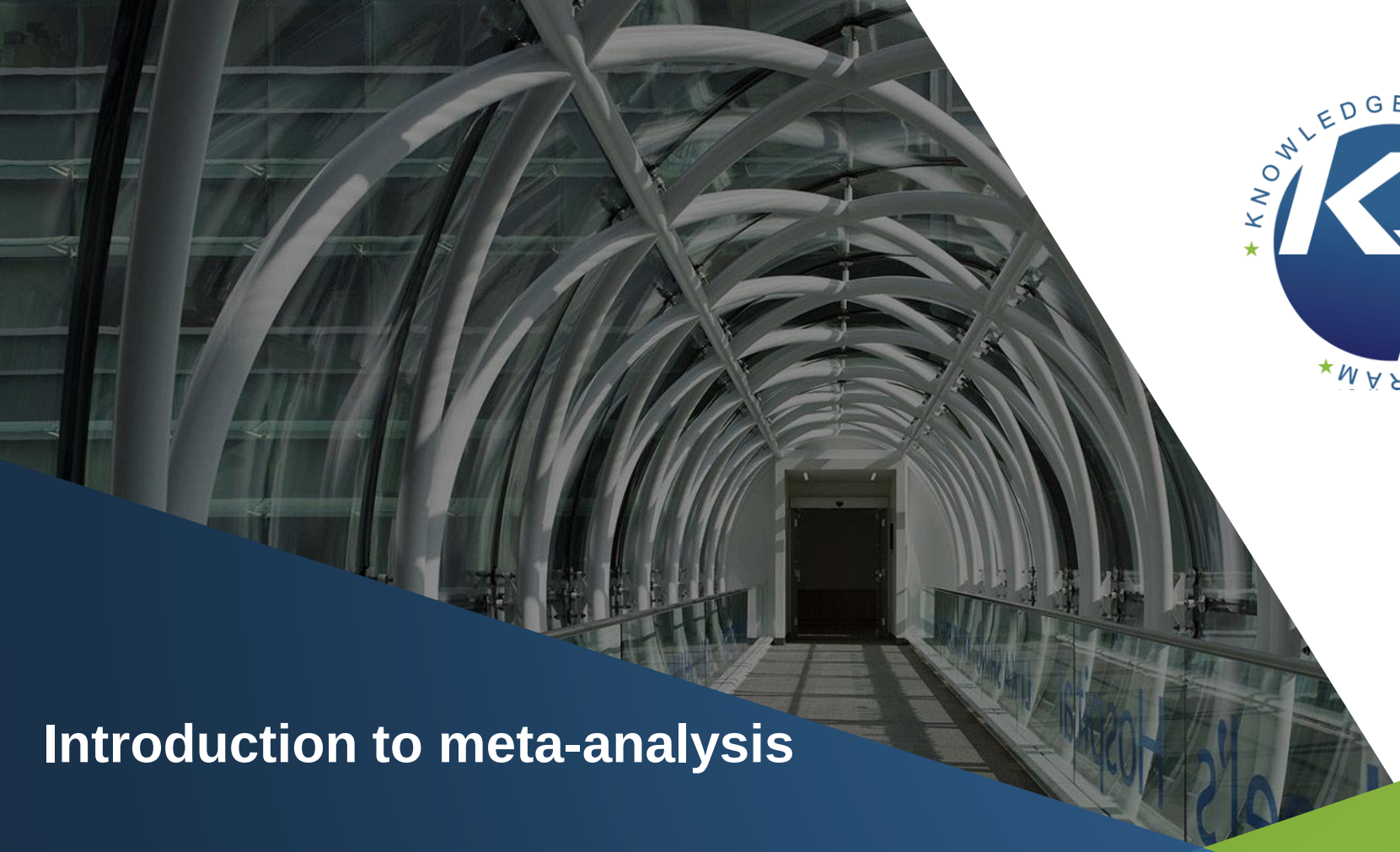

Introduction to meta-analysis

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Learning objectives

- Briefly discuss the standard systematic/rapid review process and introduce the basic principles of meta-analysis

- Describe effect measures used in meta-analysis for dichotomous and continuous data

- Explain important aspects of interpreting meta-analysis results

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Clinical trials

Patients with nausea

- Most patients undergoing chemotherapy experience nausea and vomiting
- The occurrence of post-operative nausea and vomiting among patients following some surgical procedures can be as high as 70%
- Serotonin (5-HT3) receptor antagonists were introduced as antiemetic medications
  - They inhibit vagal nerves in the central nervous system and intestinal mucosa that trigger the emetic reflex

What is the current practice in treating nausea and vomiting in patients undergoing surgery?

Clinical trials

Patients with nausea

Comparison of 2 treatment groups

Treatment Group (e.g., Granisetron)

Control Group (e.g., Placebo)

Which treatment is more effective?

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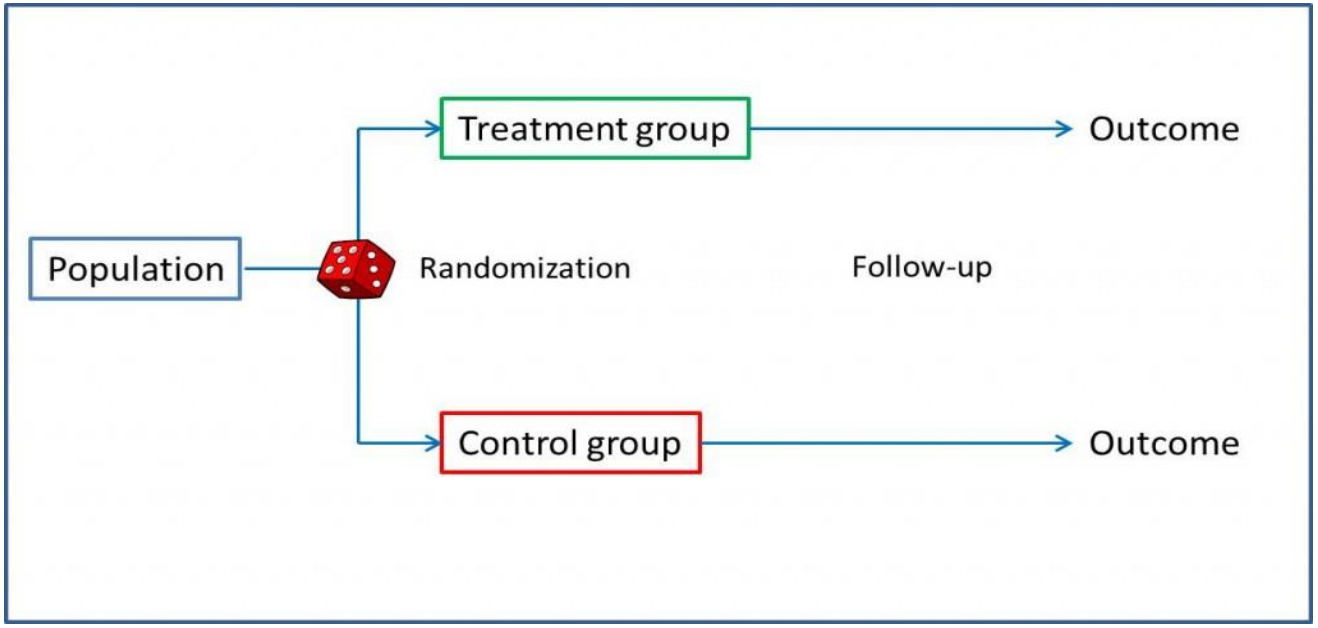
Randomized clinical trials (RCTs)

