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Systematic Reviews and Meta-analysis

Introduction to Clinical Research:
A Two-week Intensive Course
July 22, 2014

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Key messages

- Systematic reviews (SR) summarize existing evidence for a specific research question.
- SR are important to identify research gaps and limitations of previous studies, to justify new research and to inform decision makers.
- Meta-analyses provide summary estimates from different studies and are based on effect and variance estimates.

Definition of a systematic review

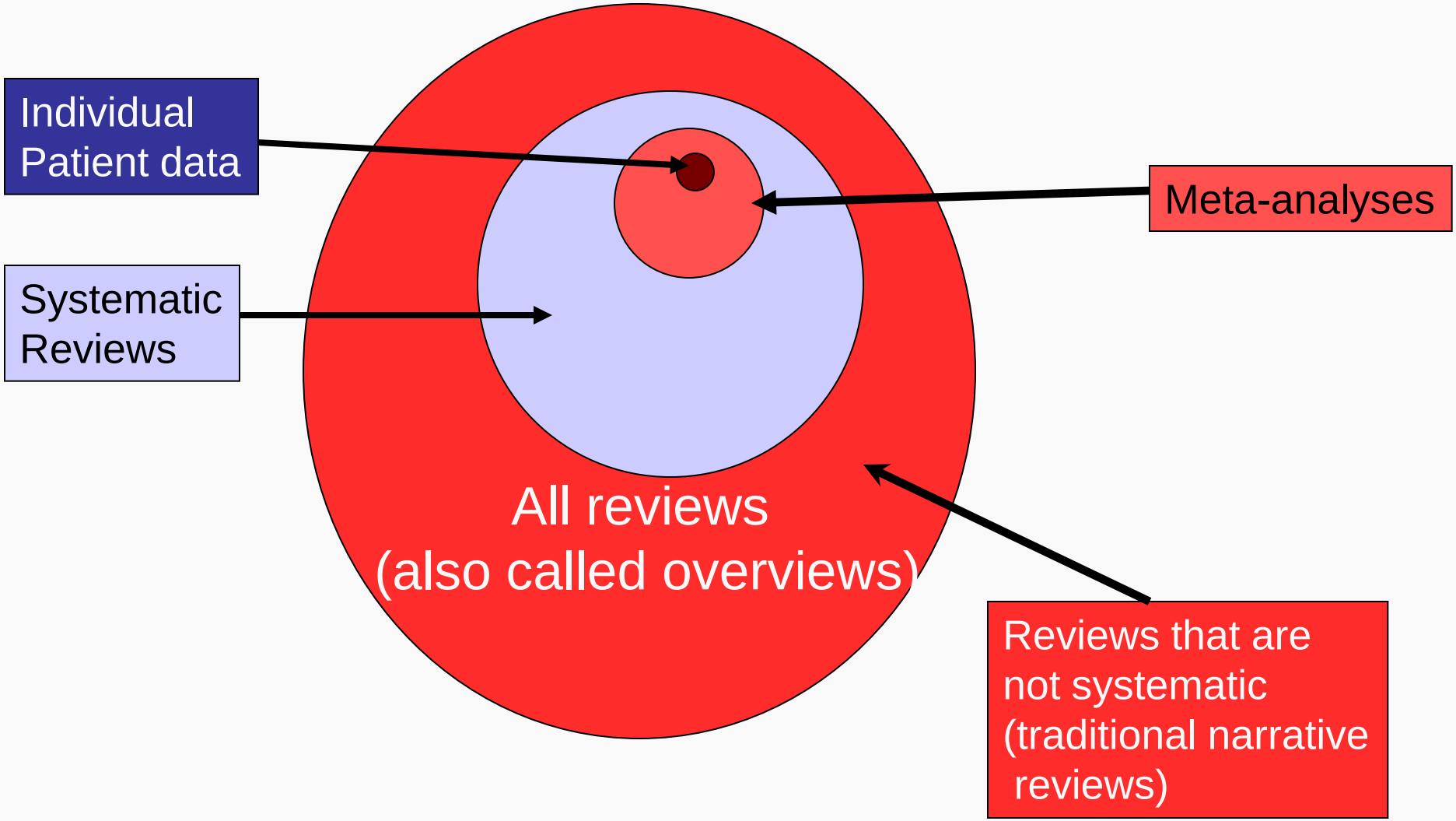
A review of existing evidence that uses a explicit and scientific methods

Contains a clear description of:

- Research question preferably using PICOTS
- Inclusion/exclusion criteria for studies
- Process used to identify studies
- Methods used to assess quality
- Methods use to abstract and summarize data

May or may not combine data quantitatively (meta-analysis)

Types of Reviews



Types of questions addressed by systematic reviews

Research questions	**Type of studies included**
Etiology (some exposure disease association)	Cohort or case-control studies
Diagnostic tests	Test accuracy studies, (RCTs)
Therapy	RCTs, observational studies
Prognosis (some predictor outcome association)	Cohort studies
Outcome measurement	Measurement studies
…	…

Roles of systematic reviews II

- Justification of new research, scientifically and ethically
- Learn about challenges of previous studies → avoid problems
- Inform decision makers
- Become an expert in topic
- Have another publication

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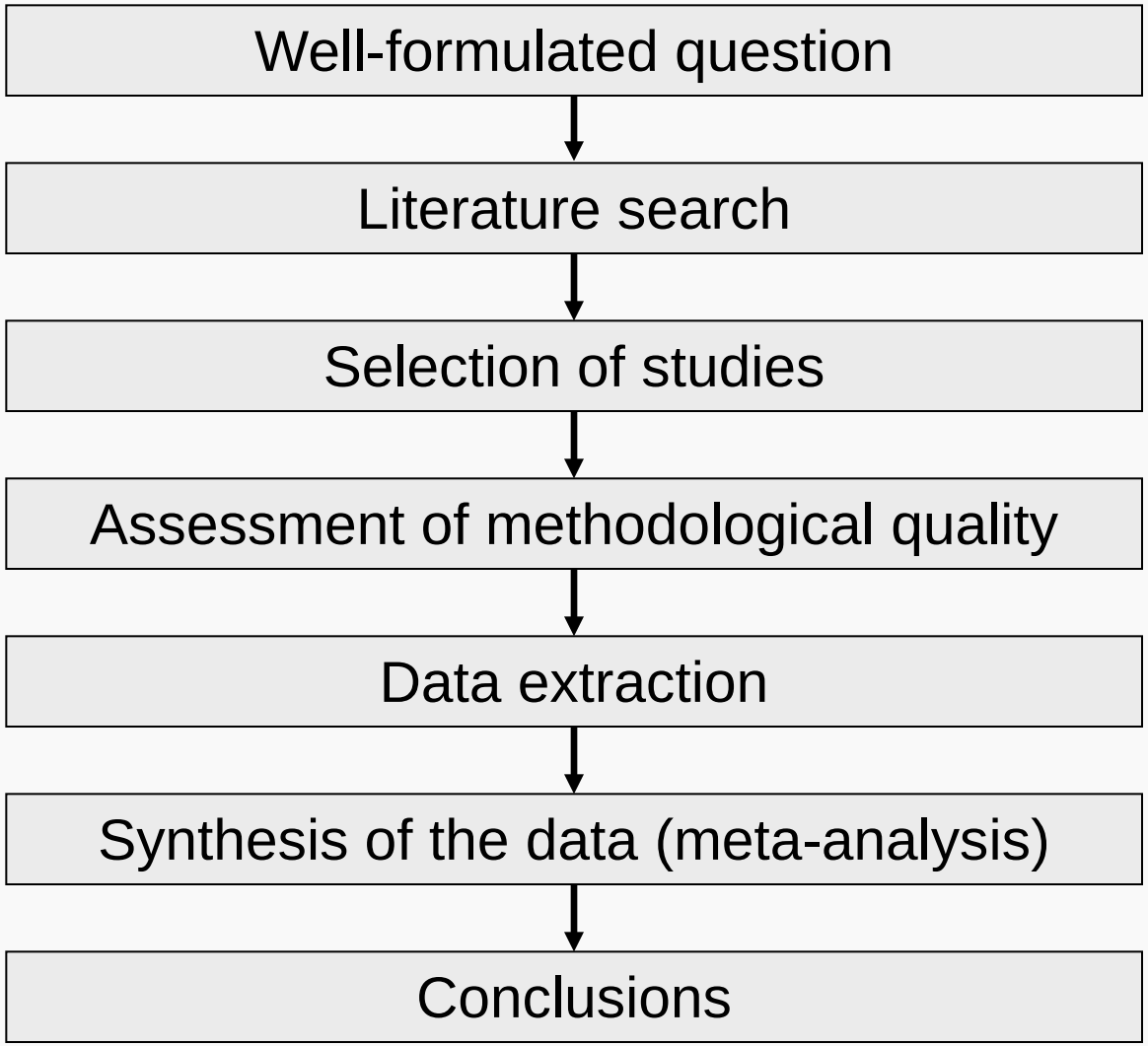
The steps of a systematic reviews

