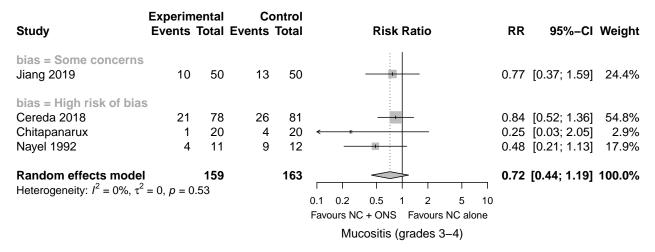
		Risk of bias domains						
		D1	D2	D3	D4	D5	Overall	
Study	Cereda 2018 – CT dose reduction	+	+	+	+	+	+	
		Domains: D1: Bias due to rando D2: Bias due to deviai D3: Bias due to missii D4: Bias due to outco D5: Bias due to select	tions from intended inten ng data. me measurement.	ervention.			Judgement + Low	

# 4.2.8 Mucositis (severe)

#### 4.2.8.1 Forest plot

```
muco_1 <- metabin(
  HNC$event.e,
  HNC$n.e,
  HNC$event.c,
  HNC$n.c,
  sm = "RR",
  method = "MH",
  RR.cochrane = TRUE,</pre>
```

```
MH.exact = FALSE,
  #allstudies = TRUE,
  HNC$studlab,
  subset = HNC$outclab == "Mucositis" & HNC$C == 1,
  byvar = HNC$bias,
  comb.fixed = FALSE,
  comb.random = TRUE
)
muco_1_d <- data.frame(muco_1)</pre>
rob_muco_1 <- merge(rob_muco_1, muco_1_d[,c("w.random", "studlab")], by = "studlab", all = TRUE)</pre>
forest(muco_1,
       xlab="Mucositis (grades 3-4)",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 2,
       digits.se = 1,
       comb.fixed = FALSE,
       #overall = FALSE,
       subgroup = FALSE,
       xlim = c(0.1, 10),
       \#xlim = "s",
       #plotwidth = "2cm",
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = C1,
       label.left = I1,
       fs.axis = 10,
       fs.lr = 10,
       hetstat = FALSE,
       overall.hetstat = TRUE
)
```

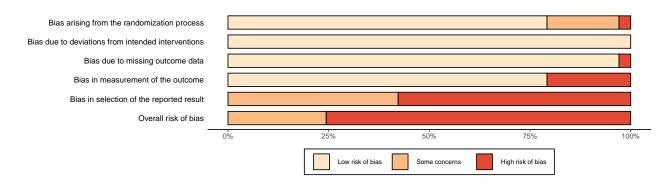


# 4.2.8.2 Proportion of information at each level of risk of bias

Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result

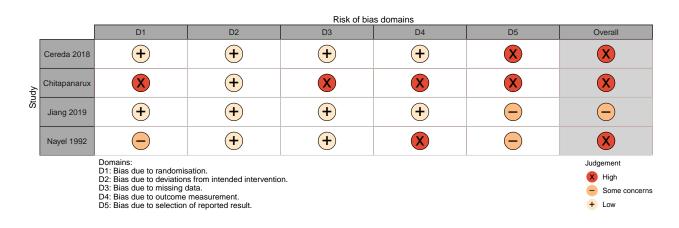
#### (when applicable)

rob\_summary(rob\_muco\_1, tool = "ROB2", weighted = TRUE, overall = TRUE, colour = "colourblind")



# 4.2.8.3 Risk of bias assessments by study

```
rob_traffic_light(rob_muco_1, tool = "ROB2", colour = "colourblind", psize = 10)
```



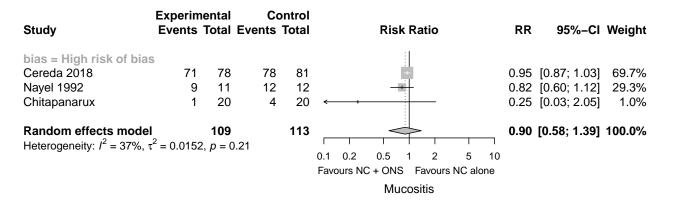
#orest(metainf(muco\_1,
# pooled = "random"))

#### 4.2.9 Mucositis (overall)

#### 4.2.9.1 Forest plot

```
muco_g_1 <- metabin(
 HNC$event.e,
 HNC$n.e,
 HNC$n.c,
 sm = "RR",
 method = "MH",
 RR.cochrane = TRUE,
 MH.exact = FALSE,
 #allstudies = TRUE,
 HNC$studlab,
 subset = HNC$outclab == "Mucositis_g" & HNC$C == 1,
 byvar = HNC$bias,
```

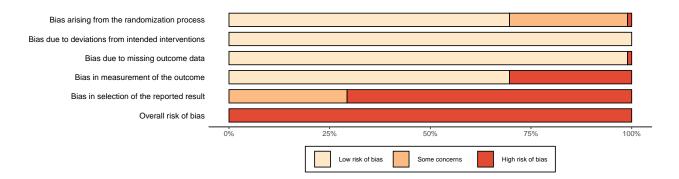
```
comb.fixed = FALSE,
  comb.random = TRUE
)
muco_g_1_d <- data.frame(muco_g_1)</pre>
rob_muco_g_1 <- merge(rob_muco_g_1, muco_g_1_d[,c("w.random", "studlab")], by = "studlab", all = TRUE)</pre>
forest(muco_g_1,
       xlab="Mucositis",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 2,
       digits.se = 1,
       comb.fixed = FALSE,
       #overall = FALSE,
       subgroup = FALSE,
       xlim = c(0.1, 10),
                = "s",
       #xlim
       #plotwidth = "2cm",
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = C1,
       label.left = I1,
       fs.axis = 10,
       fs.lr = 10,
       hetstat = FALSE,
       overall.hetstat = TRUE
)
```



#### 4.2.9.2 Proportion of information at each level of risk of bias

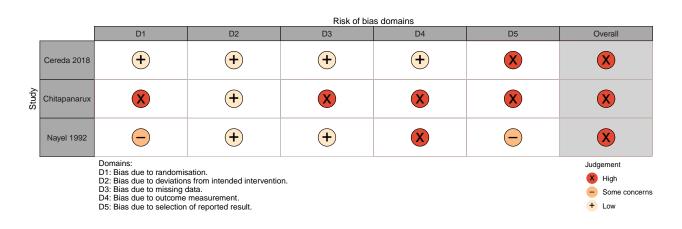
Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result (when applicable)

rob\_summary(rob\_muco\_g\_1, tool = "ROB2", weighted = TRUE, overall = TRUE, colour = "colourblind")



# 4.2.9.3 Risk of bias assessments by study

rob\_traffic\_light(rob\_muco\_g\_1, tool = "ROB2", colour = "colourblind", psize = 10)



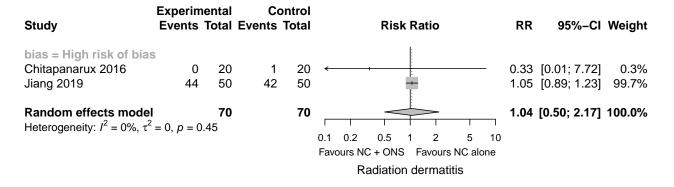
```
#forest(metainf(muco_g_1,
# pooled = "random"))
```

#### 4.2.10 Radiation dermatitis

#### 4.2.10.1 Forest plot

```
derma_1 <- metabin(</pre>
  HNC$event.e,
  HNC$n.e,
  HNC$event.c,
  HNC$n.c,
  sm = "RR",
  method = "MH",
  RR.cochrane = TRUE,
  MH.exact = FALSE,
  #allstudies = TRUE,
  HNC$studlab,
  subset = HNC$outclab == "Derma" & HNC$C == 1,
  byvar = HNC$bias,
  comb.fixed = FALSE,
  comb.random = TRUE,
)
```

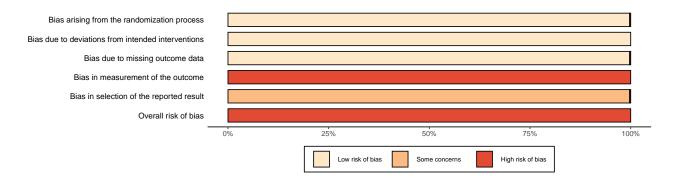
```
derma_1_d <- data.frame(derma_1)</pre>
rob_derma_1 <- merge(rob_derma_1, derma_1_d[,c("w.random", "studlab")], by = "studlab", all = TRUE)
forest(derma_1,
       xlab="Radiation dermatitis",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 2,
       digits.se = 1,
       comb.fixed = FALSE,
       #overall = FALSE,
       subgroup = FALSE,
       xlim = c(0.1, 10),
                = "s",
       #xlim
       #plotwidth = "2cm",
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = C1,
       label.left = I1,
       fs.axis = 10,
       fs.lr = 10,
       hetstat = FALSE,
       overall.hetstat = TRUE
)
```



#### 4.2.10.2 Proportion of information at each level of risk of bias

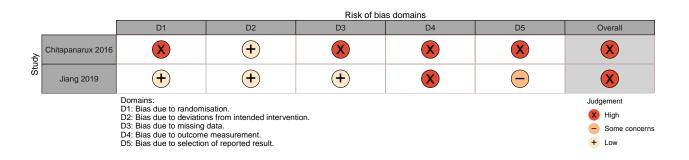
Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result (when applicable)

rob\_summary(rob\_derma\_1, tool = "ROB2", weighted = TRUE, overall = TRUE, colour = "colourblind")



# 4.2.10.3 Risk of bias assessments by study

rob\_traffic\_light(rob\_derma\_1, tool = "ROB2", colour = "colourblind", psize = 10)



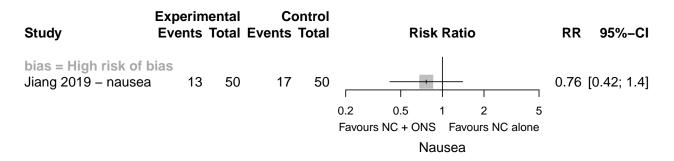
# 4.2.11 Nausea

# 4.2.11.1 Forest plot

```
nausea_1 <- metabin(</pre>
  HNC$event.e,
  HNC$n.e,
 HNC$event.c,
  HNC$n.c,
  sm = "RR",
  method = "MH",
  RR.cochrane = TRUE,
  MH.exact = FALSE,
  #allstudies = TRUE,
  HNC$studlab,
  subset = HNC$outclab == "Nausea" & HNC$C == 1,
  byvar = HNC$bias,
  comb.fixed = FALSE,
  comb.random = TRUE,
)
nausea_1_d <- data.frame(nausea_1)</pre>
rob_nausea_1 <- merge(rob_nausea_1, nausea_1_d[,c("w.random", "studlab")], by = "studlab", all = TRUE)</pre>
forest(nausea_1,
       xlab="Nausea",
       #ref = 10,
       #layout = "Revman5",
```

```
layout = "meta",
digits = 2,
digits.se = 1,
comb.fixed = FALSE,
#overall = FALSE,
subgroup = FALSE,
xlim = c(0.2, 5),
#xlim
        = "s",
#plotwidth = "2cm",
colgap.forest = "0.5 cm",
just = "right",
label.right = C1,
label.left = I1,
fs.axis = 10,
fs.lr = 10,
hetstat = FALSE,
overall.hetstat = TRUE
```

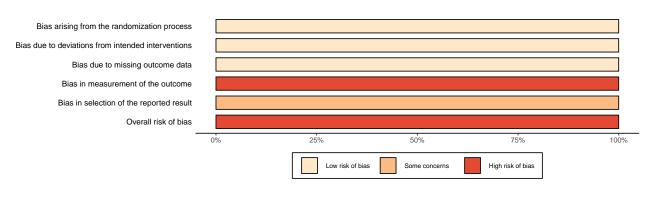
)



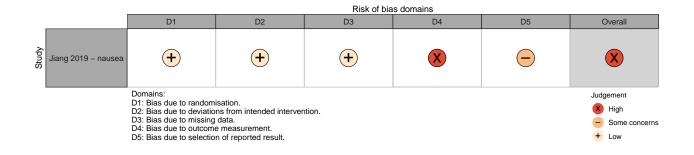
# 4.2.11.2 Proportion of information at each level of risk of bias

Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result (when applicable)









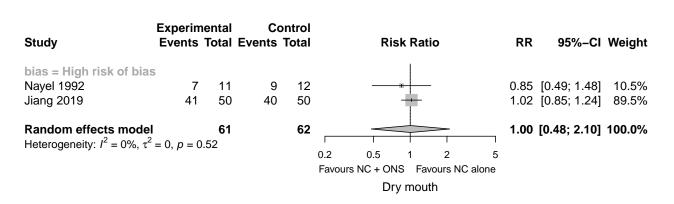
# 4.2.12 Dry mouth

```
4.2.12.1 Forest plot
```

```
mouth_dry_1 <- metabin(</pre>
  HNC$event.e,
  HNC$n.e,
  HNC$event.c.
  HNC$n.c,
  sm = "RR",
  method = "MH",
  RR.cochrane = TRUE,
  MH.exact = FALSE,
  #allstudies = TRUE,
  HNC$studlab,
  subset = HNC$outclab == "Mouth_dry" & HNC$C == 1,
  byvar = HNC$bias,
  comb.fixed = FALSE,
  comb.random = TRUE
)
mouth_dry_1_d <- data.frame(mouth_dry_1)</pre>
rob_mouth_dry_1 <- merge(rob_mouth_dry_1, mouth_dry_1_d[,c("w.random", "studlab")], by = "studlab", all
forest(mouth_dry_1,
       xlab="Dry mouth",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 2,
       digits.se = 1,
       comb.fixed = FALSE,
       #overall = FALSE,
       subgroup = FALSE,
       xlim = c(0.2, 5),
       #xlim
              = "s",
       #plotwidth = "2cm",
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = C1,
       label.left = I1,
       fs.axis = 10,
       fs.lr = 10,
```

```
hetstat = FALSE,
overall.hetstat = TRUE
```