A clinical trial in which the participants are assigned randomly (by chance alone) to different treatments



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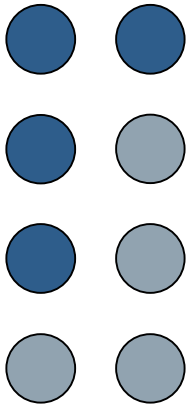
Randomized clinical trials (RCTs)

Randomization maintains the balance of baseline characteristics that could potentially confound the outcomes of the trial

Patients



Granisetron

Placebo

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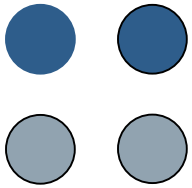
Randomized clinical trials (RCTs)

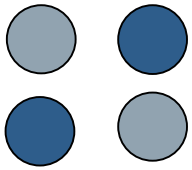
Randomization maintains the balance of baseline characteristics that could potentially confound the outcomes of the trial

Patients

Granisetron



Placebo



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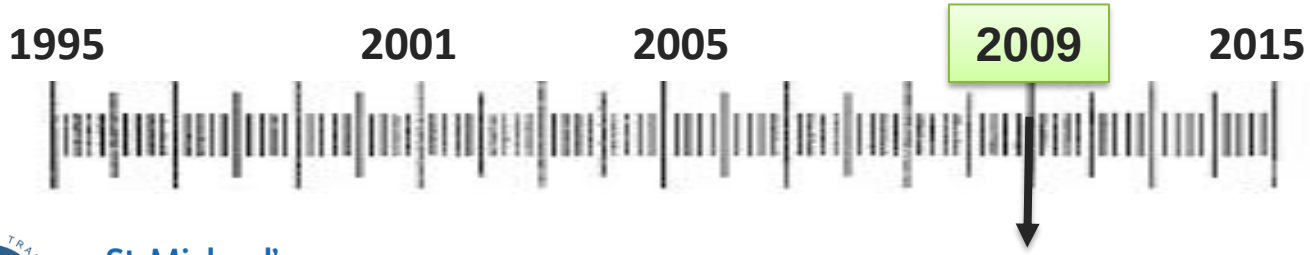
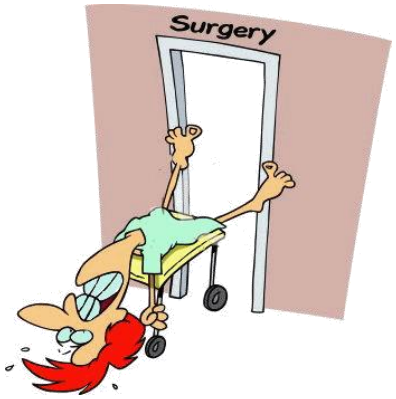
Clinical decision making

Serotonin 5-hydroxytryptamine 3 (5-HT3) receptor antagonists to relieve nausea in patients undergoing surgery

- Multiple RCTs were needed to approve granisetron in Canada
- 21 RCTs, including 1,963 patients in total, have been conducted since 1995
- The synthesis of the results of these RCTs showed a statistically significant reduction in nausea



Granisetron approved in Canada



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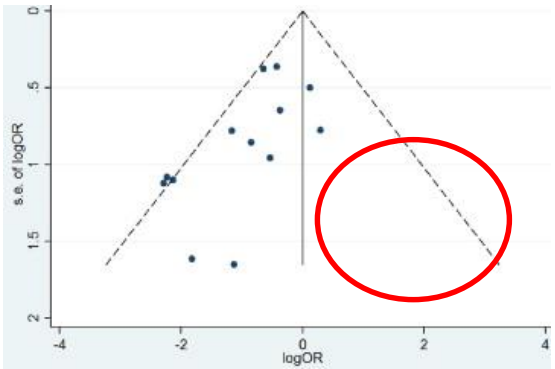
Why did it take us so long?

Because …

- The results of individual studies are not always sufficient to draw conclusions, as studies may be:
  - Small and imprecise; low power
  - Biased
  - Missing; not all studies are published and available (e.g., journals tend to publish research with positive and interesting findings)



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Why did it take us so long?

Because …

- The results of different studies may vary
  - Studies may suggest contradicting results
  - We cannot always be certain that the observed differences across studies are due to chance
- Not all questions of interest are posed by the individual studies

*"**Granisetron** tends to have a favorable trend in response rates compared with **Ondansetron**"*

*"The results indicate that **Granisetron** was significantly better than **Ondansetron**."*

*"**Granisetron** showed similar efficacy compared with **Ondansetron**,"*

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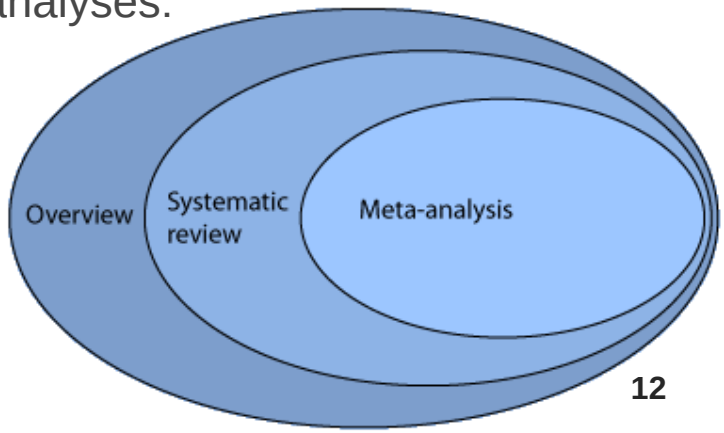
How can we improve clinical practice?

Systematic/Rapid reviews and meta-analyses

Remember …

- Systematic/Rapid reviews and meta-analyses attempt to:
  - identify all relevant studies fitting predefined criteria
  - systematically summarize the validity and findings of the studies
  - synthesize or integrate the findings
  - improve understanding of the vast amount of information
  - improve clinical practice and future research

- Rational for systematic/rapid reviews and meta-analyses:
  - Minimise bias
  - Enhance precision
  - Put results into context



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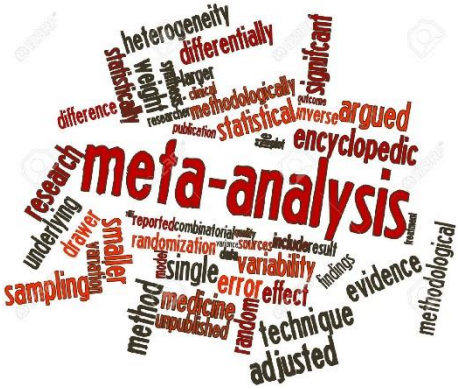
The systematic/rapid review process