Ingredients of a systematic review



Well-formulated question (PICOTS)

Example

Population	Tobacco users
Intervention	Varenicline
Comparator	Placebo or active control (Nicotine replacement therapy or bupropion
Outcome	Serious adverse cardiovascular events

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Outcomes

Primary Outcome : Any serious ischemic or arrhythmic cardiovascular event reported during the double blind period of the trial [composite]

Secondary outcome : All cause mortality

July 3, 2014

Singh S et al. CMAJ 2011;183:1359-1366

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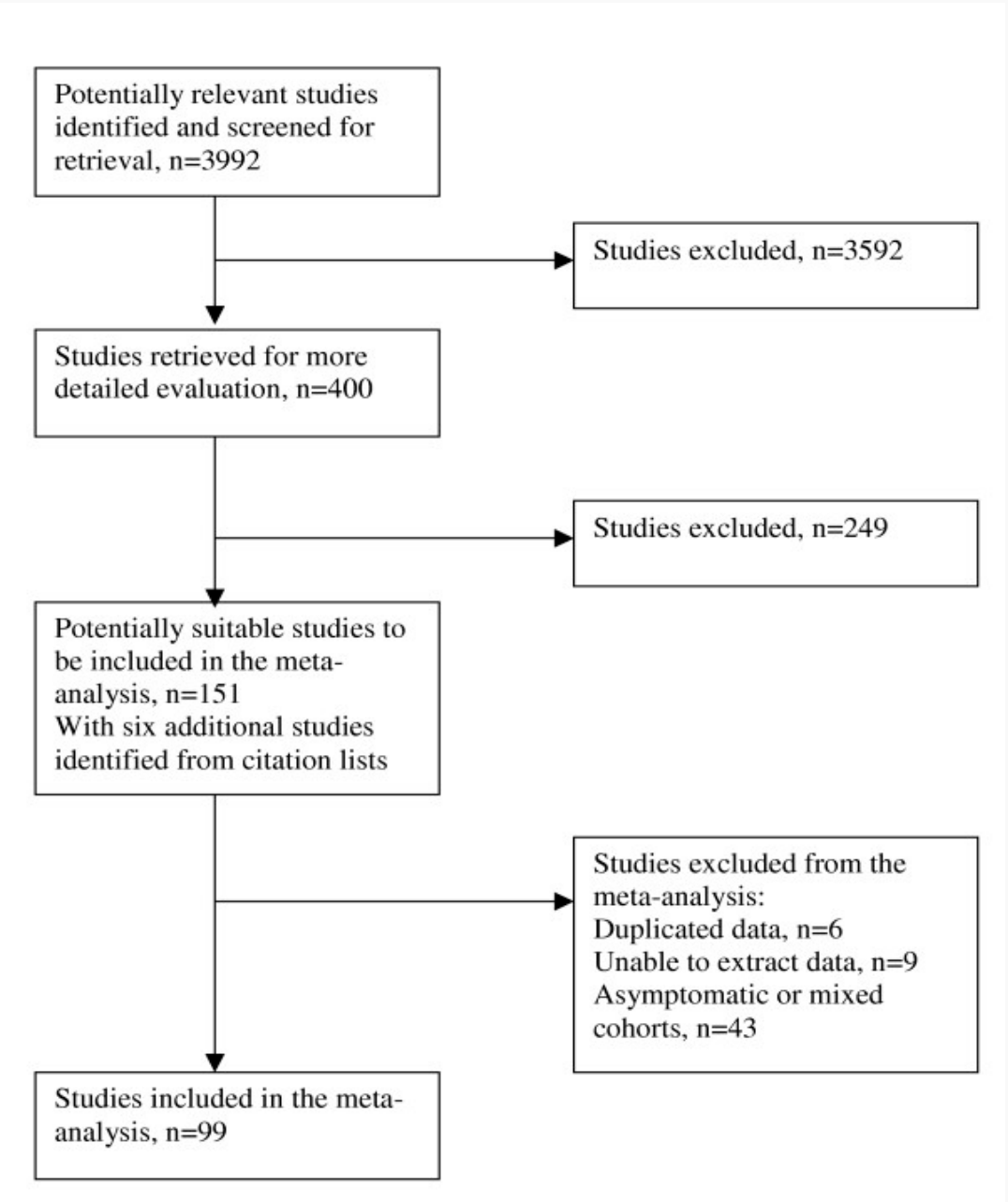
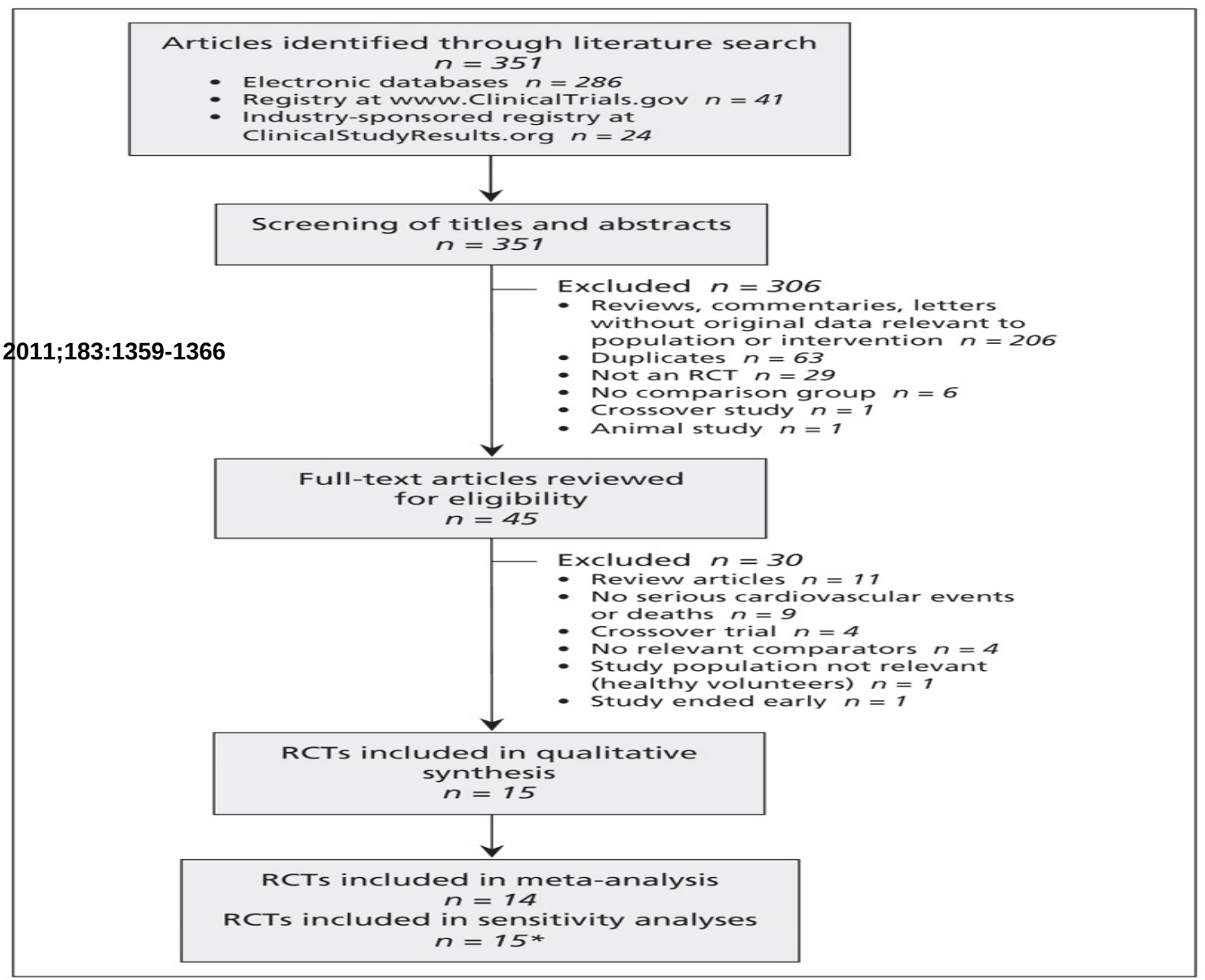
Identification of Articles

