Systematic Review and Meta-Analysis… Tools, Termites and Tricks of the Trade…

Larry Young

Sheri Keitz

Teaching Objectives

- To shun fear and learn to love forest plots
- To review principles of when it is appropriate to combine studies
- Interpret the results of a meta-analysis including forest plots
- Understand what systematic reviews can and cannot do for you
- Demonstrate teaching techniques and identify resources to assist

Extra-Special Teaching Objective

- CERTIFIED to be JARGON FREE

- Need a volunteer

Are Systematic Reviews Scary? Raise your hand if you…

- Always skip the methods section on Systematic Reviews because it sounds like gobbledy-gook
- Make your colleagues teach the systematic review session so you don't look like an idiot
- Think a "Forest Plot" might be a good buy given the current housing market.

How to decrease fear

- What strategies have you seen this week (small or large group) to decrease fear in the learning environment?

Teaching Time Out

- Simplify concepts
- Avoid numbers and Jargon
- There are tools to assist your teaching
  - TIPS Series

Tips for teachers of evidence-based medicine: 4. Assessing heterogeneity of primary studies in systematic reviews and whether to combine their results

Rose Hatala, Sheri Keitz, Peter C. Wyer, Gordon Guyatt, for the Evidence-Based Medic Teaching Tips Working Group

Clinicians wishing to quickly answer a clinical question may look for a systematic review rather than searching for primary articles. Such a review is also called a meta-analysis when the investigators have

are geared to learners who are familiar with ho tors should present the magnitude[3–5] and pr treatment effects in a study with binary outcon ratio or relative risk reduction) and who hav

Gleeful to Grief-stricken Scale

- Validated instrument for assessing levels of comfort (glee) or fear (grief) in EBM workshop participants

Reactions of people on hearing that they need to look at a meta-analysis:

Words that start with the letter "F"!

Ridicularia Exemplarum…

The best way to understand just about anything in medicine is to reflect on a patient…or other life dilemmas.

The following tale is one such dilemma…

Disclaimer

- All characters and events in this presentation are fictional.
- Any use of names (or initials) is purely unintentional and any similarities to actual persons, in this room or elsewhere, are purely coincidence.
- We cannot emphasize enough how coincidental similarities of our fictional entities to any real life individual, entity, or character are.

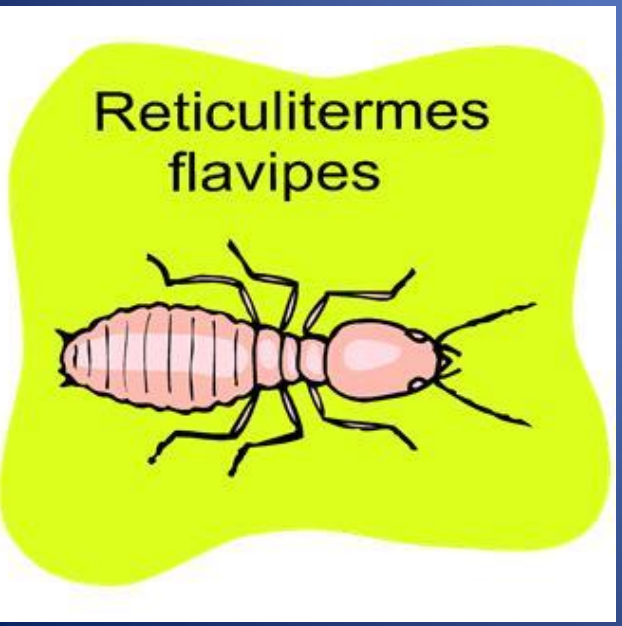
Meet Our Heroine…

- A “young” faculty member (SK) had just moved to Miami from Durham NC.
- She bought a house.

Things were going well…

- She had a great job (Some days)
- Worked with the most supportive bosses you could ask for (Some bosses)
- Nothing bad ever happened (Almost nothing)
- There were never any crises for her to manage (Definitely not written by SK)

Until one Tuesday at 1X 3 AM while lounging at the side of her pool…

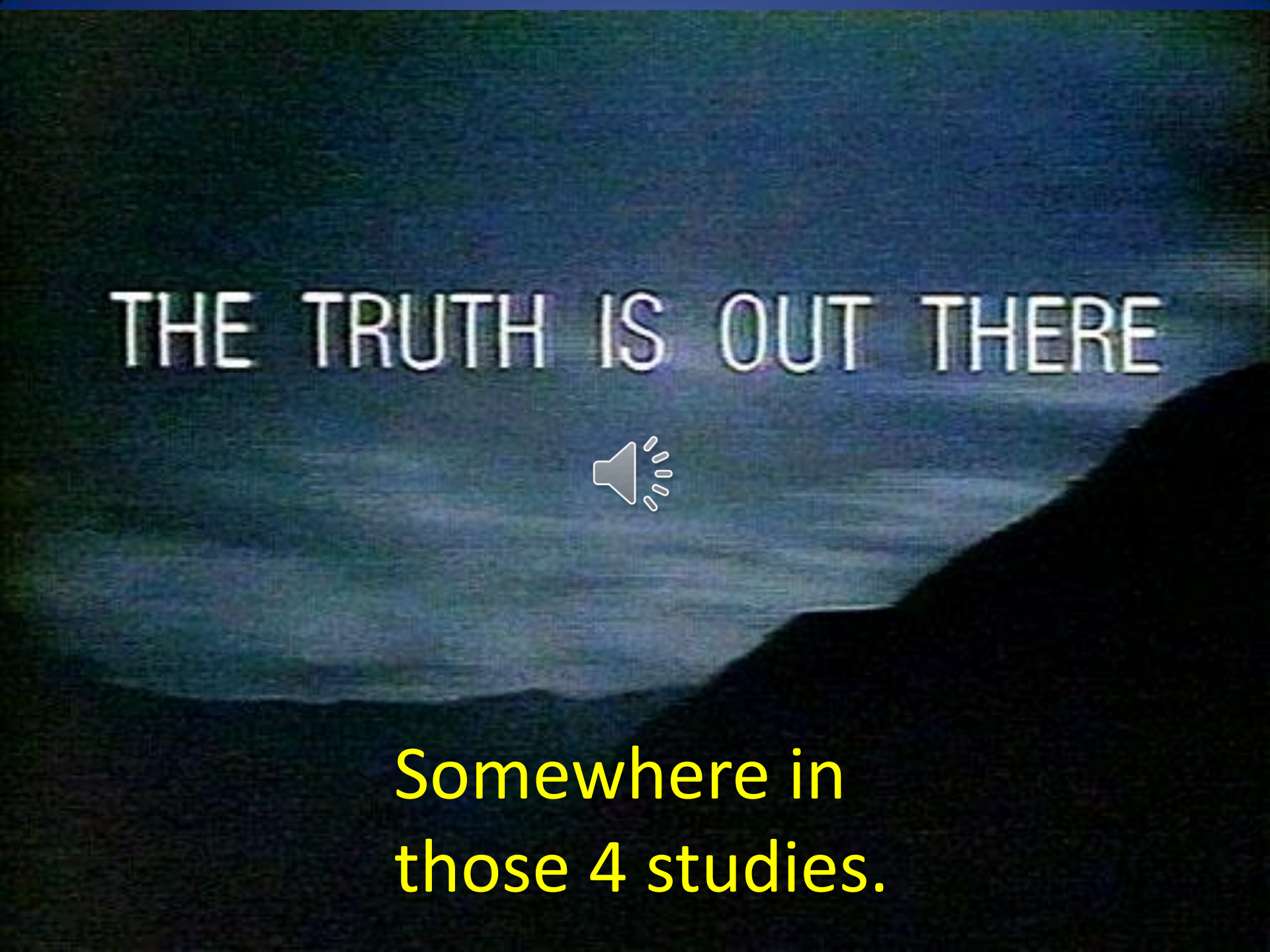


She won't lose that kitchen to termites!

- Call to her best friend, a librarian… we'll call her "Connie".
- I need to know what I can do to get rid of these termites before they destroy my kitchen island… and I want the best evidence there is.