1. Formulation of a clear question and inclusion criteria
2. Search for relevant studies
3. Data extraction and assessment of included studies
4. Synthesis of findings

Meta-analysis

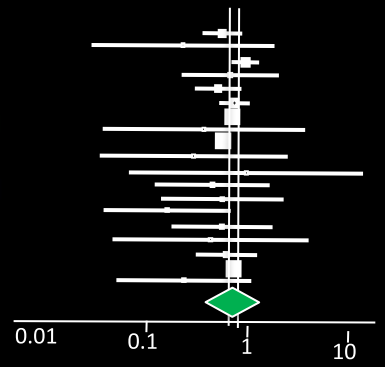
5. Interpretation

Synthesis of findings – meta-analysis

- Statistically synthesize the study results in a meta-analysis

Meta-analysis can be thought of as "conducting research about previous research"

Meta-analysis is a statistical technique for combining the findings from independent studies



It is most often used to assess the clinical effectiveness or safety of healthcare interventions

It combines data from 2 or more randomized controlled trials

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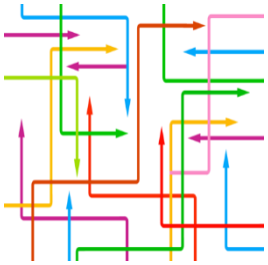
Synthesis of findings - Why apply a meta-analysis?



- To increase power and precision
- To reduce problems of interpretation due to sampling variation
- To answer questions not posed by the individual studies
- To settle controversies arising from conflicting studies and study between-study heterogeneity (generalisability of results)

Synthesis of findings - Basic principles of meta-analysis

- Participants in one study are not directly compared with those in another
- Each study is analysed separately
- Summary statistics are combined to give the meta-analysis estimate

- Each study is weighted according to the information it provides (usually the inverse of its variance)
- Larger studies are given greater weight, and hence their contribution to the meta-analysis effect is larger

To apply a meta-analysis

1. Require from each study
   - estimate of treatment effect
   - variance of estimate

$$\textbf{weight of study} = \frac{1}{\text{variance}}$$

2. Combine these using a weighted average:

$$\textbf{pooled estimate} = \frac{\text{sum of (estimate} \times \text{weight)}}{\text{sum of weights}}$$

$$\textbf{with variance} = \frac{1}{\text{sum of weights}}$$

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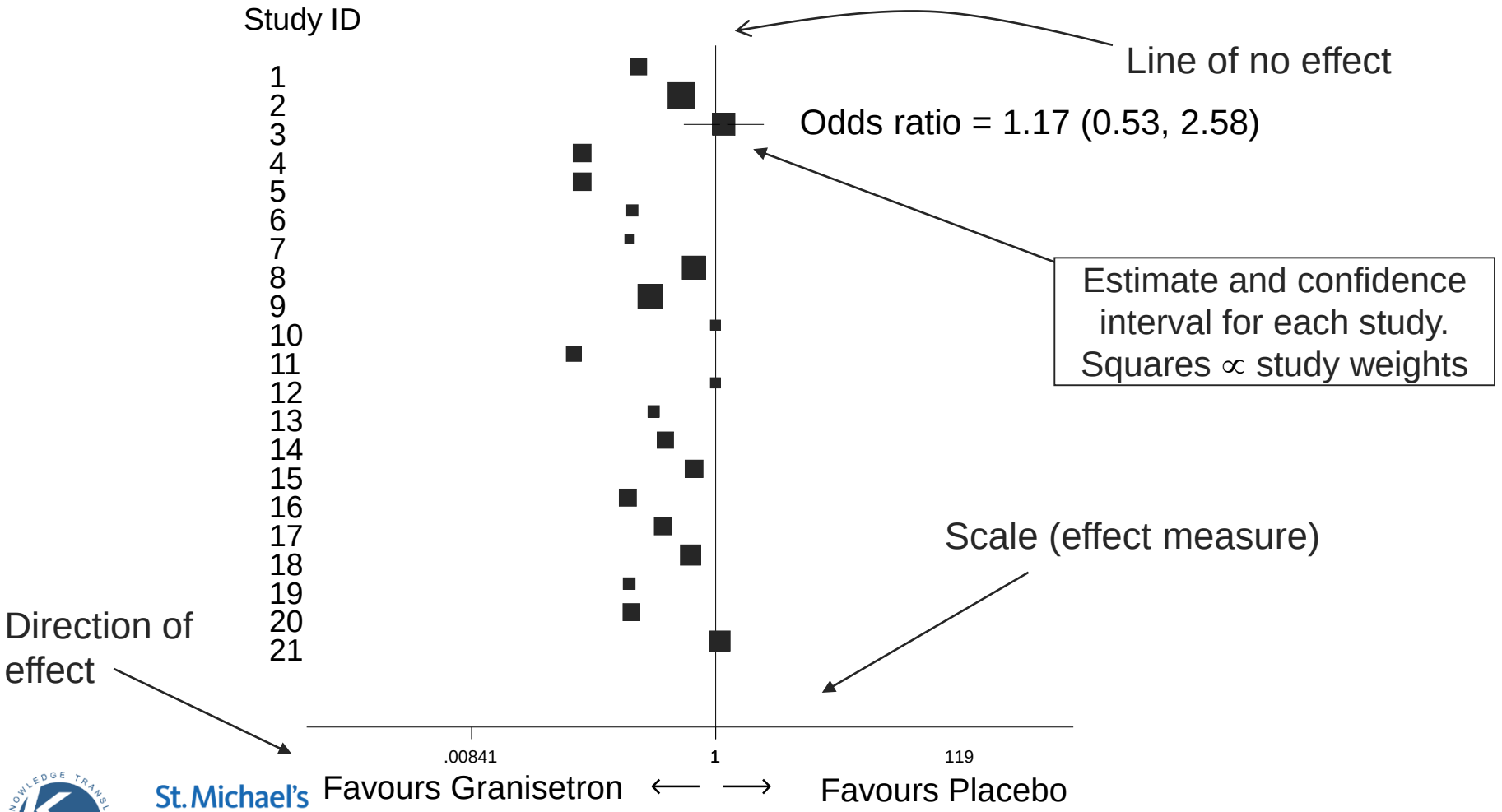
Synthesis of findings - Forest plot

Does granisetron prevent nausea?



