SUPPLEMENTARY MATERIAL:

Supplement to Methods:

Selection criteria:

Prospective non-randomized and randomized controlled trials (RCT) were included provided pre- and post-intervention data (absolute numbers) or mean difference (between pre- and post-intervention) was available. We included prospective non randomized consecutive case series but excluded case reports. Prospectively conducted multicenter cohort studies with retrospective analyses were also considered eligible for inclusion. However, retrospective cohort studies, as well as studies that reported data in median and inter-quartile range were excluded.

Trial flow:

Figure 1 summarizes the results of the inclusion and exclusion process. As a general rule, for multiple publications of the same trials, we intended to include only the most recent one. As a result, the studies by Yim et. al (E1), Toma et. al (E2), Snell et. al (E3), Hopkinson et. al (E4), and Venuta et. al (E5) were excluded as most of the data from these cohorts was in fact included in the analysis of the multicenter registry study by Wan et al (E6). However, as an exception to this rule, in order to avoid contamination bias and over-representation of study participants in our analyses, we had to exclude the most recent publication of Venuta (E7), since the two studies (E6, E7) had some of the participants in common and more importantly the short-term data by Venuta et. al (E5) was not separable from Wan et. al's study (E6). Some of the participants in the studies by Wood et. al (E8) and Sterman et. al (E9) were in common. We, therefore, included the latest publication on this cohort by Sterman et. al (E9) which also reported long term follow up data with a larger cohort. The study by Refaely et. al (E10) shared the same participants with that of Criner et. al (E11). Therefore, the former was excluded from our analyses. For analysis of bronchial thermal vapor ablation (BTVA), we shortlisted 3 studies (E12-14), however, only one study (E13) was included as this study reported the longest follow up data and the other two were publications of the same cohort.

Data abstraction:

Data were extracted on a pre-specified worksheet. This included first author's name, year of publication, number of study participants, their age and sex distribution, presence of co-morbidities besides chronic obstructive pulmonary disease (COPD), type of bronchoscope lung volume reduction (BLVR), country of origin and study design. For the analyses, we recorded the mean of pre- and post-BLVR, and where necessary the mean difference with SD or 95% CIs for the following: the forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), total lung capacity (TLC), residual volume (RV) and diffusion lung capacity of carbon monoxide (DLCO); the six minute walk distance (6 MWD) and the St. George's Respiratory Questionnaire (SGRQ). For any included study, where such information was not complete for a particular outcome of interest, this information was not included. In any included study, if outcomes were assessed at different time points, we obtained the data available for the longest follow up. Where DLCO was available in mmol/min/kPa units, we used the conversion factor of 0.335 to obtain data in ml/min/mmHg (E15). 6 MWD reported in feet (ft) was converted into m, using the formula; 1 ft = 0.3048 m. Standard errors (SE) were converted into SDs using the formula; SD = SE x ($\sqrt{n}$). For RCTs, comparing lung volume reduction with either control or an active comparator, we extracted data only for the cohort that received BLVR. Some of the datasets in the studies by Kramer et. al (E16) (NCT01181466) and Herth et. al (E15) was in fact, included in the study by Magnussen et. al (E17) (NCT00884962, NCT01051258, NCT 01181466). Therefore, for our analyses, we analyzed the data for FEV_1, FVC, 6 MWD and SGRQ only from

Magnussen et. al's study (E17) and excluded this data from Kramer et. al (E16) and Herth et. al (E15) to avoid over-representation of the same study participants. However, since Magnussen et. al (E17) did not report data on DLCO, this was separately abstracted from the studies by Herth et. al (E15) and Kramer et. al (E16). Similarly, we considered these two studies (E15, E16) separately for our analysis on safety outcomes, since Magnussen et. al's study (E17) was not designed to evaluate these. In the study by Herth et. al (E18) for one-way valves, the investigators reported separate data for cohorts with collateral ventilation either present (CV+) or absent (CV-). Therefore, the outcomes in our analyses were analyzed for these cohorts separately. The study by Criner et. al (E11) reported separate data on low dose and high dose hydrogels. We abstracted and analyzed the data separately. Only SGRQ data from the studies by Herth et. al (E19) and Slebos et. al (E20) was included for analysis, as the data for other outcomes was not available in absolute numbers.