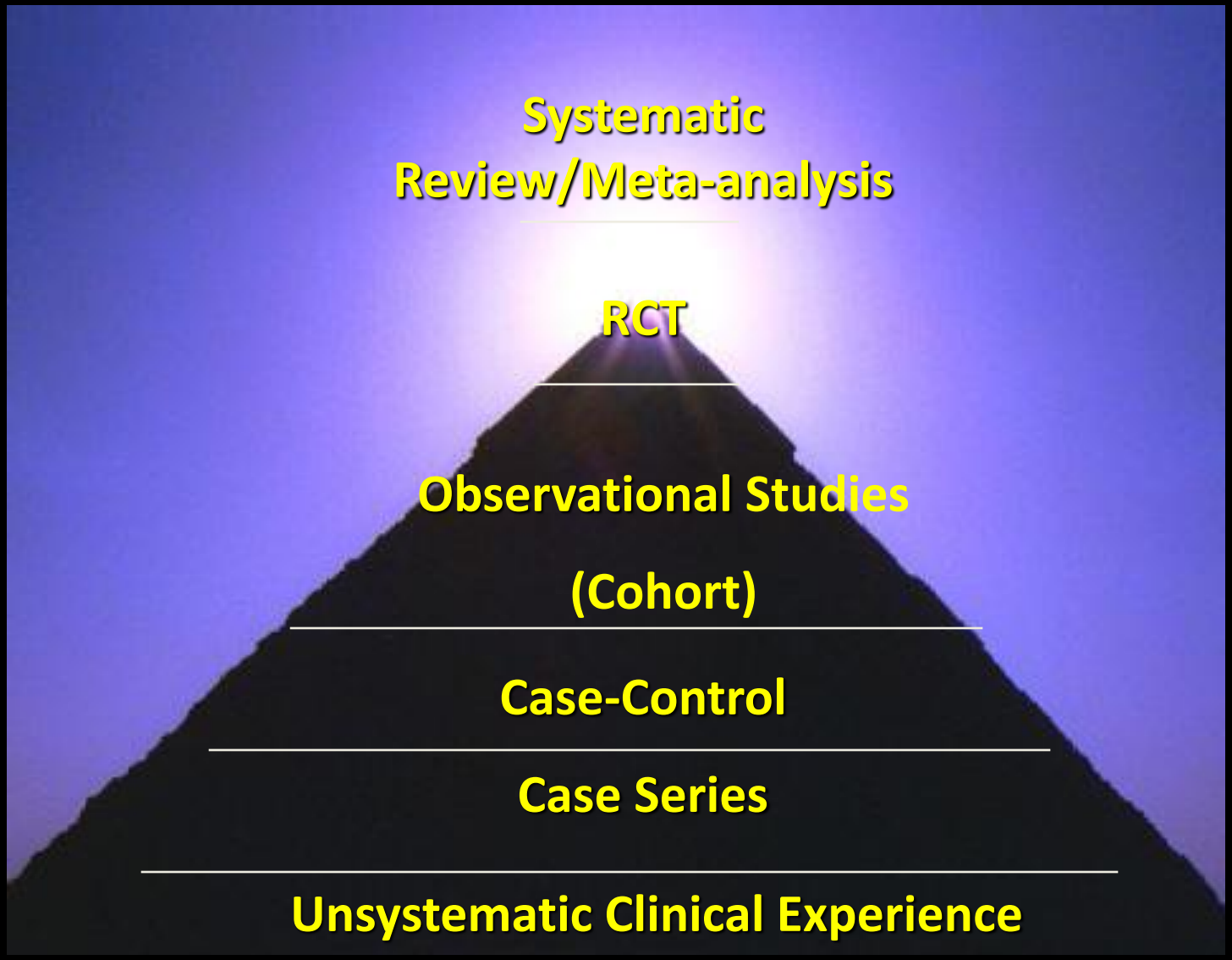
Two minutes later, Connie calls back…

- I found 4 studies on this brand new product!
- But I know you wanted the *best* evidence.



Somewhere in
those 4 studies.

The Evidence Pyramid (Of Truth)



Says Connie…

- I know you are super busy.
- As it happens we have a faculty member here at Duke who needs to publish more (we'll call him "Tom").
- I think with some help he can put this together in a meta-analysis for you.

Let's help Tom summarize each study.

	P	I	C	O	F/U
Cearras					
Villasboas					
Symes					
Brown					

First Authors Are Here If You Need Help!

	P	I	C	O	F/U
Cearras et al	Miami termites	Termicillin on walls	Placebo	Dead termites	30

	P	I	C	O	F/U
Cearras et al	Miami termites	Termicillin on walls	Placebo	Dead termites	30
Villasboas et al	Rochester termites	Termicillin on walls	Placebo	Dead termites	30

	P	I	C	O	F/U
Cearras et al	Miami termites	Termicillin on walls	Placebo	Dead termites	30
Villasboas et al	Rochester termites	Termicillin on walls	Placebo	Dead termites	30
Symes et al	Miami termites	Termicillin on walls	Termaban	Dead termites	30

	P	I	C	O	F/U
Cearras et al	Miami termites	Termicillin on walls	Placebo	Dead termites	30
Villasboas et al	Rochester termites	Termicillin on walls	Placebo	Dead termites	30
Symes et al	Miami termites	Termicillin on walls	Termaban	Dead termites	30
Brown et al	Miami termites	Termicillin aerosolized	Placebo	Termites whose wings fell off	30

Next Exercise

- Instructions to be given by a visiting celebrity scholar….
- Go to video and then do what the video tells you to do…. (use discretion in your interpretation)

Celebrity Scholar.

	P	I	C	O	F/U
Cearras et al	Miami termites	Termicillin on walls	Placebo	Dead termites	30
Villasboas et al	Rochester termites	Termicillin on walls	Placebo	Dead termites	30
Symes et al	Miami termites	Termicillin on walls	Termaban	Dead termites	30
Brown et al	Miami termites	Termicillin aerosolized	Placebo	Termites whose wings fell off	30

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Brown et al	Miami termites	Termicillin aerosolized	Placebo	Termites whose wings fell off	30

One of these things is not like the others…

Is pooling sensible?

- A priori determination of whether it makes sense to combine on a principled basis.
- You have not looked at the data yet…

The Common Sense Test

Is pooling sensible?

- MA of all kinds of treatments for all cancers?
- MA of steroid treatments for COPD?
- MA of studies looking at CT-angiogram for diagnosis of pulmonary embolism?

	P	I	C	O	F/U
Cearras et al	Miami termites	Termicillin on walls	Placebo	Dead termites	30
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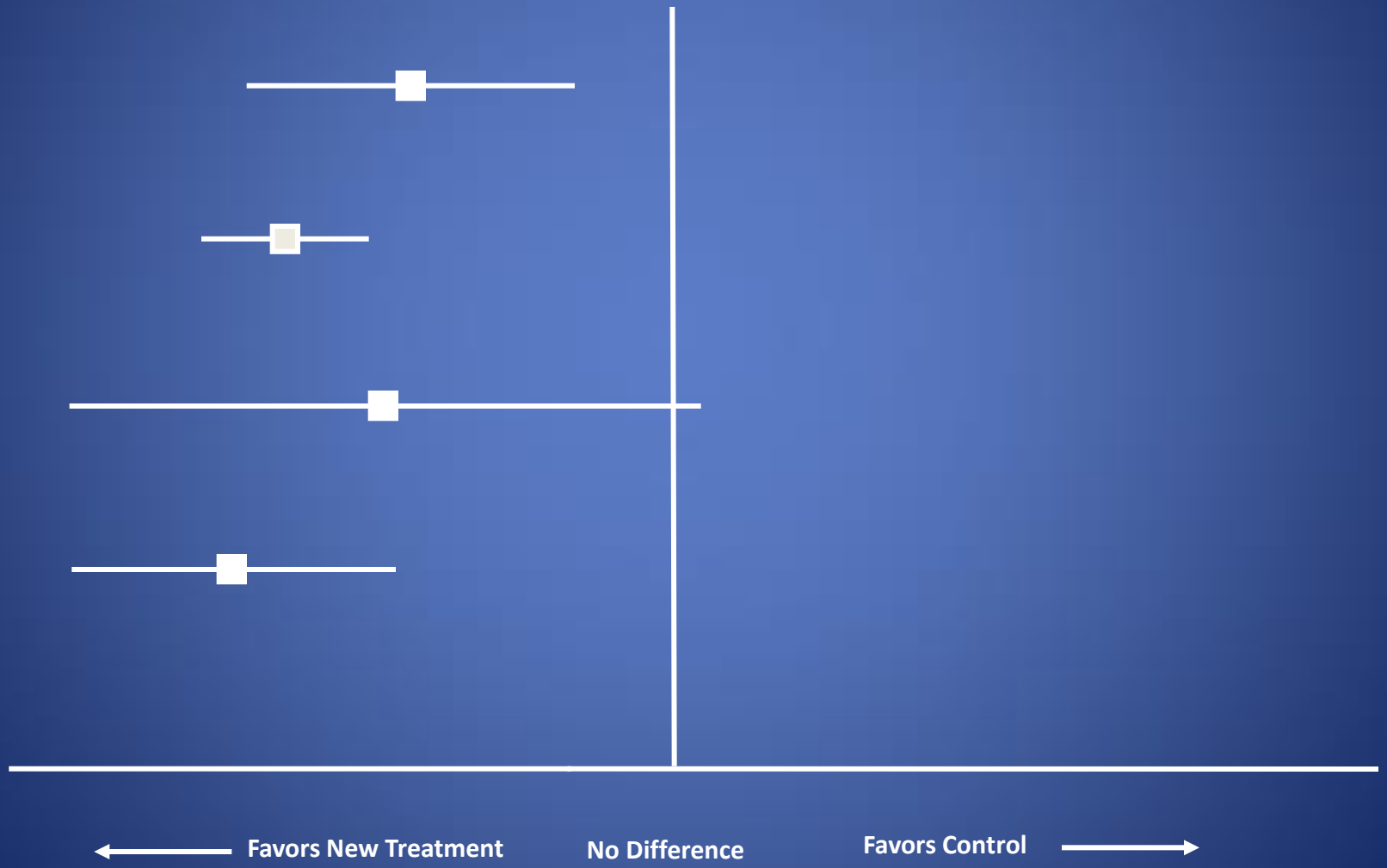
Does combining RESULTS make sense?