- Work with a librarian!
- Search in multiple databases, at least Medline and EMBASE
- Many studies not in English (>> than for RCTs)
- Hand-searching when time and resources available
- Balance sensitivity and specificity

Example for study flow



Selection of double-blind placebo-controlled randomized controlled trials (RCTs) for inclusion in the systematic review and meta-analysis



Singh S et al. CMAJ 2011;183:1359-1366

RCTs of Varenicline vs Comparators

Study	Duration of treatment, wk	Duration of study, wk	Primary outcome	Cardiac exclusions at enrolment	Drug and dose	No. of participants	Age, yr, mean (SD or range)	Males, %
Protocol A3051080, 2010[16]	12	26	Continous abstinence rate	Clinically significant CVD in last 6 mo, systolic BP > 150 mm Hg	Varenicline 1 mg bid	394	43.1 (18–69)	60.4
					Placebo	199	43.9 (20–71)	60.4‡
Protocol A3051095, 2010[17]	12	24	Continous quit rate, continous abstinence rate	No serious or unstable disease in last 6 mo	Varenicline 1 mg bid	493	43.9 (18–75)	60.3
					Placebo	166	43.2 (18–72)	60.0
Fagerstrom et al., 2010[18]	12	26	Continous quit rate	Any serious medical condition	Varenicline 1 mg bid	214	43.9 (12.0)	88.7
					Placebo	218	43.9 (12.0)	89.9
Gonzales et al., 2006[19]	12	52	Continous quit rate	CVD within last 6 mo	Varenicline 1 mg bid	352	42.5 (11.1)	50.0
					Bupropion 150 mg bid	329	42.0 (11.7)	58.4
					Placebo	344	42.6 (11.8)	54.1
Jorenby et al., 2006[20]	12	52	Continous quit rate	Clinically significant CVD in last 6 mo	Varenicline 1 mg bid	344	44.6 (11.4)	55.2
					Bupropion 150 mg bid	342	42.9 (11.9)	60.2
					Placebo	341	42.3 (11.6)	58.1
Nakamura et al., 2007[21]	12	52	Continous abstinence rate	Unstable CVD	Varenicline 1 mg bid	156	40.1 (11.6)	79.2
					Varenicline 0.5 mg bid	156	39.0 (12.0)	71.1
					Varenicline 0.25 mg bid	153	40.2 (12.3)	72.7
					Placebo	154	39.9 (12.3)	76
Niaura et al., 2008[22]	12	52	Continous abstinence rate	History of CVD	Varenicline 1 mg/d	160	41.5 (11.3)	50.3
					Placebo	160	42.1 (11.7)	53.5
Nides et al., 2006[23]	7	52	Continous abstinence rate	History of CVD	Varenicline 0.3 mg/d	128	41.9 (10.6)	50.0
					Varenicline 1 mg/d	128	42.9 (10.5)	43.7
					Varenicline 1 mg bid	127	41.9 (9.8)	50.4
					Bupropion 150 mg bid	128	40.5 (10.8)	45.2
					Placebo	127	41.6 (10.4)	52.0
Oncken et al., 2006[24]	12	52	Continous abstinence rate	History of CVD	Varenicline 1 mg bid titrated	130	42.2 (10.7)	48.5
					Varenicline 1 mg bid nontitrated	129	43.7 (10.0)	48.8
					Varenicline 0.5 mg bid titrated	130	43.5 (10.5)	53.1
					Varenicline 0.5 mg bid nontitrated	129	42.9 (10.1)	45.0
					Placebo	129	43.0 (9.4)	51.9
Rigotti et al., 2010[9]	12	52	Continous abstinence rate	Excluded if unstable CVD in last 2 mo; included with stable CVD§	Varenicline 1 mg bid	355	57.0 (8.6)	75.2
					Placebo	359	55.9 (8.3)	82.2
Tashkin et al.,† 2010[25]	12	52	Continous abstinence rate	Unstable CVD or history of CVD in last 6 mo	Varenicline 1 mg bid	250	57.2 (35–83)	62.5
					Placebo	254	57.1 (34–77)	62.2
Tonstad et al., 2006[26]	12	52	Long-term quit rate	CVD within last 6 mo	Varenicline 1 mg bid	603	45.4 (10.4)	50.2
					Placebo	607	45.3 (10.4)	48.3
Tsai et al., 2007[27]	12	24	Continous abstinence rate	Unstable CVD	Varenicline 1 mg bid	126	39.7 (9.3)	84.9
					Placebo	124	40.9 (11.1)	92.7
Williams et al., 2007[28]	52	52	Long-term safety	Clinically significant CVD in last 6 mo	Varenicline 1 mg bid	251	48.2 (12.3)	50.6
					Placebo	126	46.6 (12.1)	48.4
Aubin et al., 2008[29]	12	52	Continous abstinence rate	Serious or unstable disease in last 6 mo	Varenicline 1 mg bid	378	42.9 (10.5)	48.4
					Nicotine transdermal patch	379	42.9 (12.0)	50.0

Note: BP = blood pressure, CVD = cardiovascular disease, SD = standard deviation.
*All but one of the trials involved smokers; the study by Fagerstrom et al.[18] involved users of smokeless tobacco. Additional study characteristics are available in Appendix 2 (www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.110218/-/DC1).
†Investigators enrolled smokers with mild to moderate chronic obstructive pulmonary disease.
‡The proportion of males in study overall; the proportion in each study arm was not reported.
§The proportion of participants with cardiac disease in varenicline versus placebo groups was angina 53.2% v. 47.9%, myocardial infarction 45.9% v. 52.4%, prior coronary revascularization 46.2% v. 51.5%, and stroke 4.5% v. 6.7%.

- 14 double-blind placebo-controlled trials-13 trials enrolled smokers; one trial enrolled smokeless tobacco users.
- 13 trials excluded patients with a history of cardiovascular disease; one trial included participants with stable cardiovascular disease but excluded those with unstable cardiovascular disease.
- Sample sizes from 250 to 1210.
- The primary outcome was the continuous abstinence rate in 12 trials the long-term quit rate in 1 trial and long-term safety in 1 trial.
- Duration of treatment ranged from 7 weeks to 52 weeks, and the total duration of study, including treatment and follow-up, ranged from 24 to 52 weeks.

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Risk of Bias

Study	Adequate sequence generation	Adequate allocation concealment	Adequate blinding of personnel and participants	Adequate reporting of withdrawals and loss to follow-up	Adequate reporting of serious adverse events
Double-blind RCTs					
Protocol A3051080[16]	Unclear	Unclear	Yes	Yes	Yes
Protocol A3051095[17]	Unclear	Unclear	Yes	Yes	Yes
Fagerstrom et al.[18]	Yes	Yes	Yes	Yes	Yes
Gonzales et al.[19]	Yes	Yes	Yes	Yes	Yes
Jorenby et al.[20]	Yes	Yes	Yes	Yes	Yes
Nakamura et al.[21]	Yes	Yes	Yes	Yes	Yes
Niaura et al.[22]	Yes	Yes	Yes	Yes	Yes
Nides et al.[23]	Yes	Yes	Yes	Yes	Yes
Oncken et al.[24]	Unclear	Unclear	Yes	Yes	Yes
Rigotti et al.[9]	Yes	Yes	Yes	Yes	Yes
Tashkin et al.[25]	Unclear	Unclear	Yes	Yes	Yes
Tonstad et al.[26]	Yes	Yes	Yes	Yes	Yes
Tsai et al.[27]	Yes	Yes	Yes	Yes	Yes
Williams et al.[28]	Unclear	Unclear	Yes	Yes	Yes
Open-label RCT					
Aubin et al.[29]	Yes	Unclear	Yes	Yes	Yes

*Details of the methodology of the studies are available in Appendix 3 (w :10.1503/cmaj.110218/-/DC1).