References to Supplement text:

E1. Yim AP, Hwong TM, Lee TW, Li WW, Lam S, Yeung TK, Hui DS, Ko FW, Sihoe AD, Thung KH, Arifi AA. Early results of endoscopic lung volume reduction for emphysema. *The Journal of thoracic and cardiovascular surgery* 2004;127:1564-1573.

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E3. Snell GI, Holsworth L, Borrill ZL, Thomson KR, Kalff V, Smith JA, Williams TJ. The potential for bronchoscopic lung volume reduction using bronchial prostheses: A pilot study. *Chest* 2003;124:1073-1080.

E4. Hopkinson NS, Toma TP, Hansell DM, Goldstraw P, Moxham J, Geddes DM, Polkey MI. Effect of bronchoscopic lung volume reduction on dynamic hyperinflation and exercise in emphysema. *American journal of respiratory and critical care medicine* 2005;171:453-460.

E5. Venuta F, de Giacomo T, Rendina EA, Ciccone AM, Diso D, Perrone A, Parola D, Anile M, Coloni GF. Bronchoscopic lung-volume reduction with one-way valves in patients with heterogenous emphysema. *The Annals of thoracic surgery* 2005;79:411-416; discussion 416-417.

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E7. Venuta F, Anile M, Diso D, Carillo C, De Giacomo T, D'Andrilli A, Fraioli F, Rendina EA, Coloni GF. Long-term follow-up after bronchoscopic lung volume reduction in patients with emphysema. *The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology* 2012;39:1084-1089.

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E9. Sterman DH, Mehta AC, Wood DE, Mathur PN, McKenna RJ, Jr., Ost DE, Truwit JD, Diaz P, Wahidi MM, Cerfolio R, Maxfield R, Musani AI, Gildea T, Sheski F, Machuzak M, Haas AR, Gonzalez HX, Springmeyer SC, Team IBVVUPTR. A multicenter pilot study of a bronchial valve for the treatment of severe emphysema. *Respiration; international review of thoracic diseases* 2010;79:222-233.

E10. Refaely Y, Dransfield M, Kramer MR, Gotfried M, Leeds W, McLennan G, Tewari S, Krasna M, Criner GJ. Biologic lung volume reduction therapy for advanced homogeneous emphysema. *The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology* 2010;36:20-27.

E11. Criner GJ, Pinto-Plata V, Strange C, Dransfield M, Gotfried M, Leeds W, McLennan G, Refaely Y, Tewari S, Krasna M, Celli B. Biologic lung volume reduction in advanced upper lobe emphysema: Phase 2 results. *American journal of respiratory and critical care medicine* 2009;179:791-798.

E12. Gompelmann D, Heussel CP, Eberhardt R, Snell G, Hopkins P, Baker K, Witt C, Valipour A, Wagner M, Stanzel F, Egan J, Ernst A, Kesten S, Herth FJ. Efficacy of bronchoscopic thermal vapor ablation and lobar fissure completeness in patients with heterogeneous emphysema. *Respiration; international review of thoracic diseases* 2012;83:400-406.

E13. Herth FJ, Ernst A, Baker KM, Egan JJ, Gotfried MH, Hopkins P, Stanzel F, Valipour A, Wagner M, Witt C, Kesten S, Snell G. Characterization of outcomes 1 year after endoscopic thermal vapor ablation for patients with heterogeneous emphysema. *International journal of chronic obstructive pulmonary disease* 2012;7:397-405.

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E15. Herth FJ, Gompelmann D, Stanzel F, Bonnet R, Behr J, Schmidt B, Magnussen H, Ernst A, Eberhardt R. Treatment of advanced emphysema with emphysematous lung sealant (aeriseal(r)). *Respiration; international review of thoracic diseases* 2011;82:36-45.

E16. Kramer MR, Refaely Y, Maimon N, Rosengarten D, Fruchter O. Bilateral endoscopic sealant lung volume reduction therapy for advanced emphysema. *Chest* 2012;142:1111-1117.

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E19. Herth FJ, Eberhard R, Gompelmann D, Slebos DJ, Ernst A. Bronchoscopic lung volume reduction with a dedicated coil: A clinical pilot study. *Therapeutic advances in respiratory disease* 2010;4:225-231.

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Supplement Tables

Table E 1: Tests of heterogeneity and publication bias for primary outcomes.