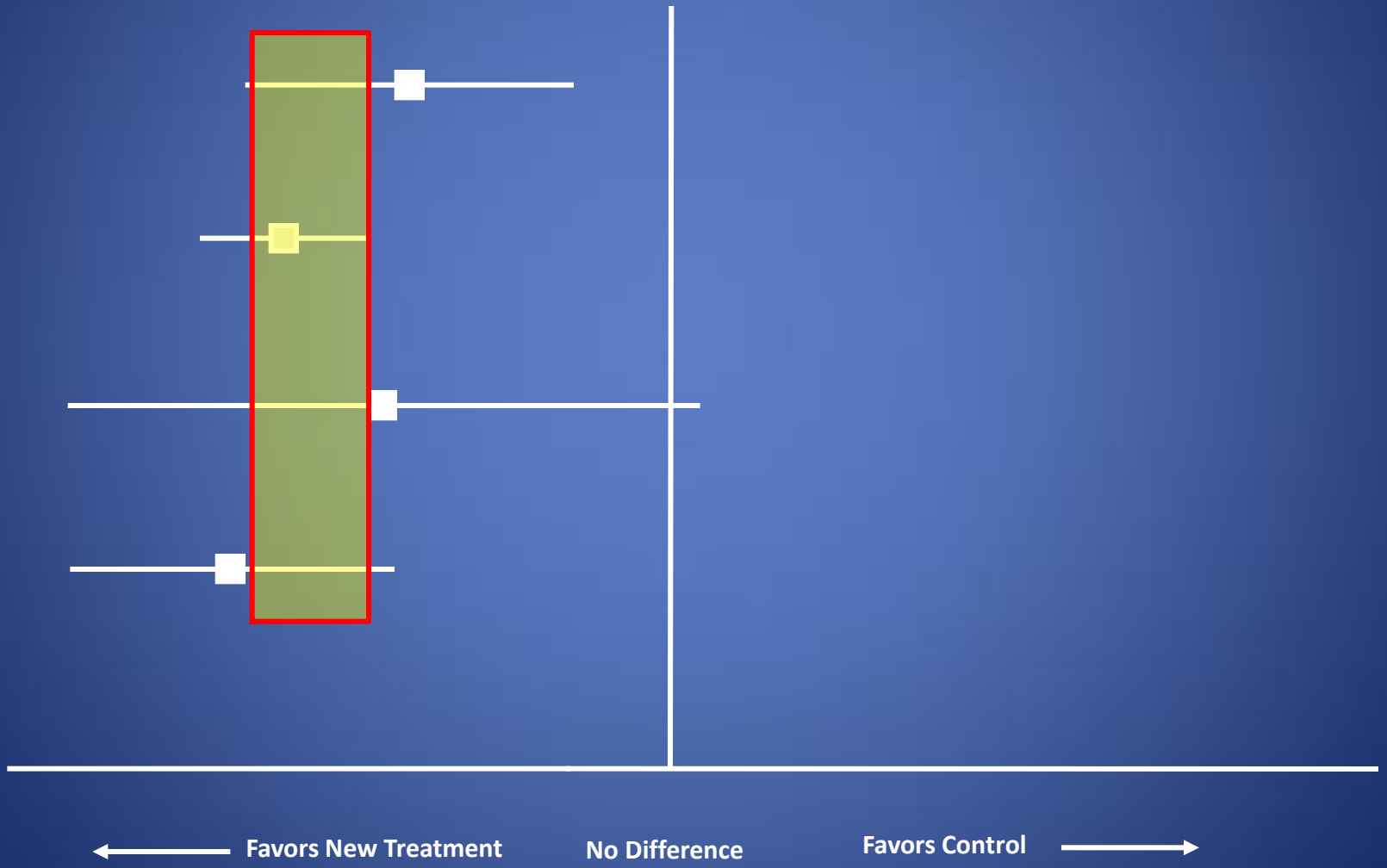
- Comes from a review of dots and lines
- What are the dots and lines in a MA?

Result 1

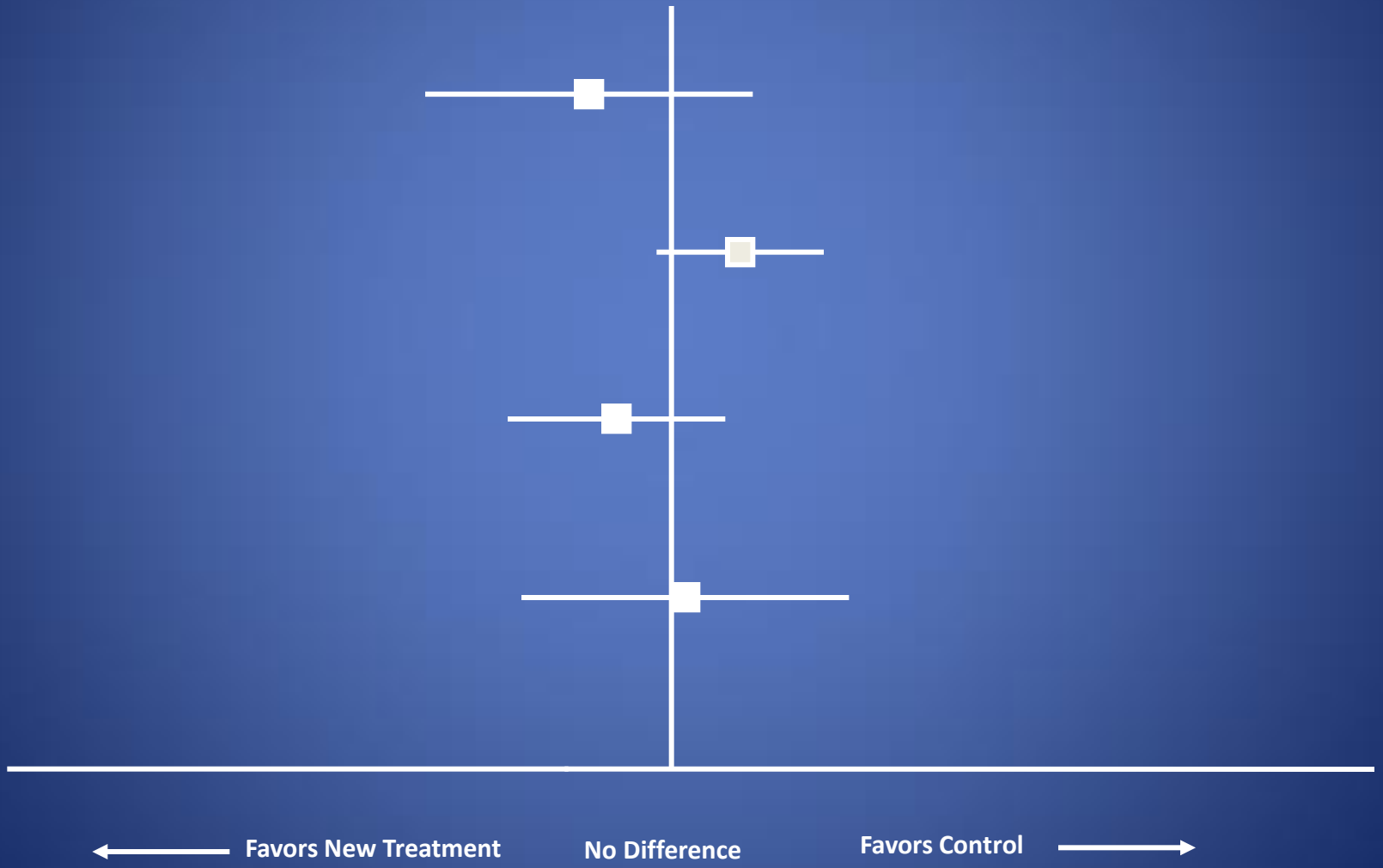


Eye-ball test

Can we combine?