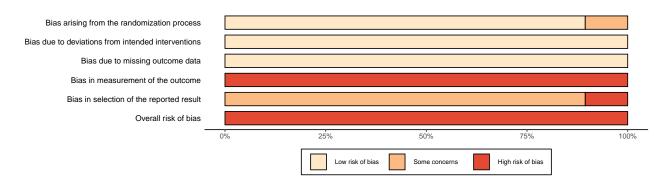
)



# 4.2.12.2 Proportion of information at each level of risk of bias

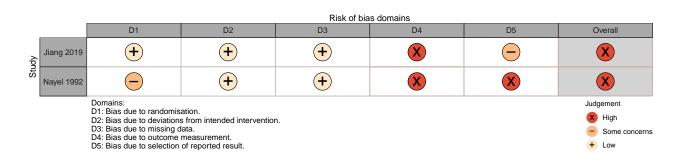
Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result (when applicable)

rob\_summary(rob\_mouth\_dry\_1, tool = "ROB2", weighted = TRUE, overall = TRUE, colour = "colourblind")



#### 4.2.12.3 Risk of bias assessments by study

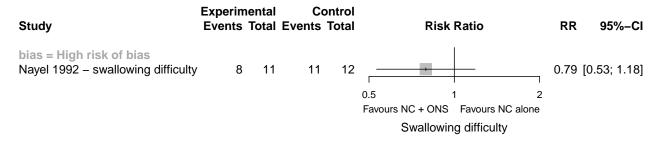
rob\_traffic\_light(rob\_mouth\_dry\_1, tool = "ROB2", colour = "colourblind", psize = 10)



#### 4.2.13 Swallowing difficulty

4.2.13.1 Forest plot

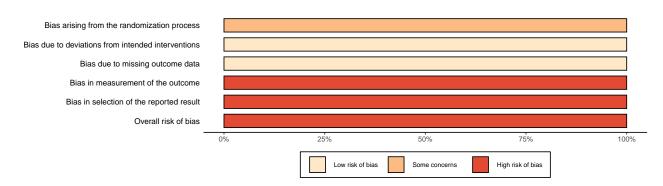
```
swallow_1 <- metabin(</pre>
  HNC$event.e,
  HNC$n.e,
  HNC$event.c,
  HNC$n.c,
  sm = "RR",
  method = "MH",
 RR.cochrane = TRUE,
 MH.exact = FALSE,
  #allstudies = TRUE,
 HNC$studlab,
  subset = HNC$outclab == "Swallow" & HNC$C == 1,
  byvar = HNC$bias,
  comb.fixed = FALSE,
  comb.random = TRUE,
)
swallow_1_d <- data.frame(swallow_1)</pre>
rob_swallow_1 <- merge(rob_swallow_1, swallow_1_d[,c("w.random", "studlab")], by = "studlab", all = TRU
forest(swallow_1,
       xlab="Swallowing difficulty",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 2,
       digits.se = 1,
       comb.fixed = FALSE,
       #overall = FALSE,
       subgroup = FALSE,
       xlim = c(0.5, 2),
       #xlim
              = "s",
       #plotwidth = "2cm",
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = C1,
       label.left = I1,
       fs.axis = 10,
       fs.lr = 10,
       hetstat = FALSE,
       overall.hetstat = TRUE
)
```



# 4.2.13.2 Proportion of information at each level of risk of bias

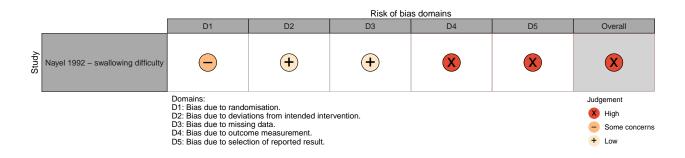
Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result (when applicable)





#### 4.2.13.3 Risk of bias assessments by study

```
rob_traffic_light(rob_swallow_1, tool = "ROB2", colour = "colourblind", psize = 10)
```



# 4.2.14 Taste and appetite changes

# 4.2.14.1 Forest plot

```
taste_app_1 <- metabin(</pre>
 HNC$event.e.
  HNC$n.e,
 HNC$event.c,
 HNC$n.c,
  sm = "RR",
  method = "MH",
  RR.cochrane = TRUE,
 MH.exact = FALSE,
  #allstudies = TRUE,
 HNC$studlab,
  subset = HNC$outclab == "Taste_App" & HNC$C == 1,
  byvar = HNC$bias,
  comb.fixed = FALSE,
  comb.random = TRUE,
)
```

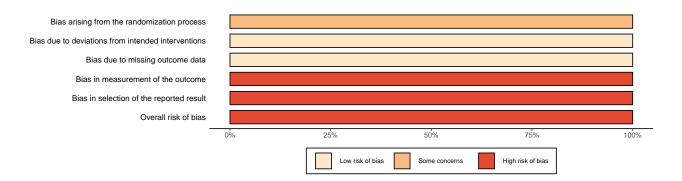
```
taste_app_1_d <- data.frame(taste_app_1)</pre>
rob_taste_app_1 <- merge(rob_taste_app_1, taste_app_1_d[,c("w.random", "studlab")], by = "studlab", all</pre>
forest(taste_app_1,
       xlab="Taste and appetite changes",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 2,
       digits.se = 1,
       comb.fixed = FALSE,
       #overall = FALSE,
       subgroup = FALSE,
       xlim = c(0.5, 2),
              = "s",
       #xlim
       #plotwidth = "2cm",
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = C1,
       label.left = I1,
       fs.axis = 10,
       fs.lr = 10,
       hetstat = FALSE,
       overall.hetstat = TRUE
)
```

Study	Experim Events			ontrol Total	Risk Ratio	R	R 95%–Cl
bias = High risk of bias Nayel 1992 – taste and appetite changes	10	11	11	12	0.5 1 Favours NC + ONS Favours NC alo Taste and appetite changes	2 ne	99 [0.77; 1.28]

#### 4.2.14.2 Proportion of information at each level of risk of bias

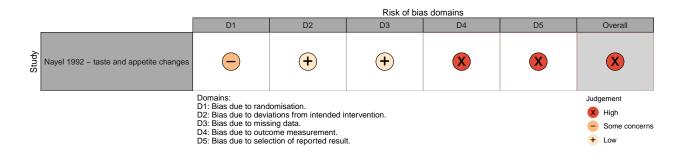
Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result (when applicable)

# rob\_summary(rob\_taste\_app\_1, tool = "ROB2", weighted = TRUE, overall = TRUE, colour = "colourblind")



#### 4.2.14.3 Risk of bias assessments by study

rob\_traffic\_light(rob\_taste\_app\_1, tool = "ROB2", colour = "colourblind", psize = 10)



#### 4.2.15 Summary of treatment tolerance outcomes

# 4.2.15.1 Results of meta-analysis

```
tol_1_b <- metabind(#rt_susp,</pre>
                     ct_susp,
                     #rt_int5,
                     #ccrt_inc,
                     #rt_dose,
                     #ct dose,
                     muco_1,
                     muco_g_1,
                     derma_1,
                     #nausea_1,
                     mouth_dry_1,
                     #swallow_1,
                     #taste_app_1,
                     name = c(#"RT suspension",
                              "CT suspension",
                              #"RT interruption >= 5 days",
                              #"Incomplete CCRT",
                              #"RT dose reduction",
                              #"CT dose reduction",
                              "Mucositis (grades 3-4)",
                              "Mucositis",
                              "Radiation dermatitis",
                              #"Nausea",
                              "Dry mouth"
                              #"Swallowing difficulties",
                              #"Taste and appetite changes"
                              ),
                     pooled = "random")
forest(tol_1_b,
       #layout = "meta",
       #leftcols = c("Subgroup"),
       digits = 2,
       digits.se = 1,
       subgroup = FALSE,
```

```
xlim = c(0.01, 100),
colgap.forest = "0.5 cm",
just = "right",
label.right = C1,
label.left = I1,
fs.axis = 10,
fs.lr = 10,
hetstat = TRUE,
overall.hetstat = FALSE,
digits.addcols.left = 0,
test.effect.subgroup.random = FALSE,
test.subgroup = FALSE,
test.overall = FALSE
```

)

Subgroup	Number of Studies	Interaction P-value	Random Effects Model (Risk Ratio)	RR	95	5%–CI
<b>CT suspension</b> <b>Some concerns</b> Heterogeneity: $I^2 = 32\%$ ,	<b>2</b> τ <sup>2</sup> = 0.3170, <i>p</i> =	- 0.22	$\longleftrightarrow \qquad \qquad$	0.79	[0.00; 14	03.55]
Mucositis (grades 3–4 Some concerns High risk of bias Heterogeneity: $I^2 = 0\%$ , $\tau^2$	1 3	0.79		0.77 0.68	[0.37; [0.25;	1.59] 1.86]
<b>Mucositis</b> High risk of bias Heterogeneity: $I^2 = 37\%$ ,	<b>3</b> τ <sup>2</sup> = 0.0152, <i>p</i> =	= 0.21	+	0.90	[0.58;	1.39]
<b>Radiation dermatitis</b> High risk of bias Heterogeneity: $I^2 = 0\%$ , $\tau^2$	<b>2</b> <sup>2</sup> = 0, p = 0.45		-	1.04	[0.50;	2.17]
<b>Dry mouth</b> <b>High risk of bias</b> Heterogeneity: $I^2 = 0\%$ , $\tau^2$	<b>2</b> <sup>2</sup> = 0, p = 0.52		0.01 0.1 0.5 1 2 10 100 Favours NC + ONS Favours NC alone	1.00	[0.48;	2.10]

4.2.15.2 Results of structured reporting (no meta-analysis)

```
"Incomplete CCRT",
                             "RT dose reduction",
                             "CT dose reduction",
                             "Nausea",
                             "Swallowing difficulties",
                             "Taste and appetite changes"
                             ),
                    pooled = "random")
forest(tol_1_c,
       #layout = "meta",
       #leftcols = c("Subgroup"),
       digits = 2,
       digits.se = 1,
       subgroup = FALSE,
       xlim = c(0.01, 100),
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = C1,
       label.left = I1,
       fs.axis = 10,
      fs.lr = 10,
      hetstat = TRUE,
      overall.hetstat = FALSE,
       digits.addcols.left = 0,
       test.effect.subgroup.random = FALSE,
       test.subgroup = FALSE,
       test.overall = FALSE
```

```
)
```

Subgroup	Number of Studies	Interaction P-value	Random Effects Model (Risk Ratio)	RR	95%–CI
<b>RT suspension</b> Some concerns Unknown Heterogeneity: not applical	1 0 ble			0.35	[0.04; 3.26]
<b>RT interruption &gt;= 5 da</b> Low risk of bias Heterogeneity: not applicat	1		+	1.14	[0.69; 1.88]
Incomplete CCRT High risk of bias Heterogeneity: not applical	1 ble			0.37	[0.12; 1.21]
RT dose reduction Low risk of bias Heterogeneity: not applical	1 ble			0.17	[0.02; 1.40]
<b>CT dose reduction</b> Low risk of bias Heterogeneity: not applical	1 ble			0.47	[0.21; 1.07]
Nausea High risk of bias Heterogeneity: not applical	1 ble		-	0.76	[0.42; 1.40]
Swallowing difficulties High risk of bias Heterogeneity: not applica	1		+	0.79	[0.53; 1.18]
Taste and appetite cha High risk of bias Heterogeneity: not applicat	1		01 0.1 0.5 1 2 10 10 avours NC + ONS Favours NC alone	00	[0.77; 1.28]
<pre>forest(rt_int, xlab="RT inter #ref = 10, #layout = "Rev layout = "meta digits = 2, digits.se = 1, comb.fixed = F pooled.events #overall = FAL subgroup = FAL hetstat = FALS outpell betato</pre>	man5", ", ALSE, = TRUE, <i>SE</i> , SE,				

overall.hetstat = FALSE,

overall = FALSE, xlim = c(0.01, 100),

```
#xlim = "s",
#plotwidth = "2cm",
colgap.forest = "0.5 cm",
just = "right",
label.right = C1,
label.left = I1,
fs.axis = 10,
fs.lr = 10
```

Study	Experim Events			ontrol Total		Ratio	RR		95%–CI
bias = Some concerns Nayel 1992 Cereda 2018	0 32	11 78	5 32			+	0.10 1.04	[0.01; [0.71;	-
bias = High risk of bias Jiang 2019	4	50	0		0.01 0.1 0.5 Favours NC + ONS		→ 9.00 100 ne	[0.50;	162.89]

