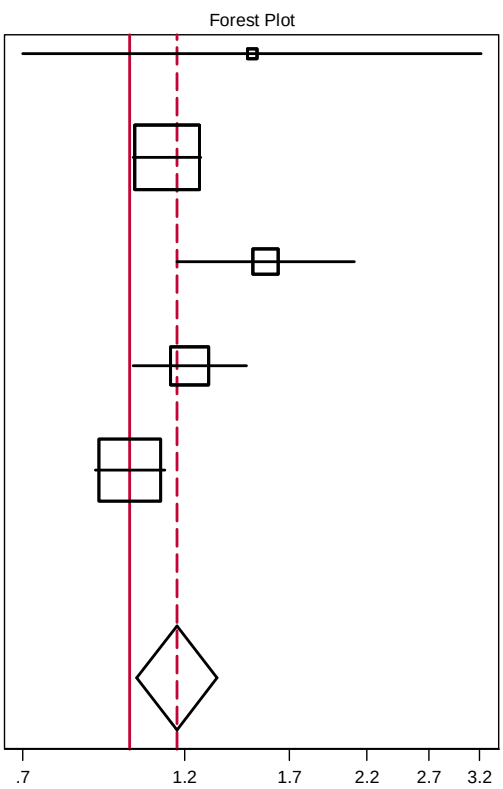
Supplemental material 1

Table 1 Study and summary risk estimates for any congenital anomalies and chlorination by-products

Study	Exposure	OR (CI95%)
Aschengrau et al 93.	Chlorin vs. chloramin.	1.5 (0.7- 3.21)
Hwang et al 02.	Chlorin. vs. No Chlorin.	1.13 (1.01- 1.25)
Bove et al 95.	>80 vs. <=20 microg/l TTHM	1.57 (1.17- 2.1)
Chisholm et al 08.	>=130 vs. <60 microg/l TTHM	1.22 (1.01- 1.48)
Hwang et al 2008.	>20 vs. 0-4 microg/l TTHM	1.00 (0.89- 1.13)
Combined effect (random)		1.17 (1.02-1.34)



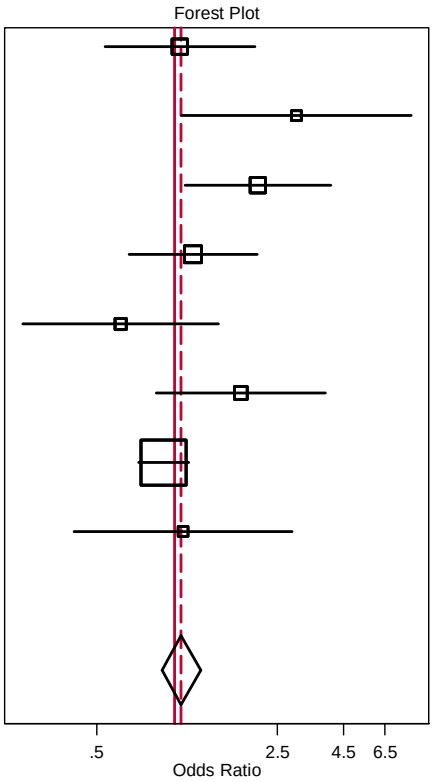
Test for heterogeneity: Q= 9.944 on 4 degrees of freedom (p= 0.041)

Egger test:
Weighted p-value for intercept 0.16

Table 2a Study and summary risk estimates for nervous system defects including neural tube defects and chlorination by-products

All

Study	Exposure	OR (CI95%)
Hwang et al 02.	Chlorin. vs. No Chlorin.	1.05 (0.54- 2.03)
Bove et al 95.	>80 vs. <=20 microg/l TTHM	2.96 (1.07- 8.2)
Klotz et al 99.	>40 vs. <5 microg/l TTHM	2.1 (1.1- 4.0)
Dodds et al 99.	100 vs. 0-49 microg/l TTHM	1.18 (0.67- 2.1)
Shaw et al 03 (1).	>=75 vs.0 microg/l TTHM	0.62 (0.26- 1.5)
Shaw et al 03 (2).	50-75 vs. 0 microg/l TTHM	1.8 (0.85- 3.7)
Nieuwenhuijsen et al 2008.	>60 vs. <30 microg/l TTHM	0.91 (0.73- 1.13)
Chisholm et al 08.	>=130 vs. <60 microg/l TTHM	1.08 (0.41- 2.85)
Combined effect (fixed)		1.06 (0.89-1.26)



Test for heterogeneity: Q= 13.658 on 7 degrees of freedom (p= 0.058)

Egger test:
Weighted p-value for intercept 0.11

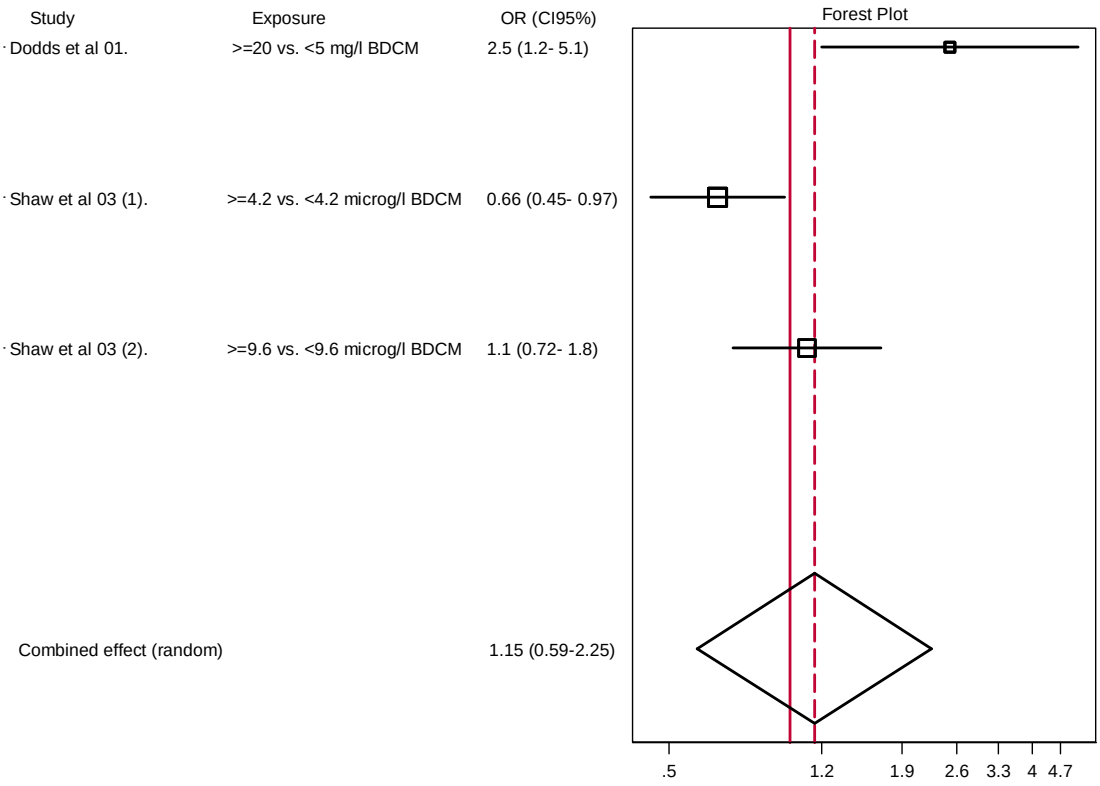
Per 10µg TTHM/L 1.02 (0.97 - 1.06)

Test for heterogeneity, Q = 5.6768, on 6 degrees of freedom (p=0.46)

Egger test:
Weighted p-value for intercept 0.20

Individual THMs

BDCM



Test for heterogeneity: Q= 10.719 on 2 degrees of freedom (p= 0.005)

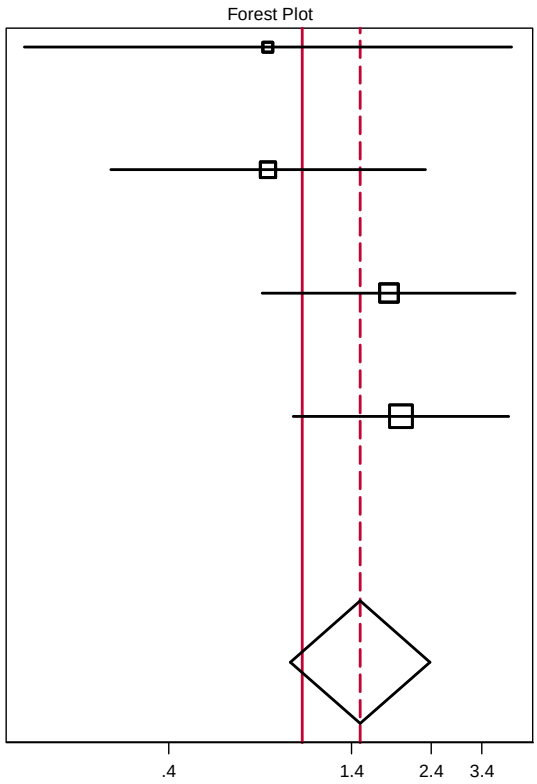
Egger test:
Weighted p-value for intercept: 0.12

Others

Shaw et al. 03	<1.7 vs. => 1.7 µg/l CDBM (1)	0.69 (0.47-1.00)
Shaw et al. 03	<3.6 vs. => 3.6 µg/l CDBM (2)	1.2 (0.73-1.8)
Nieuwen	<10 vs. >20 µg/l TBROM	0.90 (0.79-1.03)
huijsen et al. 2008	<2 vs. >4 µg/l Bromoform	0.96 (0.83-1.11)

Table 2b Study and summary risk estimates for anencephalus and chlorination by-products

Study	Exposure	OR (CI95%)
Hwang et al 02.	Chlorin. vs. No Chlorin.	0.79 (0.15- 4.23)
Shaw et al 03 (1).	>=75 vs. 0 microg/l TTHM	0.79 (0.27- 2.3)
Shaw et al 03 (2).	>=50-75 vs. 0 microg/l TTHM	1.8 (0.76- 4.4)
Hwang et al 2008.	>20 vs. 0-4 microg/l TTHM	1.96 (0.94- 4.07)
Combined effect (fixed)		1.48 (0.92-2.39)

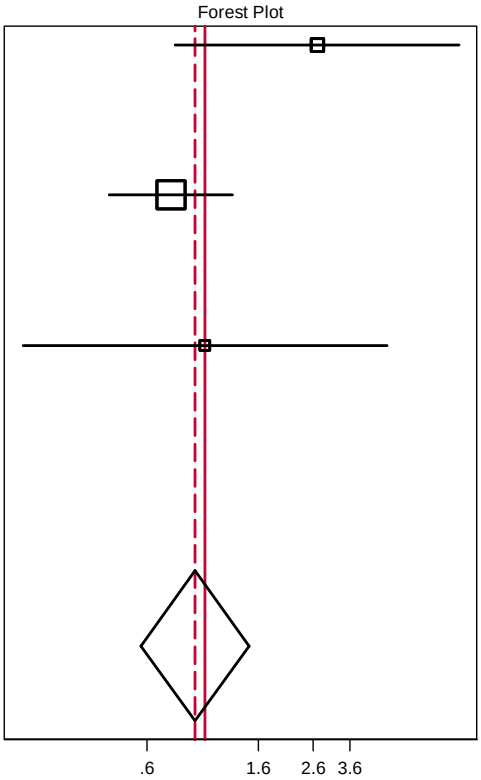


Test for heterogeneity: Q= 2.618 on 3 degrees of freedom (p= 0.454)