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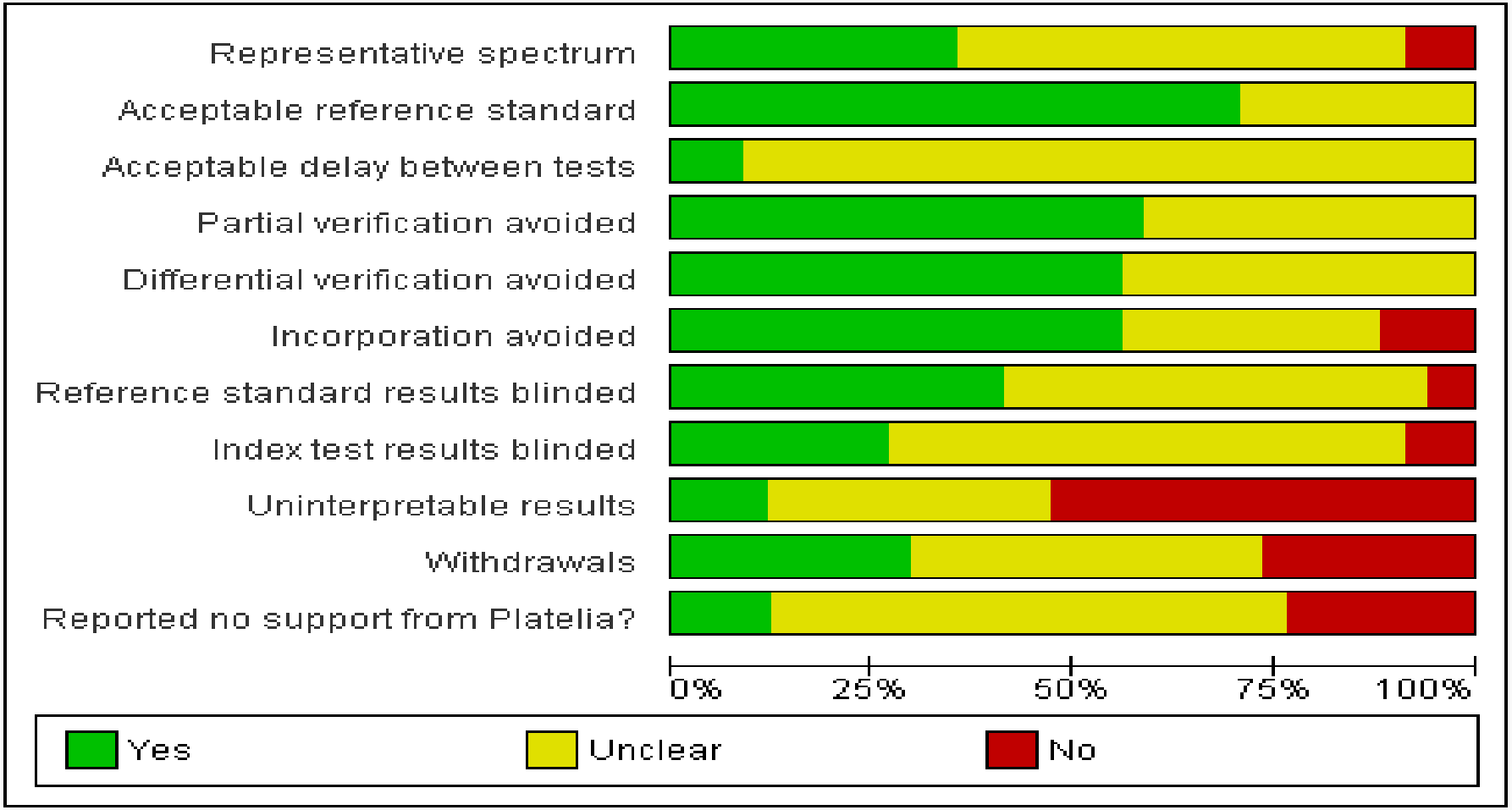
Methodological Quality Graph

QUADAS tool
(**Qu**ality **A**ssessment of **D**iagnostic **A**ccuracy **S**tudies)



Whiting et al. BMC Medical Research Methodology 2003, 3:25

Data extraction – Independently by two reviewers

First Author: | Year of publication:

A. Validity: patient spectrum

A1. Setting: setting	☐1 In-patients ☐2 Out-patients ☐55 Other	☐66 not reported
A2. Country of Investigation: Country	88	☐66 not reported
A3. Start inclusion of patients (year): StartIncl	88	☐66 not reported
A4. Eligibility/ inclusion criteria: Incl	only state page and paragraph 88	☐66 not reported
A5. Exclusion criteria: Excl	only state page and paragraph 88	☐66 not reported
A6. Were the selection criteria clearly described? SelCrit	☐1 yes ☐2 no	
A7. Consecutive series of patients: Connsec	☐1 yes ☐2 no, but random sample ☐3 no	☐66 not reported
A8. Age distribution: Age		☐66 not

Challenges because of poor reporting

- Population → purpose of test?

- Index test and reference standard → eligibility? reproducibility?

- Only test accuracy reported without precision or 2x2 table

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Meta-analysis

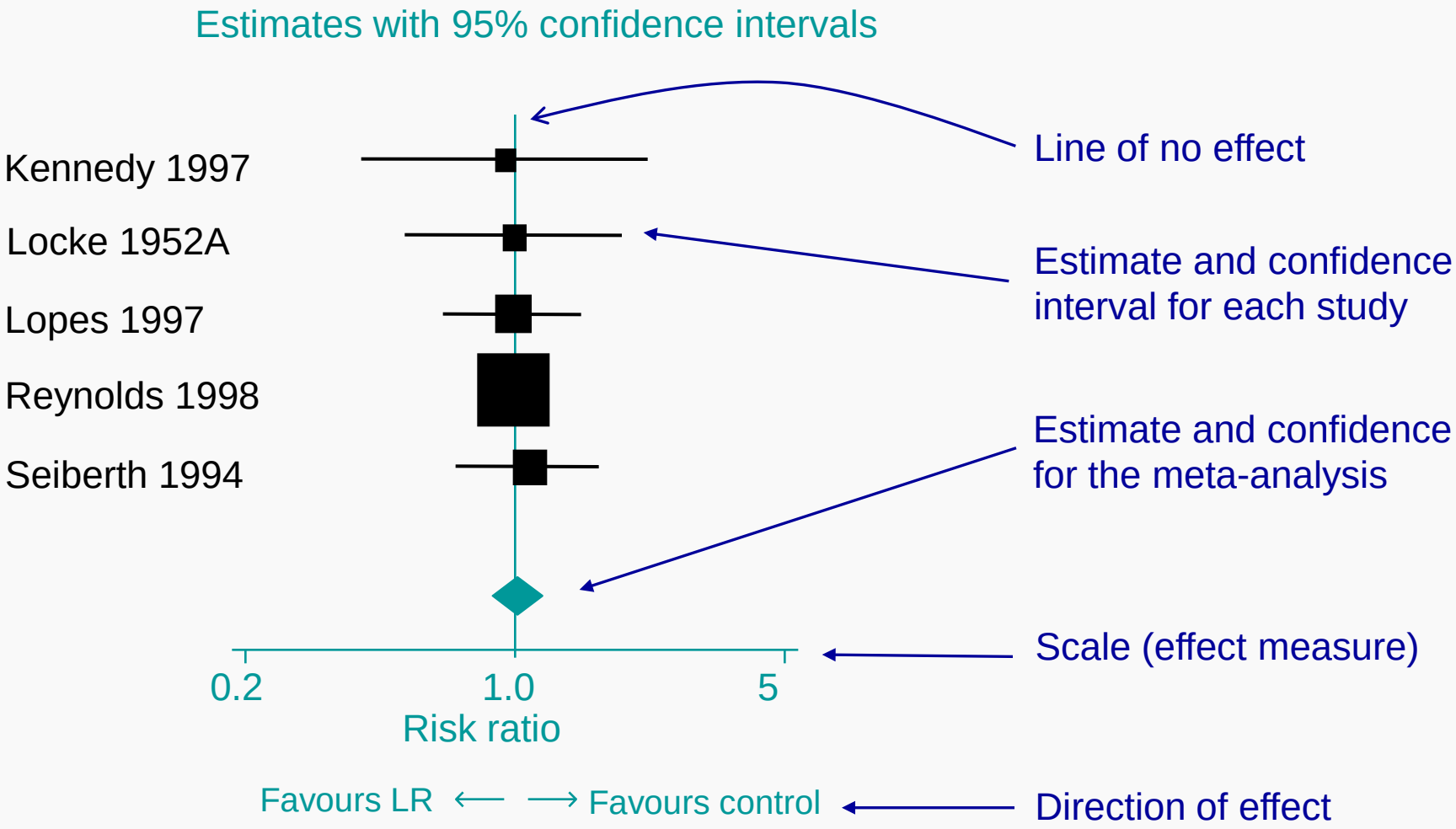
What is a Meta-analysis?