# 4.3 Quality of life (end of treatment)

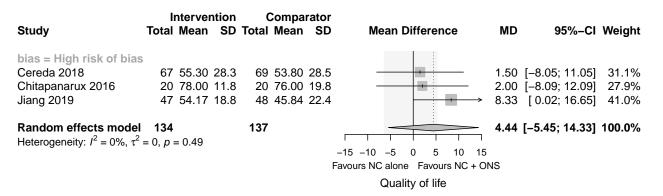
# 4.3.1 Global quality of life

```
4.3.1.1 Forest plot
```

```
QoL <- metacont(
 HNC$n.e,
  HNC$mean.e,
 HNC$sd.e,
 HNC$n.c,
 HNC$mean.c,
 HNC$sd.c,
 HNC$studlab,
 data = HNC,
 subset = HNC$outclab == "QoL" & HNC$C == 1,
 byvar = HNC$bias,
)
QoL_d <- data.frame(QoL)</pre>
rob_QoL_1_1 <- merge(rob_QoL_1_1, QoL_d[,c("w.random", "studlab")], by = "studlab", all = TRUE)</pre>
rob_QoL_1_1_S <- subset(rob_QoL_1_1,studlab != "Jiang 2019")</pre>
forest(QoL,
       xlab="Quality of life",
       layout = "meta",
       digits = 2,
       digits.se = 1,
       comb.fixed = FALSE,
       xlim = c(-15, 15),
       plotwidth = "5cm",
```

```
subgroup = FALSE,
hetstat = FALSE,
overall.hetstat = TRUE,
colgap.forest = "0.5 cm",
just = "right",
label.right = I1,
label.left = C1,
fs.axis = 10,
fs.lr = 10,
lower.equi = -6.5, # Equivalence limits
upper.equi = 5.4,
lty.equi = 1,
fill.equi = "#f5f5f5",
col.equi = "white",
lab.e = "Intervention",
lab.c = "Comparator"
```

)



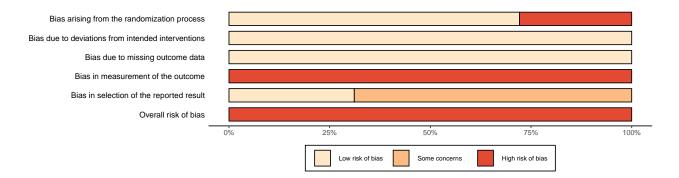
MIDs for the global health status (QL) scale for improvement (deterioration) were QL: 5.4 (- 6.5) and SF: 4.9 (- 7.7) in head and neck cancer patients (shaded area)

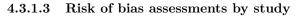
Musoro J, Coens C, Fiteni F, et al. Evidence-based approach to determine meaningful change in scores of the EORTC QLQ-C30 in breast and head and neck cancer: on behalf of the EORTC Breast, Head and Neck and Quality of Life Groups. 25th annual conference of the international society for quality of life research, Dublin, Ireland. Qual Life Res 2018;27 (Suppl 1): ab101.4, 18. https://doi.org/10.1007/s11136-018-1946-9

#### 4.3.1.2 Proportion of information at each level of risk of bias

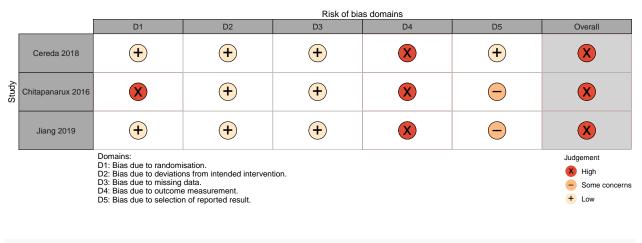
Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result (when applicable)

rob\_summary(rob\_QoL\_1\_1, tool = "ROB2", weighted = TRUE, overall = TRUE, colour = "colourblind")





rob\_traffic\_light(rob\_QoL\_1\_1, tool = "ROB2", colour = "colourblind", psize = 10)



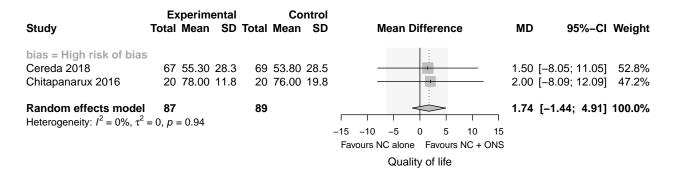
```
#forest(metainf(QoL,
# pooled = "random"))
```

## 4.3.2 Sensitivity analysis

Excluding Jiang 2019, because mean and standard deviation for this study were inputted (as described in the methods section of the primary report).

#### 4.3.2.1 Forest plot

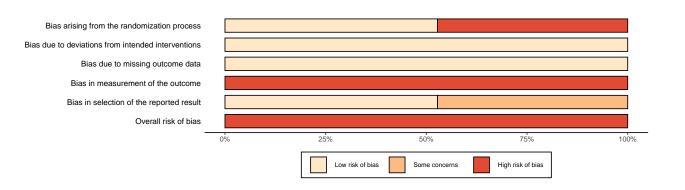
```
overall.hetstat = TRUE,
#pooled.events = TRUE,
#resid.hetstat = FALSE,
colgap.forest = "0.5 cm",
just = "right",
label.right = I1,
label.left = C1,
fs.axis = 10,
fs.lr = 10,
lower.equi = -6.5, # Equivalence limits
upper.equi = 5.4,
lty.equi = 1,
fill.equi = "#f5f5f5",
col.equi = "white",
```

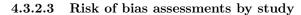


## 4.3.2.2 Proportion of information at each level of risk of bias

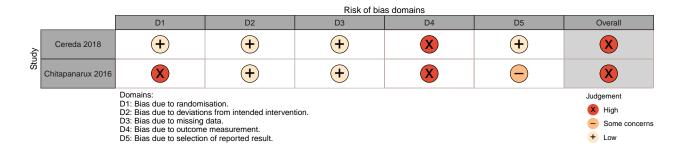
Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result (when applicable)

rob\_summary(rob\_QoL\_1\_1\_S, tool = "ROB2", weighted = TRUE, overall = TRUE, colour = "colourblind")





rob\_traffic\_light(rob\_QoL\_1\_1\_S, tool = "ROB2", colour = "colourblind", psize = 10)



#forest(metainf(bw\_1\_1,
# pooled = "random"))

4.3.3 Quality of life subscales

```
4.3.3.1 Appetite loss
```

```
QoL_Appetite <- metacont(</pre>
  HNC$n.e,
  HNC$mean.e,
  HNC$sd.e,
  HNC$n.c,
  HNC$mean.c,
  HNC$sd.c,
  HNC$studlab,
  data = HNC,
  subset = HNC$outclab == "QoL_Appetite" & HNC$C == 1,
  byvar = HNC$bias,
  sm = "SMD",
)
forest(QoL_Appetite,
       xlab="QoL_Appetite",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 1,
       digits.se = 1,
       comb.fixed = FALSE,
       xlim = c(-2, 2),
       #plotwidth = "2cm",
       subgroup = FALSE,
       hetstat = FALSE,
       overall.hetstat = FALSE,
```

```
#pooled.events = TRUE,
#resid.hetstat = FALSE,
colgap.forest = "0.5 cm",
just = "right",
label.right = C1,
label.left = I1,
fs.axis = 10,
fs.lr = 10,
overall = FALSE,
```

```
)
```

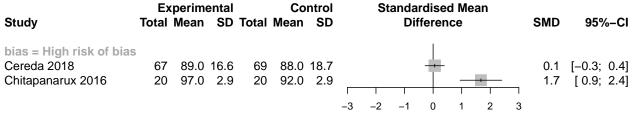
Study	 berimer Mean		ntrol SD	Standardised Mean Difference	SMD	95%–CI
bias = High risk of bias Cereda 2018 Chitapanarux 2016	27.4 3 16.0	 	30.8 5.4			[–0.4; 0.2] [–1.9; –0.6]

Favours NC + ONS Favours NC alone

```
4.3.3.2 Cognitive
```

```
QoL_Cognitive <- metacont(</pre>
 HNC<mark>$</mark>n.e,
  HNC$mean.e,
  HNC$sd.e,
  HNC$n.c,
  HNC$mean.c,
  HNC$sd.c,
  HNC$studlab,
  data = HNC,
  subset = HNC$outclab == "QoL_Cognitive" & HNC$C == 1,
  byvar = HNC$bias,
  sm = "SMD",
)
forest(QoL_Cognitive,
       xlab="QoL_Cognitive",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 1,
       digits.se = 1,
       comb.fixed = FALSE,
```

```
#plotwidth = "2cm"
xlim = c(-3, 3),
subgroup = FALSE,
hetstat = FALSE,
overall.hetstat = FALSE,
#pooled.events = TRUE,
#resid.hetstat = FALSE,
colgap.forest = "0.5 cm",
just = "right",
label.right = I1,
label.left = C1,
fs.axis = 10,
fs.lr = 10,
overall = FALSE
)
```



Favours NC alone Favours NC + ONS

#### 4.3.3.3 Constipation

```
QoL_Constipation <- metacont(</pre>
 HNC$n.e,
 HNC$mean.e,
 HNC$sd.e,
 HNC$n.c,
 HNC$mean.c,
 HNC$sd.c,
 HNC$studlab,
 data = HNC,
  subset = HNC$outclab == "QoL_Constipation" & HNC$C == 1,
 byvar = HNC$bias,
  sm = "SMD",
)
forest(QoL_Constipation,
       xlab="QoL_Constipation",
       #ref = 10,
       #layout = "Revman5",
```

```
layout = "meta",
digits = 1,
digits.se = 1,
comb.fixed = FALSE,
#plotwidth = "2cm",
xlim = c(-1, 1),
subgroup = FALSE,
hetstat = FALSE,
overall.hetstat = TRUE,
#pooled.events = TRUE,
#resid.hetstat = FALSE,
colgap.forest = "0.5 cm",
just = "right",
label.right = C1,
label.left = I1,
fs.axis = 10,
fs.lr = 10
```

Standardised Mean Experimental Control Total Mean SD Total Mean SD Study Difference SMD 95%-Cl Weight bias = High risk of bias 0.1 [-0.2; 0.5] 100.0% Cereda 2018 67 24.3 28.8 69 20.0 31.2 Chitapanarux 2016 20 5.0 20 5.0 0.0% . Random effects model 87 89 0.1 [-0.2; 0.5] 100.0% Heterogeneity:  $I^2 = NA\%$ ,  $\tau^2 = NA$ , p = NA-1 -0.5 0 0.5 1

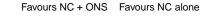
## 4.3.3.4 Diarrhoea

)

```
QoL_Diarrhoea <- metacont(
HNC$n.e,
HNC$mean.e,
HNC$sd.e,
HNC$n.c,
HNC$mean.c,
HNC$sd.c,
HNC$studlab,
data = HNC,
subset = HNC$outclab == "QoL_Diarrhoea" & HNC$C == 1,
byvar = HNC$bias,
sm = "SMD",
)
forest(QoL_Diarrhoea,
```

```
xlab="QoL_Diarrhoea",
#ref = 10,
#layout = "Revman5",
layout = "meta",
digits = 1,
digits.se = 1,
comb.fixed = FALSE,
#plotwidth = "2cm",
xlim = c(-2, 2),
subgroup = FALSE,
hetstat = FALSE,
overall.hetstat = FALSE,
#pooled.events = TRUE,
#resid.hetstat = FALSE,
colgap.forest = "0.5 cm",
just = "right",
label.right = C1,
label.left = I1,
fs.axis = 10,
fs.lr = 10,
overall = FALSE
```

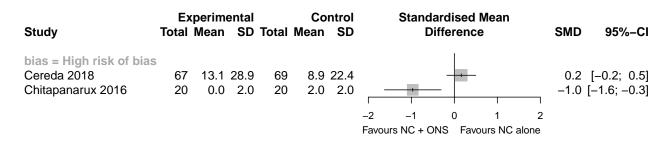
Study		kperim Mean		Total		ntrol SD	
bias = High risk of bias Cereda 2018 Chitapanarux 2016	67 20		12.8 17.2	69 20	3.0 17.0	11.5 17.2	



# 4.3.3.5 Dyspnoea

QoL\_Dyspnoea <- metacont(
HNC\$n.e,
HNC\$mean.e,
HNC\$sd.e,
HNC\$sd.e,
HNC\$n.c,
HNC\$mean.c,
HNC\$sd.c,
HNC\$studlab,
data = HNC,
subset = HNC\$outclab == "QoL\_Dyspnoea" & HNC\$C == 1,</pre>

```
byvar = HNC$bias,
  sm = "SMD",
)
forest(QoL_Dyspnoea,
       xlab="QoL_Dyspnoea",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 1,
       digits.se = 1,
       comb.fixed = FALSE,
       #plotwidth = "2cm"
       xlim = c(-2, 2),
       subgroup = FALSE,
       hetstat = FALSE,
       overall.hetstat = FALSE,
       #pooled.events = TRUE,
       #resid.hetstat = FALSE,
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = C1,
       label.left = I1,
       fs.axis = 10,
       fs.lr = 10,
       overall = FALSE
)
```