Egger test:
Weighted p-value for intercept 0.17

Table 2c Study and summary risk estimates for hydrocephalus and chlorination by-products

Study	Exposure	OR (CI95%)
Hwang et al 02.	Chlorin. vs. No Chlorin.	2.7 (0.77- 9.51)
Hwang et al 2008.	>20 vs 0-4 microg/l TTHM	0.74 (0.43- 1.28)
Kallen and Robert 00.	Chlorin vs. No chlorin	1.0 (0.2- 4.8)
Combined effect (fixed)		0.92 (0.57-1.48)

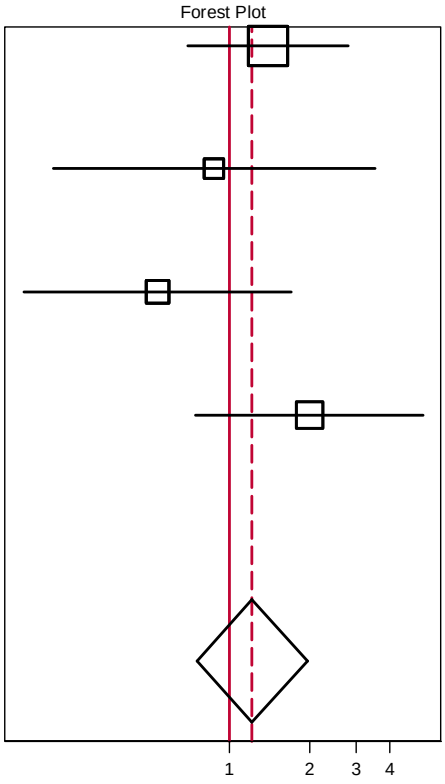


Test for heterogeneity: Q= 3.441 on 2 degrees of freedom (p= 0.18)

Egger test:
Weighted p-value for intercept 0.54

Table 2d Study and summary risk estimates for spina bifida and chlorination by-products

Study	Exposure	OR (CI95%)
Kallen and Robert 00.	Chlorin vs. Non chlorin	1.4 (0.7- 2.8)
Hwang et al 02.	Chlorin. vs. No Chlorin.	0.88 (0.22- 3.52)
Shaw et al 03 (1).	>=75 vs. 0 microg/l TTHM	0.54 (0.17- 1.7)
Shaw et al 03 (2).	>=50-75 vs. 0 microg/l TTHM	2.0 (0.75- 5.4)
Combined effect (fixed)		1.22 (0.76-1.97)



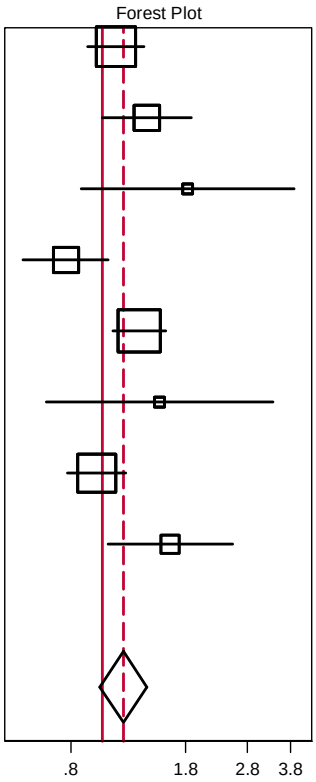
Test for heterogeneity: Q= 3.253 on 3 degrees of freedom (p= 0.35)

Egger test:
Weighted p-value for intercept 0.55

Table 3a Study and summary risk estimates for major cardiac defects and chlorination by-products

all

Study	Exposure	OR (CI95%)
Kallen and Robert 00.	Chlorin vs. No chlorin	1.1 (0.9- 1.3)
Hwang et al 02.	Chlorin. vs. No Chlorin.	1.37 (1.00- 1.89)
Bove et al 95.	>80 vs. <=20 microg/l TTHM	1.83 (0.86- 3.91)
Dodds et al 99.	>100 vs. 0-49 microg/l TTHM	0.77 (0.57- 1.04)
Cedergren et al 02.	>10 vs. <=10 microg/l TTHM	1.3 (1.08- 1.56)
Shaw et al 03.	>=50-75 vs. 0 microg/l TTHM	1.5 (0.67- 3.5)
Nieuwenhuijsen et al 2008.	>60 vs. <30 microg/l TTHM	0.96 (0.78- 1.17)
Chisholm et al 08.	>=130 vs. <60 microg/l TTHM	1.62 (1.04- 2.51)
Combined effect (random)		1.16 (0.98-1.37)



Test for heterogeneity: Q= 17.033 on 7 degrees of freedom (p= 0.017)

Egger test:
Weighted p-value for intercept 0.271

Per 10µg TTHM/L 0.99 (0.95-1.04)

Test for heterogeneity, Q = 3.3931, on 4 degrees of freedom (p=0.49)

Egger test:
Weighted p-value for intercept 0.39

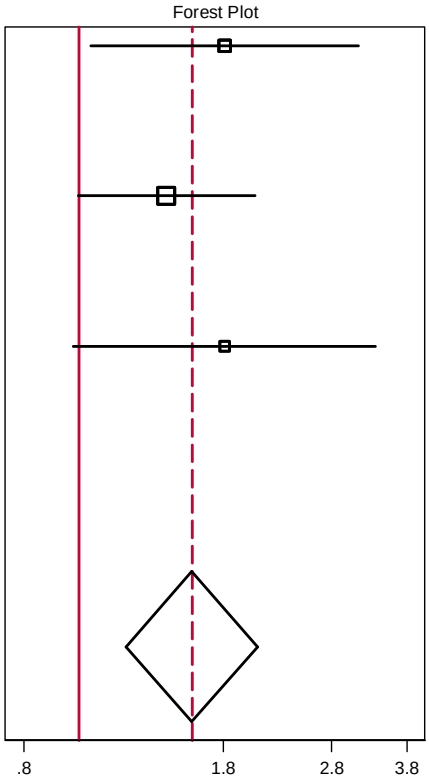
Individual THMs

Dodds et al. 01	< 5 vs. ≥20 µg/l BDCM	0.3 (0.2 -0.7)
Shaw et al. 03		
Nieuwen	<10 vs. >20 µg/l TBROM	1.13 (0.93-1.37)
huijsen et al. 2008	<2 vs. >4 µg/l Bromoform	1.04 (0.87-1.24)

Table 3b Study and summary risk estimates for ventricular septal defects and chlorination by-products

all

Study	Exposure	OR (CI95%)
Hwang et al 02.	Chlorin. vs. No Chlorin.	1.81 (1.05- 3.09)
Nieuwenhuijsen et al 2008.	>60 vs. <30 microg/l TTHM	1.43 (1.0- 2.04)
Hwang et al 2008.	>20 vs. 0-4 microg/l TTHM	1.81 (0.98- 3.35)
Combined effect (fixed)		1.59 (1.21-2.07)



Test for heterogeneity: Q= 0.732 on 2 degrees of freedom (p= 0.69)

Egger test:
Weighted p-value for intercept 0.13

Individual THMs

Nieuwen	<10 vs. >20 µg/l TBROM	1.05 (0.78-1.41)
huijsen et al. 2008*	<2 vs. >4 µg/l Bromoform	1.27 (0.89-1.82)

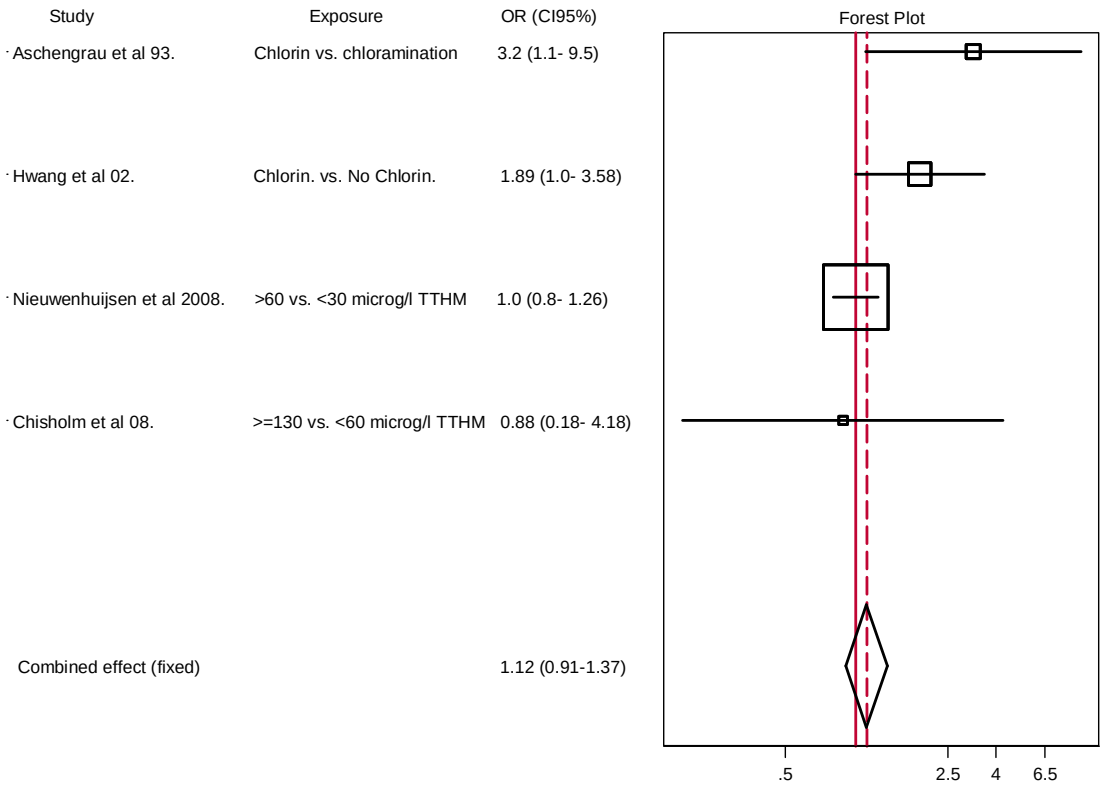
*isolated VSD

Table 3c_Study estimates for Atrial septal_and chlorination by-products

Hwang et al. 02	No chlorination/chlorination Low colour med/high colour	0.92 (0.24-1.50)
Hwang et al. 2008	0-4 vs. >20 µg/l TTHM	1.33 (0.39-4.58)

Table 4 Study and summary risk estimates for respiratory defects and chlorination by-products

all



Test for heterogeneity: Q= 7.275 on 3 degrees of freedom (p= 0.064)