Sub group analyses	Outcomes	Heterogeneity (I^2 index)	Begg and Mazumdar Rank correlation test
One-way valves	**FEV_1**	80.52	Kendall's tau b (corrected for ties, if any) is 0.32, with a 2-tailed p-value of 0.26 (based on continuity-corrected normal approximation).
	6MWD	63.77	Kendall's tau b (corrected for ties, if any) is 0.19, with a 2-tailed p-value of 0.46 (based on continuity-corrected normal approximation).
	SGRQ	98.43	In this case Kendall's tau b (corrected for ties, if any) is -0.38, with a 2-tailed p-value of 0.22 (based on continuity-corrected normal approximation).
	DLCO	37.92	In this case Kendall's tau b (corrected for ties, if any) is 0.00, with a 2-tailed p-value of 1.00 (based on continuity-corrected normal approximation).
	FVC	N/E	N/E
	TLC	94.96	In this case Kendall's tau b (corrected for ties, if any) is 0.66, with a 2-tailed p-value of 0.29 (based on continuity-corrected normal approximation).
	RV	85.97	In this case Kendall's tau b (corrected for ties, if any) is 0.00, with a 2-tailed p-value of 1.00 (based on continuity-corrected normal approximation).
BioLVR	**FEV_1**	N/E	N/E
	6MWD	0.00	In this case Kendall's tau b (corrected for ties, if any) is -0.66, with a 2-tailed p-value of 0.29 (based on continuity-corrected normal approximation).
	SGRQ	26.05	In this case Kendall's tau b (corrected for ties, if any) is 0.00, with a 2-tailed p-value of 1.0 (based on continuity-corrected normal approximation).
	DLCO	N/E	N/E
	FVC	N/E	N/E
	TLC	N/E	N/E
	RV	N/E	N/E
LVRC	**FEV_1**	N/E	N/E
	6MWD	N/E	N/E

	SGRQ	N/E		N/E	
Airway by-pass stent	**FEV$_1$**	N/E		N/E	
	6MWD	N/E		N/E	
	SGRQ	N/E		N/E	
	DLCO	N/E		N/E	
	FVC	N/E		N/E	
	TLC	N/E		N/E	
	RV	N/E		N/E	

FEV$_1$indicates forced expiratory volume in the first second
6 MWD indicates six minute walk test distance
SGRQ indicates St. George's Respiratory Questionnaire
DLCO indicates diffusion capacity of the lung for carbon monoxide
FVC indicates forced vital capacity
TLC indicates total lung capacity
RV indicates residual volume
BioLVR indicates studies using sealants.
LVRC indicates lung volume reduction coils
N/E indicates that the data was not estimable

Table E 2: Tests of heterogeneity and publication bias for secondary outcomes.

Sub group analyses	Outcomes	Heterogeneity (I^2 index)	Begg and Mazumdar Rank correlation test
One-way valves	**Pneumonia (distal to valve)**	0.00	In this case Kendall's tau b (corrected for ties, if any) is 0.09, with a 2-tailed p-value of 0.76 (based on continuity-corrected normal approximation).
	Pneumothorax	27.19	In this case Kendall's tau b (corrected for ties, if any) is 0.60, with a 2-tailed p-value of 0.03 (based on continuity-corrected normal approximation).
	Valve migration	72.16	In this case Kendall's tau b (corrected for ties, if any) is 0.28, with a 2-tailed p-value of 0.36 (based on continuity-corrected normal approximation).
BioLVR	**Pneumonia (treatment-related)**	0.00	In this case Kendall's tau b (corrected for ties, if any) is 0.66, with a 2-tailed p-value of 0.29 (based on continuity-corrected normal approximation).
	COPD exacerbations (treatment-related)	85.12	In this case Kendall's tau b (corrected for ties, if any) is 0.66, with a 2-tailed p-value of 0.29 (based on continuity-corrected normal approximation).

BioLVR indicates studies using sealants.
COPD indicates chronic obstructive pulmonary disease.

Supplement figures:

FIGURE LEGENDS FOR SUPPLEMENTARY FIGURES:

Figure E 1. Change in FVC.

The *diamond* reflects the 95% confidence interval of the pooled estimate of mean difference.

CI indicates confidence intervals.

'BioLVR' indicates studies using sealants/hydrogels.

'BTVA' indicates studies that used bronchial thermal vapor ablation.

'Stents' indicates studies using air way by-pass stents.

'Valves' indicates the subgroup of studies that used one way one-way valves.