## 4.3.3.6 Emotional

oL_Emotional <- metacont( HNC <mark>\$</mark> n.e,	
HNC <mark>\$</mark> mean.e,	
HNC <mark>\$</mark> sd.e,	
HNC <mark>\$</mark> n.c,	
HNC <mark>\$</mark> mean.c,	
HNC\$sd.c,	
HNC\$studlab,	

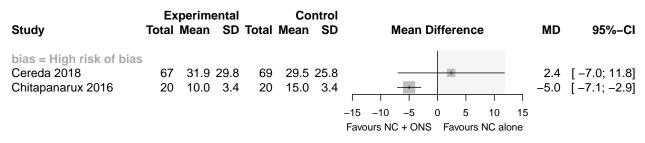
```
data = HNC,
  subset = HNC$outclab == "QoL_Emotional" & HNC$C == 1,
 byvar = HNC$bias,
  sm = "SMD",
)
forest(QoL_Emotional,
       xlab="QoL_Emotional",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 1,
       digits.se = 1,
       comb.fixed = FALSE,
       #plotwidth = "2cm"
      xlim = c(-5, 5),
       subgroup = FALSE,
      hetstat = FALSE,
       overall.hetstat = TRUE,
       #pooled.events = TRUE,
       #resid.hetstat = FALSE,
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = I1,
       label.left = C1,
       fs.axis = 10,
       fs.lr = 10
)
```

Study	Experimental Total Mean SD 1	Control Fotal Mean SD	Standardised Mean Difference	SMD 95%-CI Weight
bias = High risk of bias Cereda 2018 Chitapanarux 2016	67 72.0 23.0 20 91.0 4.6	69 75.3 28.2 20 90.0 4.6	<b>■</b> + <b>■</b> -	-0.1 [-0.5; 0.2] 77.3% 0.2 [-0.4; 0.8] 22.7%
<b>Random effects model</b> Heterogeneity: $I^2 = 0\%$ , $\tau^2$		89	-4 -2 0 2 4	-0.1 [-1.9; 1.8] 100.0%

# 4.3.3.7 Fatigue

QoL_Fatigue <- metacont( HNC\$n.e,	
HNC <mark>\$</mark> mean.e,	
HNC\$sd.e,	
HNC\$n.c,	
HNC <sup>\$</sup> mean.c,	
HNC <sup>\$</sup> sd.c,	

```
HNC$studlab,
  data = HNC,
  subset = HNC$outclab == "QoL_Fatigue" & HNC$C == 1,
  byvar = HNC$bias
)
forest(QoL_Fatigue,
       xlab="QoL_Fatigue",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 1,
       digits.se = 1,
       comb.fixed = FALSE,
       #plotwidth = "2cm"
       xlim = c(-15, 15),
       subgroup = FALSE,
       hetstat = FALSE,
       overall.hetstat = FALSE,
       #pooled.events = TRUE,
       #resid.hetstat = FALSE,
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = C1,
       label.left = I1,
       fs.axis = 10,
       fs.lr = 10,
       lower.equi = 0, # Equivalence limits
       upper.equi = 12,
       lty.equi = 1,
       fill.equi = "#f5f5f5",
       col.equi = "white",
       overall = FALSE
)
```



MID: 12.0 (deteriorate)

Musoro J, Coens C, Fiteni F, et al. Minimally important differences for interpreting EORTC QLQ-C30 scores in melanoma, breast cancer and head and neck cancer patients on behalf of the EORTC breast, Head and Neck, Melanoma and Quality of life groups. ISPOR Europe 2018 Barcelona, November, 2018.

```
4.3.3.8 Financial
```

```
QoL_Financial <- metacont(</pre>
  HNC$n.e,
  HNC$mean.e,
  HNC$sd.e,
  HNC$n.c,
  HNC$mean.c,
  HNC$sd.c,
  HNC$studlab,
  data = HNC,
  subset = HNC$outclab == "QoL_Financial" & HNC$C == 1,
 byvar = HNC$bias,
  sm = "SMD",
)
forest(QoL_Financial,
       xlab="QoL_Financial",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 1,
       digits.se = 1,
       comb.fixed = FALSE,
       #plotwidth = "2cm"
       xlim = c(-2, 2),
       subgroup = FALSE,
       hetstat = FALSE,
       overall.hetstat = TRUE,
       #pooled.events = TRUE,
       #resid.hetstat = FALSE,
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = C1,
       label.left = I1,
       fs.axis = 10,
       fs.lr = 10
```

)

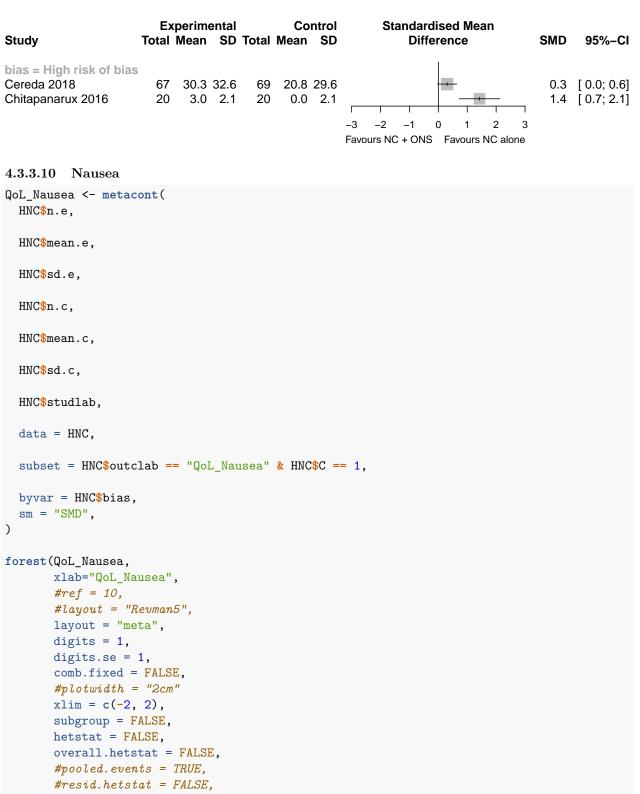
	Ex	perime	ental		Co	ntrol	Standardised Mean		
Study	Total	Mean	SD	Total	Mean	SD	Difference	SMD	95%–CI Weight
bias = High risk of bias	6								
Cereda 2018	67	7.7	16.8	69	6.5	17.3		0.1	[-0.3; 0.4] 77.6%
Chitapanarux 2016	20	18.0	7.3	20	15.0	7.3		0.4	[-0.2; 1.0] 22.4%
Random effects model				89				0.1	[–1.6; 1.9] 100.0%
Heterogeneity: $I^2 = 0\%$ , $\tau^2$	= 0, <i>p</i> =	= 0.36							
							-2 -1 0 1 2		

#### 4.3.3.9 Insomnia

```
QoL_Insomnia <- metacont(</pre>
  HNC$n.e,
  HNC$mean.e,
  HNC$sd.e,
  HNC$n.c,
  HNC$mean.c,
  HNC$sd.c,
  HNC$studlab,
  data = HNC,
  subset = HNC$outclab == "QoL_Insomnia" & HNC$C == 1,
 byvar = HNC$bias,
  sm = "SMD",
)
forest(QoL_Insomnia,
       xlab="QoL_Insomnia",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 1,
       digits.se = 1,
       comb.fixed = FALSE,
       #plotwidth = "2cm"
       xlim = c(-3, 3),
       subgroup = FALSE,
       hetstat = FALSE,
       overall.hetstat = FALSE,
       #pooled.events = TRUE,
       #resid.hetstat = FALSE,
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = C1,
       label.left = I1,
       fs.axis = 10,
```

```
fs.lr = 10,
overall = FALSE
```

)



```
colgap.forest = "0.5 cm",
just = "right",
label.right = C1,
label.left = I1,
fs.axis = 10,
fs.lr = 10,
overall = FALSE
```

Study		cperimo Mean			 ntrol SD			ardised N ifference		:	SMD	95%–Cl
bias = High risk of bias Cereda 2018 Chitapanarux 2016	67 20	10.5 12.0	22.4 4.4	69 20	 20.3 4.4	–2 Favo	-1 ours NC + O	0 NS Favou	1 I Ins NC alc	2 Dne		[–0.3; 0.4] [ 0.2; 1.5]

# 4.3.3.11 Pain

1,

```
subgroup = FALSE,
hetstat = FALSE,
overall.hetstat = FALSE,
#pooled.events = TRUE,
#resid.hetstat = FALSE,
colgap.forest = "0.5 cm",
just = "right",
label.right = C1,
label.left = I1,
fs.axis = 10,
fs.lr = 10,
overall = FALSE
```

)

Study		perime Mean		Co Mean	ntrol SD	Standardised Mean Difference	SMD	95%–CI
bias = High risk of bias Cereda 2018 Chitapanarux 2016	67 20	26.3 9.0	34.2 3.8	 27.6 13.0				[-0.4; 0.3] -1.7; -0.4]

# 4.3.3.12 Physical

```
QoL_Physical <- metacont(</pre>
 HNC$n.e,
  HNC$mean.e,
 HNC$sd.e,
  HNC$n.c,
  HNC$mean.c,
 HNC$sd.c,
 HNC$studlab,
 data = HNC,
  subset = HNC$outclab == "QoL_Physical" & HNC$C == 1,
 byvar = HNC$bias,
)
forest(QoL_Physical,
       xlab="QoL_Physical",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 1,
```

```
digits.se = 1,
comb.fixed = FALSE,
#plotwidth = "2cm"
xlim = c(-15, 15),
subgroup = FALSE,
hetstat = FALSE,
overall.hetstat = FALSE,
#pooled.events = TRUE,
#resid.hetstat = FALSE,
colgap.forest = "0.5 cm",
just = "right",
label.right = I1,
label.left = C1,
fs.axis = 10,
fs.lr = 10,
lower.equi = -7.3, # Equivalence limits
upper.equi = 0,
lty.equi = 1,
fill.equi = "#f5f5f5",
col.equi = "white",
overall = FALSE
```

```
)
```

Study		perime Mean	Total	Co Mean	ntrol SD	
bias = High risk of bias Cereda 2018 Chitapanarux 2016	67 20	74.1 95.0	 	78.1 91.0	-	

MID: -7.3 (deteriorate)

# 4.3.3.13 Role

```
QoL_Role <- metacont(
   HNC$n.e,</pre>
```

HNC\$mean.e,

HNC\$sd.e,

HNC<mark>\$</mark>n.c,

HNC\$mean.c,

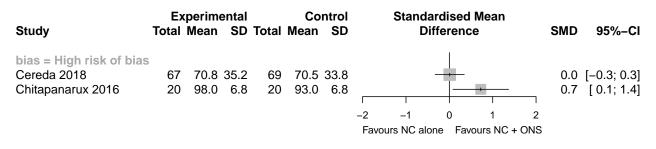
HNC**\$**sd.c,

HNC\$studlab,

data = HNC,

subset = HNC\$outclab == "QoL\_Role" & HNC\$C == 1,

```
byvar = HNC$bias,
  sm = "SMD",
)
forest(QoL_Role,
       xlab="QoL_Role",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 1,
       digits.se = 1,
       comb.fixed = FALSE,
       #plotwidth = "2cm"
       xlim = c(-2, 2),
       subgroup = FALSE,
       hetstat = FALSE,
       overall.hetstat = FALSE,
       #pooled.events = TRUE,
       #resid.hetstat = FALSE,
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = I1,
       label.left = C1,
       fs.axis = 10,
       fs.lr = 10,
       overall = FALSE
)
```



4.3.3.14 Social

DL_Social <- metacont( HNC\$n.e,
HNC\$mean.e,
HNC <sup>\$</sup> sd.e,
HNC\$n.c,
HNC <sup>\$</sup> mean.c,
HNC\$sd.c,
HNC <sup>\$</sup> studlab,

```
data = HNC,
  subset = HNC$outclab == "QoL Social" & HNC$C == 1,
  byvar = HNC$bias
)
forest(QoL Social,
       xlab="QoL Social",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 1,
       digits.se = 1,
       comb.fixed = FALSE,
       #plotwidth = "2cm"
       xlim = c(-30, 30),
       subgroup = FALSE,
       hetstat = FALSE,
       overall.hetstat = TRUE,
       #pooled.events = TRUE,
       #resid.hetstat = FALSE,
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = I1,
       label.left = C1,
       fs.axis = 10,
       fs.lr = 10,
       lower.equi = -7.3, # Equivalence limits
       upper.equi = 6.1,
       lty.equi = 1,
       fill.equi = "#f5f5f5",
       col.equi = "white",
)
```

Study	Experime Total Mean		Control an SD	Mean Difference	MD 95%-CI Weight
bias = High risk of bias Cereda 2018 Chitapanarux 2016	67 87.8 20 89.0		3.1 17.4 8.0 3.6		-5.3 [-12.2; 1.6] 9.6% -9.0 [-11.3; -6.7] 90.4%
<b>Random effects model</b> Heterogeneity: $I^2 = 0\%$ , $\tau^2$		89	-30		<b>-8.6 [-22.5; 5.2] 100.0%</b>