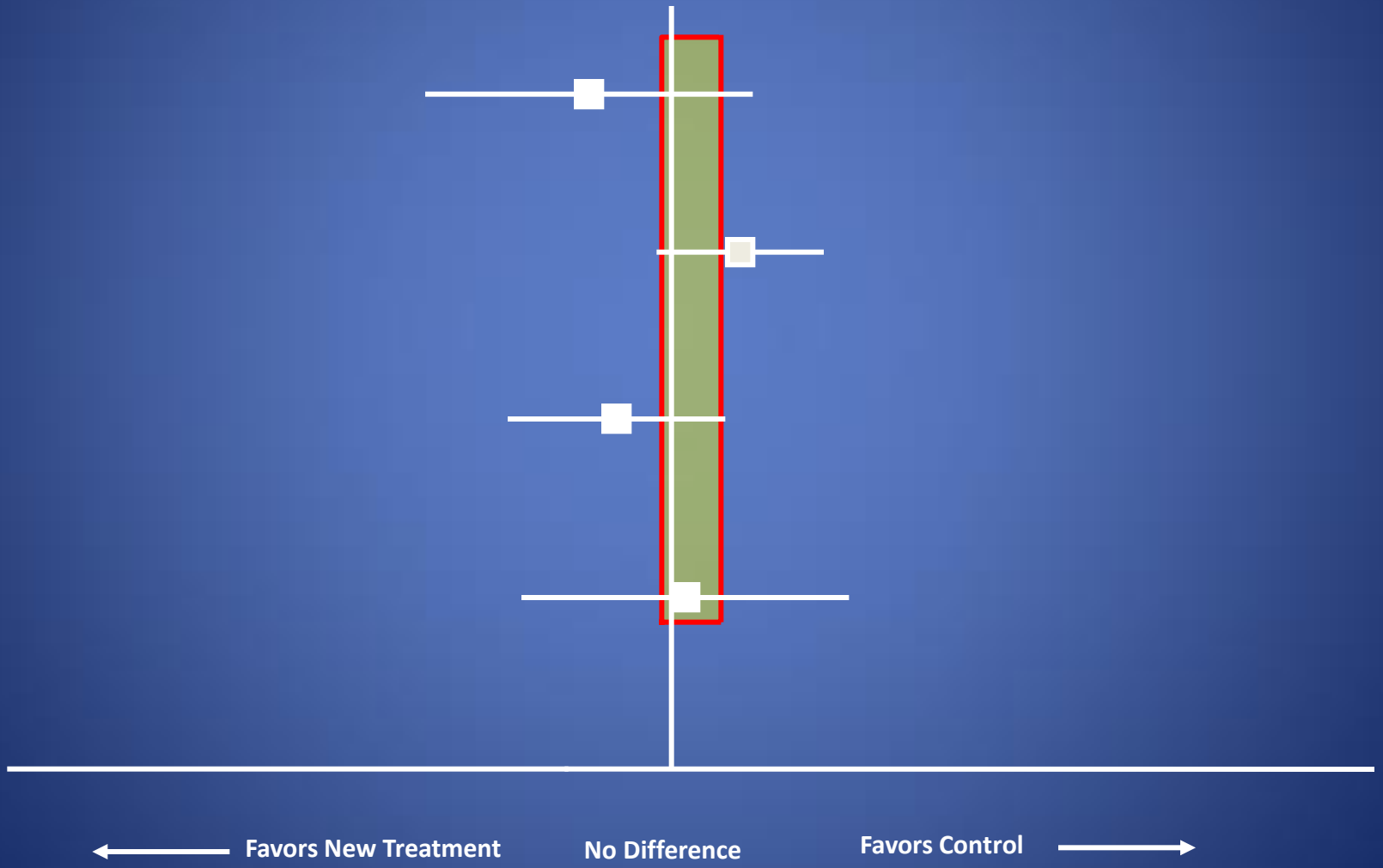


Result 2

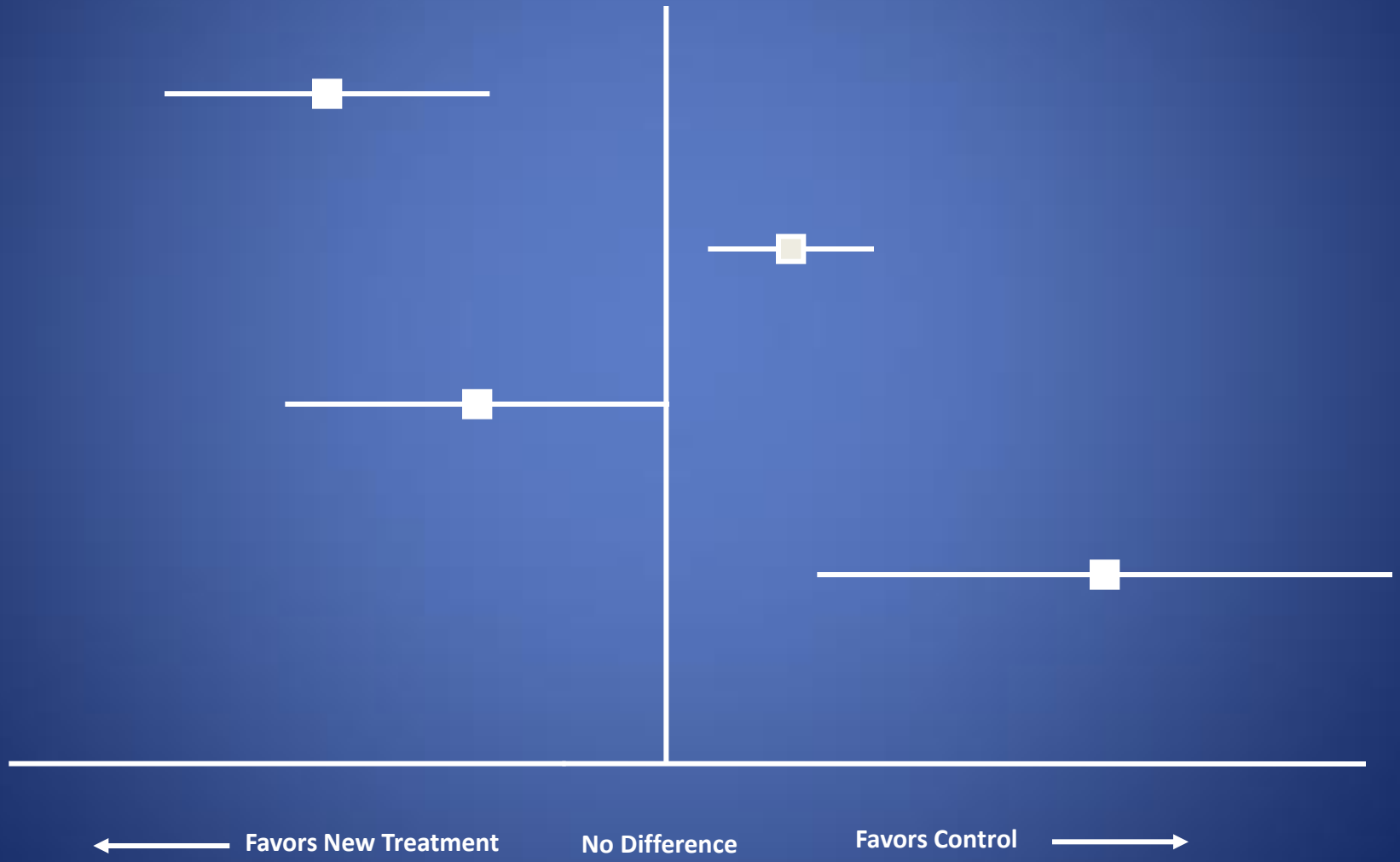


Eye-ball test

Can we combine?