- An ***optional*** component of a systematic review

- Definition:

  “the statistical analysis of a large collection of analysis results from individual studies for the purpose of integrating the findings.” (Glass 1976)

Presentation: the Forest Plot



Inverse-variance Weighted Average

- Require from each study
  - estimate of treatment effect; and
  - standard error (or variance) of estimate
- Combine these using a weighted average:

$$weighted\ average = \frac{sum\ of\ (estimate \times wiehgt)}{sum\ of\ weights} = \frac{\sum Y_i W_i}{\sum W_i}$$

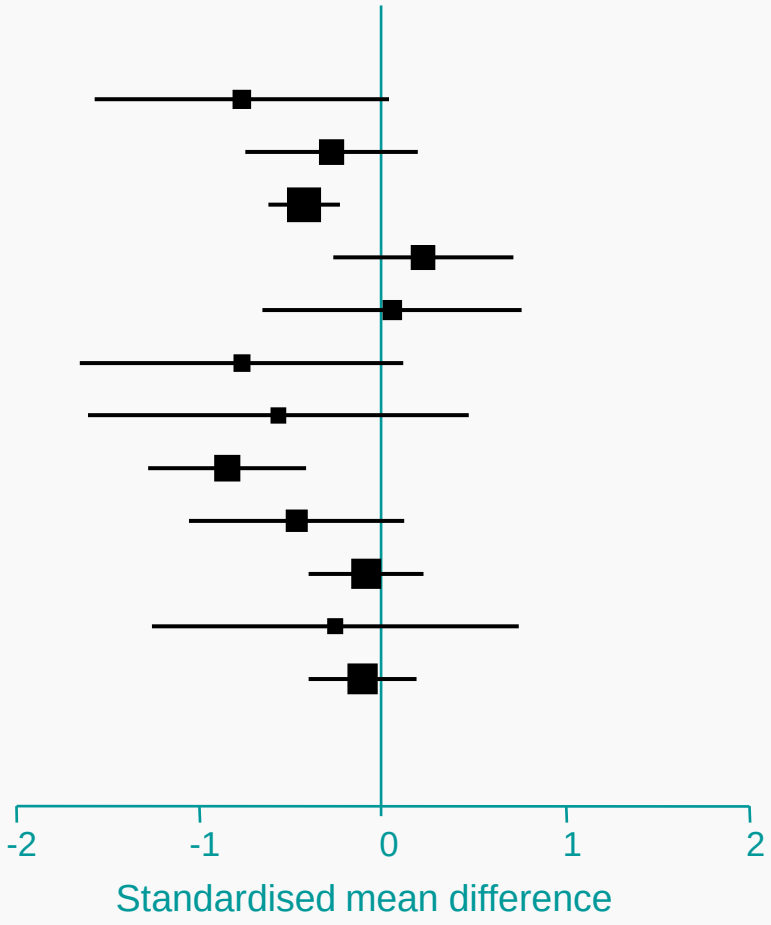
$$Variance\ (weighted\ average) = \frac{1}{sum\ of\ weights} = \frac{1}{\sum W_i}$$

Y_i - intervention effect estimated in the *i* th study
W_i - weight given to the *i* th study, and is usually chosen to be the inverse of the variance of the effect estimate

Why Do a Meta-analysis (cont'd)?

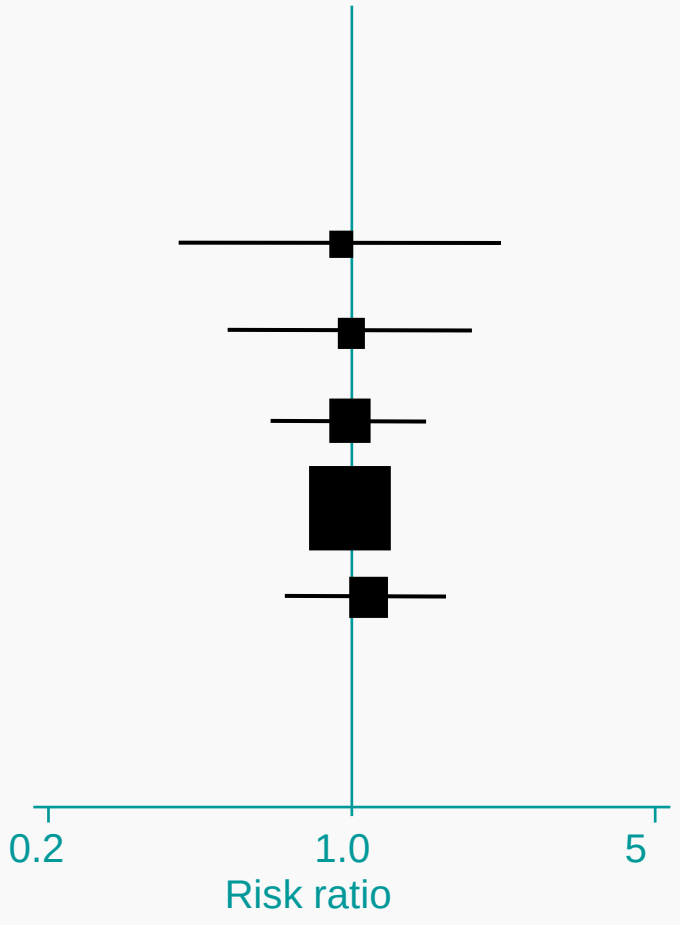
Opioids for Breathlessness

Estimates with 95% confidence intervals



Early Light Reduction for Retinopathy of prematurity

Estimates with 95% confidence intervals

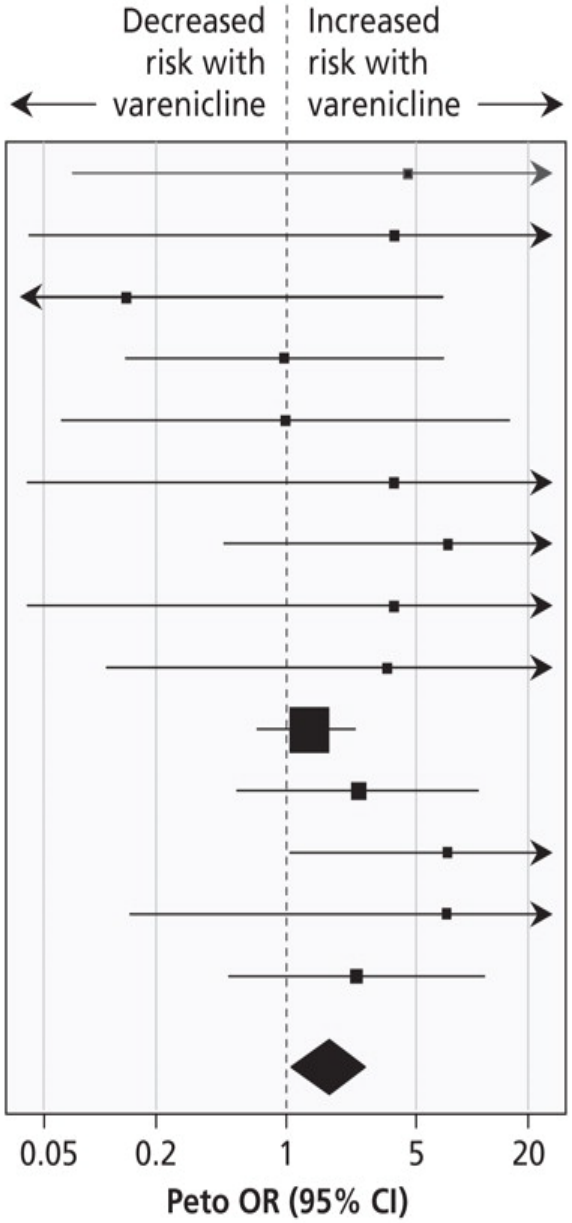


Why Do a Meta-analysis (cont'd)?