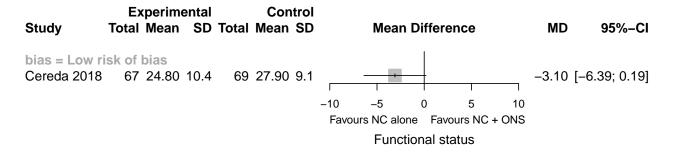
MIDs for the social functioning (SF) scale for improvement (deterioration) were SF: 6.1 (- 7.3) in HNC

Musoro J, Coens C, Fiteni F, et al. Evidence-based approach to determine meaningful change in scores of the EORTC QLQ-C30 in breast and head and neck cancer: on behalf of the EORTC Breast, Head and Neck and Quality of Life Groups. 25th annual conference of the international society for quality of life research, Dublin, Ireland. Qual Life Res 2018;27 (Suppl 1): ab101.4, 18. https://doi.org/10.1007/s11136-018-1946-9

# 4.4 Functional status (end of treatment)

```
4.4.1 Forest plot
```

```
functional <- metacont(</pre>
  HNC$n.e,
  HNC$mean.e,
  HNC$sd.e,
  HNC$n.c,
  HNC$mean.c,
  HNC$sd.c,
 HNC$studlab,
  data = HNC,
  subset = HNC$outclab == "Functional status" & HNC$C == 1,
  byvar = HNC$bias
)
functional_d <- data.frame(functional)</pre>
rob_functional_1_1 <- merge(rob_functional_1_1, functional_d[,c("w.random", "studlab")], by = "studlab"</pre>
forest(functional,
       xlab="Functional status",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 2,
       digits.se = 1,
       comb.fixed = FALSE,
       xlim = c(-10, 10),
       #plotwidth = "2cm",
       subgroup = FALSE,
       hetstat = FALSE,
       overall.hetstat = TRUE,
       #pooled.events = TRUE,
       #resid.hetstat = FALSE,
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = I1,
       label.left = C1,
       fs.axis = 10,
       fs.lr = 10
)
```



# 4.4.2 Proportion of information at each level of risk of bias

Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result (when applicable)

```
rob_summary(rob_functional_1_1, tool = "ROB2", weighted = TRUE, overall = TRUE, colour = "colourblind")
```



#### 4.4.3 Risk of bias assessments by study

```
rob_traffic_light(rob_functional_1_1, tool = "ROB2", colour = "colourblind", psize = 10)
```

		Risk of bias domains										
	D1	D2	D3	D4	D5	Overall						
Apn Cereda 2018	(+)	(+)	(+)	+	(+)	+						
	Domains: D1: Bias due to randomisation. D2: Bias due to deviations from intended intervention. D3: Bias due to missing data. D4: Bias due to outcome measurement. D5: Bias due to selection of reported result.											

# 4.5 Body weight (end of treatment)

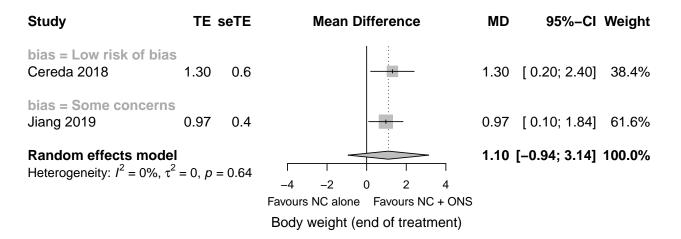
# 4.5.1 Main analysis

Including only results at most at some concerns of bias.

## 4.5.1.1 Forest plot

```
bw_1_1 <- metagen(
    HNC$TE,</pre>
```

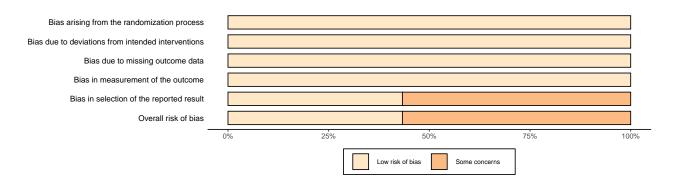
```
HNC$seTE,
  sm = "MD",
  HNC$studlab,
  data = HNC,
  subset = HNC$outclab == "Body weight" & HNC$C == 1,
 byvar = HNC$bias,
)
bw_1_1_d <- data.frame(bw_1_1)</pre>
rob_bw_1_1 <- merge(rob_bw_1_1, bw_1_1_d[,c("w.random", "studlab")], by = "studlab", all = TRUE)</pre>
rob_bw_1_1_S <- subset(rob_bw_1_1, Overall != "High")</pre>
rob_bw_1_1_S_2 <- subset(rob_bw_1_1,studlab != "Chitapanarux 2016")</pre>
bw_1_1_LB <- update.meta(bw_1_1, subset = HNC$outclab == "Body weight" & HNC$C == 1 & HNC$bias != "High
forest(bw_1_1_LB,
       xlab="Body weight (end of treatment)",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 2,
       digits.se = 1,
       comb.fixed = FALSE,
       xlim = c(-5, 5),
       #leftcols = c("studlab", "n.e", "n.c", "TE", "seTE", "random.w"),
       \#xlim = "s",
       #plotwidth = "2cm",
       subgroup = FALSE,
       hetstat = FALSE,
       overall.hetstat = TRUE,
       #pooled.events = TRUE,
       #resid.hetstat = FALSE,
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = I1,
       label.left = C1,
       fs.axis = 10,
       fs.lr = 10
)
```



#### 4.5.1.2 Proportion of information at each level of risk of bias

Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result (when applicable)

rob\_summary(rob\_bw\_1\_1\_S, tool = "ROB2", weighted = TRUE, overall = TRUE, colour = "colourblind")

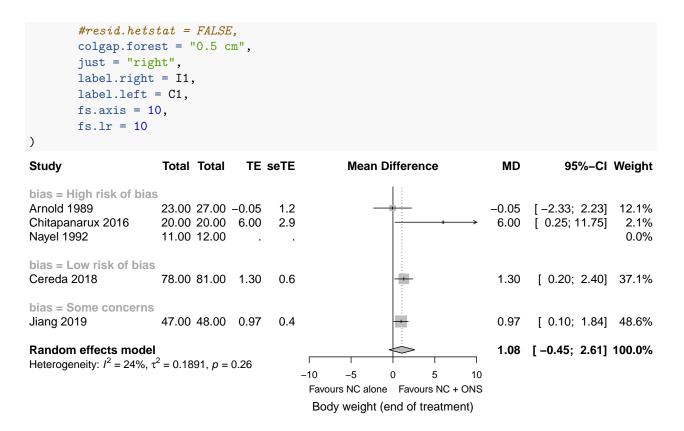


# 4.5.2 Sensitivity analysis 1

Including all available results.

## 4.5.2.1 Forest plot

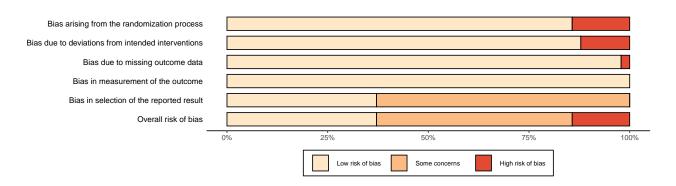
```
forest(bw_1_1,
       xlab="Body weight (end of treatment)",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 2,
       digits.se = 1,
       comb.fixed = FALSE,
       xlim = c(-10, 10),
       leftcols = c("studlab", "n.e", "n.c", "TE", "seTE"),
       #xlim
               = "s",
       #plotwidth = "2cm",
       subgroup = FALSE,
       hetstat = FALSE,
       overall.hetstat = TRUE,
       #pooled.events = TRUE,
```



#### 4.5.2.2 Proportion of information at each level of risk of bias

Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result (when applicable)

rob\_summary(rob\_bw\_1\_1, tool = "ROB2", weighted = TRUE, overall = TRUE, colour = "colourblind")



4.5.2.3 Risk of bias assessments by study

rob\_traffic\_light(rob\_bw\_1\_1, tool = "ROB2", colour = "colourblind", psize = 10)

	Risk of bias domains									
		D1	D2	D3	D4	D5	Overall			
	Arnold 1989	X	X	+	+	-	×			
	Cereda 2018	+	+	+	+	+	+			
Study	Chitapanarux 2016	X	+	X	+	-	×			
	Jiang 2019	+	+	+	+	-	$\overline{}$			
	Nayel 1992	$\overline{}$	+	+	+	X	×			
	Domains: D1: Bias due to randomisation. D2: Bias due to deviations from intended intervention. D3: Bias due to missing data. D4: Bias due to outcome measurement. D5: Bias due to selection of reported result.									
# #	<pre>#forest(metainf(bw_1_1, # pooled = "random"))</pre>									

# 4.5.3 Sensitivity analysis 2

Excluding Chitapanarux 2016, because mean and standard deviation for this study were inputted (as described in the methods section of the primary report).

#### 4.5.3.1 Forest plot

bw\_1\_1\_S\_2 <- update.meta(bw\_1\_1, subset = HNC\$outclab == "Body weight" & HNC\$C == 1 & HNC\$studlab != "

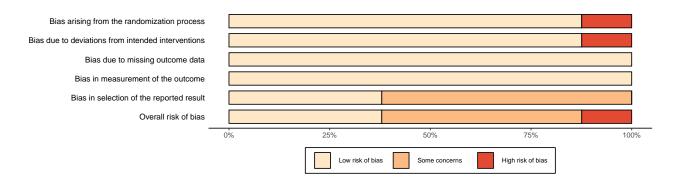
```
forest(bw_1_1_S_2,
       xlab="Body weight (end of treatment)",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 2,
       digits.se = 1,
       comb.fixed = FALSE,
       xlim = c(-10, 10),
       leftcols = c("studlab", "n.e", "n.c", "TE", "seTE"),
       #xlim
              = "s",
       #plotwidth = "2cm",
       subgroup = FALSE,
       hetstat = FALSE,
       overall.hetstat = TRUE,
       #pooled.events = TRUE,
       #resid.hetstat = FALSE,
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = I1,
       label.left = C1,
       fs.axis = 10,
       fs.lr = 10
)
```

Study	Total Tota	TE seTE	Mean Difference	MD	95%-CI Weight
bias = High risk of bias Arnold 1989 Nayel 1992	s 23.00 27.00 11.00 12.00			-0.05	[-2.33; 2.23] 8.2% 0.0%
bias = Low risk of bias Cereda 2018	78.00 81.00	) 1.30 0.6		1.30	[ 0.20; 2.40] 35.2%
bias = Some concerns Jiang 2019	47.00 48.00	0.97 0.4		0.97	[ 0.10; 1.84] 56.6%
<b>Random effects mode</b> Heterogeneity: $l^2 = 0\%$ , $\tau^2$	-		-10 -5 0 5 10 Favours NC alone Favours NC + ONS Body weight (end of treatment)	1.00	[–0.06; 2.07] 100.0%

# 4.5.3.2 Proportion of information at each level of risk of bias

Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result (when applicable)

rob\_summary(rob\_bw\_1\_1\_S\_2, tool = "ROB2", weighted = TRUE, overall = TRUE, colour = "colourblind")



4.5.3.3	Risk of bias	assessments	by study
---------	--------------	-------------	----------

rob\_traffic\_light(rob\_bw\_1\_1\_S\_2, tool = "ROB2", colour = "colourblind", psize = 10)

				Risk of bia	s domains		
		D1	D2	D3	D4	D5	Overall
	Arnold 1989	×	X	+	+	-	×
Study	Cereda 2018	+	+	+	+	+	+
Stu	Jiang 2019	+	+	+	+	-	-
	Nayel 1992	-	+	+	+	×	×
		Domains: D1: Bias due to randomis D2: Bias due to deviation D3: Bias due to missing o D4: Bias due to outcome D5: Bias due to selection	s from intended interventio data. measurement.	n.			Judgement High Some concerns + Low

```
#forest(metainf(bw_1_1,
# pooled = "random"))
```

# 4.6 Adverse effects

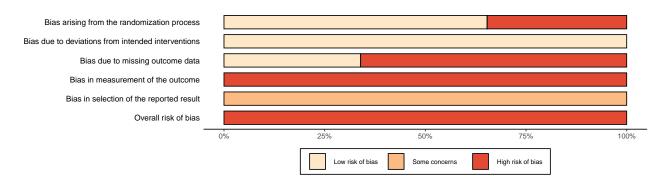
```
4.6.1 Forest plot
ae <- metabin(
 HNC$event.e,
  HNC$n.e,
  HNC$event.c,
  HNC$n.c.
  sm = "RR",
  method = "MH",
  RR.cochrane = TRUE,
  MH.exact = FALSE,
  allstudies = FALSE,
 HNC<sup>$</sup>studlab,
  subset = HNC$outclab == "Adverse events" & HNC$C == 1,
  byvar = HNC$bias,
)
ae d <- data.frame(ae)</pre>
rob_ae_1 <- merge(rob_ae_1, ae_d[,c("w.random", "studlab")], by = "studlab", all = TRUE)</pre>
forest(ae,
       xlab="Adverse effects (nausea, vomiting, feeling of fullness)",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 2,
       digits.se = 1,
       comb.fixed = FALSE,
       xlim = c(0.001, 1000),
              = "s",
       #xlim
       #plotwidth = "2cm",
       subgroup = FALSE,
       hetstat = FALSE,
       overall.hetstat = TRUE,
       pooled.events = TRUE,
       #resid.hetstat = FALSE,
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = C1,
       label.left = I1,
       fs.axis = 10,
       fs.lr = 10
)
```