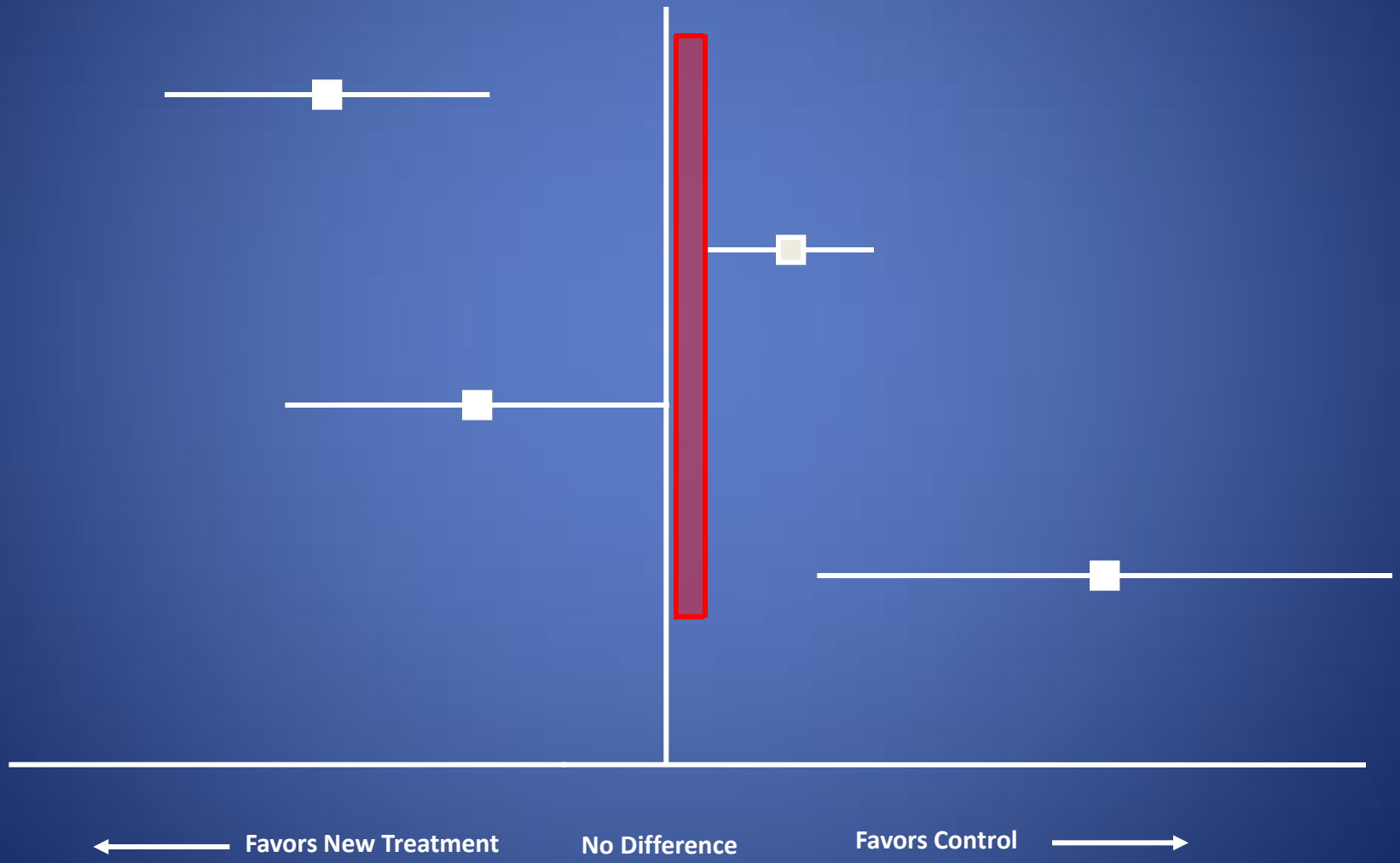


Result 3



Eye-ball test

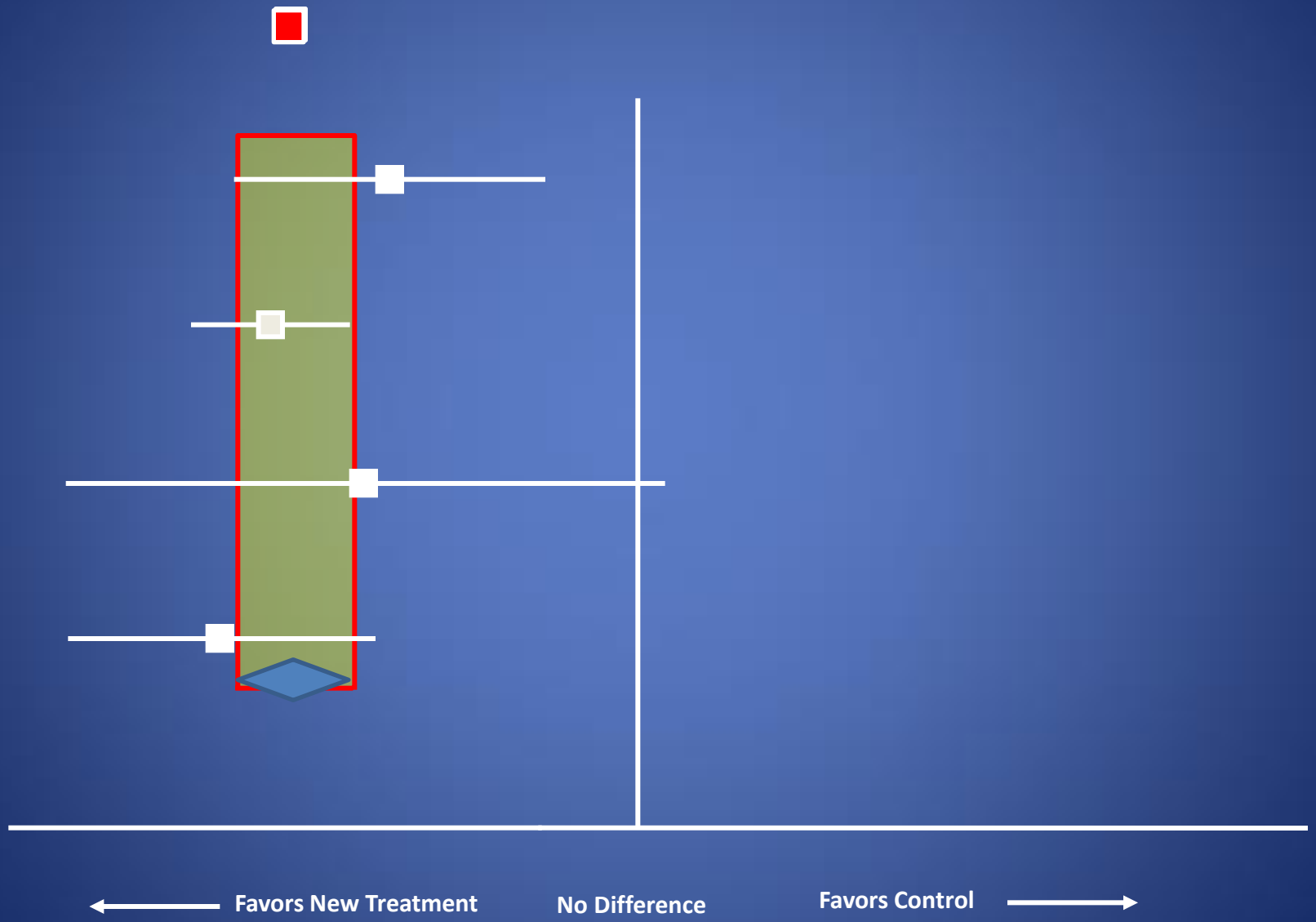
Can we combine?



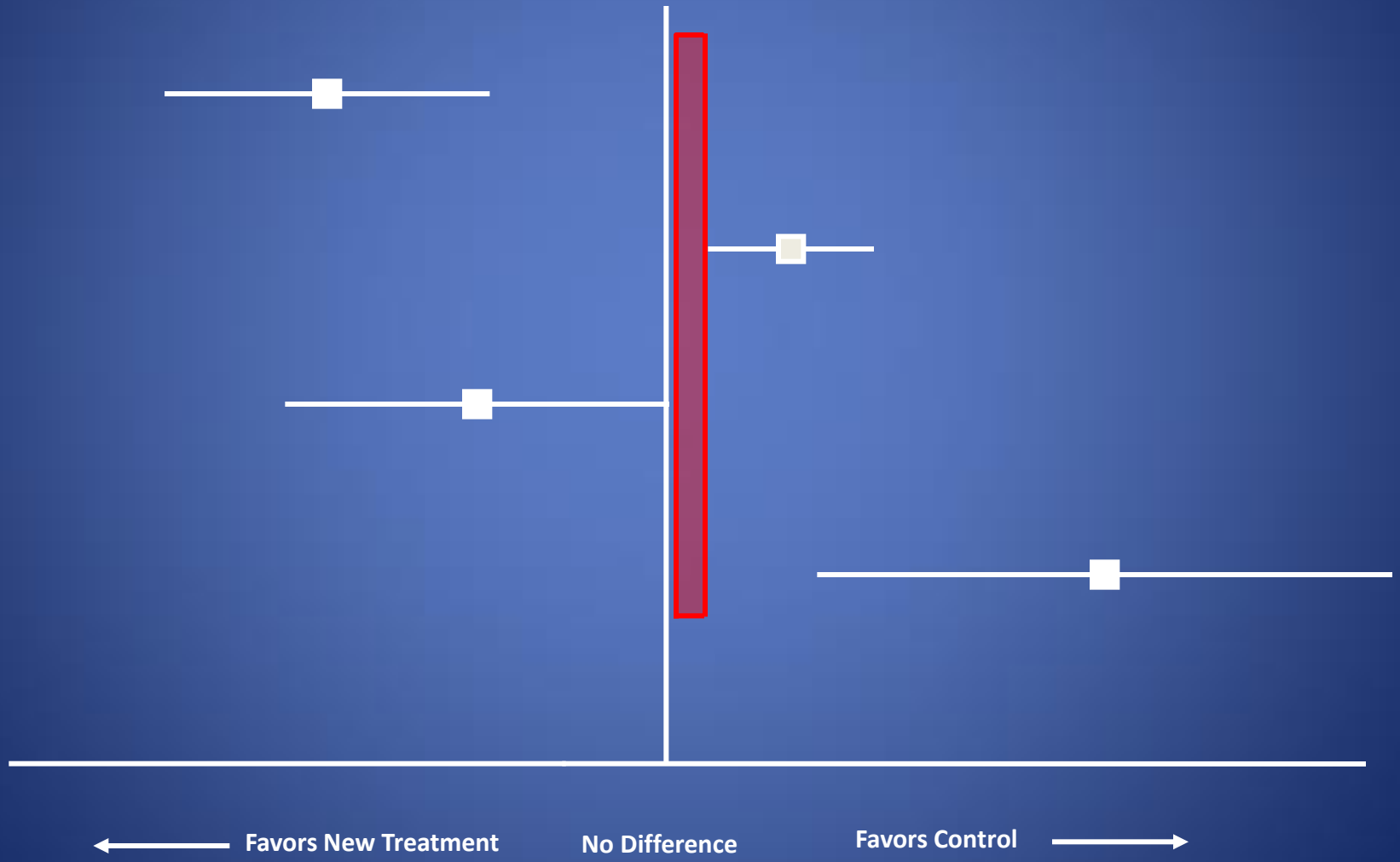
Okay: What is the "Eye-ball test"?

Eye-ball test

- Visual impression of degree of overlap of each study's results (find a common neighborhood of truth)
- Visual impression of where the estimates of study "effects" themselves lie (where are the dots)


Favors New Treatment
No Difference
Favors Control

Back to result 3: if not, why not?