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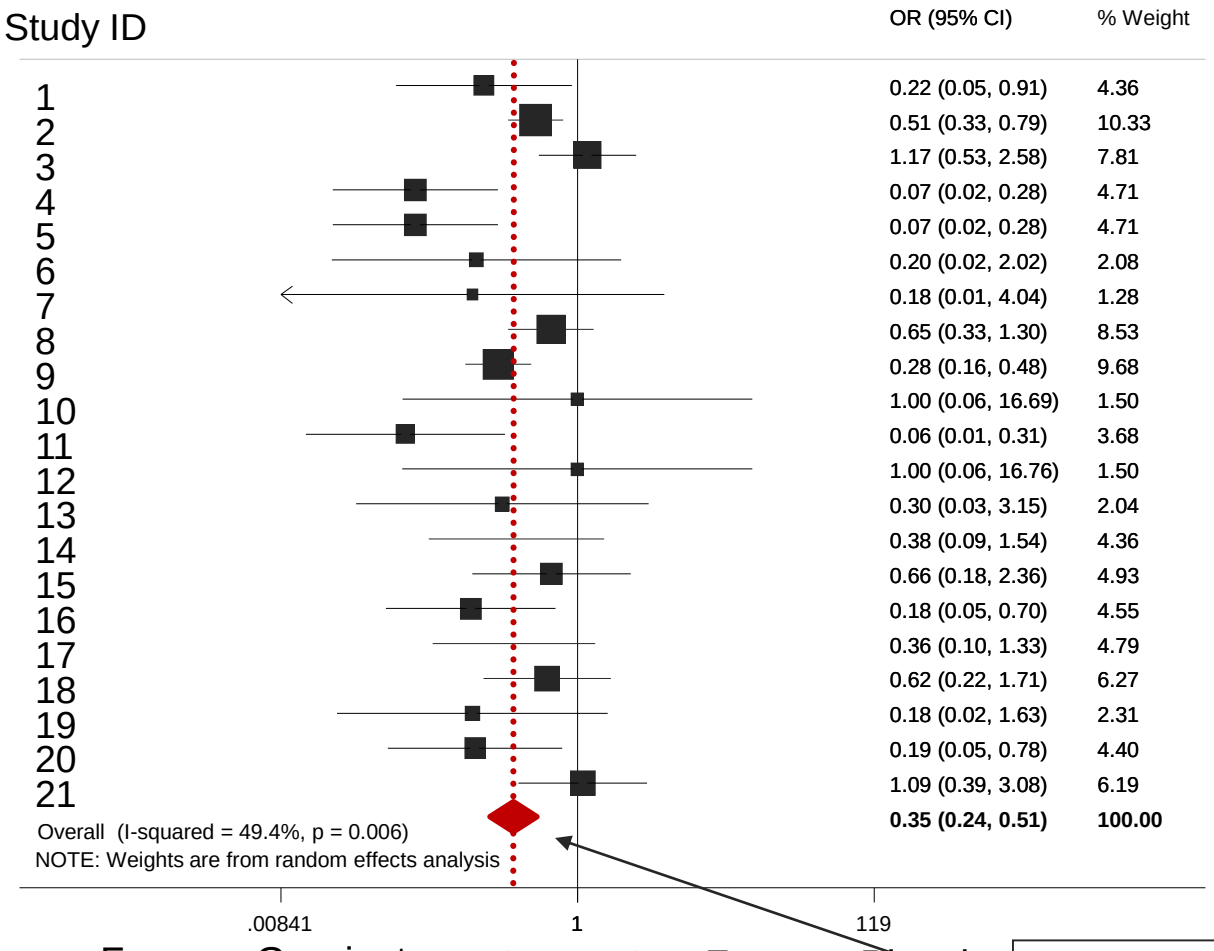
Synthesis of findings - Forest plot



Estimate and confidence for the meta-analysis

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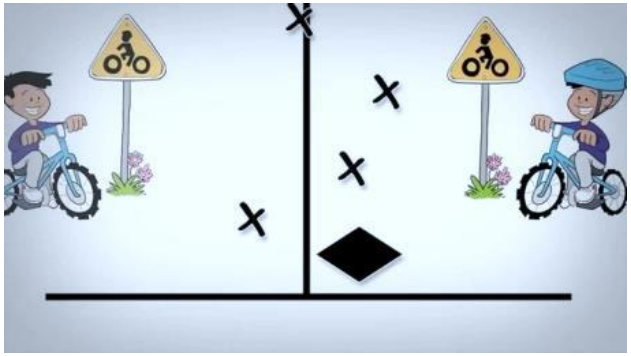
How to start a meta-analysis

1. Identify the data type for the outcome measurements
2. Use an effect size to compare the outcomes between the interventions



Results of experiments or observations

- Studies usually compare outcomes between intervention groups
  - The risk of nausea with and without granisetron

	Nausea	**Non-nausea**	Total
Granisetron	**3**	**27**	30
Placebo	**10**	**20**	30
Total	13	47	200

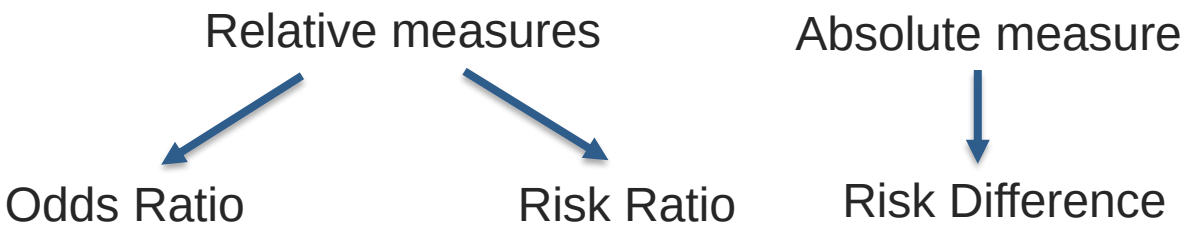
Question: How can we **compare the outcomes** between the interventions?

→ Using **Effect Sizes**

Results of experiments or observations

- Effect size: a value reflecting the magnitude of the treatment effect

	Nausea	Non-nausea	Total
Granisetron	**3**	**27**	30
Placebo	**10**	**20**	30
Total	13	47	200



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Group discussion

Have you ever conducted a meta-analysis?

Dichotomous data

Dichotomous data

Consider a single study:

	Event	*No-Event*	*Total*
Treatment	**a**	**b**	m_1
Control	**c**	**d**	m_2
Total	N_1	N_2	N

Control Group Risk (CGR)= $\frac{c}{m_2}$

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Dichotomous data

- Two components
  - Number of events per group
  - Sample size per group

	Dead	*Alive*	*Total*
Treatment	**10**	**90**	100
Control	**14**	**86**	100
Total	24	176	200

Effect measures for dichotomous data

- We can compare the two groups in several ways:
  - Odds ratio (OR)
  - Risk ratio (RR) = Relative Risk
  - Risk difference (RD) = Absolute Risk Reduction (ARR)

- All estimates are uncertain and should be presented with a confidence interval, variance or standard error

- Risks and odds are just different ways of expressing how likely an event is

Risks and odds

- Risk is defined as the probability of having an event

$$\text{risk} = \frac{\text{number of events of interest}}{\text{total number of observations}}$$

- Example: What is the probability of today to be Tuesday?
  - 1 day of the week is Tuesday / 7 days of the week = 1/7

- Odds is defined as the ratio of two probabilities: the probability of having an event over the probability of not having an event

$$\text{odds} = \frac{\text{number of events}}{\text{number of no events}}$$

- Example: What are the odds of today to be Tuesday?
  - (1/7)/(6/7) = (1 day of the week is Tuesday / 7 days of the week) / (6 days of the week are not Tuesday / 7 days of the week) = 1/6

Risks and odds

Risk : The probability with which an event will occur

Odds : The ratio of the probability that a particular event will occur to the probability that it will not occur