Egger test:
Weighted p-value for intercept 0.29

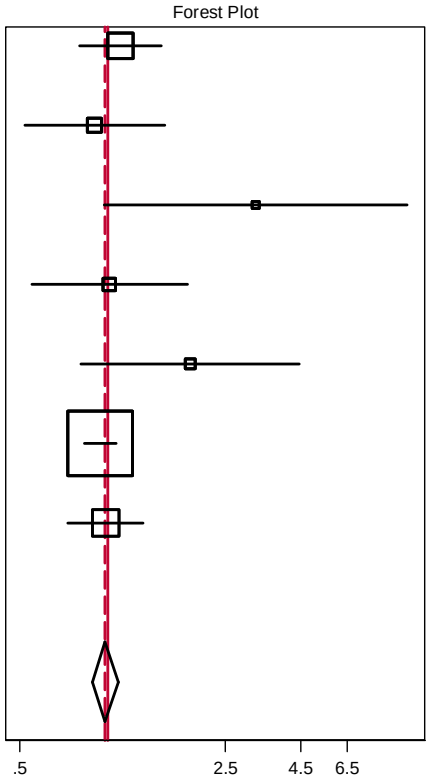
Individual THMs

Nieuwen	<10 vs. >20 µg/l TBROM	1.09 (0.80-1.49)
huijsen et al. 2008	<2 vs. >4 µg/l Bromoform	0.98 (0.78-1.23)

Table 5a Study and summary risk estimates for oral cleft or cleft palate defects and chlorination by-products

All

Study	Exposure	OR (CI95%)
Kallen and Robert 00.	Chlorin vs. Non chlorin.	1.1 (0.8- 1.6)
Hwang et al 02.	Chlorin. vs. No Chlorin.	0.9 (0.52- 1.58)
Bove et al 95.	>100 vs. <=20 microg/l TTHM	3.17 (0.97- 10.32)
Dodds et al 99.	>100 vs. 0-49 microg/l TTHM	1.01 (0.55- 1.86)
Shaw et al 03.	>=50-75 vs.0 microg/l TTHM	1.9 (0.81- 4.5)
Nieuwenhuijsen et al 2008.	>60 vs. <30 microg/l TTHM	0.94 (0.83- 1.06)
Hwang et al 08.	>20 vs. 0-4 microg/l TTHM	0.98 (0.73- 1.32)
Combined effect (fixed)		0.98 (0.88-1.08)



Test for heterogeneity: Q= 7.047 on 6 degrees of freedom (p= 0.32)

Egger test:
Weighted p-value for intercept 0.067

Per 10µg TTHM/L 1.00 (0.96-1.05)

Test for heterogeneity, Q = 3.7503, on 4 degrees of freedom (p=0.44)

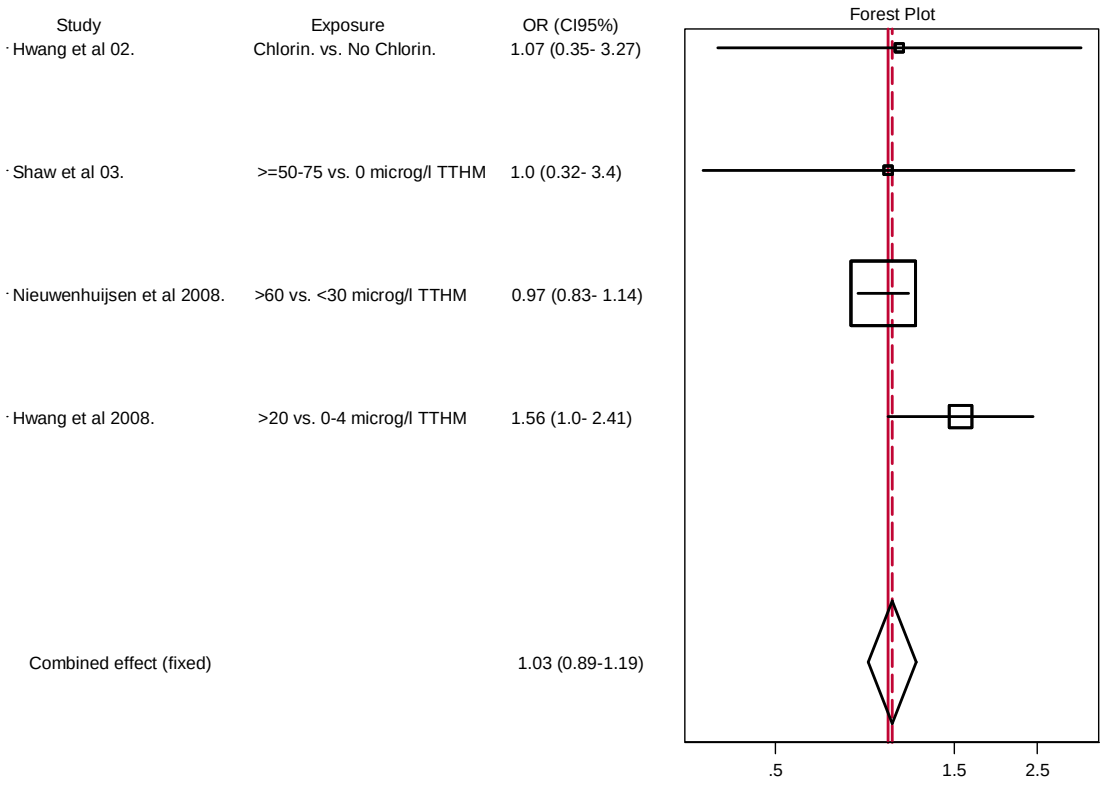
Egger test:
Weighted p-value for intercept 0.04

Individual THMs

Dodds and King 01	<5 vs. ≥ 20 µg/l BDCM	0.6 (0.2 -1.9)
Shaw et al. 03**	<9.6 vs. => 9.6 µg/l BDCM (2)	0.96 (0.56-1.7)
Shaw et al. 03¨**	<3.6 vs. => 3.6 µg/l CDBM (2)	0.87 (0.49-1.5)
Nieuwen	<10 vs. >20 µg/l TBROM	0.96 (0.86-1.07)
huijsen et al. 2008	<2 vs. >4 µg/l Bromoform	1.01 (0.88-1.16)

Table 5b_Study and summary risk estimates for cleft palate only and chlorination by-products

all



Test for heterogeneity: Q= 3.974 on 3 degrees of freedom (p= 0.26)

Egger test:
Weighted p-value for intercept 0.53

Individual THMs

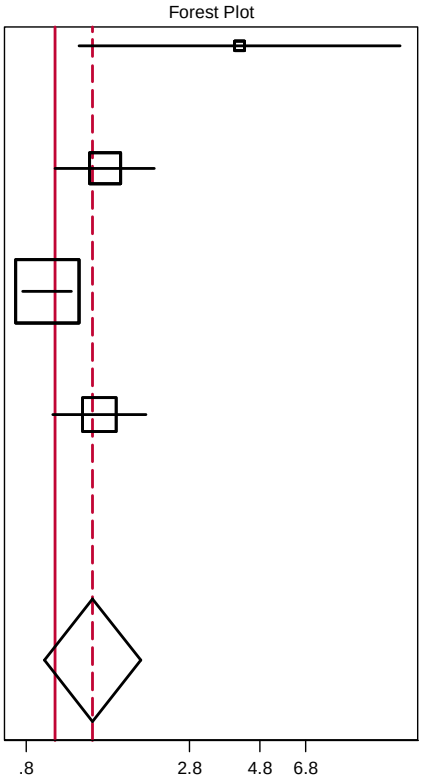
Shaw et al. 03**	<9.6 vs. => 9.6 µg/l BDCM (2)	0.77 (0.36-1.7)
Shaw et al. 03¨**	<3.6 vs. => 3.6 µg/l CDBM (2)	1.00 (0.50-2.1)
Nieuwen	<10 vs. >20 µg/l TBROM	0.96 (0.84-1.11)
huijsen et al. 2008	<2 vs. >4 µg/l Bromoform	0.98 (0.82-1.19)

** isolated

Table 6a Study and summary risk estimates for urinary tract defects and chlorination by-products

all

Study	Exposure	OR (CI95%)
Aschengrau et al 93.	Chlorin. vs. Chloramination	4.1 (1.2- 14.1)
Hwang et al 02.	Chlorin. vs. No Chlorin.	1.46 (1.0- 2.13)
Nieuwenhuijsen et al 2008.	>60 vs. <30 microg/l TTHM	0.94 (0.78- 1.14)
Chisholm et al 08.	>=130 vs. <60 microg/l TTHM	1.4 (0.98- 1.99)
Combined effect (random)		1.33(0.92-1.92)



Test for heterogeneity: Q= 10.939 on 3 degrees of freedom (p= 0.012)

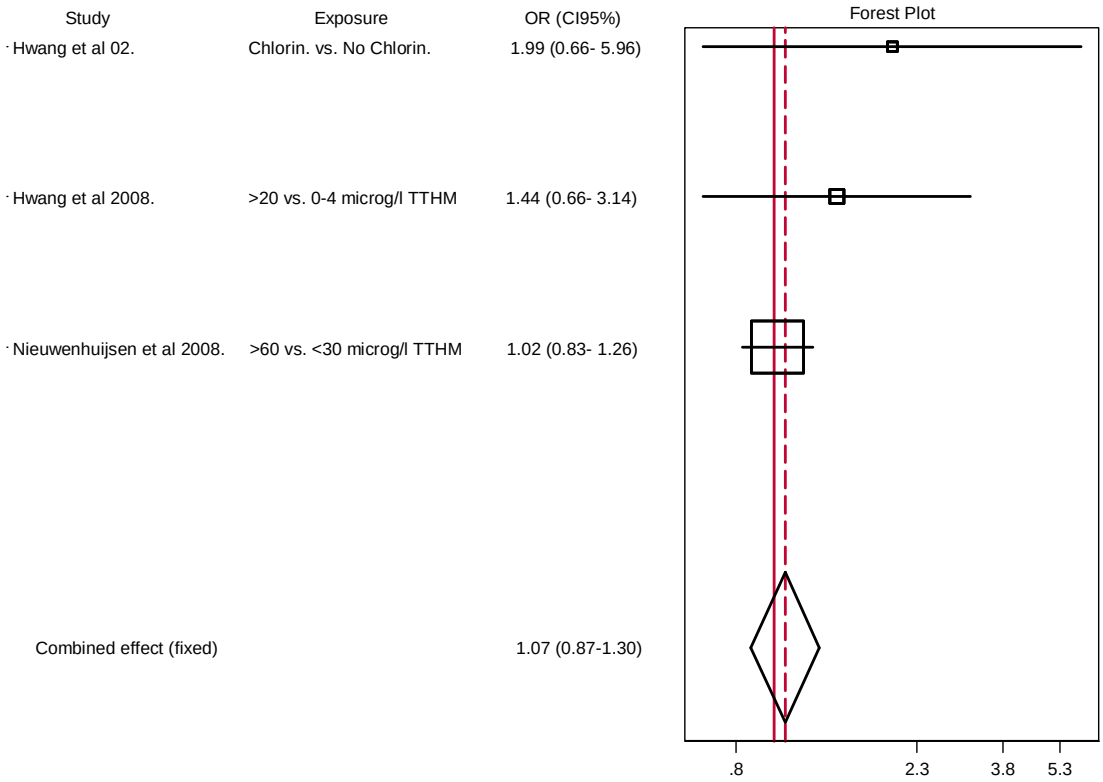
Egger test:
Weighted p-value for intercept 0.002