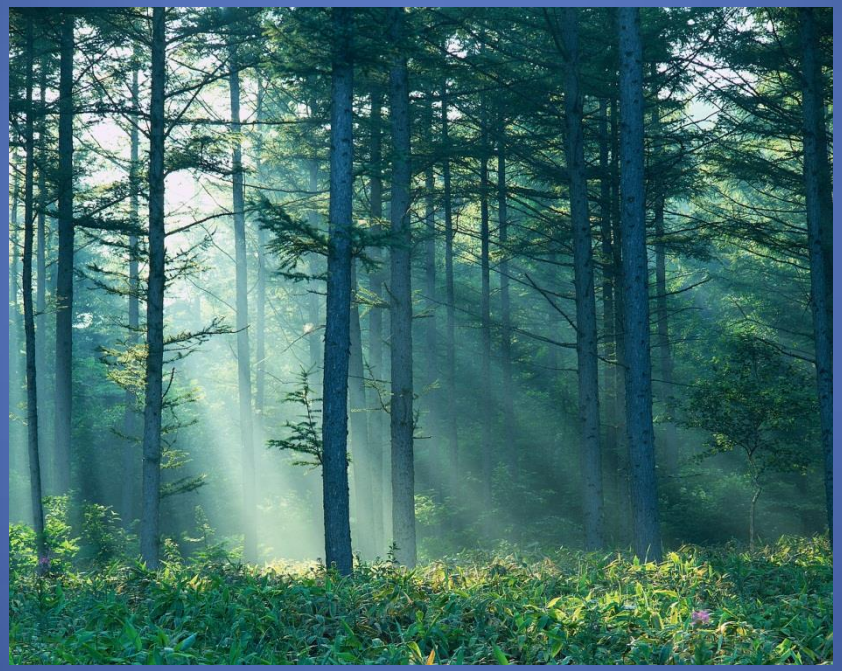
Why might things be different

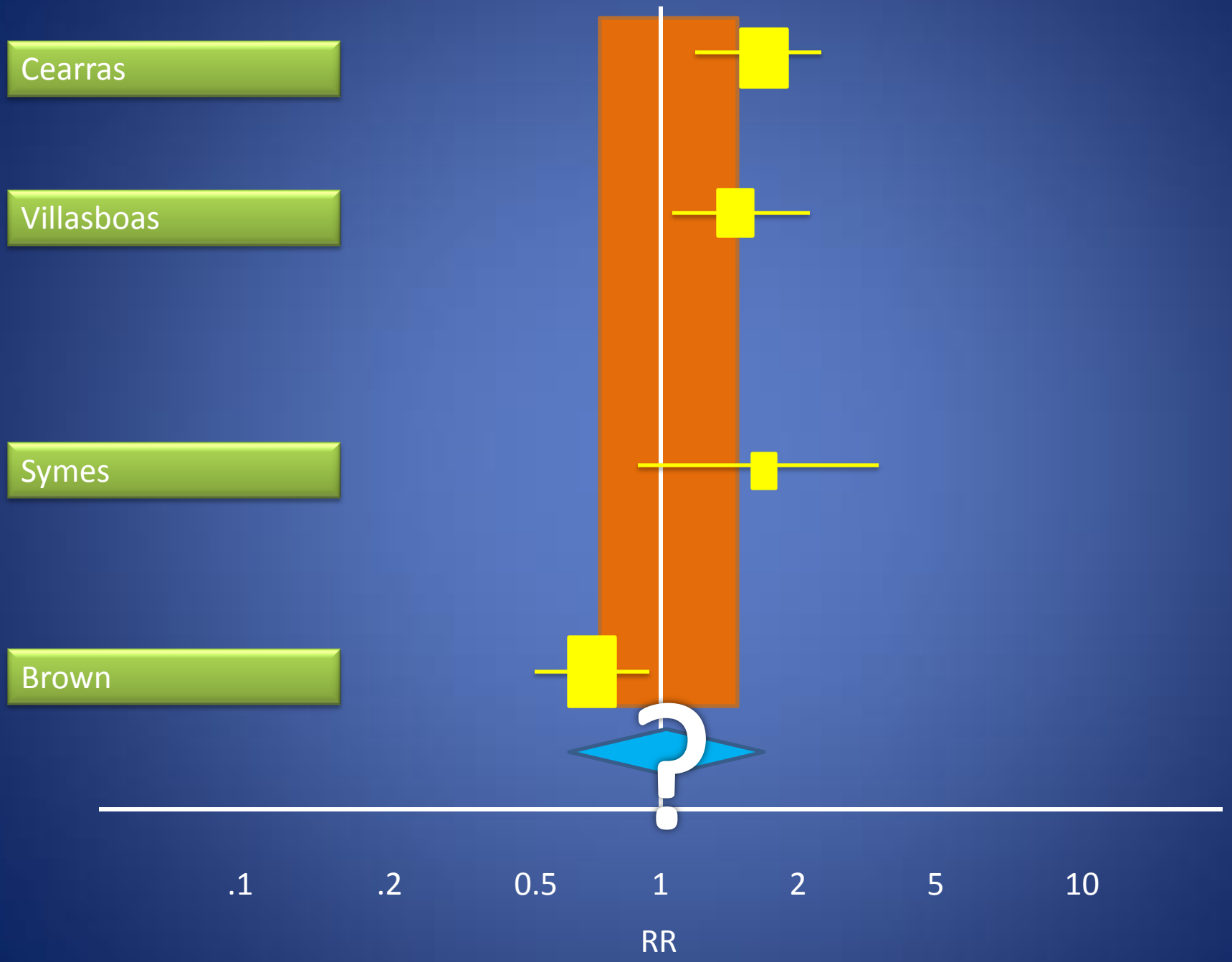
- P: Termites born in different climates
- I: Preparations of brand new drug
- C: Active control / placebo
- O: dead termites vs. lost wings
- T: Treatment Question
- T: RCT or Meta-analysis of well done RCTs

Should We Combine?

						Results.				
						% dead termites/larvae				
						Intervention Group	Comparison Group	RR	95% CI	
	Population	**Intervention**	**Comparison**	**Outcome**	**Follow Up (days)**				Lower	Upper
Cearras et al	Miami termites	Termicillin on walls	Placebo	Dead termites	30	87	50	1.74	1.2	2.6
Villasboas et al	Rochester termites	Termicillin on walls	Placebo	Dead termites	30	85	57	1.491228	1.04	2.4
Symes et al	Miami termites	Termicillin on walls	Termaban	Dead termites	30	80	45	1.777778	0.9	3.97
Brown et al	Miami termites	Termicillin aerosolized	Placebo	Termites whose wings fell off	30	40	50	0.8	0.5	0.9
Summary								1.70	0.98	3.2

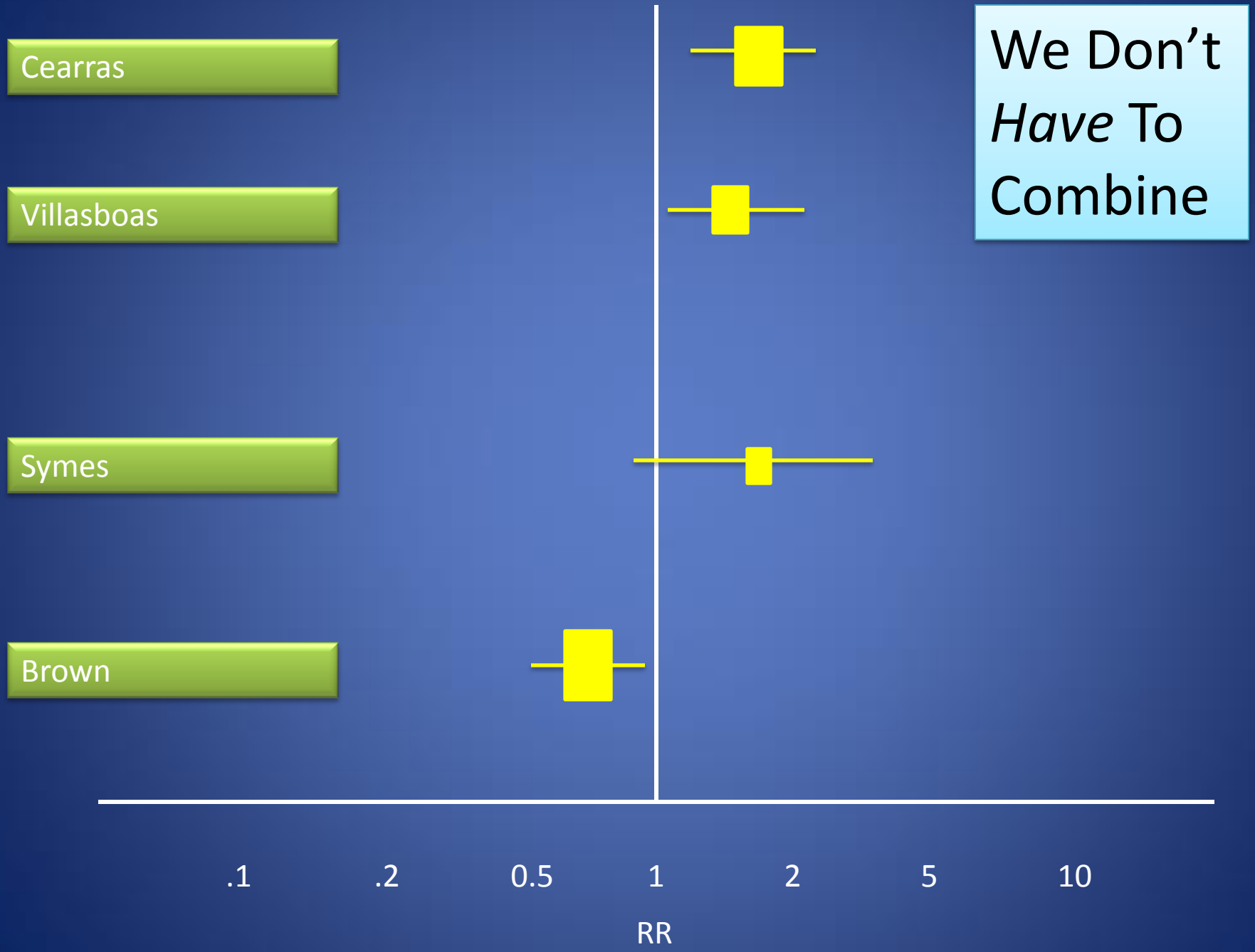
Let’s help Tom build a Forest plot.