The difference between risk and odds is small when the event is rare but can be large for common events

$$Risk = \frac{Odds}{1+Odds}$$

$$Odds = \frac{Risk}{1-Risk}$$

Event	Total	Risk	Odds
5	100	0.05	0.0526
50	100	0.5	1
95	100	0.95	19

Risk ratio and odds ratio

$$\text{risk ratio} = \frac{\text{risk in treatment group}}{\text{risk in control group}}$$

$$\text{odds ratio} = \frac{\text{odds in treatment group}}{\text{odds in control group}}$$

	Event	*No-Event*	*Total*
Treatment	**a**	**b**	m_1
Control	**c**	**d**	m_2
Total	N_1	N_2	N

$$\text{risk ratio} = \frac{a/(a+b)}{c/(c+d)}$$

$$\text{odds ratio} = \frac{a/b}{c/d}$$

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Risk ratio

	Dead	*Alive*	*Total*
Treatment	**10**	**90**	100
Control	**14**	**86**	100
Total	24	176	200

Risk of event in treatment
= 10/100

Risk of event in control
= 14/100

$$\text{Risk Ratio} = \frac{10/100}{14/100} = \frac{0.10}{0.14} = 0.71$$

$$= \frac{\text{risk in treatment group}}{\text{risk in control group}}$$

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Odds ratio

	Dead	*Alive*	*Total*
Treatment	**10**	**90**	100
Control	**14**	**86**	100
Total	24	176	200

Odds of event in treatment
= 10/90

Odds of event in control
= 14/86

$$\text{Odds Ratio} = \frac{10/90}{14/86} = \frac{0.11}{0.16} = 0.69$$

$$= \frac{\text{odds in treatment group}}{\text{odds in control group}}$$

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Risk ratio

	Event	*No-Event*	*Total*
Treatment	**90**	**10**	100
Control	**30**	**70**	100
Total	120	80	200

A risk ratio of 3 ($RR = 3$) implies:

- Events are *3 times more likely* in the treatment group
- The treatment *increases* the risk of events by

$$100 \times (RR - 1)\% = 200\%$$

$$RR = \frac{90/(90+10)}{30/(30+70)}$$

A risk ratio of 0.25 ($RR = 0.25$) implies:

- The probability of an event in the treatment group is 1/4 of the probability in the control group
- The treatment *reduces* the risk of events by

$$100 \times (1 - RR)\% = 75\%$$

$$RR = \frac{10/(10+90)}{40/(40+60)}$$

	Event	*No-Event*	*Total*
Treatment	**10**	**90**	100
Control	**40**	**60**	100
Total	50	150	200

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Risk ratio and odds ratio

- $RR = 1$ → there is *no* *difference* in risk of event between the two groups
- $RR < 1$ → the *event rate* *is lower* in the group in the numerator
- $RR > 1$ → the *event rate* *is larger* in the group in the numerator

* Similarly, this holds for an OR, but we use odds instead of event rate

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Zero events/non-events

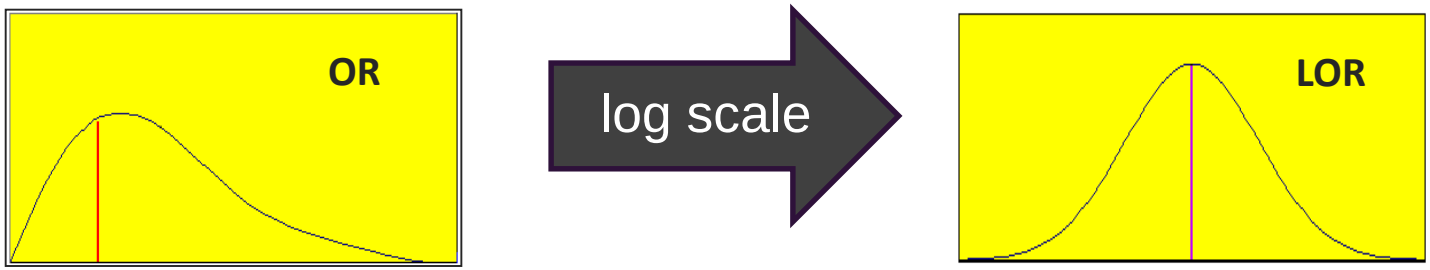
- If some cells contain zeros, then add *0.5* correction to each cell

$$\text{Risk Ratio} = \frac{\frac{a}{a+b}}{\frac{c}{c+d}} \qquad \text{Odds Ratio} = \frac{\frac{a}{b}}{\frac{c}{d}}$$

- If $a = c = 0$ or $b = d = 0$ then OR and RR are not defined and it is valid to exclude the study from the analysis

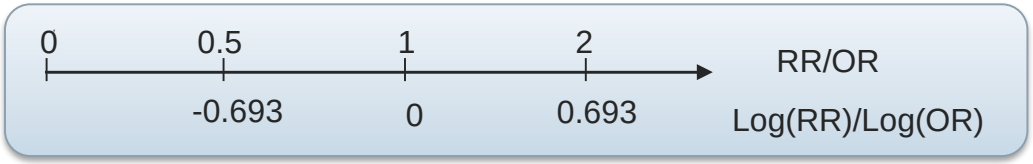
Treatment effects on the log-scale: Why?

- RR, OR are *not* symmetric



- log(OR) and log(RR)
  - are symmetric
    - log(OR) follows the normal distribution
    - log(RR) has a better approximation with the normal distribution than RR
  - no effect at zero (neutral value)
  - easier to compare positive with negative values
    - Log(OR) takes values in (-∞, ∞)
    - Log(RR) takes values in (-∞, $\log(1/CGR)$)

✓ **Typically the natural log transformation (log base e, written 'ln') is used**



Log-risk ratio (LogRR)

$$logRR = log\frac{\frac{a}{a+b}}{\frac{c}{c+d}} = log\left(\frac{a(c+d)}{c(a+b)}\right)$$

$$var(logRR) = \frac{1}{a} + \frac{1}{a+b} + \frac{1}{c} + \frac{1}{c+d}$$

- When $logRR = 0$, there is no difference between the groups

Log-Risk Ratio (LogRR)

	Dead	Alive	Total
Treatment	10	90	100
Control	14	86	100
	24	176	200

Calculate Risk Ratio

$$\boldsymbol{RR} = \frac{\frac{10}{100}}{\frac{14}{100}} = \frac{10}{14} = 0.71$$

- Where risk ratio = 1, this implies no difference in effect

Introduce in meta-analysis

$\boldsymbol{log(RR)} = log(0.71) = -0.34$ and $\boldsymbol{var(logRR)} = \frac{1}{10} + \frac{1}{100} + \frac{1}{14} + \frac{1}{100} = 0.194$

or $\boldsymbol{SE(logRR)} = \sqrt{var(logRR)} = \sqrt{0.19} = 0.44$

Calculate a 95% C.I. for logRR

$\boldsymbol{95\%\ CI\ for\ logRR}$: $logRR \pm 1.96 \times SE(logRR) = (-1.20, 0.52)$