Study	Experim Events		Co Events	ntrol Total	Risk Ratio	RR	95%-CI Weight
bias = High risk of bias Cereda 2018 Chitapanarux 2016 Jiang 2019 Nayel 1992	9 7 3 0	78 20 50 11	0 0 0 0	81 20 50 12		15.00	[1.17; 333.18] 33.9% [0.91; 246.20] 34.6% [0.37; 132.10] 31.4% 0.0%
<b>Random effects model</b> Heterogeneity: $I^2 = 0\%$ , $\tau^2$		<b>159</b> 87	<b>0</b> Ad	-	0.001 0.01 0.1 1 10 100 1000 Favours NC + ONS Favours NC alone effects (nausea, vomiting, feeling of	)	<b>[3.48; 48.19] 100.0%</b> δ)

# 4.6.2 Proportion of information at each level of risk of bias

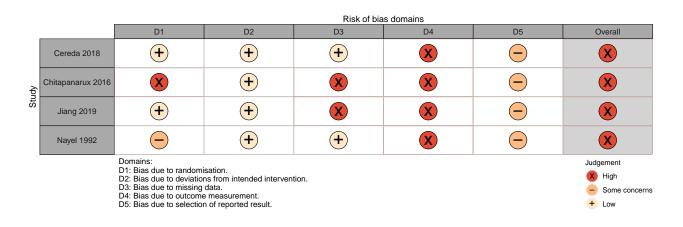
Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result (when applicable)

rob\_summary(rob\_ae\_1, tool = "ROB2", weighted = TRUE, overall = TRUE, colour = "colourblind")



#### 4.6.3 Risk of bias assessments by study

rob\_traffic\_light(rob\_ae\_1, tool = "ROB2", colour = "colourblind", psize = 10)



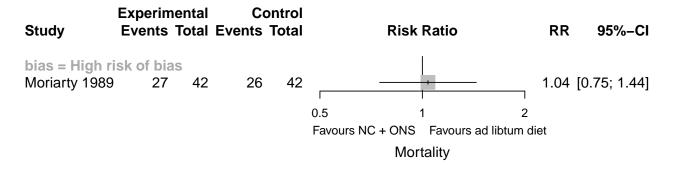
# 5 Comparison 2

# 5.1 Mortality

# 5.1.1 Forest plot

```
mort_2 <- metabin(</pre>
 HNC$event.e,
 HNC$n.e,
 HNC$event.c,
 HNC$n.c,
  sm = "RR",
  method = "MH",
  RR.cochrane = TRUE,
 MH.exact = FALSE,
 allstudies = FALSE,
 HNC$studlab,
  subset = HNC$outclab == "Mortality" & HNC$C == 2,
  byvar = HNC$bias
)
mort_2d <- data.frame(mort_2)</pre>
rob_mort_2 <- merge(rob_mort_2, mort_2d[,c("w.random", "studlab")], by = "studlab", all = TRUE)</pre>
forest(mort_2,
       xlab="Mortality",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 2,
       digits.se = 1,
       comb.fixed = FALSE,
       xlim = c(0.5, 2),
       \#xlim = "s",
       #plotwidth = "2cm",
       subgroup = FALSE,
       hetstat = FALSE,
       overall.hetstat = TRUE,
       #pooled.events = TRUE,
       #resid.hetstat = FALSE,
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = C1,
       label.left = I1,
       fs.axis = 10,
       fs.lr = 10
```

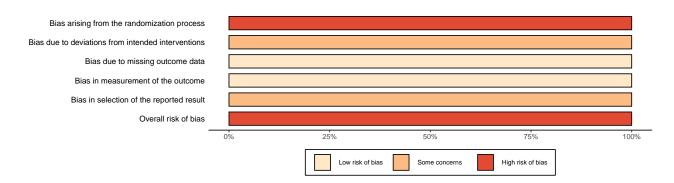
)



# 5.1.2 Proportion of information at each level of risk of bias

Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result (when applicable)





# 5.1.3 Risk of bias assessments by study

```
rob_traffic_light(rob_mort_2, tool = "ROB2", colour = "colourblind", psize = 10)
```

			Risk of bias domains										
		D1	D2	D3	D4	D5	Overall						
Study	Moriarty 1989	×	-	+	+	-	×						
		Domains: D1: Bias due to randomisation. D2: Bias due to deviations from intended intervention. D3: Bias due to missing data. D4: Bias due to outcome measurement. D5: Bias due to selection of reported result.											

# 5.2 Quality of life (end of treatment)

## 5.2.1 Global quality of life

# 5.2.1.1 Forest plot

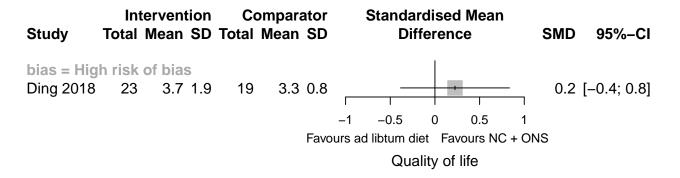
# QoL\_2 <- metacont( HNC\$n.e,</pre>

#### HNCon.e,

HNC<mark>\$</mark>mean.e,

```
HNC$sd.e,
  HNC$n.c,
  HNC$mean.c,
  HNC$sd.c,
  HNC$studlab,
  data = HNC,
  subset = HNC$outclab == "QoL" & HNC$C == 2,
 sm = "SMD",
 byvar = HNC$bias
)
QoL_2_d <- data.frame(QoL_2)</pre>
rob_QoL_2_1 <- merge(rob_QoL_2_1, QoL_2_d[,c("w.random", "studlab")], by = "studlab", all = TRUE)</pre>
forest(QoL_2,
       xlab="Quality of life",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 1,
       digits.se = 1,
       comb.fixed = FALSE,
       plotwidth = "5cm",
       xlim = c(-1, 1),
       subgroup = FALSE,
       hetstat = FALSE,
       overall.hetstat = TRUE,
       #pooled.events = TRUE,
       #resid.hetstat = FALSE,
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = I1,
       label.left = C1,
       fs.axis = 10,
       fs.lr = 10,
       lab.e = "Intervention",
       lab.c = "Comparator",
)
```

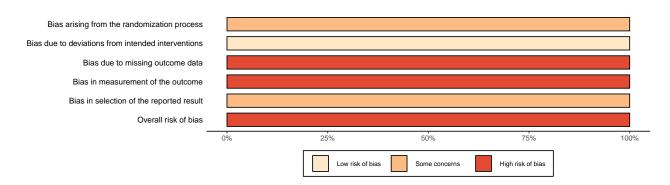
69



# 5.2.1.2 Proportion of information at each level of risk of bias

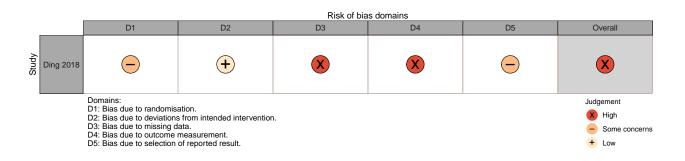
Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result (when applicable)

rob\_summary(rob\_QoL\_2\_1, tool = "ROB2", weighted = TRUE, overall = TRUE, colour = "colourblind")



# 5.2.1.3 Risk of bias assessments by study

rob\_traffic\_light(rob\_QoL\_2\_1, tool = "ROB2", colour = "colourblind", psize = 10)

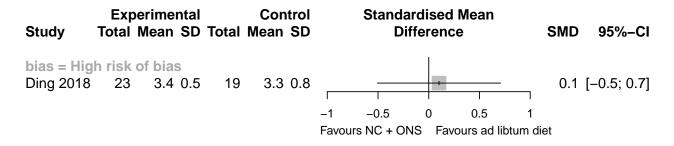


## 5.2.2 Quality of life subscales

#### 5.2.2.1 Appetite loss

```
QoL_Appetite_2 <- metacont(
   HNC$n.e,
   HNC$mean.e,</pre>
```

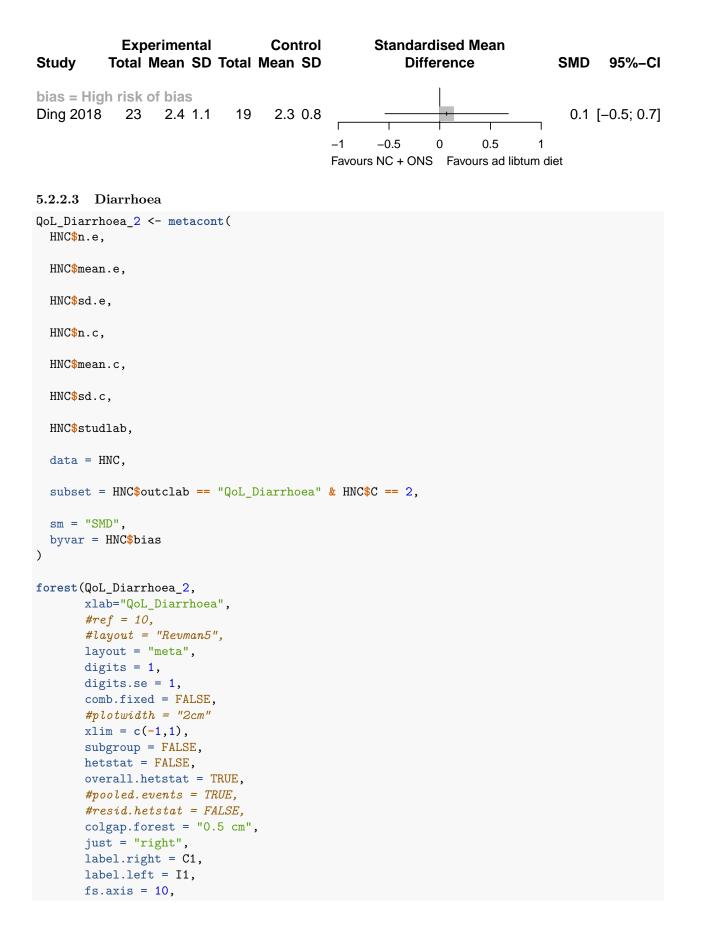
```
HNC$sd.e,
 HNC$n.c,
 HNC$mean.c,
 HNC$sd.c,
 HNC$studlab,
  data = HNC,
  subset = HNC$outclab == "QoL_Appetite" & HNC$C == 2,
  sm = "SMD",
  byvar = HNC$bias
)
forest(QoL_Appetite_2,
       xlab="QoL_Appetite",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 1,
       digits.se = 1,
       comb.fixed = FALSE,
       xlim = c(-1, 1),
       #plotwidth = "2cm",
       subgroup = FALSE,
       hetstat = FALSE,
       overall.hetstat = TRUE,
       #pooled.events = TRUE,
       #resid.hetstat = FALSE,
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = C1,
       label.left = I1,
       fs.axis = 10,
       fs.lr = 10
)
```



## 5.2.2.2 Constipation

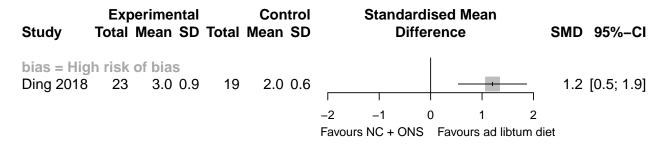
```
QoL_Constipation_2 <- metacont(</pre>
  HNC$n.e,
  HNC$mean.e,
  HNC$sd.e,
  HNC$n.c,
  HNC$mean.c,
  HNC$sd.c,
  HNC$studlab,
  data = HNC,
  subset = HNC$outclab == "QoL_Constipation" & HNC$C == 2,
  sm = "SMD",
  byvar = HNC$bias
)
forest(QoL_Constipation_2,
       xlab="QoL_Constipation",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 1,
       digits.se = 1,
       comb.fixed = FALSE,
       #plotwidth = "2cm"
       xlim = c(-1, 1),
       subgroup = FALSE,
       hetstat = FALSE,
       overall.hetstat = TRUE,
       #pooled.events = TRUE,
       #resid.hetstat = FALSE,
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = C1,
       label.left = I1,
       fs.axis = 10,
       fs.lr = 10
```

)



fs.lr = 10) Experimental **Standardised Mean** Control Study Total Mean SD Total Mean SD Difference SMD 95%-CI bias = High risk of bias -0.3 [-0.9; 0.3] Ding 2018 1.2 0.4 19 23 1.3 0.5 -0.5 0 -1 0.5 1 Favours NC + ONS Favours ad libtum diet 5.2.2.4 Nausea QoL\_Nausea\_2 <- metacont(</pre> HNC\$n.e, HNC\$mean.e, HNC\$sd.e, HNC\$n.c, HNC\$mean.c, HNC\$sd.c, HNC\$studlab, data = HNC, subset = HNC\$outclab == "QoL\_Nausea" & HNC\$C == 2, sm = "SMD", byvar = HNC\$bias ) forest(QoL\_Nausea\_2, xlab="QoL\_Nausea", #ref = 10,#layout = "Revman5", layout = "meta", digits = 1, digits.se = 1, comb.fixed = FALSE, #plotwidth = "2cm" xlim = c(-2, 2),subgroup = FALSE, hetstat = FALSE, overall.hetstat = TRUE, #pooled.events = TRUE, #resid.hetstat = FALSE, colgap.forest = "0.5 cm",