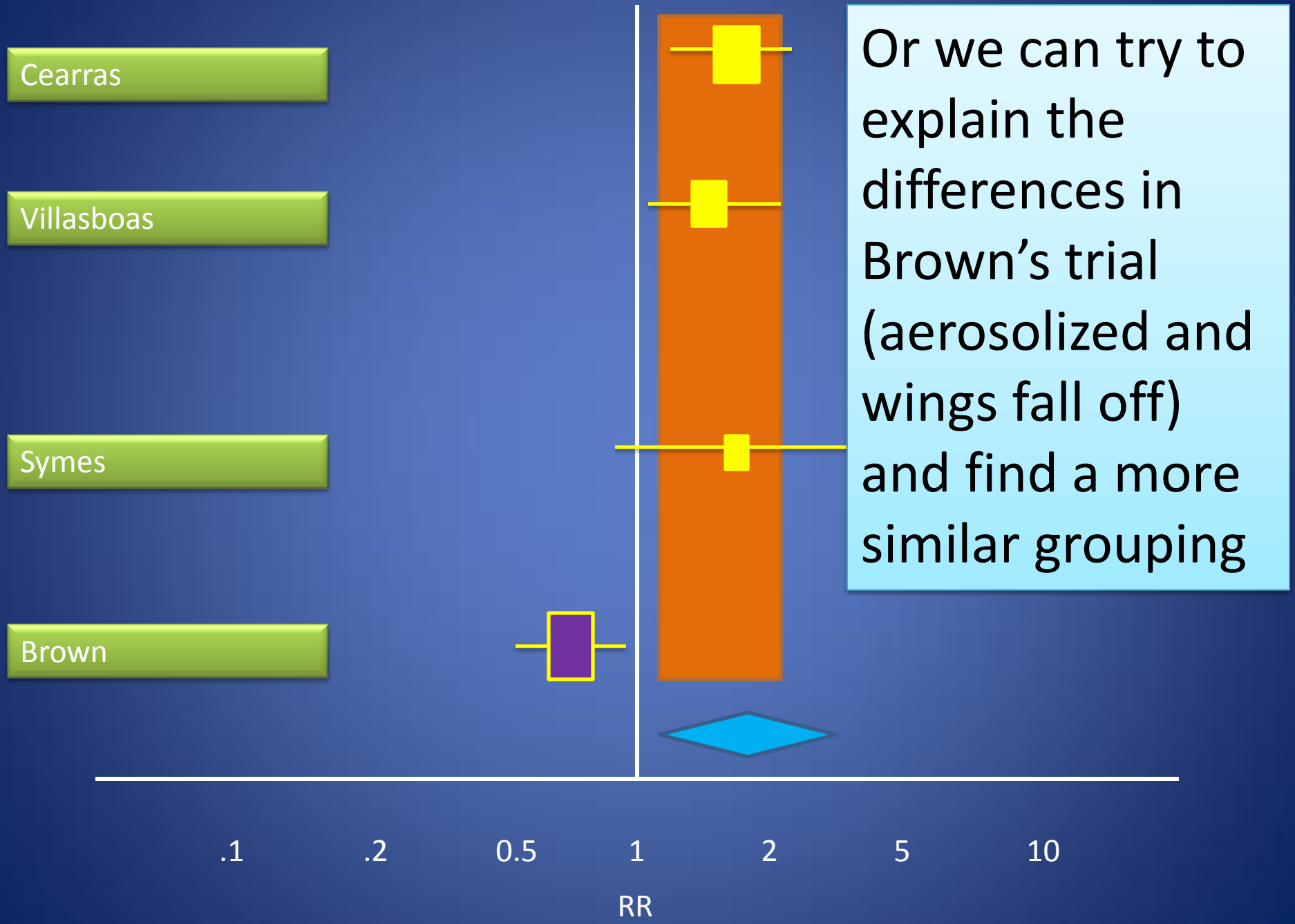

Cearras
Villasboas
Symes
Brown
?
.1
.2
0.5
1
2
5
10
RR

To Combine Or Not To Combine?

- Systematic review vs. meta-analysis
- Disbelievers be comforted…



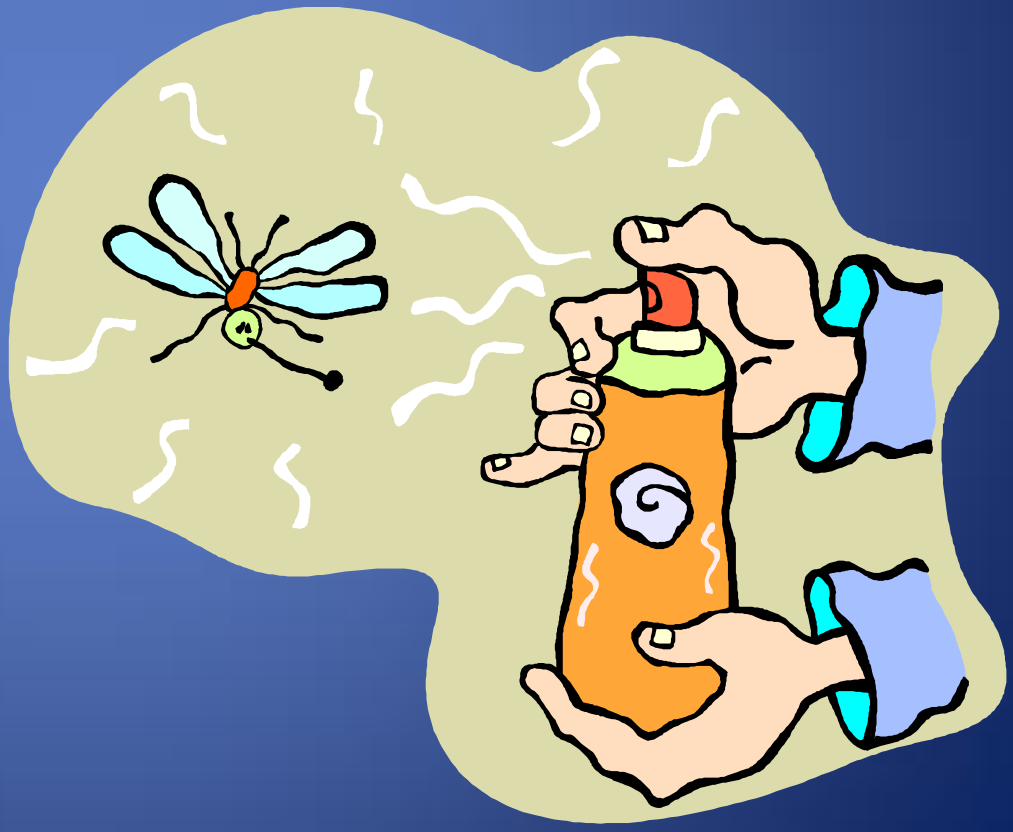
We Don't *Have* To Combine



Or we can try to explain the differences in Brown's trial (aerosolized and wings fall off) and find a more similar grouping

Back To Our Heroine.

- I guess it works!
- Where do I get some?

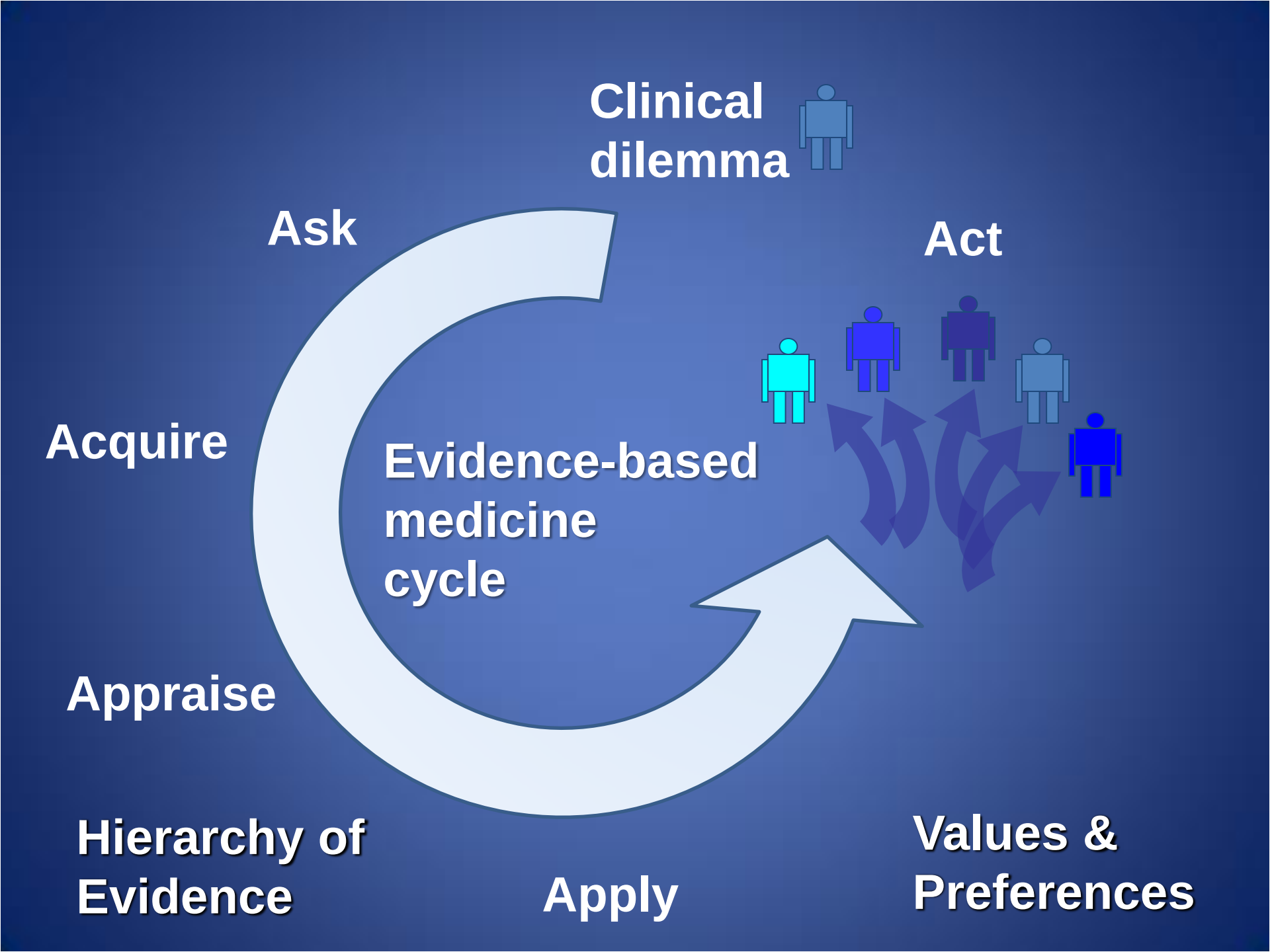


Tips for minimizing learner fear

- Use non-medical examples
- Use common sense approach explanations rather than statistical ones