Back-calculate to the original scale

$\boldsymbol{95\%\ CI\ for\ RR}$: $(e^{-1.20}, e^{0.52}) = (0.30, 1.68)$

Log-odds ratio (LogOR)

$$logOR = log\frac{\frac{a}{b}}{\frac{c}{d}} = log\left(\frac{a}{b}\right) - log\left(\frac{c}{d}\right)$$

$$= log\left(\frac{ad}{bc}\right)$$

$$var(logOR) = \frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}$$

- When $logOR = 0$, there is no difference between the groups

Log-Odds Ratio (LogOR)

	Dead	Alive	Total
Treatment	10	90	100
Control	14	86	100
	24	176	200

Calculate Odds Ratio

$$OR = \frac{\frac{10}{90}}{\frac{14}{86}} = 0.68$$

- Where odds ratio = 1, this implies no difference in effect

$log(OR)$	$var(logOR) = \frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}$	$SE(logOR) = \sqrt{var(logOR)}$	95% CI for logOR $logOR \pm 1.96 \times SE(logOR)$
-0.38	0.191	0.44	(-1.24 , 0.48)

Back-calculate to the original scale

$95\%\ CI\ for\ OR:\ (e^{-1.24}, e^{0.48}) = (0.29, 1.62)$

Risk difference (RD)

- The difference in the probability between the treated and control groups

$$RD = TGR - CGR = \frac{a}{a+b} - \frac{c}{c+d}$$

- A measure easy to interpret but clinical interpretation depends on context (RD is not a relative treatment effect)
  - A treatment reduces the probability of death RD= 2% from 70% risk goes to 68% or from 3% to 1%?
- Gives improbable values if applied in different populations
  - RD of -10% applied to a population with 7% CGR gives –3% TGR

TGR: Treatment Group Risk; CGR: Control Group Risk

Risk difference (RD)

$$RD = \frac{a}{a+b} - \frac{c}{c+d}$$

$$var(RD) = \frac{ab}{(a+b)^3} + \frac{cd}{(c+d)^3}$$

- When $RD = 0$, there is no difference between the groups

Group discussion

Have you ever worked with dichotomous data?

Continuous data

Outcomes from a study

- Three components
  - Mean value per group
  - Measure of variation per group
  - Sample size per group

	Mean	*SD*	*Sample Size*
Treatment	$\boldsymbol{m_t}$	$\boldsymbol{s_t}$	$\boldsymbol{n_t}$
Control	$\boldsymbol{m_c}$	$\boldsymbol{s_c}$	$\boldsymbol{n_c}$
Total			$\boldsymbol{n}$

Outcomes from a study

- Zachariah et al. 2011: Type 1 diabetes and weight gain
- Detemir vs. NPH

	Mean	*SD*	*Sample Size*
Detemir	$\mathbf{-0.69}$	$\mathbf{1.85}$	$\mathbf{23}$
NPH	$\mathbf{1.7}$	$\mathbf{2.46}$	$\mathbf{23}$
Total			$\mathbf{46}$

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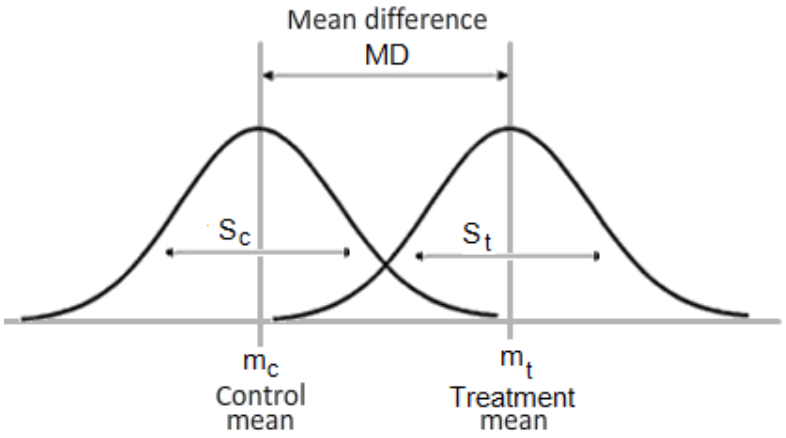
Difference in means (MD)



$$MD = m_t - m_c$$

$$Var(MD) \cong \frac{s_t^2}{n_t} + \frac{s_c^2}{n_c}$$

sample standard deviations of each group

- **When mean difference = 0, there is no difference between the groups**

Mean Difference

	Mean	*SD*	*Sample Size*
Detemir	-0.69	1.85	23
NPH	1.7	2.46	23
Total			46

Mean in Detemir group
= -0.69

Mean in NPH group
= 1.7

Mean Difference = – 0.69 – 1.7 = – 2.39 kg

= mean in treatment group – mean in control group

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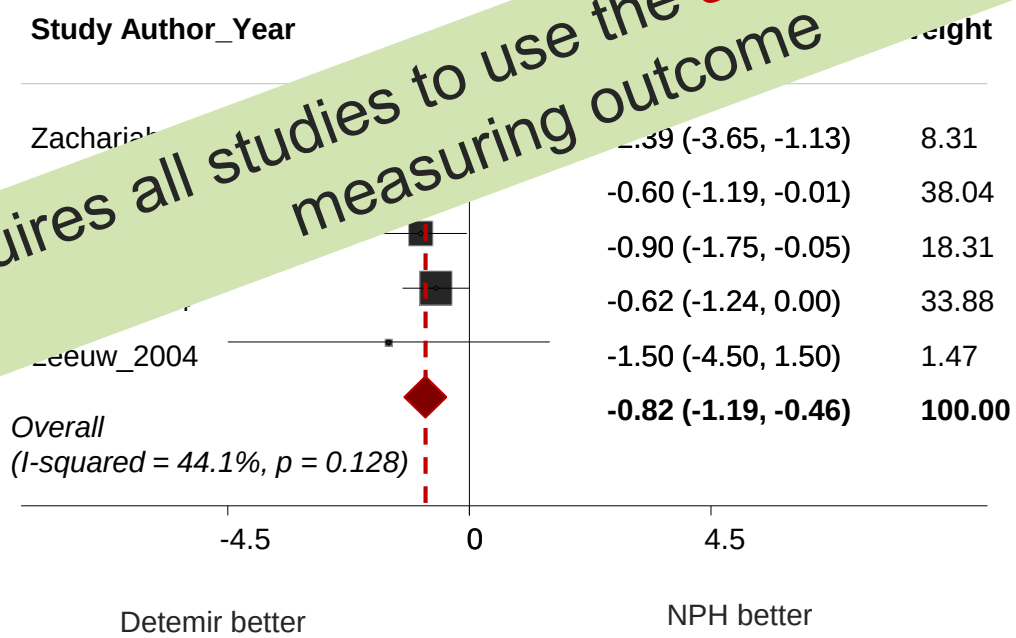
Detemir vs. NPH for preventing weight gain in patients with type 1 diabetes

	NPH [od/bid]			Detemir [od/bid]		
Study	mean	sd	n	mean	sd	n
Zachariah_2011	1.7	2.46	23	-0.69	1.85	23
Pieber_2005	0.7	2.4232	129	0.1	2.4232	
Vague_2003	71.8	3.97	145	70.9		
Home_2004	0.86	2.64	132	0.24		
Leeuw_2004	72.7	13.1	99			116