FVC indicates forced vital capacity in liters.

Figure E 2. Change in TLC.

The *diamond* reflects the 95% confidence interval of the pooled estimate of mean difference.

CI indicates confidence intervals.

'BioLVR' indicates studies using sealants/hydrogels.

'Stents' indicates studies using air way by-pass stents.

'Valves' indicates the subgroup of studies that used one way one-way valves.

TLC indicates total lung capacity in liters.

Figure E 3. Change in RV.

The *diamond* reflects the 95% confidence interval of the pooled estimate of mean difference.

CI indicates confidence intervals.

'BioLVR' indicates studies using sealants/hydrogels.

'BTVA' indicates studies that used bronchial thermal vapor ablation.

'Stents' indicates studies using air way by-pass stents.

‘Valves’ indicates the subgroup of studies that used one way one-way valves.

RV indicates residual volume in liters.

Figure E 4. Change in DLCO.

The *diamond* reflects the 95% confidence interval of the pooled estimate of mean difference.

CI indicates confidence intervals.

‘BioLVR’ indicates studies using sealants/hydrogels.

‘BTVA’ indicates studies that used bronchial thermal vapor ablation.

‘Valves’ indicates the subgroup of studies that used one way one-way valves.

DLCO indicates diffusion capacity of the lung for carbon monoxide measured in ml/min/mmHg.

Figure E 5. Incidence rate of Pneumonia (distal to valve).

The *diamond* reflects the 95% confidence interval of the pooled estimate of mean incidence rate.

CI indicates confidence intervals.

Figure E 6. Incidence rate of Pneumothorax (valve or procedure related).

The *diamond* reflects the 95% confidence interval of the pooled estimate of mean incidence rate.

CI indicates confidence intervals.

Figure E 7. Incidence rate of valve migration.

The *diamond* reflects the 95% confidence interval of the pooled estimate of mean incidence rate.

CI indicates confidence intervals.

Figure E 8. Incidence rate of treatment related COPD exacerbations with BioLVR.

The *diamond* reflects the 95% confidence interval of the pooled estimate of mean incidence rate.

CI indicates confidence intervals.

BioLVR indicates studies using sealants/hydrogels.

COPD indicates chronic obstructive pulmonary disease.

Figure E 9. Incidence rate of treatment related COPD exacerbations with LVRC.

The *diamond* reflects the 95% confidence interval of the pooled estimate of mean incidence rate.

CI indicates confidence intervals.

COPD indicates chronic obstructive pulmonary disease.

LVRC indicates studies using lung volume reduction coils.

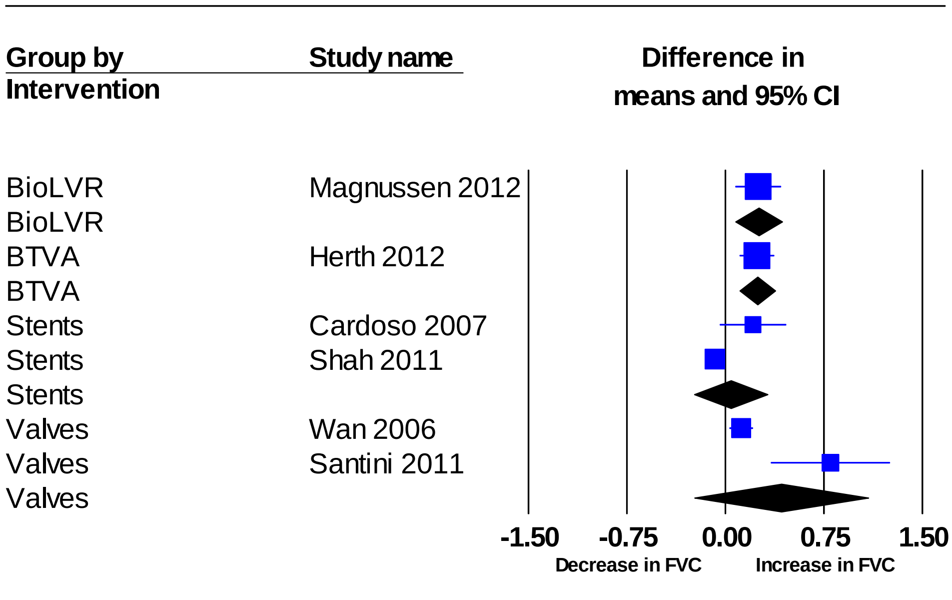
Figure E 10. Incidence rate of treatment related Pneumonia with BioLVR.