Individual THMs

Nieuwen	<10 vs. >20 µg/l TBROM	1.05 (0.89-1.25)
huijsen et al. 2008	<2 vs. >4 µg/l Bromoform	0.96 (0.78-1.18)

Table 6b_Study and summary risk estimates for obstructive urinary defects only and chlorination by-products

all



Test for heterogeneity: Q= 1.979 on 2 degrees of freedom (p= 0.37)

Egger test:
Weighted p-value for intercept 0.12

Individual THMs

Nieuwen	<10 vs. >20 µg/l TBROM	0.96 (0.81-1.14)
huijsen et al. 2008*	<2 vs. >4 µg/l Bromoform	0.84 (0.68-1.04)

*isolated

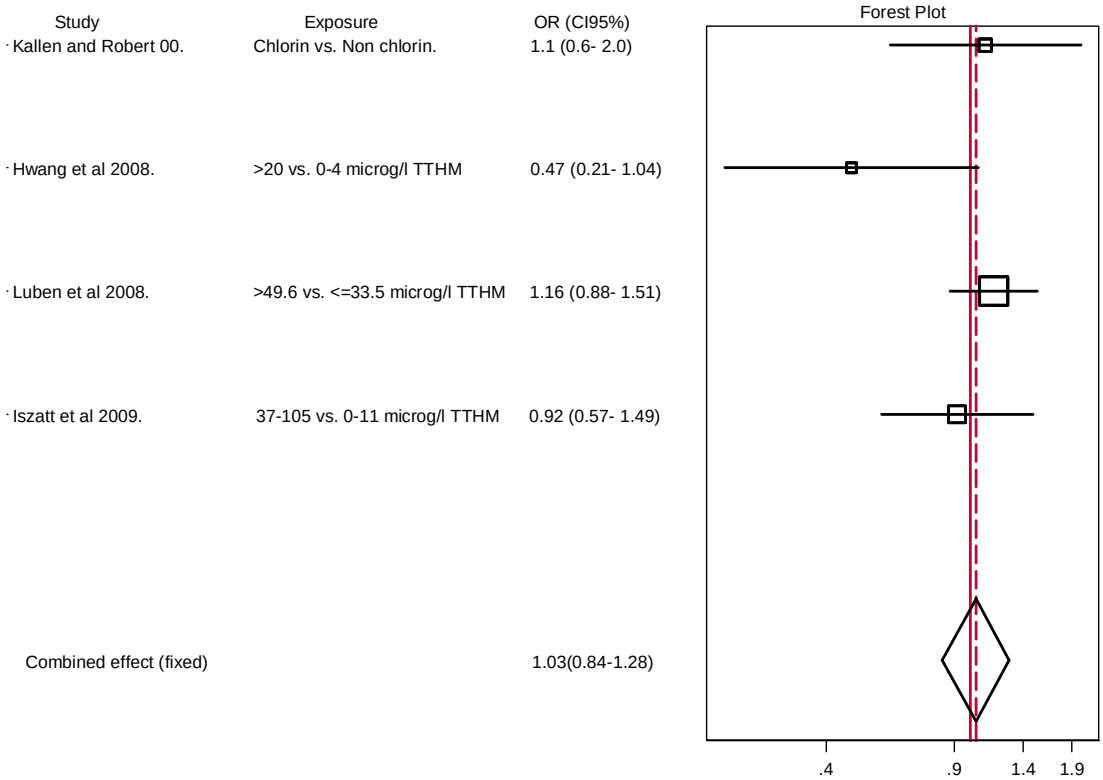
Table 7 Risk estimates for abdominal wall defects and chlorination by-products

Study	**Exposure**	**Risk estimate**
Källen and Robert 00*	Chlorin. vs. non chlorin.	1.3 (0.4 -4.4)
Nieuwen huijsen et al. 2008	<30 vs. > 60 µg/l TTHM	0.81 (0.68-0.95)
Individual THMs		
Nieuwen huijsen et al. 2008	<10 vs. >20 µg/l TBROM	1.02 (0.89-1.17)
	<2 vs. >4 µg/l Bromoform	1.15 (0.82-1.62)

*abdominal wall hernia

Table 8 Study and summary risk estimates for hypospadias and chlorination by-products

all



Test for heterogeneity: Q= 4.697 on 3 degrees of freedom (p= 0.20)

Egger test:
Weighted p-value for intercept 0.17

Ingestion of THMs		
Iszatt et al. 2009	1st vs. 4th quartile brom THMs	1.61 (0.95-2.75)
Iszatt et al. 2009	1st vs. 4th quartile BDCM	1.69 (1.04-2.73)
Luben et al. 2008	0 vs. >0-32.5 µg/day	2.79 (1.01-7.72)
Haloacetic acids		
Luben et al. 2008	<=22.8 vs. >32 µg/l HAA5	1.22 (0.92-1.62)
Total THM uptake		
Luben et al. 2008*	1st vs. 3rd tertile TTHM uptake	1.68 (0.55-5.13)
Iszatt et al. 2009	1st vs. 4th quartile TTHM uptake	0.98 (0.60-1.59)

*subset analyses

Supplementary material 2 Funnel plots for high versus low DBP exposure analyses of congenital anomalies

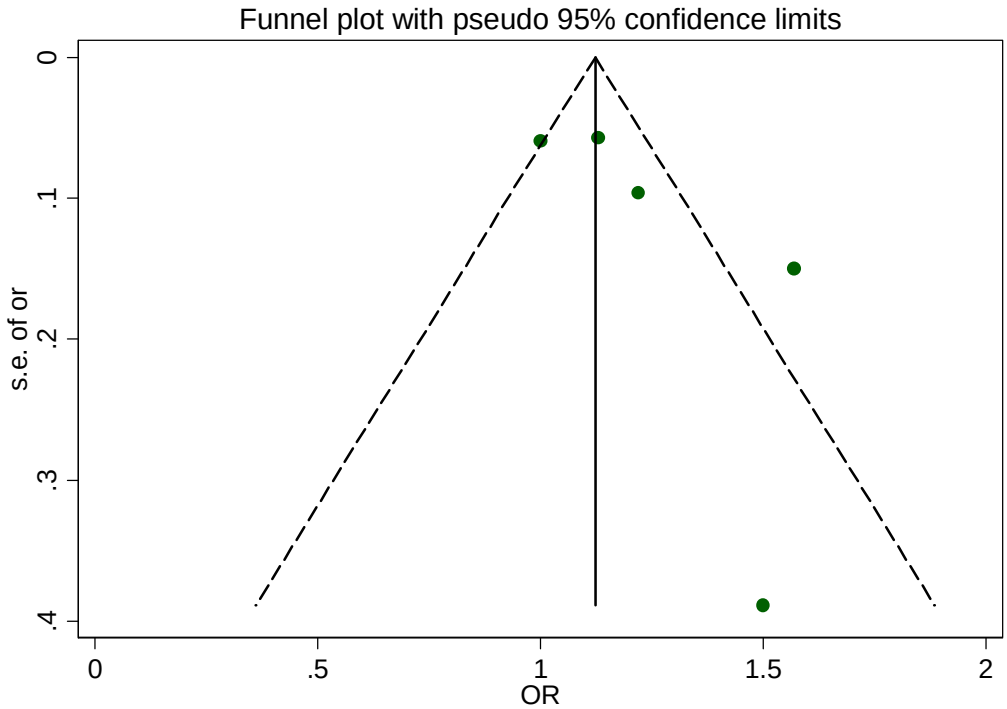


Figure 1 Funnel plot Meta-analyses any congenital anomalies and chlorination by-products

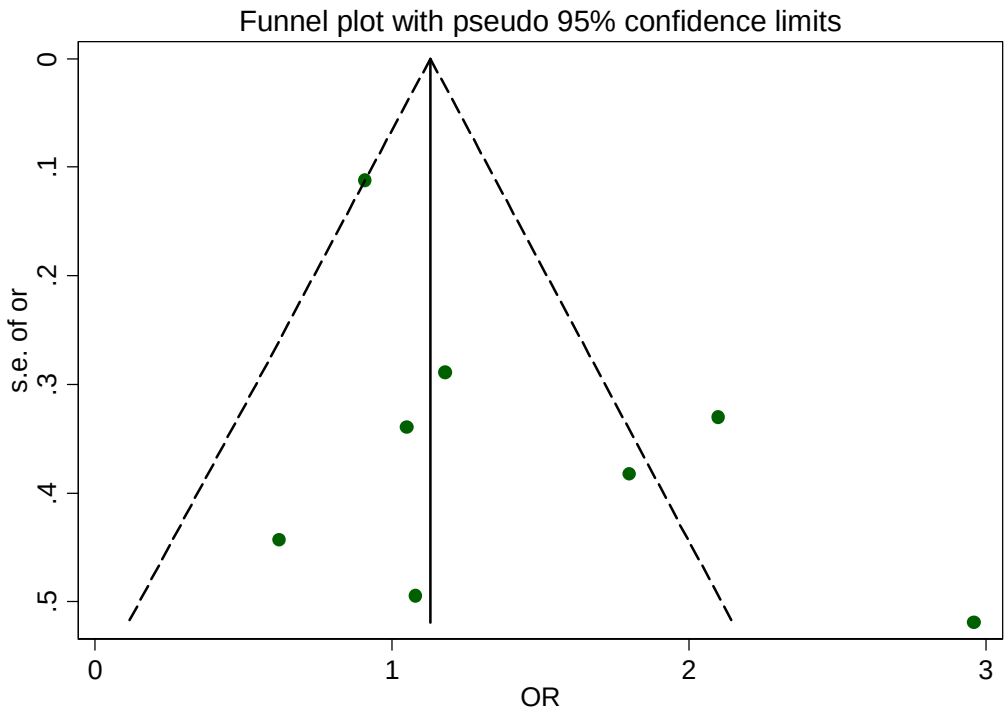


Figure 2 Funnel Plot Meta-analyses Neural tube defects and chlorination by-products