Requires all studies to use the same scale for the measuring outcome



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Standardized difference in means (SMD)

$$SMD = \frac{m_t - m_c}{s_{pooled}}$$

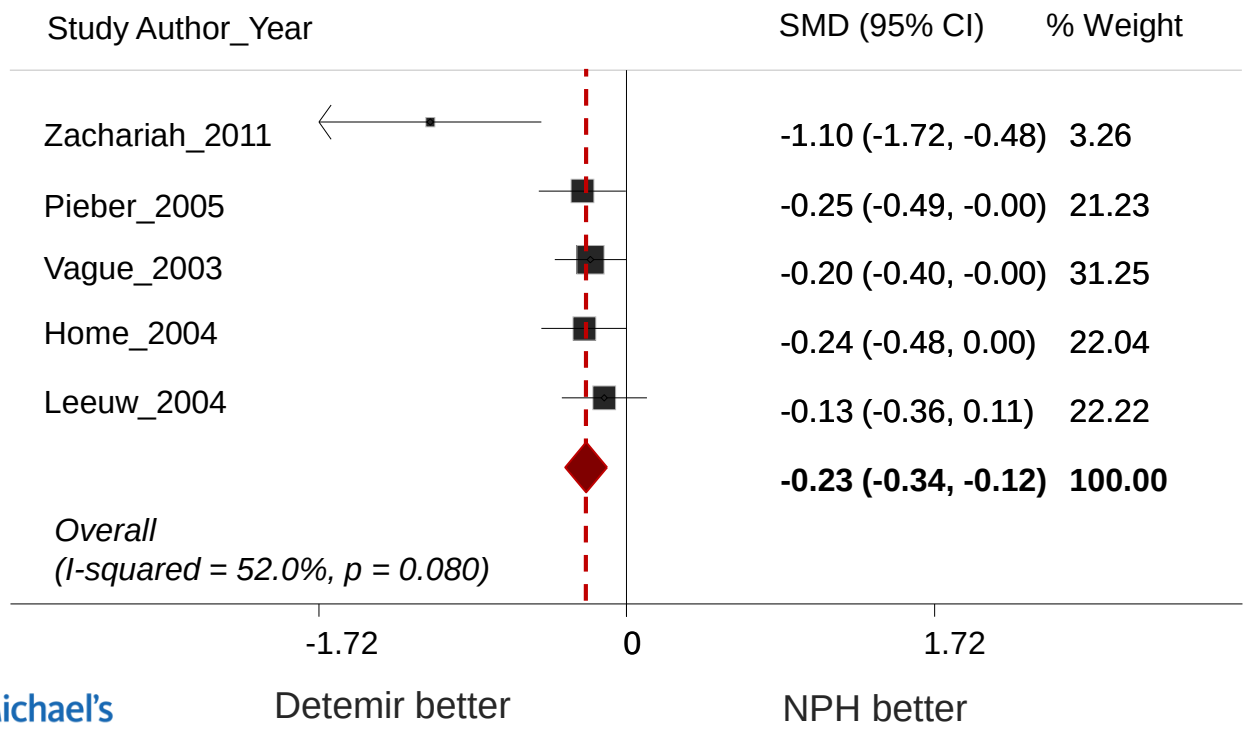
$$Var(SMD) \cong \frac{1}{n_t} - \frac{1}{n_c} + \frac{SMD^2}{2(n-2)}$$

$$s_{pooled} = \sqrt{\frac{(n_t - 1)s_t^2 + (n_t - 1)s_c^2}{n - 2}}$$

- When standardized mean difference = 0, there is no difference between the groups

NPH vs. Detemir for preventing weight gain in patients with type 1 diabetes

Treatment Effect	SMD
small	0.2
medium	0.5
large	0.8



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Group discussion

Have you ever worked with continuous data?

Interpretation of meta-analysis results

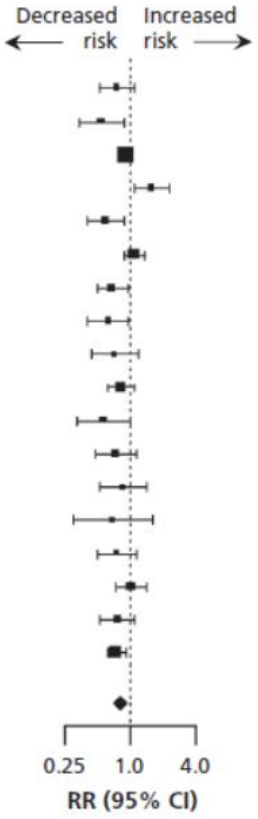
- Conventional Interpretations
  1. Statistical Significance and Direction
  2. Magnitude of the pooled estimate
  3. Width of the confidence interval

- Heterogeneity
  - Too much heterogeneity challenges the meaning of the diamond

- Quality of the included studies

Interpretation of meta-analysis results

Study	Treatment n/N	Control n/N	RR (95% CI)
Beck et al.[51]	35/160	47/161	0.75 (0.51 to 1.09)
Botha et al.[25]	13/32	18/24	0.54 (0.34 to 0.87)
Burns et al.[45]	210/353	228/355	0.93 (0.82 to 1.04)
Franklin et al.[60]	62/213	38/204	1.56 (1.10 to 2.23)
Lafave et al.[53]	13/24	37/41	0.60 (0.41 to 0.88)
Puschner et al.[29]	108/241	103/250	1.09 (0.89 to 1.33)
Rich et al.[55]	41/142	59/140	0.69 (0.50 to 0.95)
Salkever et al.[48]	27/91	25/53	0.63 (0.41 to 0.96)
Rich et al.[58]	21/63	16/35	0.73 (0.44 to 1.20)
Kasper et al.[43]	47/102	55/98	0.82 (0.62 to 1.08)
Courtney et al.[30]	13/49	27/58	0.57 (0.33 to 0.98)
Castro et al.[40]	20/50	25/46	0.74 (0.48 to 1.13)
Burns et al.[26]	17/110	56/313	0.86 (0.53 to 1.42)
Koehler et al.[32]	6/20	9/21	0.70 (0.30 to 1.61)
Ruchlewska et al.[28]	24/70	33/73	0.76 (0.50 to 1.14)
Laramee et al.[41]	49/131	46/125	1.02 (0.74 to 1.40)
Stewart et al.[50]	24/49	31/48	0.76 (0.53 to 1.08)
Lichtenberg et al.[34]	71/122	74/95	0.75 (0.62 to 0.90)
Overall Heterogeneity: I^2 = 58%			0.81 (0.72 to 0.91)




RESEARCH

CMAJ

Effectiveness of quality improvement strategies for coordination of care to reduce use of health care services: a systematic review and meta-analysis

Andrea C. Tricco PhD, Jesmin Antony MSc, Noah M. Ivers MD PhD, Huda M. Ashoor BSc, Paul A. Khan PhD, Erik Blondal BSc, Marco Ghassemi MSc, Heather MacDonald MLIS, Maggie H. Chen PhD, Lianne Kark Ezer MS

"Significantly fewer patients in the intervention group than in the control group were admitted to hospital (relative risk [RR] 0.81, 95% confidence interval [CI] 0.72–0.91)."