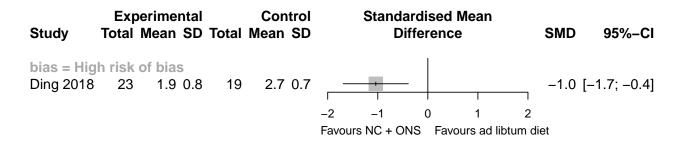
```
just = "right",
label.right = C1,
label.left = I1,
fs.axis = 10,
fs.lr = 10
```



5.2.2.5 Pain

```
QoL_Pain_2 <- metacont(</pre>
  HNC$n.e,
  HNC$mean.e,
  HNC$sd.e,
  HNC$n.c,
  HNC$mean.c,
  HNC$sd.c,
  HNC$studlab,
  data = HNC,
  subset = HNC$outclab == "QoL_Pain" & HNC$C == 2,
  sm = "SMD",
  byvar = HNC$bias
)
forest(QoL_Pain_2,
       xlab="QoL_Pain",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 1,
       digits.se = 1,
       comb.fixed = FALSE,
       #plotwidth = "2cm"
       xlim = c(-2, 2),
       subgroup = FALSE,
       hetstat = FALSE,
```

```
overall.hetstat = TRUE,
#pooled.events = TRUE,
#resid.hetstat = FALSE,
colgap.forest = "0.5 cm",
just = "right",
label.right = C1,
label.left = I1,
fs.axis = 10,
fs.lr = 10
```



# 5.3 Body weight (end of treatment)

#### 5.3.1 Forest plot

```
bw_2_1 <- metacont(</pre>
 HNC$n.e,
 HNC$mean.e,
 HNC$sd.e,
 HNC$n.c,
 HNC$mean.c,
 HNC$sd.c,
 HNC$studlab,
 data = HNC,
 subset = HNC$outclab == "Body weight" & HNC$C == 2,
 byvar = HNC$bias,
)
bw_2_1_d <- data.frame(bw_2_1)</pre>
rob_bw_2_1 <- merge(rob_bw_2_1, bw_2_1_d[,c("w.random", "studlab")], by = "studlab", all = TRUE)</pre>
rob_bw_2_1_x <- subset(rob_bw_2_1, studlab != "Moriarty 1989")</pre>
forest(bw_2_1,
       xlab="Body weight (end of treatment)",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 2,
       digits.se = 1,
       comb.fixed = FALSE,
       xlim = c(-15, 15),
       #leftcols = c("studlab", "n.e", "n.c", "TE", "seTE", "random.w"),
       \#xlim = "s",
       #plotwidth = "2cm",
```

```
subgroup = FALSE,
hetstat = FALSE,
overall.hetstat = TRUE,
#pooled.events = TRUE,
#resid.hetstat = FALSE,
colgap.forest = "0.5 cm",
just = "right",
label.right = I1,
label.left = C1,
fs.axis = 10,
fs.lr = 10
```

)

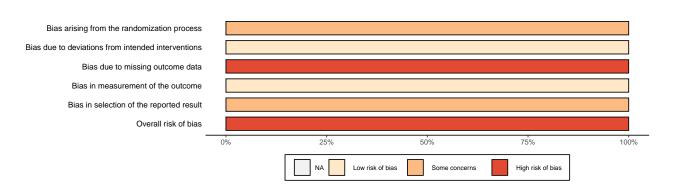
Study	Experimental Total Mean SD	Control Total Mean SD	Mean Difference	MD 95%-CI Weight
bias = High risk of bias Ding 2018	23 61.38 12.3	19 58.05 10.6		3.33 [-3.6; 10.26] 100.0%
bias = Unknown Moriarty 1989	42	42		0.0%
<b>Random effects model</b> Heterogeneity: $l^2 = NA\%$ , $\gamma$			15 -10 -5 0 5 10 15 rours ad libtum diet Favours NC + ONS Body weight (end of treatment)	

Moriarty 1981 measured body weight but only reported the result as statistically non-significant, so it could not be included in a meta-analysis.

# 5.3.2 Proportion of information at each level of risk of bias

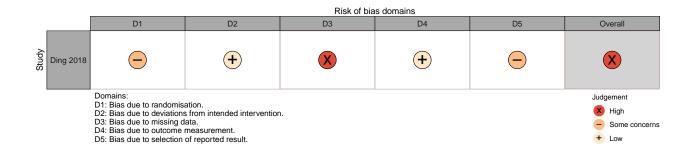
Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result (when applicable)

```
rob_summary(rob_bw_2_1, tool = "ROB2", weighted = TRUE, overall = TRUE, colour = "colourblind")
```



5.3.3 Risk of bias assessments by study

rob\_traffic\_light(rob\_bw\_2\_1\_x, tool = "ROB2", colour = "colourblind", psize = 10)



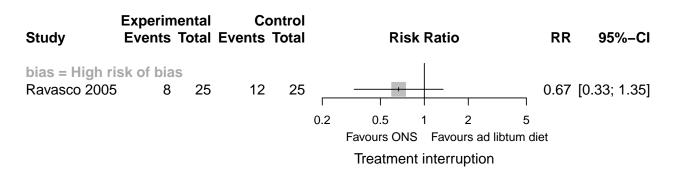
# 6 Comparison 3

# 6.1 Mortality

# 6.1.1 Forest plot

```
mort_3 <- metabin(</pre>
  HNC$event.e,
  HNC$n.e,
  HNC$event.c,
  HNC$n.c,
  sm = "RR",
  method = "MH",
  RR.cochrane = TRUE,
  MH.exact = FALSE,
  allstudies = TRUE,
 HNC$studlab,
  subset = HNC$outclab == "Mortality" & HNC$C == 3,
  byvar = HNC$bias,
  comb.fixed = FALSE,
)
mort_3_d <- data.frame(mort_3)</pre>
rob_mort_3 <- merge(rob_mort_3, mort_3_d[,c("w.random", "studlab")], by = "studlab", all = TRUE)</pre>
forest(mort_3,
       xlab="Treatment interruption",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 2,
       digits.se = 1,
       comb.fixed = FALSE,
       #overall = FALSE,
       #subgroup = FALSE,
       xlim = c(0.2, 5),
               = "s",
       #xlim
       #plotwidth = "2cm",
       subgroup = FALSE,
       hetstat = FALSE,
       overall.hetstat = TRUE,
       #pooled.events = TRUE,
```

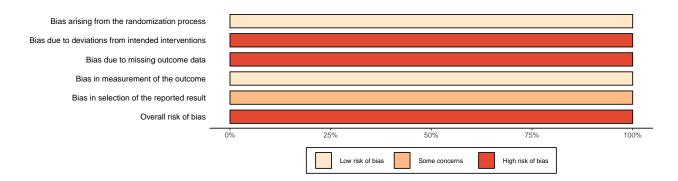
```
#resid.hetstat = FALSE,
colgap.forest = "0.5 cm",
just = "right",
label.right = C1,
label.left = I1,
fs.axis = 10,
fs.lr = 10
```



#### 6.1.2 Proportion of information at each level of risk of bias

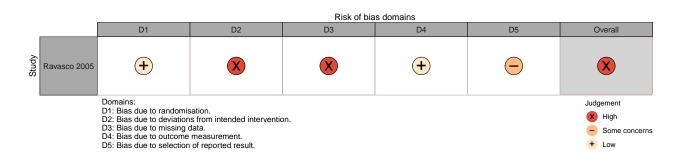
Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result (when applicable)

rob\_summary(rob\_mort\_3, tool = "ROB2", weighted = FALSE, overall = TRUE, colour = "colourblind")



#### 6.1.3 Risk of bias assessments by study

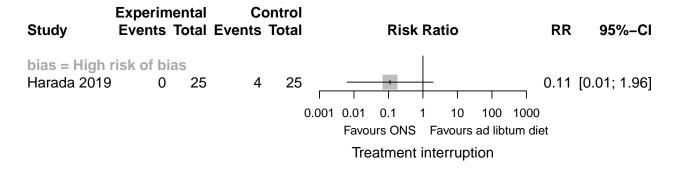
```
rob_traffic_light(rob_mort_3, tool = "ROB2", colour = "colourblind", psize = 10)
```



# 6.2 Interruption of treatment

#### 6.2.1 Forest plot

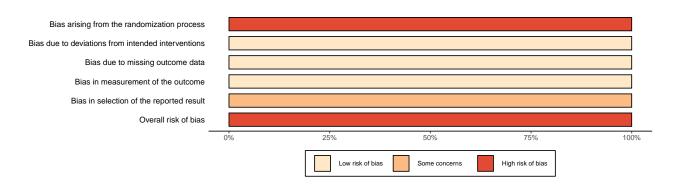
```
int_3 <- metabin(</pre>
 HNC$event.e,
 HNC$n.e,
 HNC$event.c.
 HNC$n.c,
 sm = "RR",
 method = "MH",
 RR.cochrane = TRUE,
 MH.exact = FALSE,
 allstudies = TRUE,
 HNC$studlab,
 subset = HNC$outclab == "Interruption of anti-cancer treatment" & HNC$C == 3,
 byvar = HNC$bias,
 comb.fixed = FALSE,
)
int_3_d <- data.frame(int_3)</pre>
rob_int_3 <- merge(rob_int_3, int_3_d[,c("w.random", "studlab")], by = "studlab", all = TRUE)</pre>
forest(int_3,
       xlab="Treatment interruption",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 2,
       digits.se = 1,
       comb.fixed = FALSE,
       #overall = FALSE,
       #subgroup = FALSE,
       xlim = c(0.001, 1000),
       \#xlim = "s",
       #plotwidth = "2cm",
       subgroup = FALSE,
       hetstat = FALSE,
       overall.hetstat = TRUE,
       #pooled.events = TRUE,
       #resid.hetstat = FALSE,
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = C1,
       label.left = I1,
       fs.axis = 10,
       fs.lr = 10
)
```



#### 6.2.2 Proportion of information at each level of risk of bias

Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result (when applicable)

rob\_summary(rob\_int\_3, tool = "ROB2", weighted = FALSE, overall = TRUE, colour = "colourblind")



#### 6.2.3 Risk of bias assessments by study

```
rob_traffic_light(rob_int_3, tool = "ROB2", colour = "colourblind", psize = 10)
```

		Risk of bias domains								
		D1	D2	D3	D4	D5	Overall			
Study	Harada 2019	×	+	+	+	-	×			
Domains: D1: Bias due to randomisation. D2: Bias due to deviations from intended intervention. D3: Bias due to missing data. D4: Bias due to outcome measurement. D5: Bias due to selection of reported result.										

# 6.3 Summary of non-hematological toxicity outcomes

# 6.3.1 Forest plot

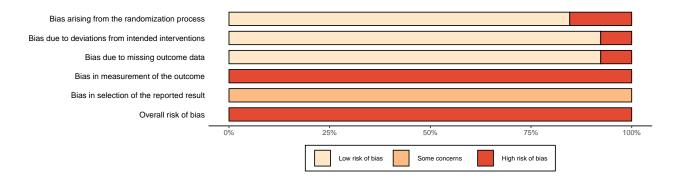
```
tol_3 <- metabin(
  HNC$event.e,
  HNC$n.e,
  HNC$event.c,</pre>
```

```
HNC$n.c,
  sm = "RR",
  method = "MH",
  RR.cochrane = TRUE,
  MH.exact = FALSE,
  #allstudies = TRUE,
  HNC$studlab,
  subset = HNC$outclab == "Tolerance" & HNC$C == 3,
  byvar = HNC$bias,
  comb.fixed = FALSE,
  comb.random = FALSE,
)
forest(tol_3,
       xlab="Non-hematological toxicity",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 2,
       digits.se = 1,
       comb.fixed = FALSE,
       #overall = FALSE,
       #subgroup = FALSE,
       xlim = c(0.1, 10),
       #plotwidth = "2cm",
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = C1,
       label.left = I1,
       fs.axis = 10,
       fs.lr = 10
)
```

	Experim	ental	Co	ntrol		
Study	Events	Total	Events	Total	Risk Ratio	RR 95%–Cl
bias = High risk of bias						
Harada 2019 – mucositis (grades 3–4)	3	25	16	25	← +	0.19 [0.06; 0.56]
Harada 2019 – mucositis (grades 1–2)	22	25	9	25		2.44 [1.42; 4.20]
Ravasco 2005 – anorexia (grade 1)	9	25	9	25		1.00 [0.48; 2.09]
Ravasco 2005 – anorexia (grade 2)	5	25	7	25		0.71 [0.26; 1.95]
Ravasco 2005 – dysguesia (grade 1)	10	25	11	25		0.91 [0.47; 1.75]
Ravasco 2005 – dysguesia (grade 2)	11	25	12	25		0.92 [0.50; 1.67]
Ravasco 2005 – nausea/vomiting (grade 1)		25	3	25		1.00 [0.22; 4.49]
Ravasco 2005 – nausea/vomiting (grade 2)		25	2	25		1.00 [0.15; 6.55]
Ravasco 2005 – odynophagia/dysphagia (grade 1)		25	12	25		1.00 [0.56; 1.78]
Ravasco 2005 – odynophagia/dysphagia (grade 2)	10	25	12	25		0.83 [0.44; 1.56]
Ravasco 2005 – xerostomia (grade 1)	10	25	10	25		1.00 [0.51; 1.97]
Ravasco 2005 – xerostomia (grade 2)		25	7	25		0.86 [0.34; 2.19]
Ravasco 2005 - permanent xerostomia and/or taste alterations	i 12	17	10	13		0.92 [0.60; 1.41]
						-
					0.1 0.2 0.5 1 2 5 1	-
					Favours ONS Favours ad libtum	diet
					Non-hematological toxicity	