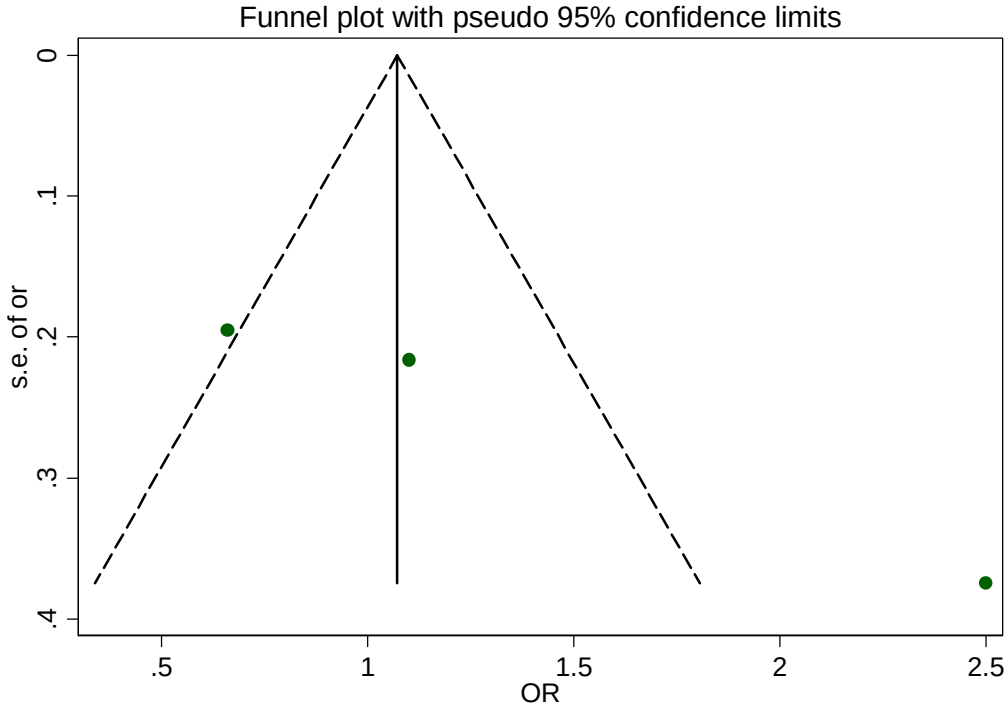


Figure 3 Funnel plot Meta-analyses Neural tube defects (BDCM)

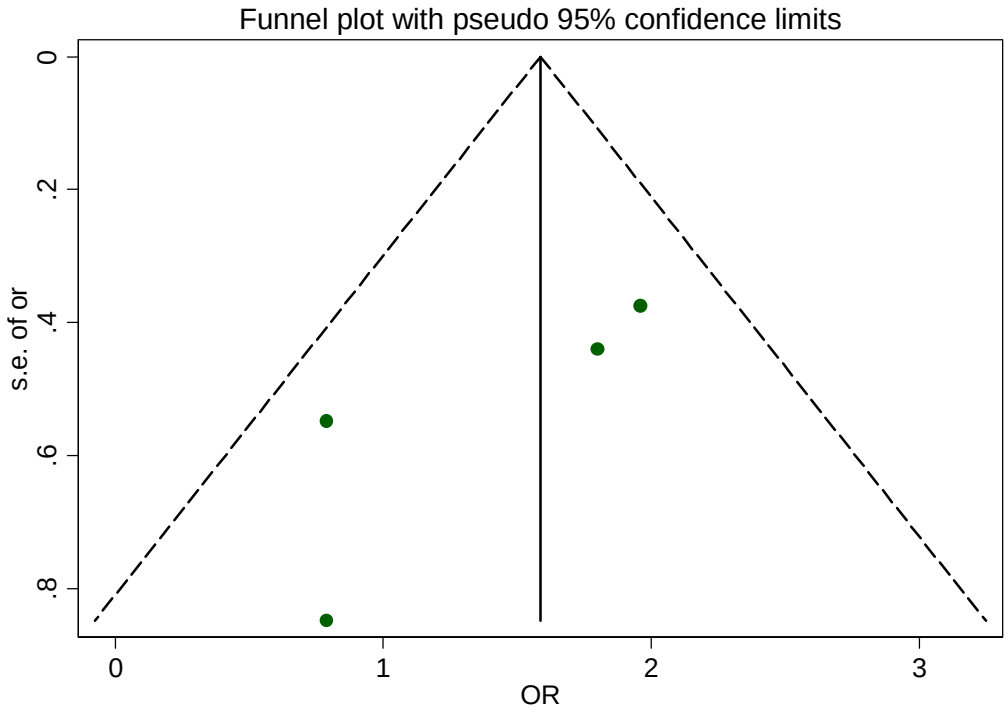


Figure 4 Funnel plot Meta-analyses Anencephalus

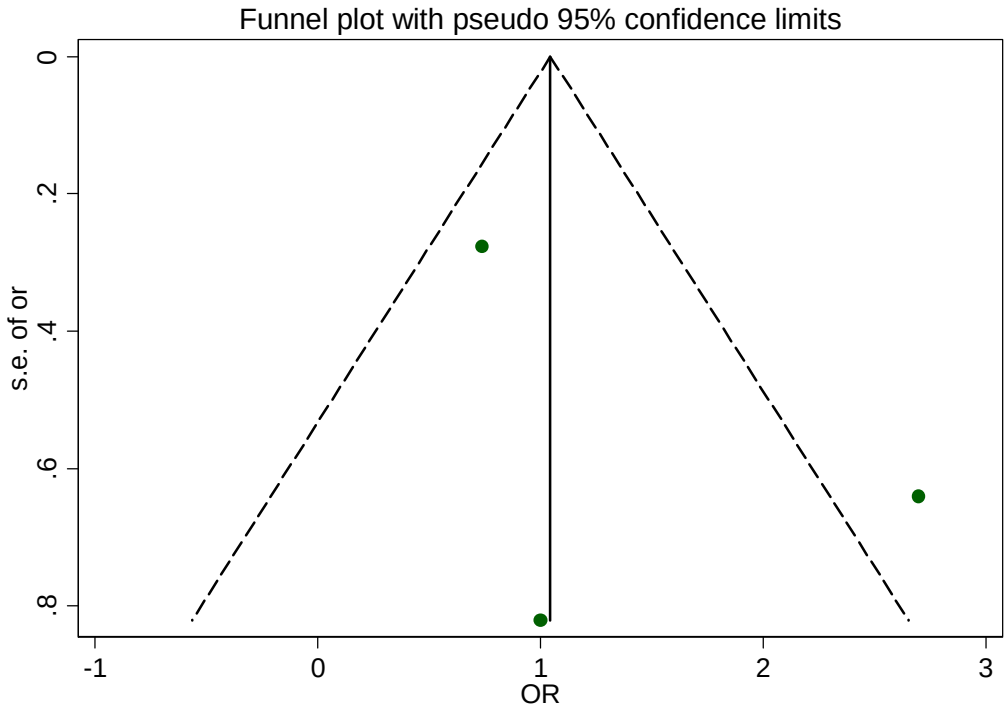
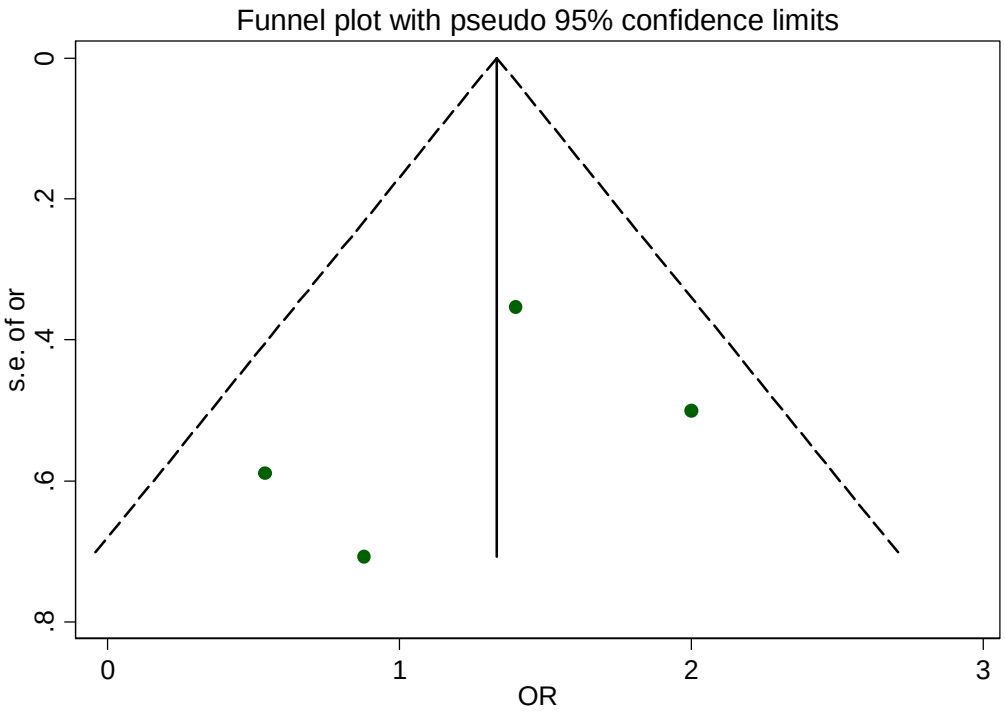


Figure 5 Funnel plot Meta-analyses Hydrocephalus



F Figure 6unnel plot Meta-analyses Spina Bifida

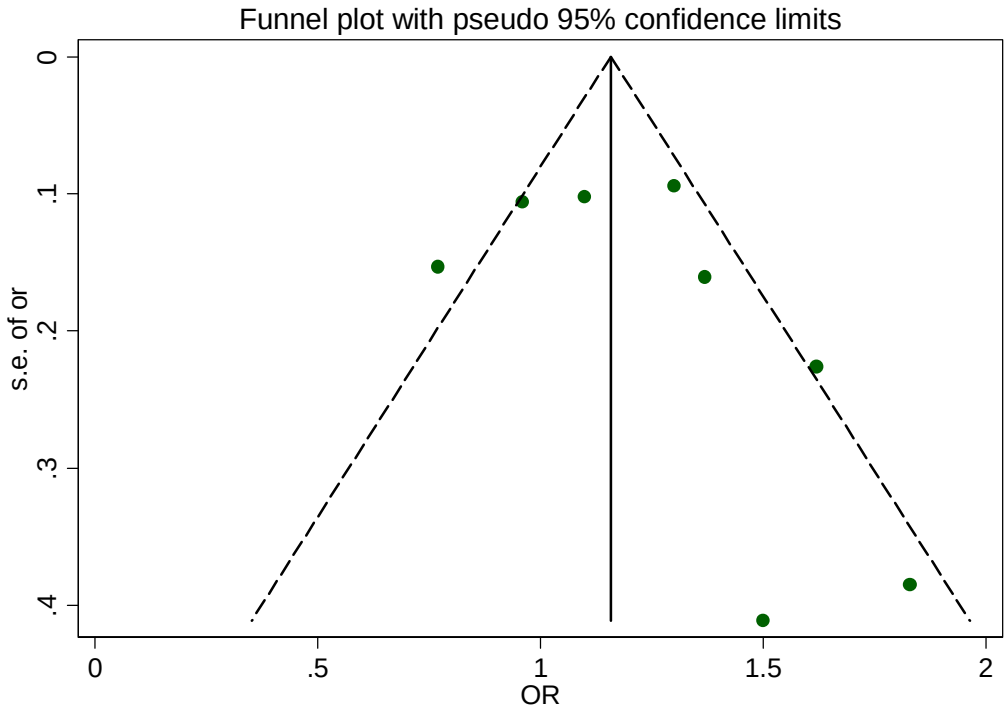


Figure 7 Funnel plot Meta-analyses Major Cardiac defects (a)