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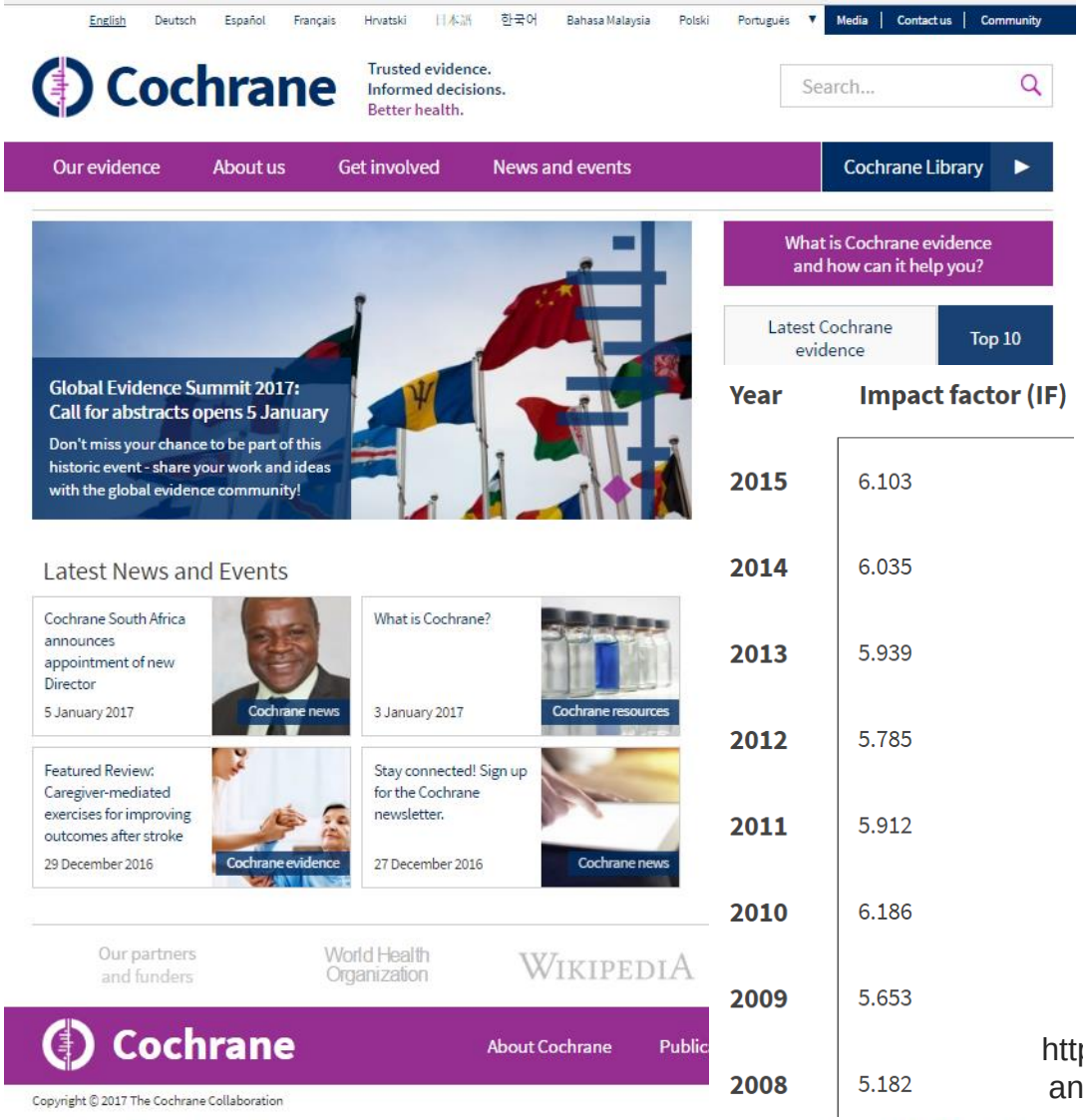
The Cochrane Collaboration



Year	Impact factor (IF)
2015	6.103
2014	6.035
2013	5.939
2012	5.785
2011	5.912
2010	6.186
2009	5.653
2008	5.182

Number of Cochrane reviews and protocols published by issue

2015	Total reviews	Total protocols	Total reviews and protocols
Issue 1	6275	2356	8631
Issue 2	6307	2370	8677
Issue 3	6355	2380	8735
Issue 4	6388	2411	8799
Issue 5	6421	2420	8841
Issue 6	6466	2437	8901
Issue 7	6505	2432	8937
Issue 8	6538	2425	8963
Issue 9	6583	2432	9017
Issue 10	6621	2429	9050

http://www.cochranelibrary.com/cochrane-database-of-systematic-reviews/

The Cochrane Collaboration

- The Cochrane collaboration is one of the greatest databases of RCTs (CENTRAL)

www.cochrane.org

- Provides a free software for systematic reviews and meta-analyses (Review Manager; RevMan) – For a practical to RevMan see:

  https://www.youtube.com/watch?v=I6gqY5GkwMs

- See also the **Cochrane Handbook** (http://community.cochrane.org/handbook) that describes in detail the process of preparing and maintaining Cochrane systematic reviews on the effects of healthcare interventions.
  - For video about systematic reviews, also visit: http://www.cochrane.org/what-is-cochrane-evidence

For more details on the Knowledge Translation Tools, please visit our website: http://knowledgetranslation.net/

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Group discussion

Why apply meta-analysis?

What factors should you keep in mind when interpreting MA data?

Resources

- *Cochrane Handbook for Systematic Reviews of Interventions*
  - Higgins and Green (eds); Wiley 2008, updated online
- *RevMan Tutorial* and *User Guide*
  - www.cc-ims.net/RevMan/documentation.htm
- *Introduction to Meta-analysis*
  - Borenstein, Hedge, Higgins and Rothwell; Wiley 2009
- *Meta-Analysis of Controlled Clinical Trials*
  - Whitehead; Wiley 2002
- *Handbook of Research Synthesis and Meta-analysis*
  - Cooper, Hedges and Valentine; Sage 2009
- *Methods for Meta-Analysis on Medical Research*
  - Alex J.Sutton et al.,John Wiley & Sons, Ltd. (2000)
- *Statistical Methods for Meta-Analysis*
  - Larry V. Hedges and Ingrim Olgin, Academic Press, Inc. (1985)

Additional reading:

- Borrenstein M, Higgins JPT, Hedges LV, Rothstein H. Basics of meta-analysis: I^2 is not an absolute measure of heterogeneity. Res. Syn. Meth., 2017 (early view)
- DerSimonian R, Laird NM. Meta-analysis in clinical trials. Controlled Clinical Trials 1986. 7: 177–188.
- Riley RD, Higgins JPT, Deeks JJ. Interpretation of random effects meta-analyses. BMJ. 2011. 342: d549.
- Veroniki, A. A., Jackson, D., Viechtbauer, W., Bender, R., Bowden, J., Knapp, G., Kuss, O., Higgins, J. PT., Langan, D., and Salanti, G. Methods to estimate the between-study variance and its uncertainty in meta-analysis. Res. Syn. Meth., 2016 7: 55–79.

Questions?

Thank you for your attention!

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