Supplemental Digital Content 1

```
> citation()
R Core Team (2014). R: A language and environment for statistical computing. R Foundation
for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/.

> sessionInfo()
R version 3.1.0 (2014-04-10)
Platform: x86_64-apple-darwin13.1.0 (64-bit)
locale:
[1] en_US.UTF-8/en_US.UTF-8/en_US.UTF-8/C/en_US.UTF-8/en_US.UTF-8
attached base packages:
[1] stats     graphics  grDevices utils     datasets  methods   base
other attached packages:
[1] mmeta_2.2      metaLik_0.41.0 metafor_1.9-3  Matrix_1.1-4   Formula_1.1-1
loaded via a namespace (and not attached):
```

```
[1] grid_3.1.0      lattice_0.20-29 tools_3.1.0
```

```
> citation('metafor')
```

Wolfgang Viechtbauer (2010). Conducting meta-analyses in R with the metafor package. Journal of Statistical Software, 36(3), 1-48. URL http://www.jstatsoft.org/v36/i03/.

```
> citation('MetaLik')
```

Annamaria Guolo, Cristiano Varin (2012). The R Package metaLik for Likelihood Inference in Meta-Analysis. Journal of Statistical Software, 50(7), 1-14. URL http://www.jstatsoft.org/v50/i07/.

Guolo, A. (2012). Higher-order likelihood inference in meta-analysis and meta-regression. Statistics in Medicine 31, 313-327.

```
> citation('mmeta')
```

Sheng Luo, Yong Chen, Xiao Su, Haitao Chu (2014). mmeta: An R Package for Multivariate Meta-Analysis. Journal of Statistical Software, 56(11), 1-26.

Data from Peyton et al Table 1

> N2O.df

	studlab	duration	ci	n2i	ai	n1i	year
1	Lonie 1986	39	20	46	20	41	1986
2	Kortilla 1987	102	25	55	30	55	1987
3	Melnick 1987	13	1	28	8	32	1987
4	Muir 1987	73	67	181	67	178	1987
5	Muir 1987	78	62	186	65	173	1987
6	Bloomfield 1988	96	5	31	11	32	1988
7	Sengupta 1988	23	10	31	13	33	1988
8	Hovorka 1989	38	26	50	53	100	1989
9	Eger 1990	178	63	147	64	133	1990
10	Scheinin 1990	266	5	20	5	20	1990
11	Ranta 1991	121	12	24	13	26	1991
12	Wrigley 1991	29	3	13	6	14	1991
13	Rapp 1992	53	9	22	10	24	1992

14	Taylor	1992	87	13	24	9	26	1992
15	Akhtar	1993	10	2	50	6	50	1993
16	Graham	1993	24	11	15	4	15	1993
17	Jensen	1993	165	10	23	11	19	1993
18	Lebenborn-Mansour	1993	86	2	16	7	14	1993
19	Pedersen	1993	95	6	19	5	17	1993
20	Sukhani	1994	81	5	36	2	34	1994
21	Bloomfield	1997	139	26	59	12	60	1997
22	Vanacker	1999	120	6	30	17	30	1999
23	Arellano	2000	13	22	467	9	468	2000
24	Arellano	2000	31	70	241	63	242	2000
25	Apfel	2004	108	638	2050	721	2036	2004
26	Fleischmann	2005	202	26	206	39	208	2005
27	Myles	2007	222	104	997	229	997	2007
28	El-Galley	2007	138	4	16	6	12	2007
29	Mraovic	2008	73	7	46	20	91	2008

```
# estimate RR
N2O.df <- escalc(measure = 'RR', ai = ai, n1i = n1i, ci = ci, n2i = n2i, data = N2O.df,
                 append = T, replace = T)
```

```
>  N2O.df
```

	studlab	duration	ci	n2i	ai	n1i	year	yi	vi
1	Lonie 1986	39	20	46	20	41	1986	0.1151	0.0539
2	Kortilla 1987	102	25	55	30	55	1987	0.1823	0.0370
3	Melnick 1987	13	1	28	8	32	1987	1.9459	1.0580
4	Muir 1987	73	67	181	67	178	1987	0.0167	0.0187
5	Muir 1987	78	62	186	65	173	1987	0.1197	0.0204
6	Bloomfield 1988	96	5	31	11	32	1988	0.7567	0.2274
7	Sengupta 1988	23	10	31	13	33	1988	0.1998	0.1144
8	Hovorka 1989	38	26	50	53	100	1989	0.0190	0.0273
9	Eger 1990	178	63	147	64	133	1990	0.1158	0.0172
10	Scheinin 1990	266	5	20	5	20	1990	0.0000	0.3000