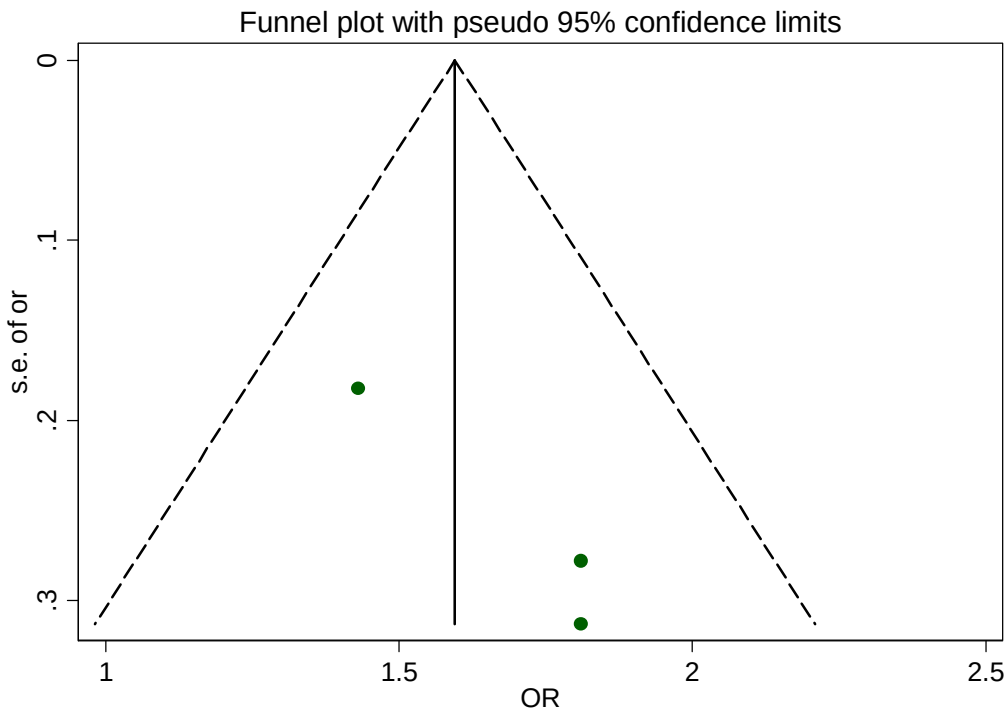


Figure 8 Funnel plot Meta-analyses Ventricular septal defects

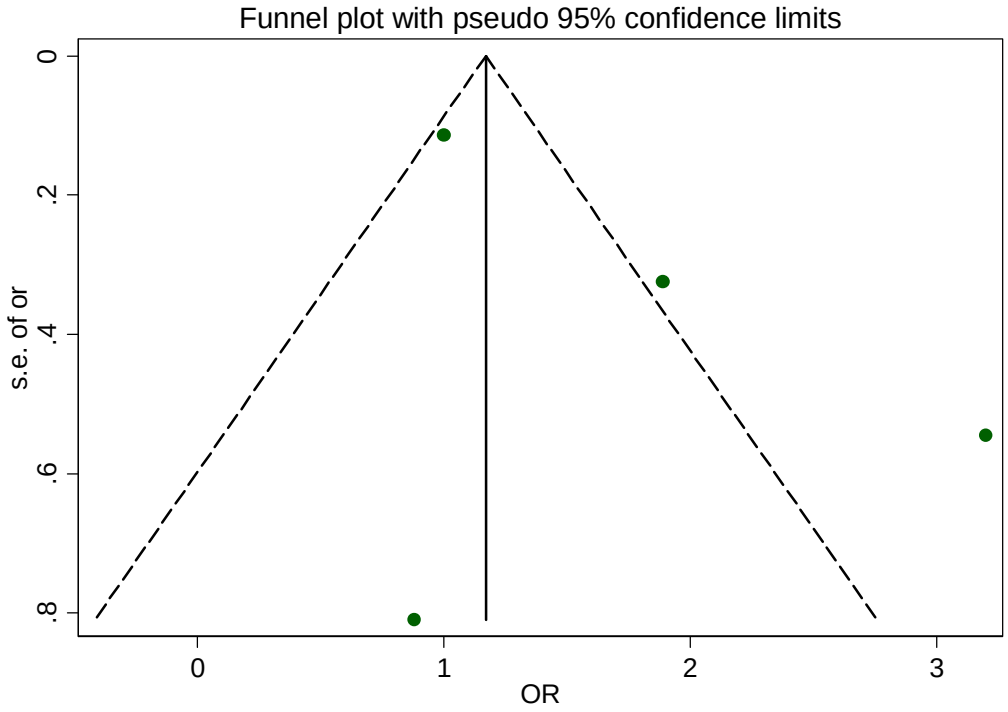


Figure 9 Funnel plot Meta-analyses Respiratory defects

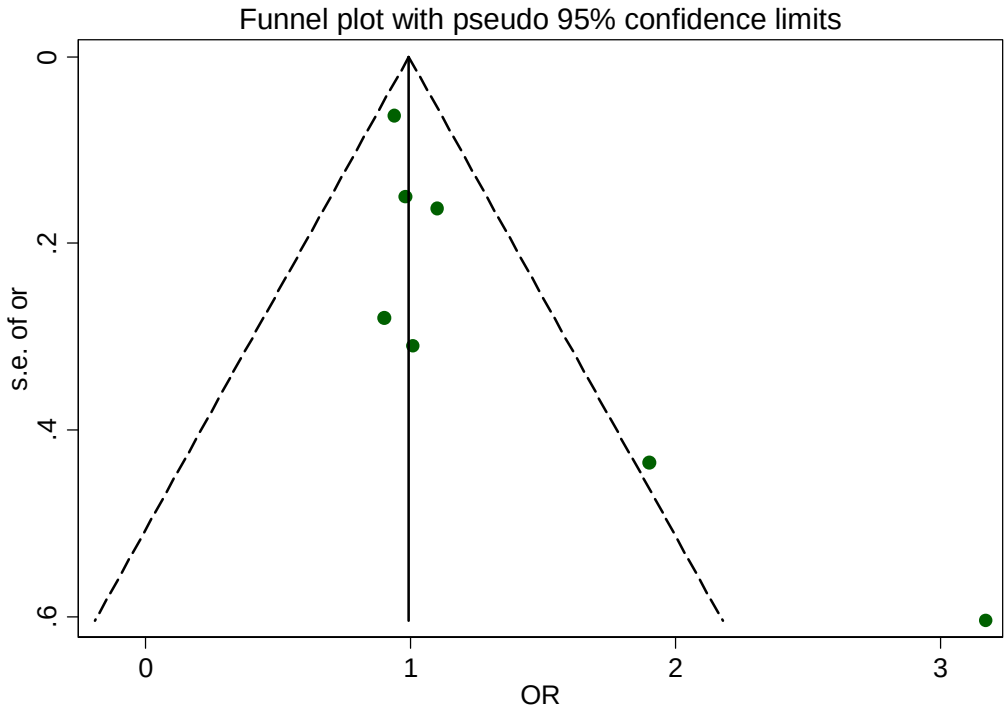


Figure 10 Funnel plot Meta-analyses oral cleft or cleft palate defects

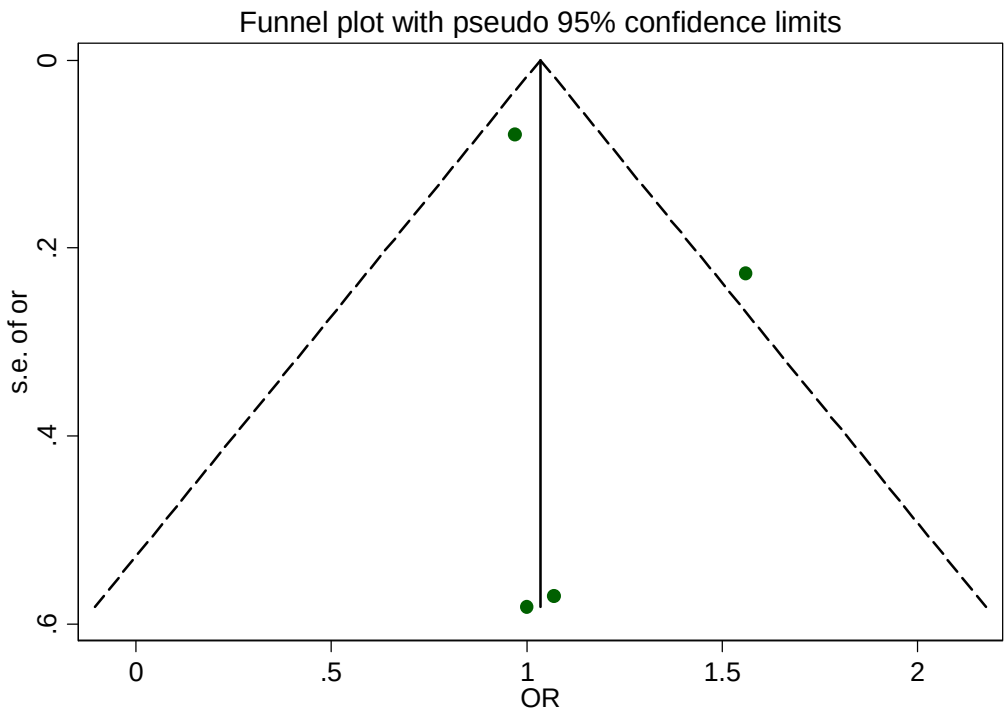


Figure 12 Funnel plot Meta-analyses cleft palate

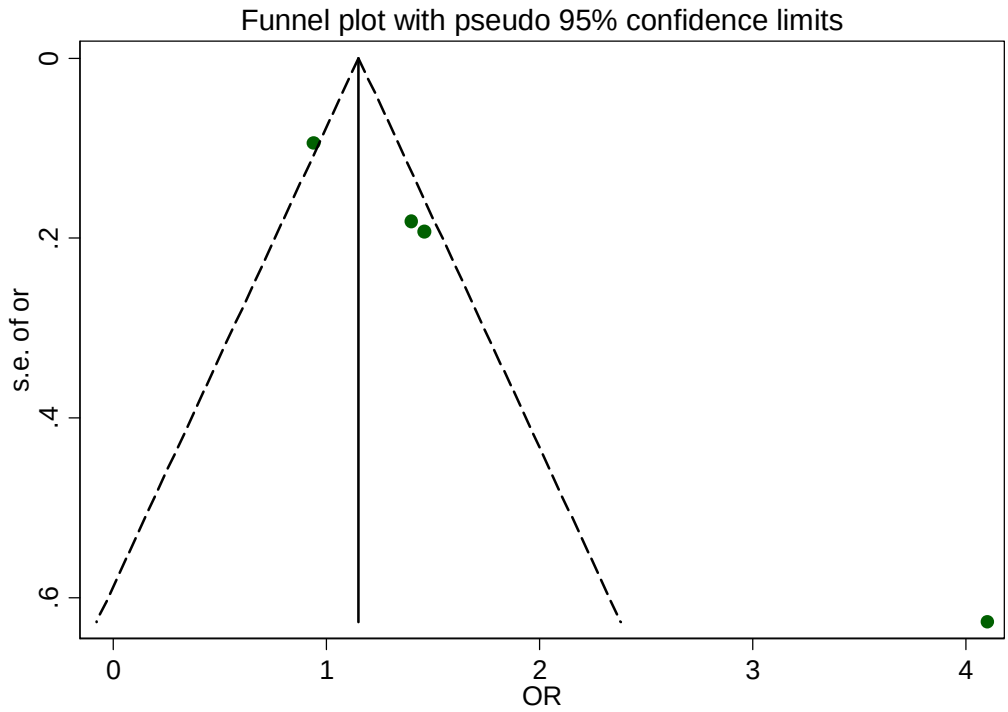


Figure 13 Funnel plot Meta-analyses Urinary tract defects

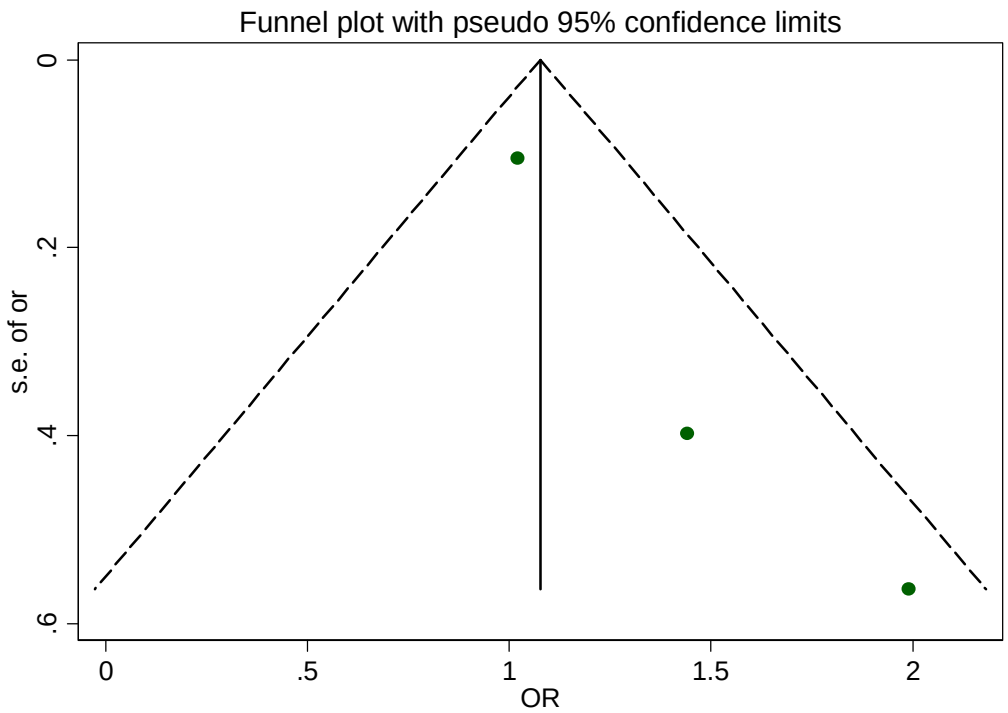


Figure 14 Funnel plot Meta-analyses obstructive urinary defects only