The *diamond* reflects the 95% confidence interval of the pooled estimate of mean incidence rate.

CI indicates confidence intervals.

BioLVR indicates studies using sealants/hydrogels.

Figure E 1.



Group by Intervention
Study name
Difference in means and 95% CI
BioLVR
Magnussen 2012
BioLVR
BTVA
Herth 2012
BTVA
Stents
Cardoso 2007
Stents
Shah 2011
Stents
Valves
Wan 2006
Valves
Santini 2011
Valves
-1.50
-0.75
0.00
0.75
1.50
Decrease in FVC
Increase in FVC

Figure E 2.

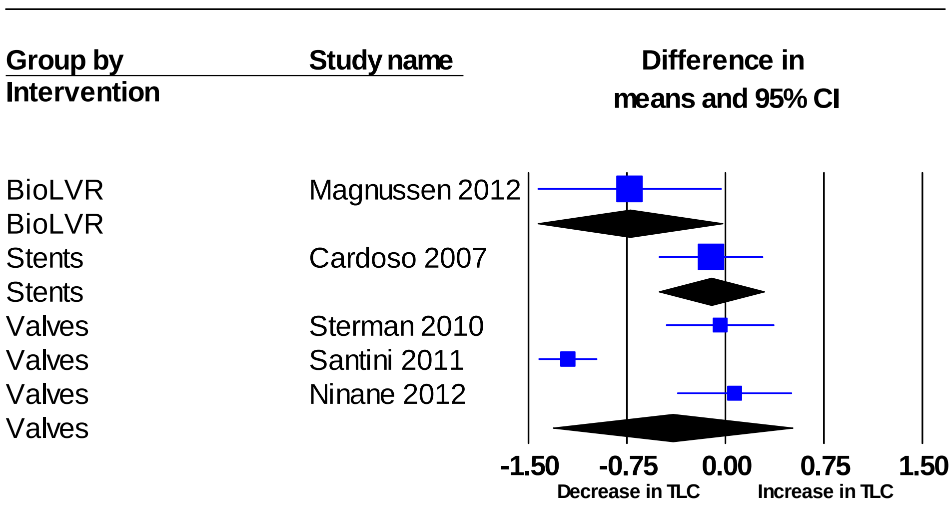

Group by Intervention
Study name
Difference in means and 95% CI
BioLVR
Magnussen 2012
BioLVR
Stents
Cardoso 2007
Stents
Valves
Sterman 2010
Valves
Santini 2011
Valves
Ninane 2012
Valves
-1.50
-0.75
0.00
0.75
1.50
Decrease in TLC
Increase in TLC

Figure E 3.