11	Ranta	1991	121	12	24	13	26	1991	0.0000	0.0801
12	Wrigley	1991	29	3	13	6	14	1991	0.6190	0.3516
13	Rapp	1992	53	9	22	10	24	1992	0.0183	0.1240
14	Taylor	1992	87	13	24	9	26	1992	-0.4478	0.1079
15	Akhtar	1993	10	2	50	6	50	1993	1.0986	0.6267
16	Graham	1993	24	11	15	4	15	1993	-1.0116	0.2076
17	Jensen	1993	165	10	23	11	19	1993	0.2864	0.0948
18	Lebenborn-Mansour	1993	86	2	16	7	14	1993	1.3863	0.5089
19	Pedersen	1993	95	6	19	5	17	1993	-0.0711	0.2552
20	Sukhani	1994	81	5	36	2	34	1994	-0.8591	0.6428
21	Bloomfield	1997	139	26	59	12	60	1997	-0.7900	0.0882
22	Vanacker	1999	120	6	30	17	30	1999	1.0415	0.1588
23	Arellano	2000	13	22	467	9	468	2000	-0.8960	0.1523
24	Arellano	2000	31	70	241	63	242	2000	-0.1095	0.0219
25	Apfel	2004	108	638	2050	721	2036	2004	0.1292	0.0020
26	Fleischmann	2005	202	26	206	39	208	2005	0.3958	0.0544