- **To increase power and precision**
  - detect effect as statistically significant; narrower CIs
- **To quantify effect sizes and their uncertainty**
  - reduce problems of interpretation due to sampling variation
- **To assess homogeneity/heterogeneity of results**
  - quantify between-study variation
- **To answer questions not posed by the individual studies**
  - factors that differ across studies
- **To settle controversies arising from conflicting studies**
  - generate new hypotheses

Study	Cardiovascular events, *n/N*		Weight, %	Peto OR (95% CI)
	Varenicline	Placebo		
Protocol A3051080[16]	1/394	0/199	1.2	4.50 (0.07–285.96)
Protocol A3051095[17]	1/493	0/166	1.0	3.81 (0.04–347.82)
Fagerstrom et al.[18]	0/214	1/218	1.4	0.14 (0.00–6.95)
Gonzales et al.[19]	2/352	2/344	5.4	0.98 (0.14–6.97)
Jorenby et al.[20]	1/344	1/341	2.7	0.99 (0.06–15.88)
Nakamura et al.[21]	1/465	0/154	1.0	3.79 (0.04–352.44)
Niaura et al.[22]	2/160	0/160	2.7	7.44 (0.46–119.40)
Nides et al.[23]	1/383	0/127	1.0	3.79 (0.04–352.09)
Oncken et al.[24]	2/518	0/129	1.7	3.49 (0.11–112.44)
Rigotti et al.[9]	25/355	20/359	57.3	1.28 (0.70–2.34)
Tashkin et al.[25]	5/250	2/254	9.4	2.42 (0.55–10.74)
Tonstad et al.[26]	4/603	0/607	5.4	7.48 (1.05–53.20)
Tsai et al.[27]	1/126	0/124	1.4	7.27 (0.14–366.57)
Williams et al.[28]	6/251	1/126	8.3	2.40 (0.49–11.67)
Overall	**52/4908**	**27/3308**	**100.0**	**1.72 (1.09–2.71)**

Heterogeneity: $I^2 = 0\%$



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Sensitivity analysis	Statistical model	No. of RCTs	Group; no. of events, *n/N*		OR (95% CI)
			Varenicline	Control	
Placebo comparator					
Reciprocal of the treatment arm size					
Continuity correction	Fixed (MH)	14[9,16–28]	52/4908	27/3308	1.67 (1.06–2.64)
No continuity correction	Fixed (MH)	14[9,16–28]	52/4908	27/3308	1.77 (1.09–2.88)
Use of unadjudicated cardiovascular event data from one trial	Peto OR	14[9,16–28]	61/4908	29/3308	1.91 (1.25–2.94)
Exclusion of most influential study	Peto OR	13[16–28]	27/4553	7/2949	2.54 (1.26–5.12)
Placebo or active† comparator	Peto OR	15[9,16–29]	52/5286	30/4486	1.67 (1.07–2.62)

Note: CI = confidence interval, OR = odds ratio, MH = Mantel–Haenszel test, RCT = randomized controlled trial.
*Statistical heterogeneity was I^2 = 0% for all sensitivity analyses.
†Bupropion or nicotine replacement therapy.

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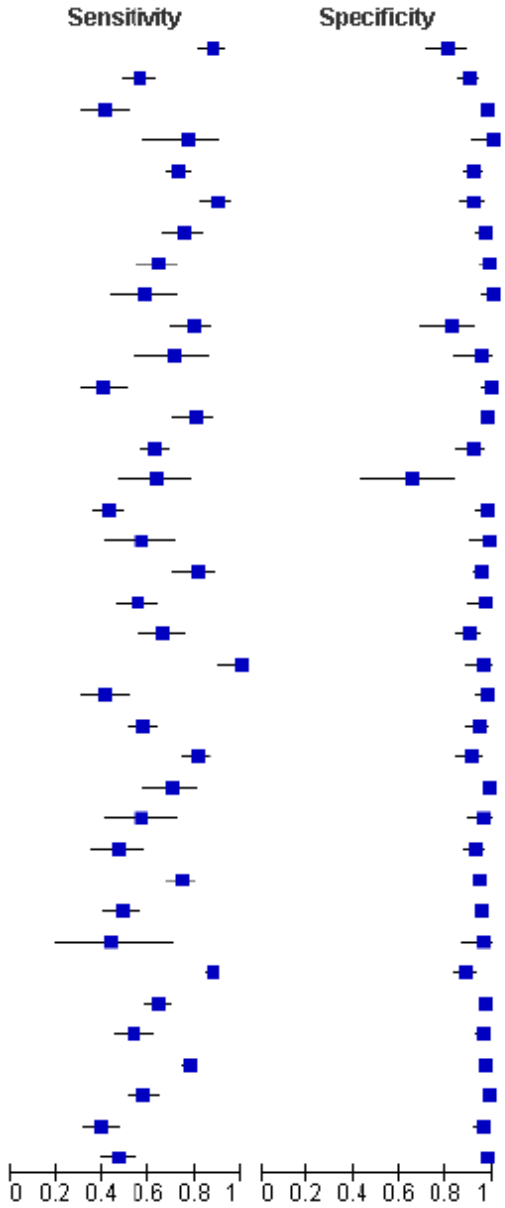
Forest plots: Example for diagnostic studies