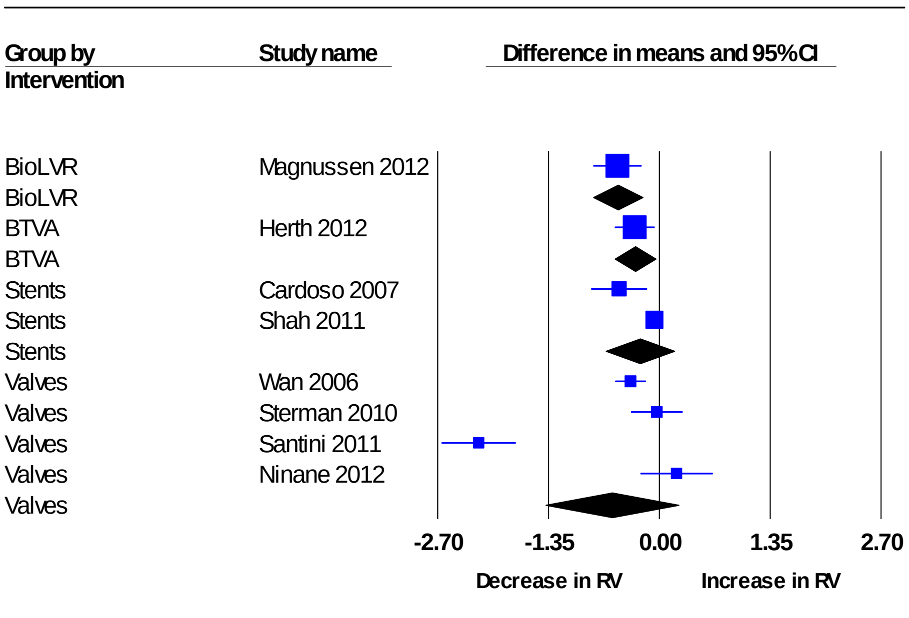

Group by Intervention
Study name
Difference in means and 95%CI
BioLVR
Magnussen 2012
BioLVR
BTVA
Herth 2012
BTVA
Stents
Cardoso 2007
Stents
Shah 2011
Stents
Valves
Wan 2006
Valves
Sterman 2010
Valves
Santini 2011
Valves
Ninane 2012
Valves
-2.70
-1.35
0.00
1.35
2.70
Decrease in RV
Increase in RV

Figure E 4.

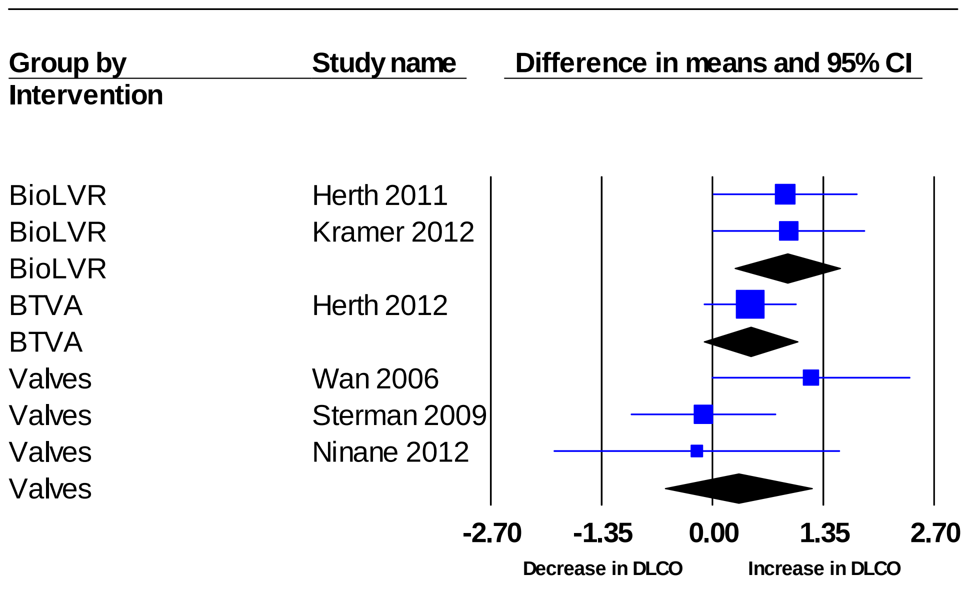

Group by Intervention
Study name
Difference in means and 95% CI
BioLVR
Herth 2011
BioLVR
Kramer 2012
BioLVR
BTVA
Herth 2012
BTVA
Valves
Wan 2006
Valves
Sterman 2009
Valves
Ninane 2012
Valves
-2.70
-1.35
0.00
1.35
2.70
Decrease in DLCO
Increase in DLCO

Figure E 5.

Study name	Rate	p-Value	Total
Wan 2006	0.021	0.480	0 / 24
Sterman 2010	0.066	0.014	6 / 91
Sciurba 2010	0.039	0.157	2 / 51
Chung 2010	1.563	0.317	1 / 1
Santini 2011	0.100	0.480	0 / 5
Ninane 2012	0.051	0.480	0 / 9
Herth 2012	0.063	0.008	7 / 111
	0.050	0.000	