27	Myles	2007	222	104	997	229	997	2007	0.7893	0.0120
28	El-Galley	2007	138	4	16	6	12	2007	0.6931	0.2708
29	Mraovic	2008	73	7	46	20	91	2008	0.3676	0.1601

```
# function code
# glmm OR models

N2O0.rma.glmm <- rma.glmm(ai = ai, n1i = n1i, ci = ci, n2i = n2i, measure = 'OR', data =
N2O.df,
                          slab = as.character(studlab), model = 'CM.EL', method = 'ML',
tdist = T)

N2O1.rma.glmm <- rma.glmm(ai = ai, n1i = n1i, ci = ci, n2i = n2i, measure = 'OR', data =
N2O.df, mods = duration,
                    slab = as.character(studlab), model = 'CM.EL', method = 'ML', tdist =
T)

summary(N2O0.rma.glmm)

summary(N2O1.rma.glmm)
```

```
predict(N2O0.rma.glmm, transf = exp)

predict(N2O1.rma.glmm, newmods = c(0, 60, 120), transf = exp)

# linear mixed effects RR models

N2O0.rma.uni <- rma.uni(yi = yi, vi = vi, method = 'REML', data = N2O.df,
                        slab = as.character(studlab), knha = T)

N2O1.rma.uni <- rma.uni(yi = yi, vi = vi,  mods = duration, method = 'REML', data =
N2O.df,
                        slab = as.character(studlab), knha = T)

summary(N2O0.rma.uni)
```

```
predict(N2O0.rma.uni, transf = exp)

summary(N2O1.rma.uni)

predict(N2O1.rma.uni, transf = exp, newmods = c(0, 60, 120))

#
### metaLik (higher order likelihoods) model
#

require(metaLik)

N2O0.metaLik <- metaLik(formula = yi ~ 1, data  = N2O.df, sigma2 = vi)

N2O1.metaLik <- metaLik(formula = yi ~ duration, data  = N2O.df, sigma2 = vi)
```

```
summary(N2O0.metaLik)

summary(N2O1.metaLik)



# calculation of pairwise RR 95% CI

exp(coefficients(N2O0.metaLik))
exp(profile(N2O0.metaLik)$lower.rskow)
exp(profile(N2O0.metaLik)$upper.rskow)

#
### mmeta (exact Bayesian) model
#

require(dplyr)
```

```
N2O.mmeta.df <- select(N2O.df, y1 = ci, n1 = n2i, y2 = ai, n2 = n1i, studynames =
studlab)

require(mmeta)

N2O0.OR.multipletables <- multipletables(data = N2O.mmeta.df, measure = 'OR',
                                         model = 'Independent', method = 'exact')

summary(N2O0.OR.multipletables)

N2O0.RR.multipletables <- multipletables(data = N2O.mmeta.df, measure = 'RR',
                                            model = 'Independent', method = 'exact')

summary(N2O0.RR.multipletables)
```

```
# statistical output
> summary(N2O0.rma.glmm)

Random-Effects Model (k = 29; tau^2 estimator: ML)
Model Type: Conditional Model with Exact Likelihood

  logLik  deviance       AIC       BIC      AICc
-80.6163   61.3471  165.2325  165.6941  167.9671

tau^2 (estimated amount of total heterogeneity): 0.2332 (SE = 0.1297)
tau (square root of estimated tau^2 value):      0.4829
I^2 (total heterogeneity / total variability):   73.17%
H^2 (total variability / sampling variability):  3.73

Tests for Heterogeneity:
Wld(df = 28) = 85.5000, p-val < .0001
```

```
LRT(df = 28) = 92.7126, p-val < .0001

Model Results:

estimate       se     tval     pval    ci.lb    ci.ub
  0.2103   0.1248   1.6853   0.1030  -0.0453   0.4659

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

>
> summary(N2O1.rma.glmm)

Mixed-Effects Model (k = 29; tau^2 estimator: ML)
Model Type: Conditional Model with Exact Likelihood
```

```
  logLik  deviance       AIC       BIC      AICc
-79.6050   59.3245  165.2100  166.1700  169.3119

tau^2 (estimated amount of residual heterogeneity):     0.1403 (SE = 0.1230)
tau (square root of estimated tau^2 value):             0.3746
I^2 (residual heterogeneity / unaccounted variability): 60.00%
H^2 (unaccounted variability / sampling variability):   2.50

Tests for Residual Heterogeneity:
Wld(df = 27) = 55.4480, p-val = 0.0010
LRT(df = 27) = 61.8525, p-val = 0.0002

Test of Moderators (coefficient(s) 2):
F(df1 = 1, df2 = 27) = 2.5058, p-val = 0.1251

Model Results:
```

```
                    se     tval    pval    ci.lb   ci.ub
intrcpt  -0.0675  0.2073  -0.3256  0.7472  -0.4929  0.3579
mods      0.0027  0.0017   1.5830  0.1251  -0.0008  0.0062

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

>
> predict(N2O0.rma.glmm, transf = exp)
   pred  ci.lb  ci.ub  cr.lb  cr.ub
 1.2340 0.9557 1.5934 0.4442 3.4281
>
> predict(N2O1.rma.glmm, newmods = c(0, 60, 120), transf = exp)
    pred  ci.lb  ci.ub  cr.lb  cr.ub
1 0.9347 0.6109 1.4303 0.3883 2.2499
```

```
2 1.1005 0.8415 1.4391 0.4876 2.4837

3 1.2956 1.0301 1.6295 0.5810 2.8893

>

> summary(N2O0.rma.uni)


Random-Effects Model (k = 29; tau^2 estimator: REML)


  logLik  deviance       AIC       BIC      AICc

-22.8325   45.6649   49.6649   52.3293   50.1449


tau^2 (estimated amount of total heterogeneity): 0.1007 (SE = 0.0487)

tau (square root of estimated tau^2 value):      0.3174

I^2 (total heterogeneity / total variability):   72.40%

H^2 (total variability / sampling variability):  3.62


Test for Heterogeneity:
```

```
Q(df = 28) = 85.8655, p-val < .0001

Model Results:

estimate       se     tval     pval    ci.lb    ci.ub

  0.1303   0.0921   1.4152   0.1680  -0.0583   0.3189

---

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

>

> predict(N2O0.rma.uni, transf = exp)

   pred  ci.lb  ci.ub  cr.lb  cr.ub

 1.1392 0.9434 1.3757 0.5789 2.2417

>

> summary(N2O1.rma.uni)
```

```
Mixed-Effects Model (k = 29; tau^2 estimator: REML)

  logLik  deviance       AIC       BIC      AICc
-20.7828   41.5655   47.5655   51.4530   48.6090

tau^2 (estimated amount of residual heterogeneity):     0.0477 (SE = 0.0306)
tau (square root of estimated tau^2 value):             0.2185
I^2 (residual heterogeneity / unaccounted variability): 54.41%
H^2 (unaccounted variability / sampling variability):   2.19
R^2 (amount of heterogeneity accounted for):            52.62%

Test for Residual Heterogeneity:
QE(df = 27) = 57.6410, p-val = 0.0005

Test of Moderators (coefficient(s) 2):
```

```
F(df1 = 1, df2 = 27) = 4.1107, p-val = 0.0526

Model Results:

                    se     tval    pval    ci.lb   ci.ub
intrcpt  -0.1318  0.1532  -0.8606  0.3970  -0.4461  0.1825
mods      0.0026  0.0013   2.0275  0.0526  -0.0000  0.0052  .

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

>
> predict(N2O1.rma.uni, transf = exp, newmods = c(0, 60, 120))
    pred  ci.lb  ci.ub  cr.lb  cr.ub
1 0.8765 0.6401 1.2002 0.5070 1.5153
2 1.0221 0.8374 1.2476 0.6258 1.6693
```

```
3 1.1919 1.0051 1.4135 0.7379 1.9254
> summary(N2O0.metaLik)

Likelihood inference in random-effects meta-analysis models

Call:
metaLik(formula = yi ~ 1, data = N2O.df, sigma2 = vi)

Estimated heterogeneity parameter tau2 = 0.0912
Test for heterogeneity Q = 85.87 (pval < 0.0001)

Fixed-effects:
             estimate  std.err.  signed logLRT  p-value  Skovgaard  p-value
(Intercept)    0.1301    0.0811          1.555   0.1199       1.45   0.1471

Log-likelihood: 3.7114
```

```
>
> summary(N2O1.metaLik)

Likelihood inference in random-effects meta-analysis models

Call:
metaLik(formula = yi ~ duration, data = N2O.df, sigma2 = vi)

Estimated heterogeneity parameter tau2 = 0.02801
Test for heterogeneity Q = 57.64 (pval = 0.000533)

Fixed-effects:
             estimate  std.err.  signed logLRT  p-value  Skovgaard  p-value
(Intercept)   -0.1490    0.1182        -1.1507   0.2499    -0.7199   0.4716
duration       0.0027    0.0010         2.2176   0.0266     1.7201   0.0854
```

```
Log-likelihood: 6.1702
>
> # calculation of pairwise RR 95% CI
>
> exp(coefficients(N2O0.metaLik))
(Intercept)
    1.13899
> exp(profile(N2O0.metaLik)$lower.rskow)
0.9525714
> exp(profile(N2O0.metaLik)$upper.rskow)
1.365702
> summary(N2O0.OR.multipletables)
Model: Independent Beta-Binomial Model
Overall Odds ratio
Estimate: 1.212
95% CI:[0.803,1.83]
```