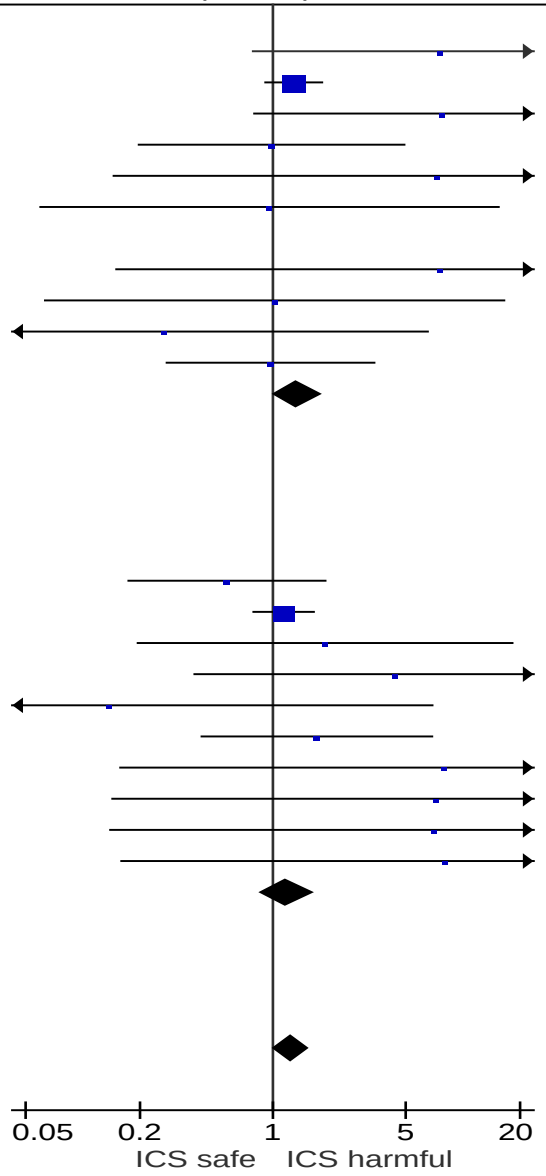
Study	TP	FP	FN	TN	Generation	Sensitivity	Specificity
Aotsuka 2005	115	17	16	73	CCP2	0.88 [0.81, 0.93]	0.81 [0.71, 0.89]
Bas 2003	110	24	86	215	CCP1	0.56 [0.49, 0.63]	0.90 [0.85, 0.93]
Bizzaro 2001	40	5	58	227	CCP1	0.41 [0.31, 0.51]	0.98 [0.95, 0.99]
Bombardieri 2004	23	0	7	39	CCP2	0.77 [0.58, 0.90]	1.00 [0.91, 1.00]
Choi 2005	236	20	88	231	CCP2	0.73 [0.68, 0.78]	0.92 [0.88, 0.95]
Correa 2004	74	11	8	130	CCP2	0.90 [0.82, 0.96]	0.92 [0.86, 0.96]
De Rycke 2004	89	4	29	142	CCP2	0.75 [0.67, 0.83]	0.97 [0.93, 0.99]
Dubucquoi 2004	90	2	50	129	CCP2	0.64 [0.56, 0.72]	0.98 [0.95, 1.00]
Fernandez-Suarez 2005	31	0	22	75	CCP2	0.58 [0.44, 0.72]	1.00 [0.95, 1.00]
Garcia-Berrocal 2005	69	8	18	38	CCP2	0.79 [0.69, 0.87]	0.83 [0.69, 0.92]
Girelli 2004	25	2	10	40	CCP2	0.71 [0.54, 0.85]	0.95 [0.84, 0.99]
Goldbach-Mansky 2000	43	1	63	120	CCP1	0.41 [0.31, 0.51]	0.99 [0.95, 1.00]
Greiner 2005	70	5	17	228	CCP2	0.80 [0.71, 0.88]	0.98 [0.95, 0.99]
Grootenboer-Mignot 2004	167	8	98	88	CCP2	0.63 [0.57, 0.69]	0.92 [0.84, 0.96]
Hitchon 2004	26	8	15	15	CCP2	0.63 [0.47, 0.78]	0.65 [0.43, 0.84]
Jansen 2003	110	3	148	118	CCP1	0.43 [0.37, 0.49]	0.98 [0.93, 0.99]
Kamali 2005	26	1	20	56	CCP2	0.57 [0.41, 0.71]	0.98 [0.91, 1.00]
Kumagai 2004	64	14	15	293	CCP2	0.81 [0.71, 0.89]	0.95 [0.92, 0.97]
Kwok 2005	71	2	58	66	CCP2	0.55 [0.46, 0.64]	0.97 [0.90, 1.00]
Lee 2003	68	14	35	132	CCP2	0.66 [0.56, 0.75]	0.90 [0.84, 0.95]
Lopez-Hoyos 2004	38	3	0	73	CCP2	1.00 [0.91, 1.00]	0.96 [0.89, 0.99]
Nell 2005	42	2	60	96	CCP2	0.41 [0.32, 0.51]	0.98 [0.93, 1.00]
Nielen 2005	149	7	109	114	CCP2	0.58 [0.51, 0.64]	0.94 [0.88, 0.98]
Quinn 2006	147	10	35	106	CCP2	0.81 [0.74, 0.86]	0.91 [0.85, 0.96]
Rantapaa-Dahlqvist 2003	47	7	20	375	CCP2	0.70 [0.58, 0.81]	0.98 [0.96, 0.99]
Raza 2005	24	3	18	79	CCP2	0.57 [0.41, 0.72]	0.96 [0.90, 0.99]
Saraux 2003	40	11	46	146	CCP1	0.47 [0.36, 0.58]	0.93 [0.88, 0.96]
Sauerland 2005	171	26	60	443	CCP2	0.74 [0.68, 0.80]	0.94 [0.92, 0.96]
Schellekens 2000	72	14	77	298	CCP1	0.48 [0.40, 0.57]	0.96 [0.93, 0.98]
Soderlin 2004	7	2	9	51	CCP2	0.44 [0.20, 0.70]	0.96 [0.87, 1.00]
Suzuki 2003	481	23	68	185	CCP2	0.88 [0.85, 0.90]	0.89 [0.84, 0.93]
Vallbracht 2004	190	12	105	408	CCP2	0.64 [0.59, 0.70]	0.97 [0.95, 0.99]
van Gaalen 2005	82	13	71	301	CCP2	0.54 [0.45, 0.62]	0.96 [0.93, 0.98]
van Venrooij 2004	865	79	252	2218	CCP2	0.77 [0.75, 0.80]	0.97 [0.96, 0.97]
Vincent 2002	139	7	101	464	CCP1	0.58 [0.51, 0.64]	0.99 [0.97, 0.99]
Vittecoq 2004	69	5	107	133	CCP2	0.39 [0.32, 0.47]	0.96 [0.92, 0.99]
Zeng 2003	90	7	101	313	CCP1	0.47 [0.40, 0.54]	0.98 [0.96, 0.99]



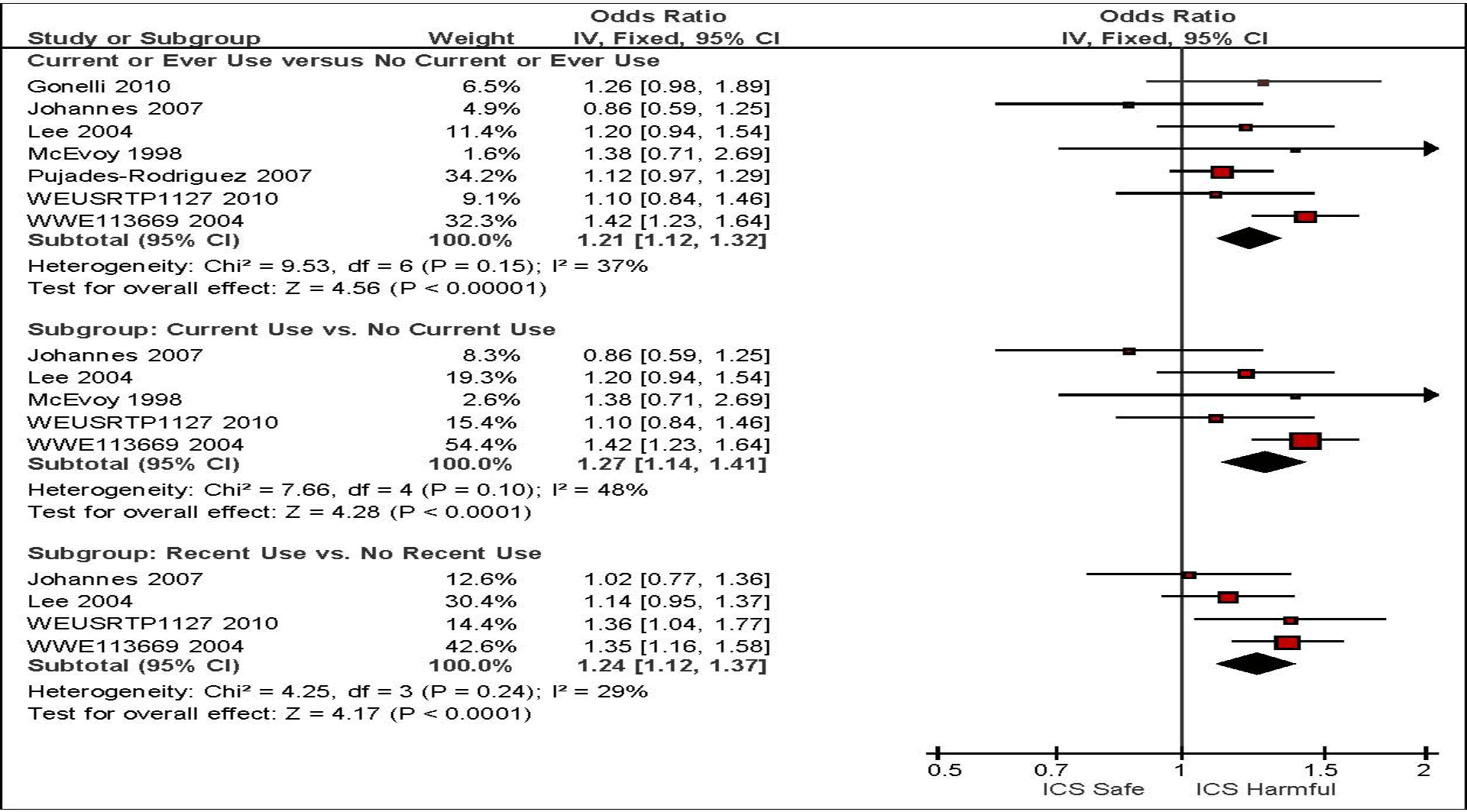
Nishimura Ket al. *Ann Intern Med* 2007; 146: 797-808.