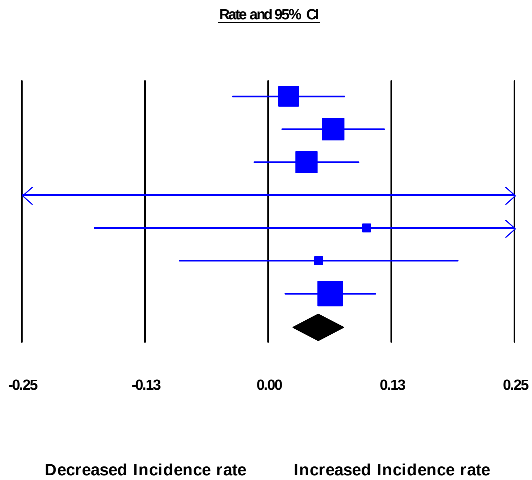
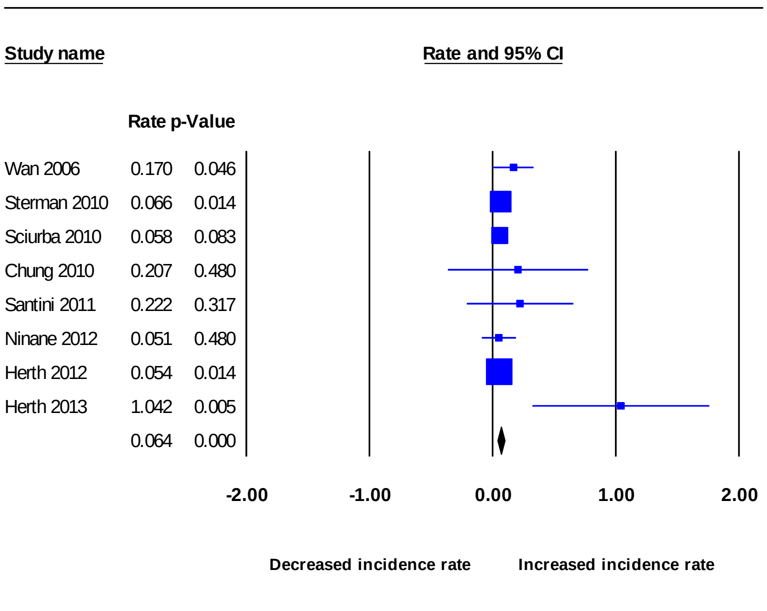


Figure E 6.



Study name
Rate and 95% CI
Rate p-Value
Wan 2006 0.170 0.046
Sterman 2010 0.066 0.014
Sciurba 2010 0.058 0.083
Chung 2010 0.207 0.480
Santini 2011 0.222 0.317
Ninane 2012 0.051 0.480
Herth 2012 0.054 0.014
Herth 2013 1.042 0.005
0.064 0.000
-2.00
-1.00
0.00
1.00
2.00
Decreased incidence rate
Increased incidence rate

Figure E 7.

Study name	Rate	p-Value
Wan 2006	0.021	0.480
Sterman 2010	0.005	0.480
Sciurba 2010	0.195	0.002
Chung 2010	1.563	0.317
Santini 2011	0.100	0.480
Ninane 2012	0.051	0.480
Herth 2012	0.117	0.000
	0.015	0.035

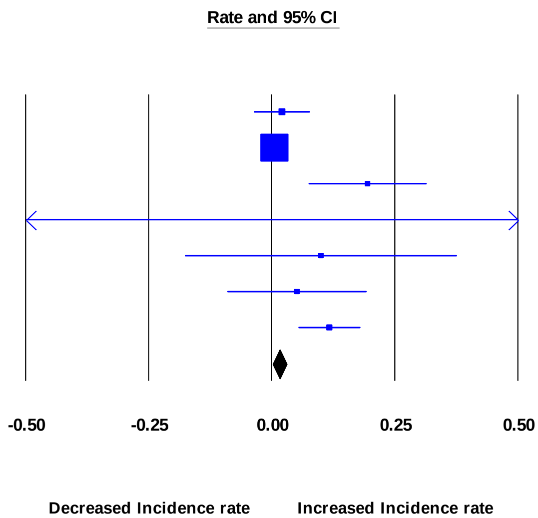


Figure E 8.