Maximum likelihood estimates of hyperparameters:

a1 =2.168, b1 =5.23, a2 =2.745, b2 =5.464, rho =0

Likelihood ratio test for within-group correlation (H0: rho=0):

chi2: 2.344; p-value: 0.13

Study-SpecifcOdds ratio:

	Mean	Lower Bound	Upper Bound
14	1.321	0.563	2.689
12	1.486	0.675	2.822
15	5.588	1.085	19.374
17	1.060	0.677	1.579
17	1.235	0.789	1.841
4	2.726	0.807	7.015
23	1.499	0.527	3.435
10	1.162	0.587	2.098
6	1.255	0.771	1.929

22	1.299	0.308	3.580
20	1.177	0.380	2.804
27	2.586	0.529	8.169
21	1.232	0.382	3.047
25	0.619	0.199	1.445
1	3.004	0.708	9.314
9	0.329	0.073	0.923
11	1.796	0.531	4.535
13	5.151	1.001	16.741
19	1.198	0.291	3.337
24	0.762	0.160	2.222
5	0.395	0.169	0.779
26	4.523	1.469	11.121
3	0.493	0.222	0.912
3	0.887	0.589	1.294
2	1.216	1.068	1.378

```
8       1.636       0.944       2.687
18      2.561       1.974       3.256
7       2.780       0.606       8.274
16      1.620       0.636       3.581
Overall 1.212       0.803       1.830


>
> N2O0.RR.multipletables <- multipletables(data = N2O.mmeta.df, measure = 'RR',
+                                          model = 'Independent', method = 'exact')
There were 50 or more warnings (use warnings() to see the first 50)
>
> summary(N2O0.RR.multipletables)
Model: Independent Beta-Binomial Model
Overall Relative risk
Estimate: 1.141
95% CI:[0.859,1.515]
```

Maximum likelihood estimates of hyperparameters:

a1 =2.168, b1 =5.23, a2 =2.745, b2 =5.464, rho =0

Likelihood ratio test for within-group correlation (H0: rho=0):

chi2: 2.344; p-value: 0.13

Study-SpecifcRelative risk:

	Mean	Lower Bound	Upper Bound
14	1.148	0.715	1.747
12	1.216	0.826	1.760
15	4.231	1.093	13.907
17	1.030	0.779	1.324
17	1.137	0.853	1.492
4	2.071	0.884	4.438
23	1.280	0.656	2.303
10	1.066	0.777	1.475
6	1.130	0.868	1.446

22	1.179	0.424	2.644
20	1.062	0.602	1.758
27	1.848	0.664	4.508
21	1.101	0.545	2.014
25	0.735	0.373	1.252
1	2.642	0.720	7.536
9	0.512	0.213	0.964
11	1.334	0.716	2.291
13	3.096	1.035	8.239
19	1.087	0.416	2.332
24	0.768	0.197	1.972
5	0.519	0.282	0.839
26	2.614	1.258	5.197
3	0.500	0.229	0.918
3	0.915	0.680	1.203
2	1.140	1.044	1.241

8	1.506	0.955	2.275
18	2.198	1.779	2.704
7	1.859	0.724	4.180
16	1.475	0.702	2.889
Overall	1.141	0.859	1.515