Meta-analysis of RCTs of ICS & Fractures

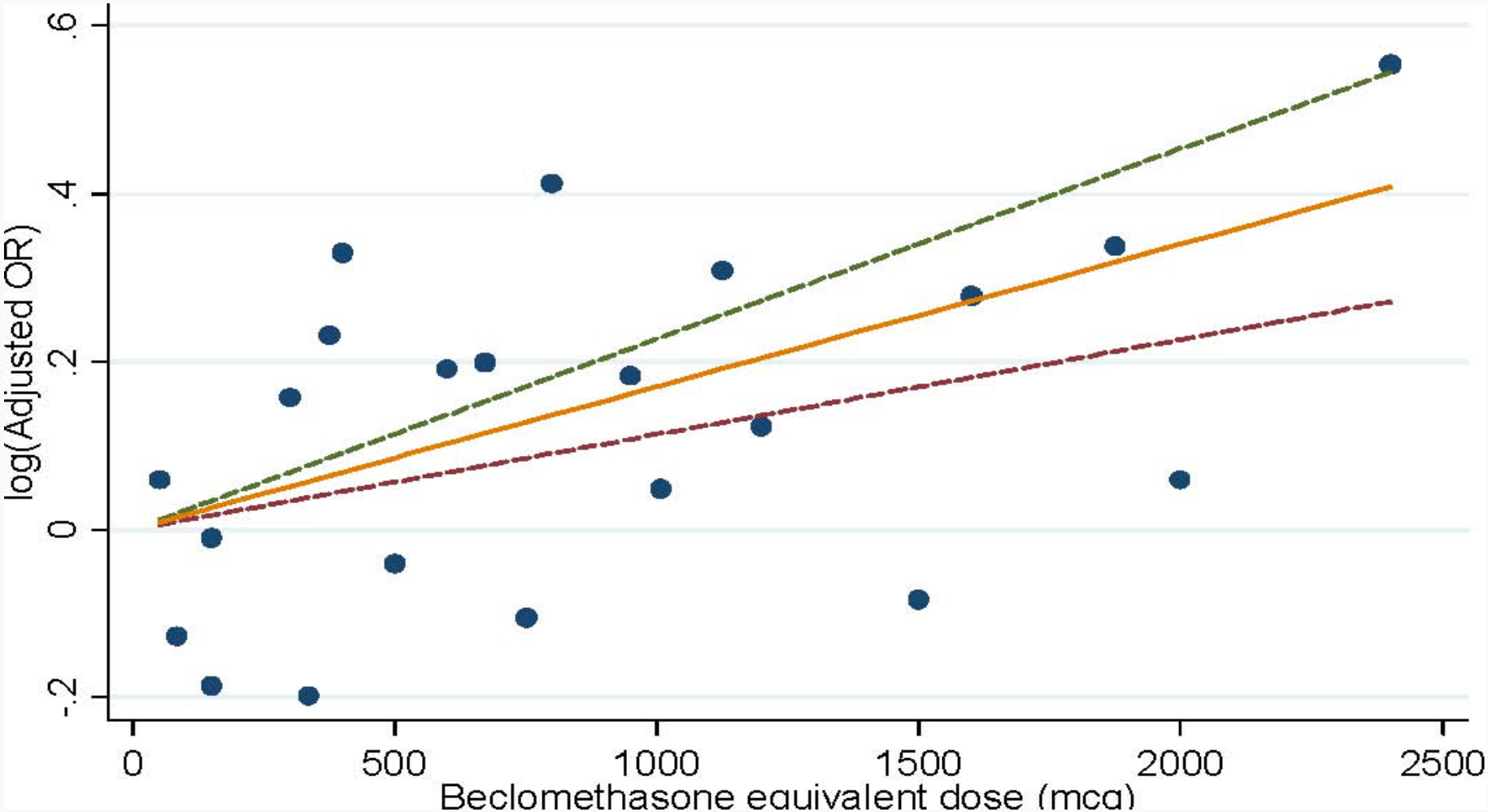
Study or Subgroup	ICS Events	ICS Total	No ICS Events	No ICS Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
4.2.1 ICS-LABA vs. LABA						
Anzueto SCO100250 2009	3	394	0	403	1.0%	7.60 [0.79, 73.27]
Calverley SCO30003 2007	78	1546	61	1542	43.0%	1.29 [0.92, 1.81]
Calverley SFCB3024 2003	3	358	0	372	1.0%	7.73 [0.80, 74.55]
Ferguson SCO40043 2008	3	394	3	388	1.9%	0.98 [0.20, 4.90]
Hannania SFCA3007 2003	1	178	0	177	0.3%	7.35 [0.15, 370.30]
Kardos SCO30006 2007	1	507	1	487	0.6%	0.96 [0.06, 15.39]
Mahler SFCA3006 2002	0	165	0	160		Not estimable
SCO100470 2006	1	518	0	532	0.3%	7.59 [0.15, 382.72]
SCO40041 2008	1	92	1	94	0.6%	1.02 [0.06, 16.46]
Tashkin 2008	1	845	1	284	0.5%	0.27 [0.01, 6.52]
Wouters SCO40002 2005	5	189	5	184	3.2%	0.97 [0.28, 3.41]
Subtotal (95% CI)		**5186**		**4623**	**52.5%**	**1.34 [0.99, 1.82]**
Total events	97		72			
Heterogeneity: Chi² = 7.54, df = 9 (P = 0.58); I² = 0%						
Test for overall effect: Z = 1.86 (P = 0.06)						
4.2.2 ICS alone vs. Placebo						
Burge FLTB3054 2000	4	376	7	375	3.5%	0.57 [0.17, 1.89]
Calverley SCO30003 2007	65	1552	57	1544	38.0%	1.14 [0.79, 1.64]
Calverley SFCB3024 2003	2	374	1	361	1.0%	1.88 [0.20, 18.17]
FLTA3025 2005	3	434	0	206	0.8%	4.39 [0.39, 49.66]
Hannania SFCA3007 2003	0	183	1	185	0.3%	0.14 [0.00, 6.90]
Johnell 2002	5	322	3	331	2.6%	1.70 [0.42, 6.87]
Mahler SFCA3006 2002	1	168	0	181	0.3%	7.98 [0.16, 403.44]
Paggiaro FLIT97 1998	1	142	0	139	0.3%	7.23 [0.14, 364.68]
SFCT01 2005	1	131	0	125	0.3%	7.06 [0.14, 356.10]
Tashkin 2008	1	275	0	300	0.3%	8.09 [0.16, 409.34]
Subtotal (95% CI)		**3957**		**3747**	**47.5%**	**1.19 [0.86, 1.64]**
Total events	83		69			
Heterogeneity: Chi² = 7.62, df = 9 (P = 0.57); I² = 0%						
Test for overall effect: Z = 1.05 (P = 0.29)						
Total (95% CI)		**9143**		**8370**	**100.0%**	**1.27 [1.01, 1.58]**
Total events	180		141			
Heterogeneity: Chi² = 15.43, df = 19 (P = 0.69); I² = 0%						
Test for overall effect: Z = 2.07 (P = 0.04)						
Test for subgroup differences: Chi² = 0.28, df = 1 (P = 0.60), I² = 0%						



Meta-analysis of Observational Studies of ICS and fractures in COPD



Dose Response Meta-Regression of ICS and Fractures in Observational Studies



- Each 500 mcg increase in beclometasone dose equivalents was associated with a 9 % increase in the risk of fractures OR: 1.09 (95% CI 1.06 to 1.12; p<0.001).

When Not to Do a Meta-analysis

- **“Garbage in - garbage out”**
  - a meta-analysis is only as good as the studies in it
  - narrower confidence interval around combination of biased studies worse than the biased studies on their own
  - beware of reporting biases (e.g. publication bias)
- **“Mixing apples with oranges”**
  - not useful for learning about apples, although useful for learning about fruit!
  - studies must address the same question
    - though the question can, *and usually must,* be broader

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Number Needed to Harm for Cardiovascular Events based on Meta-analysis

Population	Source of baseline risk	Baseline Risk	Annualized Number Needed to Harm
Smokers without CVD	Control event rate of Meta-analysis	0.82%	167
Smokers with stable CVD	Control event rate of trial among smokers with CVD	5.8%	28

Singh S et al. CMAJ 2011;183:1359-1366

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Limitations

- Trials did not use adjudicated CV definitions
- Could not conduct time to event analysis due to individual patient data

Conclusions

- Among smokers exposure to varenicline is associated with a statistically significant increased risk of CV events

Key messages

- Systematic reviews (SR) summarize existing evidence for a specific research question.
- SR are important to identify research gaps and limitations of previous studies, to justify new research and to inform decision makers.
- Meta-analyses provide summary estimates from different studies and are based on effect and variance estimates.