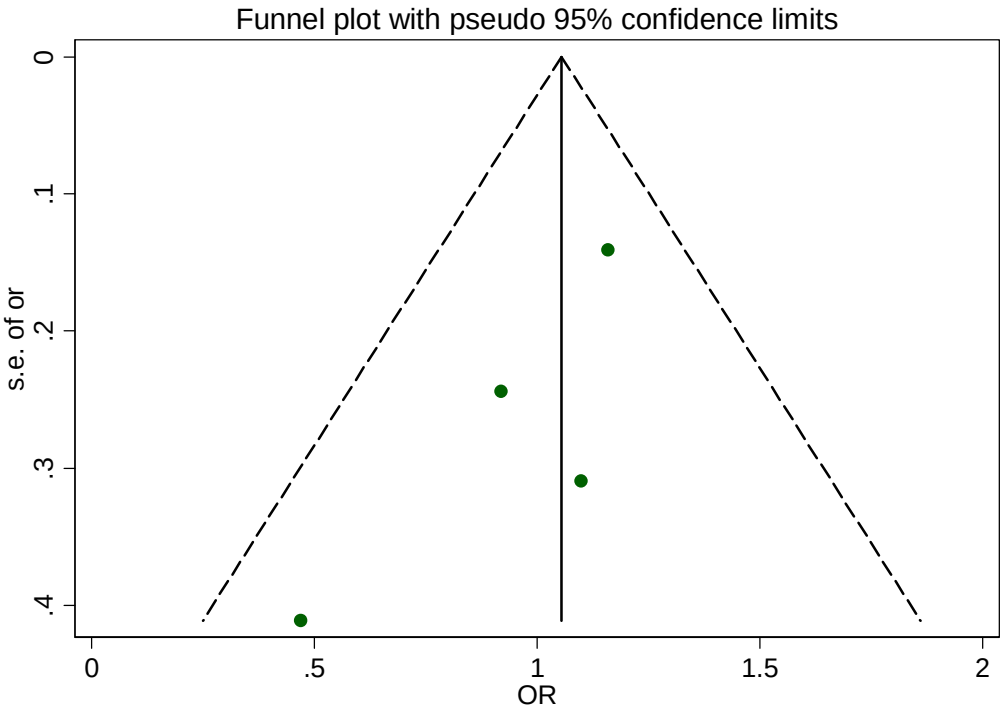


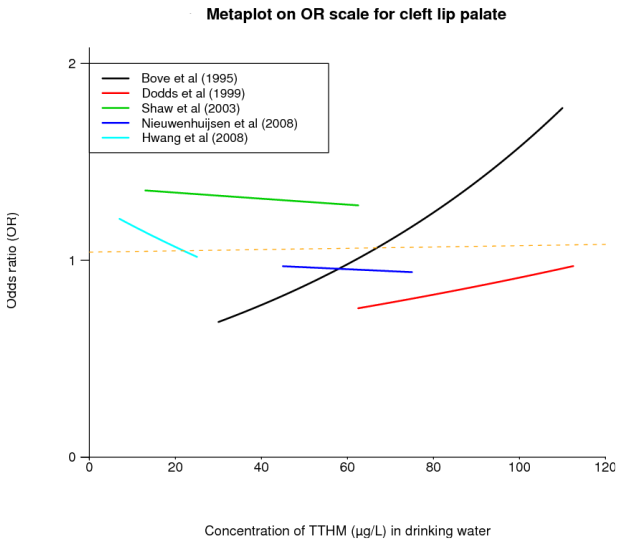
Figure 15 Funnel plot Meta-analyses hypospadias

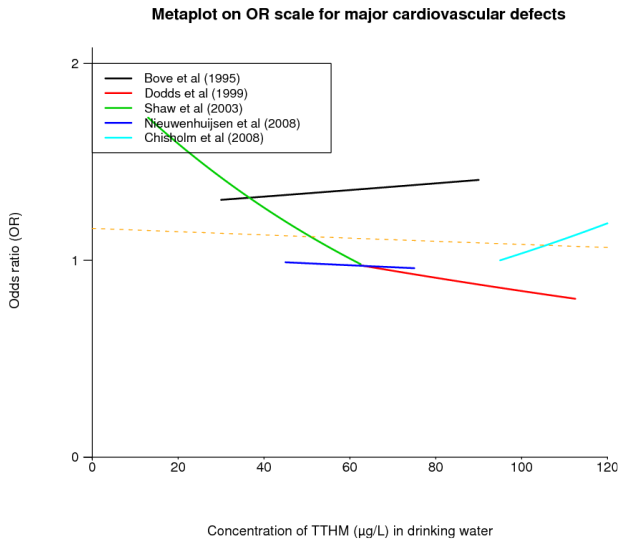
Supplementary material 3

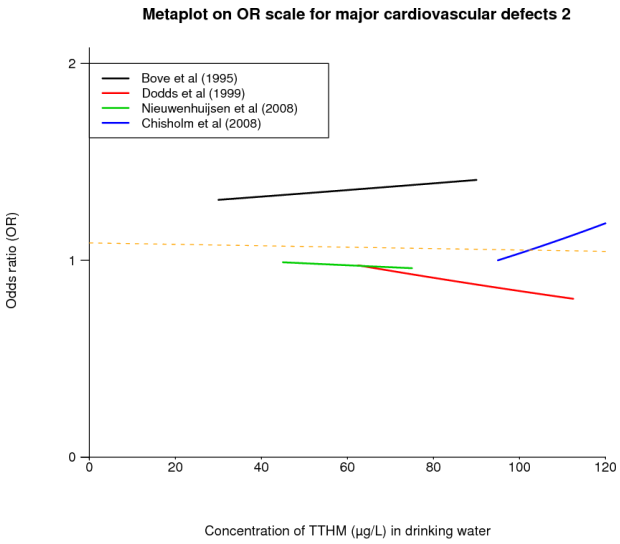
Figure 1 Exposure-response relationship of the meta-analyses per 10 μg/L total trihalomethane (TTHM) analyses

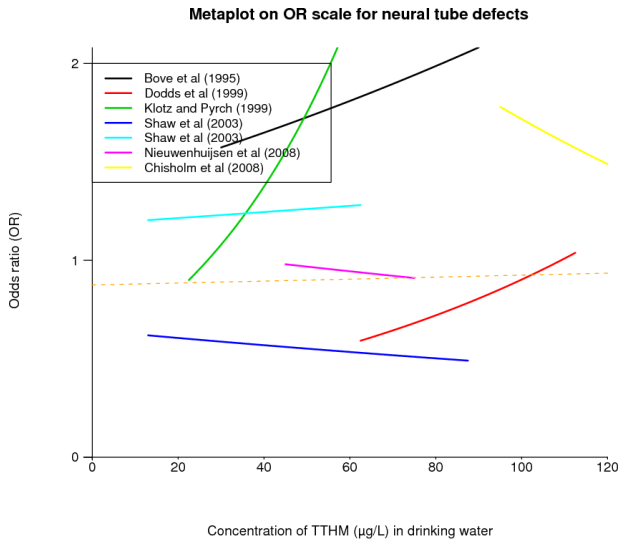
Figure 2 Forest plots of the meta-analyses per 10 μg/L total trihalomethane (TTHM) analyses

Figure 3 Funnel plots of the meta-analyses per 10 μg/L total trihalomethane (TTHM) analyses