#### 6.3.2 Proportion of the summary at each level of risk of bias

rob\_summary(rob\_tol\_3, tool = "ROB2", weighted = FALSE, overall = TRUE, colour = "colourblind")



### 6.3.3 Risk of bias assessments by study

rob\_traffic\_light(rob\_tol\_3, tool = "ROB2", colour = "colourblind", psize = 10)

		Risk of bias domains							
		D1	D2	D3	D4	D5	Overall		
	Harada 2019 – mucositis (grades 3–4)	×	+	+	X	-	X		
	Harada 2019 – mucositis (grades 1–2)	×	+	+	X	-	X		
	Ravasco 2005 – anorexia (grade 1)	+	+	+	X	$\overline{}$	X		
	Ravasco 2005 – anorexia (grade 2)	+	+	+	X	$\overline{}$	X		
	Ravasco 2005 – dysguesia (grade 1)		+	+	X	-	X		
	Ravasco 2005 – dysguesia (grade 2)	+	+	+	X	-	X		
Study	Ravasco 2005 – nausea/vomiting (grade 1)	+	+	+	X	$\overline{}$	X		
	Ravasco 2005 – nausea/vomiting (grade 2)	+	+	+	X	-	X		
	Ravasco 2005 – odynophagia/dysphagia (grade 1)	+	+	+	X	-	X		
	Ravasco 2005 – odynophagia/dysphagia (grade 2)	+	+	+	X	-	X		
	Ravasco 2005 – xerostomia (grade 1)	+	+	+	X	$\overline{}$	X		
	Ravasco 2005 – xerostomia (grade 2)	+	+	+	X	-	X		
	Ravasco 2005 - permanent xerostomia and/or taste alterations	+	X	X	X	-	X		
		Domains: D1: Bias due to I	randomination				Judgement		
		D1: Bias due to D2: Bias due to		X High					

D1: Blas due to randomisation.
D2: Blas due to deviations from intended intervention.
D3: Blas due to missing data.
D4: Blas due to outcome measurement.
D5: Blas due to selection of reported result.

 Some concerns + Low

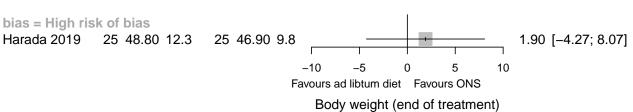
 $#labbe.metabin(x = tol_1,$ bg = "grey", # # studlab = TRUE, # comb.random = FALSE, # cex.studlab = 0.4)

#### 6.4Body weight (end of treatment)

# 6.4.1 Forest plot

```
bw_3_1 <- metacont(</pre>
 HNC$n.e,
```

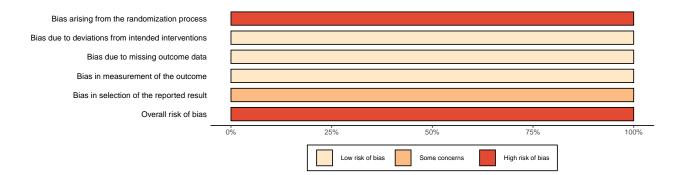
```
HNC$mean.e,
  HNC$sd.e,
  HNC$n.c,
  HNC$mean.c,
 HNC$sd.c,
 HNC$studlab,
 data = HNC,
 subset = HNC$outclab == "Body weight" & HNC$C == 3,
  byvar = HNC$bias,
)
bw_3_1_d <- data.frame(bw_3_1)</pre>
rob_bw_3_1 <- merge(rob_bw_3_1, bw_3_1_d[,c("w.random", "studlab")], by = "studlab", all = TRUE)</pre>
forest(bw_3_1,
       xlab="Body weight (end of treatment)",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 2,
       digits.se = 1,
       comb.fixed = FALSE,
       xlim = c(-10, 10),
       #leftcols = c("studlab", "n.e", "n.c", "TE", "seTE", "random.w"),
       #xlim
               = "s",
       #plotwidth = "2cm",
       subgroup = FALSE,
       hetstat = FALSE,
       overall.hetstat = TRUE,
       #pooled.events = TRUE,
       #resid.hetstat = FALSE,
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = I1,
       label.left = C1,
       fs.axis = 10,
       fs.lr = 10
)
               Experimental
                                    Control
Study
            Total Mean SD Total Mean SD
                                                    Mean Difference
                                                                              MD
                                                                                      95%-CI
```



#### 6.4.2 Proportion of information at each level of risk of bias

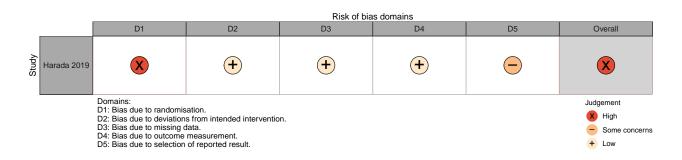
Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result (when applicable)

# rob\_summary(rob\_bw\_3\_1, tool = "ROB2", weighted = FALSE, overall = TRUE, colour = "colourblind")



#### 6.4.3 Risk of bias assessments by study

rob\_traffic\_light(rob\_bw\_3\_1, tool = "ROB2", colour = "colourblind", psize = 10)



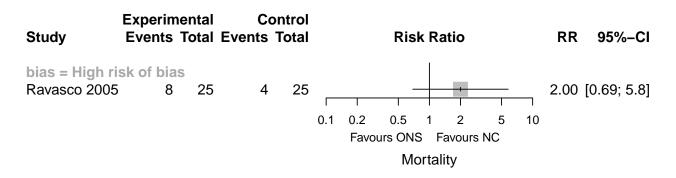
# 7 Comparison 4

# 7.1 Mortality

#### 7.1.1 Forest plot

```
mort_4 <- metabin(</pre>
  HNC$event.e,
  HNC$n.e,
  HNC$event.c,
  HNC$n.c,
  sm = "RR",
  method = "MH",
  RR.cochrane = TRUE,
  MH.exact = FALSE,
  allstudies = TRUE,
  HNC$studlab,
  subset = HNC$outclab == "Mortality" & HNC$C == 4,
  byvar = HNC$bias,
  comb.fixed = FALSE,
)
forest(mort_4,
```

```
xlab="Mortality",
#ref = 10,
#layout = "Revman5",
layout = "meta",
digits = 2,
digits.se = 1,
comb.fixed = FALSE,
#overall = FALSE,
#subgroup = FALSE,
xlim = c(0.1, 10),
         = "s",
#xlim
#plotwidth = "2cm",
subgroup = FALSE,
hetstat = FALSE,
overall.hetstat = TRUE,
#pooled.events = TRUE,
#resid.hetstat = FALSE,
colgap.forest = "0.5 cm",
just = "right",
label.right = C1,
label.left = I1,
fs.axis = 10,
fs.lr = 10
```

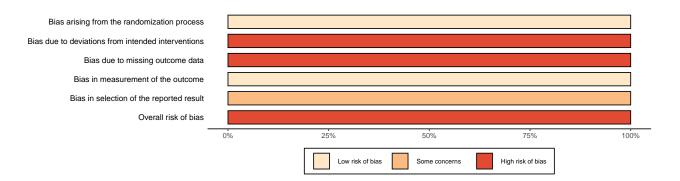


# 7.1.2 Proportion of information at each level of risk of bias

)

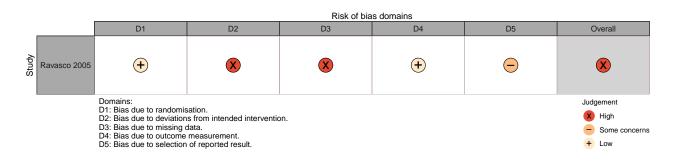
Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result (when applicable)





#### 7.1.3 Risk of bias assessments by study

```
rob_traffic_light(rob_mort_4, tool = "ROB2", colour = "colourblind", psize = 8)
```



# 7.2 Summary of non-hematological toxicity outcomes

# 7.2.1 Forest plot

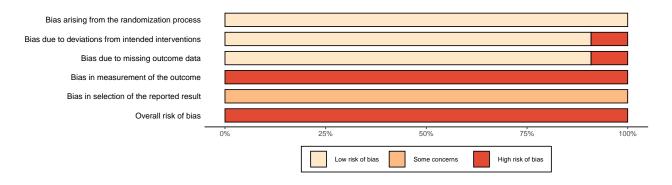
```
tol_4 <- metabin(</pre>
 HNC$event.e,
 HNC$n.e,
 HNC$event.c,
 HNC$n.c,
  sm = "RR",
 method = "MH",
 RR.cochrane = TRUE,
 MH.exact = FALSE,
  #allstudies = TRUE,
 HNC$studlab,
  subset = HNC$outclab == "Tolerance" & HNC$C == 4,
  byvar = HNC$bias,
  comb.fixed = FALSE,
  comb.random = FALSE,
)
forest(tol 4,
       xlab="Non-hematological toxicity",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 2,
       digits.se = 1,
       comb.fixed = FALSE,
       #overall = FALSE,
       #subgroup = FALSE,
       xlim = c(0.1, 10),
       #lim = "s",
       #plotwidth = "2cm",
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = C1,
       label.left = I1,
```

```
fs.axis = 10,
fs.lr = 10
```

)							
Study	Experime Events			ntrol Fotal	Risk Ratio	RR	95%-CI
bias = High risk of bias							
Ravasco 2005 – anorexia (grade 1)	9	25	10	25			[0.44; 1.83]
Ravasco 2005 – anorexia (grade 2)	5	25	2	25			[0.53; 11.70]
Ravasco 2005 – dysguesia (grade 1)	10	25	10	25		1.00	[0.51; 1.97]
Ravasco 2005 – dysguesia (grade 2)	11	25	7	25		1.57	[0.73; 3.39]
Ravasco 2005 – nausea/vomiting (grade 1)	3	25	4	25		0.75	[0.19; 3.01]
Ravasco 2005 – nausea/vomiting (grade 2)	2	25	1	25		2.00	[0.19; 20.67]
Ravasco 2005 – odynophagia/dysphagia (grade 1)	12	25	14	25		0.86	[0.50; 1.46]
Ravasco 2005 – odynophagia/dysphagia (grade 2)	10	25	8	25		1.25	[0.59; 2.64]
Ravasco 2005 – xerostomia (grade 1)	10	25	12	25			[0.44; 1.56]
Ravasco 2005 – xerostomia (grade 2)	6	25	3	25			[0.56; 7.12]
Ravasco 2005 – permanent xerostomia and/or taste alterations	s 12	17	10	19			[0.79; 2.27]
							[0110, 2121]
				0	0.1 0.2 0.5 1 2 5 1	0	
					Favours ONS Favours NC		
					Non-hematological toxicity		

# 7.2.2 Proportion of the summary at each level of risk of bias

rob\_summary(rob\_tol\_4, tool = "ROB2", weighted = FALSE, overall = TRUE, colour = "colourblind")



7.2.3 Risk of bias assessments by study

```
rob_traffic_light(rob_tol_4, tool = "ROB2", colour = "colourblind", psize = 10)
```

		Risk of bias domains						
		D1	D2	D3	D4	D5	Overall	
	Ravasco 2005 – anorexia (grade 1)	+	+	+	×	$\overline{}$	×	
	Ravasco 2005 – anorexia (grade 2)	+	+	+	X	-	X	
	Ravasco 2005 – dysguesia (grade 1)	+	+	+	×	-	X	
	Ravasco 2005 – dysguesia (grade 2)	+	+	+	×	-	X	
	Ravasco 2005 – nausea/vomiting (grade 1)	+	+	+	×	-	X	
Study	Ravasco 2005 – nausea/vomiting (grade 2)	+	+	+	X	-	X	
	Ravasco 2005 – odynophagia/dysphagia (grade 1)	+	+	+	×	-	×	
	Ravasco 2005 – odynophagia/dysphagia (grade 2)	+	+	+	×	$\overline{}$	×	
	Ravasco 2005 - xerostomia (grade 1)	+	+	+	×	-	×	
	Ravasco 2005 - xerostomia (grade 2)	+	+	+	×	-	X	
	Ravasco 2005 - permanent xerostomia and/or taste alterations	+	X	×	×	-	X	
		Domains:					Judgement	

 Domains:

 D1: Bias due to randomisation.

 D2: Bias due to deviations from intended intervention.

 D3: Bias due to missing data.

 D4: Bias due to outcome measurement.

 D5: Bias due to selection of reported result.

X High - Some concerns

+ Low