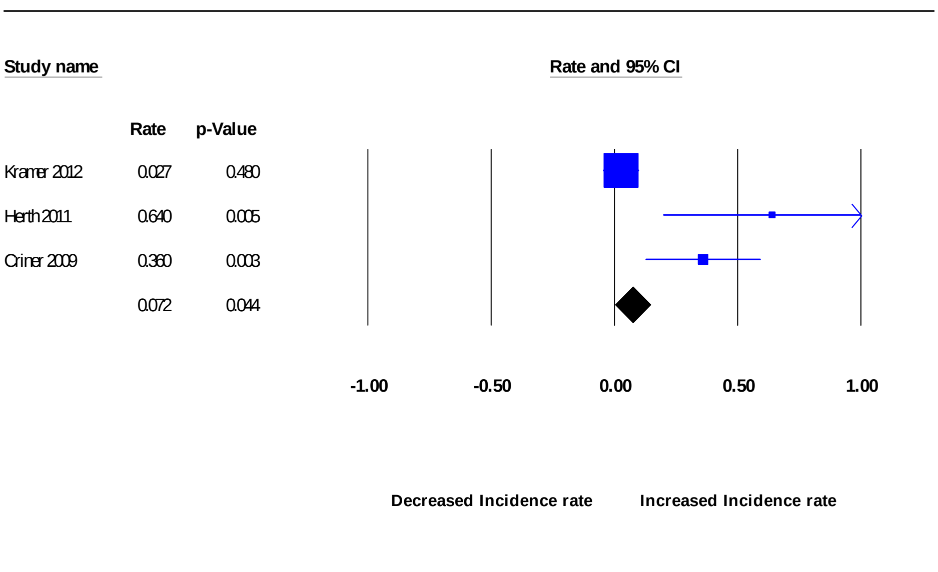

Study name
Rate and 95% CI
Rate
p-Value
Kramer 2012
0.027
0.480
Herth 2011
0.640
0.005
Criner 2009
0.360
0.003
0.072
0.044
-1.00
-0.50
0.00
0.50
1.00
Decreased Incidence rate
Increased Incidence rate

Figure E 9.

Study name	Rate	p-Value
Herth 2010	1.000	0.083
Slebos 2012	4.688	0.014
	1.308	0.018

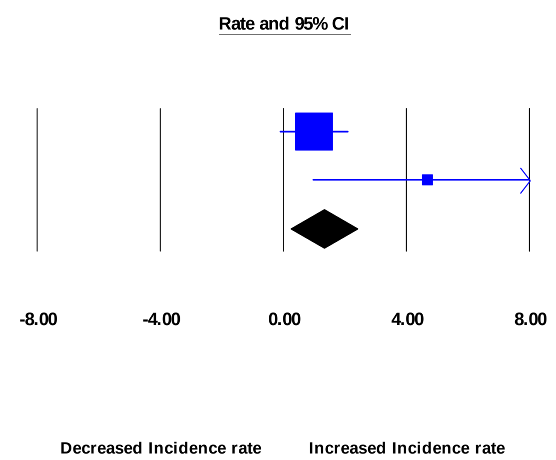
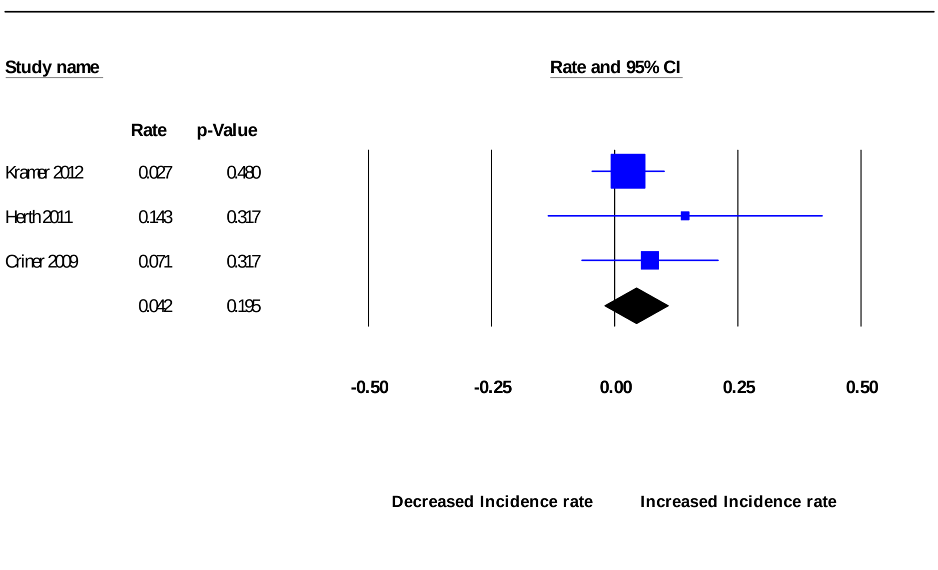


Figure E 10.


Study name
Rate and 95% CI
Rate
p-Value
Kramer 2012
0.027
0.480
Herth 2011
0.143
0.317
Criner 2009
0.071
0.317
0.042
0.195
-0.50
-0.25
0.00
0.25
0.50
Decreased Incidence rate
Increased Incidence rate