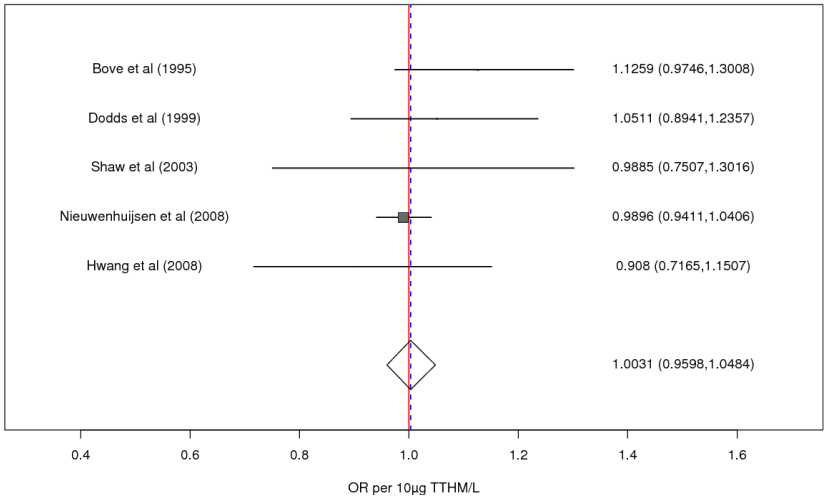

Metaplot on OR scale for cleft lip palate
Bove et al (1995)
Dodds et al (1999)
Shaw et al (2003)
Nieuwenhuijsen et al (2008)
Hwang et al (2008)
Odds ratio (OR)
Concentration of TTHM (µg/L) in drinking water


Metaplot on OR scale for major cardiovascular defects
Bove et al (1995)
Dodds et al (1999)
Shaw et al (2003)
Nieuwenhuijsen et al (2008)
Chisholm et al (2008)
Odds ratio (OR)
Concentration of TTHM (µg/L) in drinking water

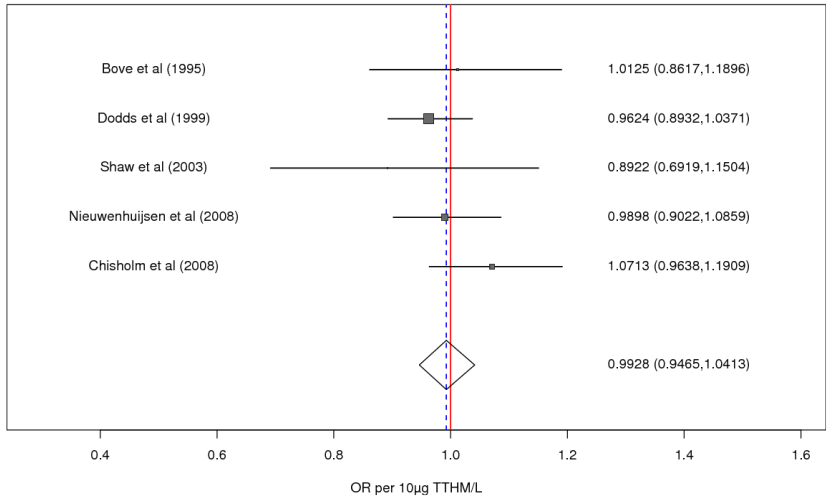

Metaplot on OR scale for major cardiovascular defects 2
Bove et al (1995)
Dodds et al (1999)
Nieuwenhuijsen et al (2008)
Chisholm et al (2008)
Odds ratio (OR)
Concentration of TTHM (µg/L) in drinking water


Metaplot on OR scale for neural tube defects
Bove et al (1995)
Dodds et al (1999)
Klotz and Pyrch (1999)
Shaw et al (2003)
Shaw et al (2003)
Nieuwenhuijsen et al (2008)
Chisholm et al (2008)
Odds ratio (OR)
Concentration of TTHM (µg/L) in drinking water

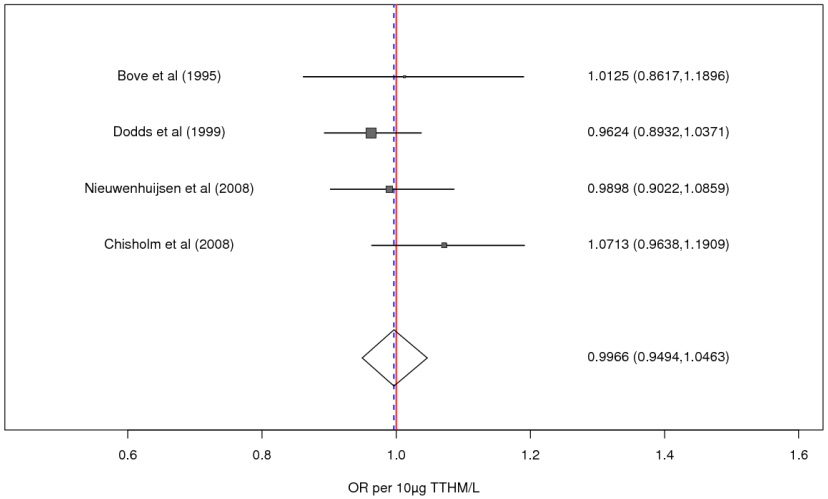
Forest plot of OR per 10µg TTHM/L for cleft lip palate



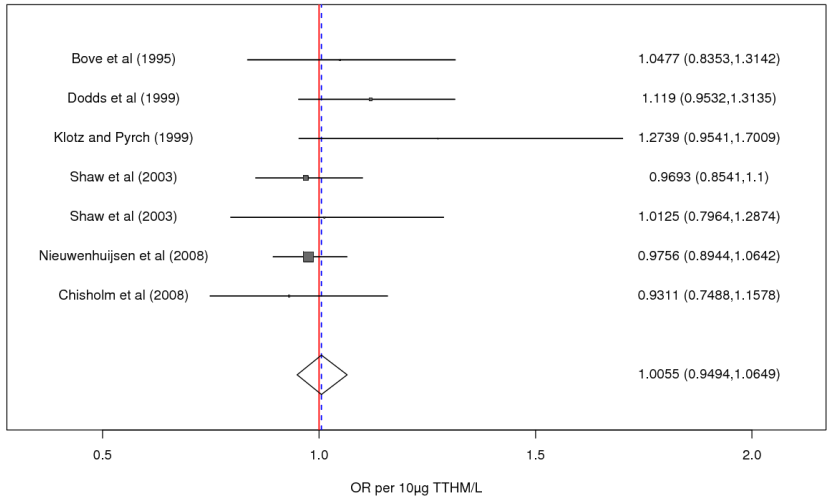
Forest plot of OR per 10µg TTHM/L for major cardiovascular defects

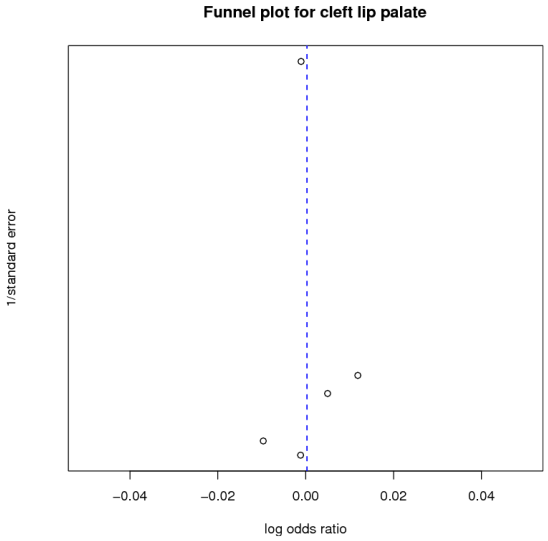


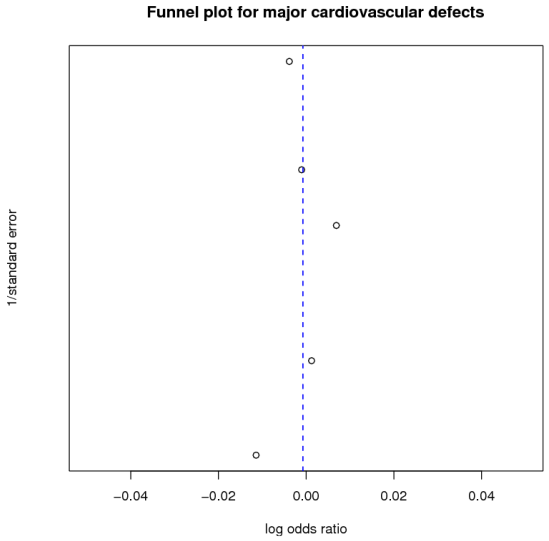
Forest plot of OR per 10µg TTHM/L for major cardiovascular defects 2

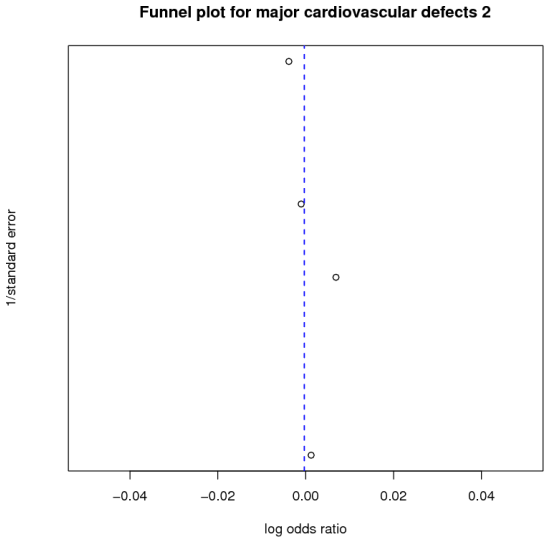


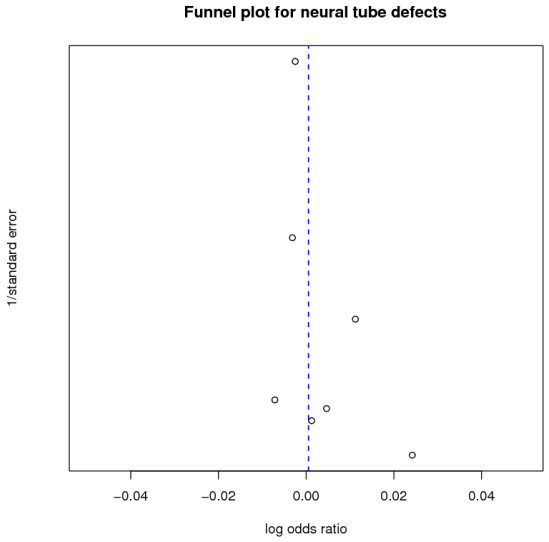
Forest plot of OR per 10µg TTHM/L for neural tube defects




Funnel plot for cleft lip palate
1/standard error
−0.04
−0.02
0.00
0.02
0.04
log odds ratio


Funnel plot for major cardiovascular defects
1/standard error
−0.04
−0.02
0.00
0.02
0.04
log odds ratio


Funnel plot for major cardiovascular defects 2
1/standard error
−0.04
−0.02
0.00
0.02
0.04
log odds ratio


Funnel plot for neural tube defects
1/standard error
−0.04
−0.02
0.00
0.02
0.04
log odds ratio