Back to case scenario

Right after this commercial message
(bathroom break)


Clinical dilemma
Ask
Act
Acquire
Evidence-based medicine cycle
Appraise
Hierarchy of Evidence
Apply
Values & Preferences

Case Scenario: “My Husband Has What!”

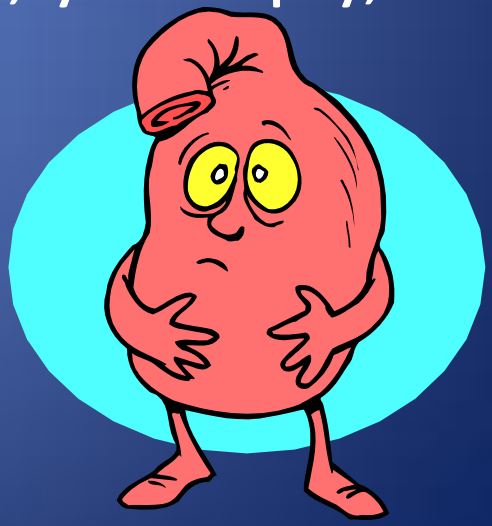
- It’s Friday night and you have finally returned from work at 9:37 PM.
- On your answering machine is a frantic message from your best friend from college.
- Her husband has just returned from his annual physical. He had complained about epigastric pain.
- The doctor ran some tests, and…

“My Husband Has A Bacteria!”

- He was found to have *H. pylori.*
- After much time reassuring her that this was not the end of the world (not as if her house had termites, after all), she tells you that he has been given 3 different medications to take for 14 days.
- But he’s worse than the 9 month old and gets diarrhea and “belly pain” when he takes any medication.

The Question.

- She asks if there is anything that they can do to prevent him (and her) from suffering for the next 2 weeks.
- She has heard that *probiotics* might work.
- Being the EBM expert that you are, you reply, "I'll find out and get back to you!"
- What's our first step?



Those 6 Letters Again.

- **P**atients with H. pylori receiving triple therapy for eradication.
- **I**: probiotics (micro-organisms that have beneficial effects for the host).
- **C**: placebo or no additional treatment.
- **O**: cure rate, diarrhea, abdominal pain.
- **T**: therapy/prevention.
- **T**: RCT or MA of well done RCTs.

Success!

Connie

THERAPEUTICS

Review: Eradication therapy supplemented by probiotics increased eradication rates and reduced side effects in *H. pylori* infection

Tong JL, Ran ZH, Shen J, Zhang CX, Xiao SD. **Meta-analysis: the effect of supplementation with probiotics on eradication rates and adverse events during *Helicobacter pylori* eradication therapy.** Aliment Pharmacol Ther. 2007;25:155-68.

Clinical impact ratings: Gastroenterology ★★★★★★☆ Infectious Disease ★★★★★☆☆

QUESTION

In patients with *Helicobacter pylori* infection, do probiotics improve eradication rates and reduce side effects of anti-*H. pylori* treatment?

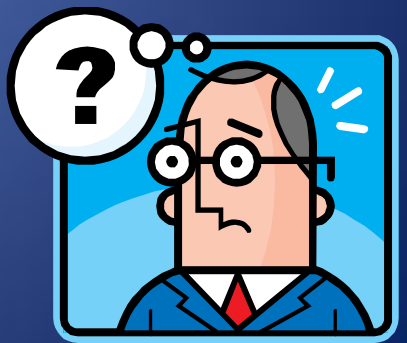
Outcomes: *H. pylori* eradication rates and side effects.

MAIN RESULTS

toms of diarrhea, epigastric pain, nausea, and taste disturbance (Table).

CONCLUSION

Let's appraise the article together… in 5 minutes?



Words that start with the letter “F”.

- **FRAME IT**
  - Did the authors define (frame) a sensible clinical question using PICO framework?

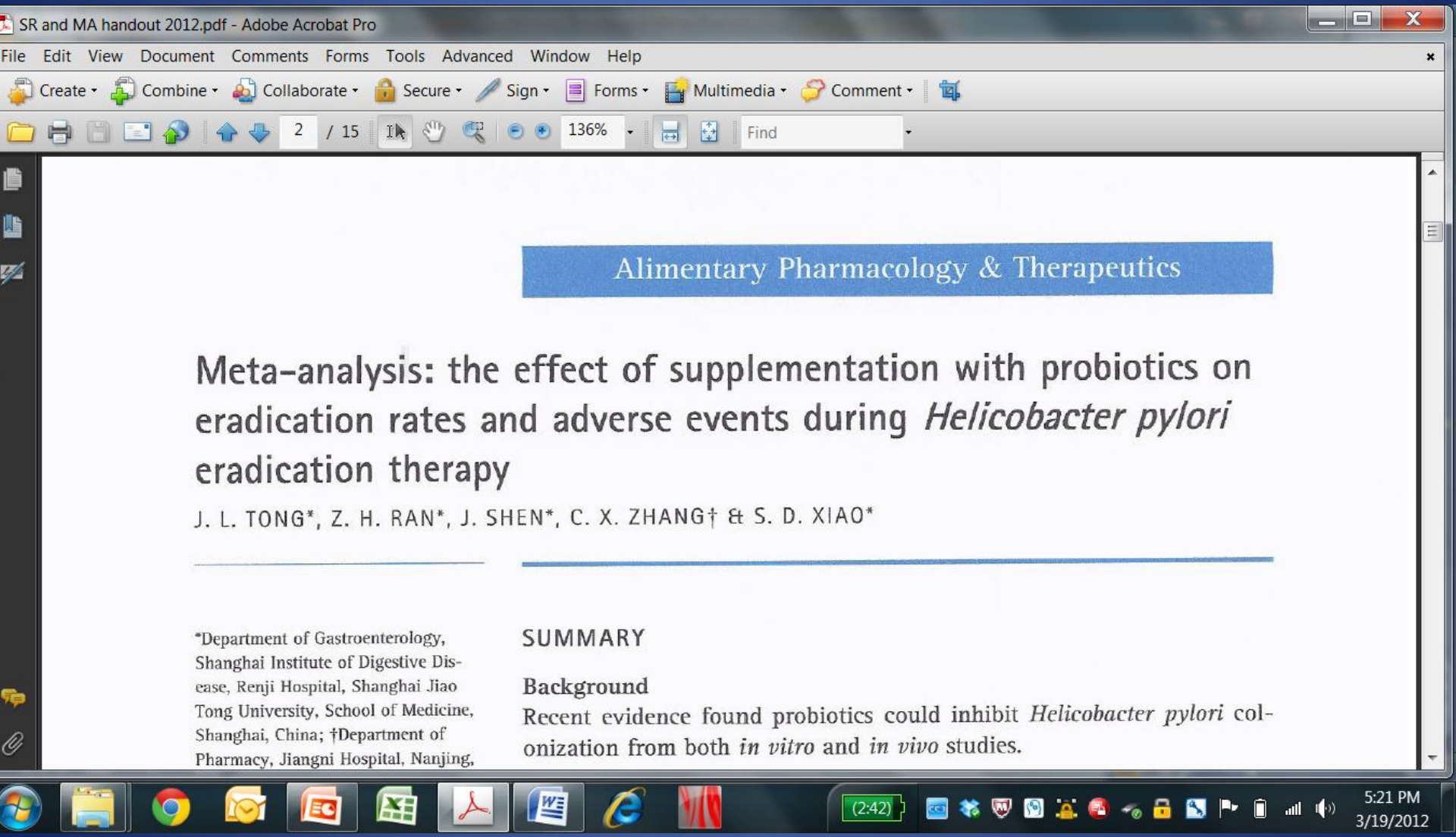
- **FIND IT**
  - Did the authors do a detailed and exhaustive search (find) that is unlikely to systematically miss important relevant studies?

"F"our-step plan for teaching

- **Filter and Fetch**
  - Did authors select studies based on inclusion criteria, assess risk of bias, collect data from individual studies in a reproducible manner?

- **Findings and Forest Plots**
  - Review findings of a systematic review and the forest plots or summary statistics if graphs are not provided for meta-analysis.

Success (2)… Appraisal



What are the results

- Everyone: look at Figure 2 (page 162).
- Describe the dots and lines

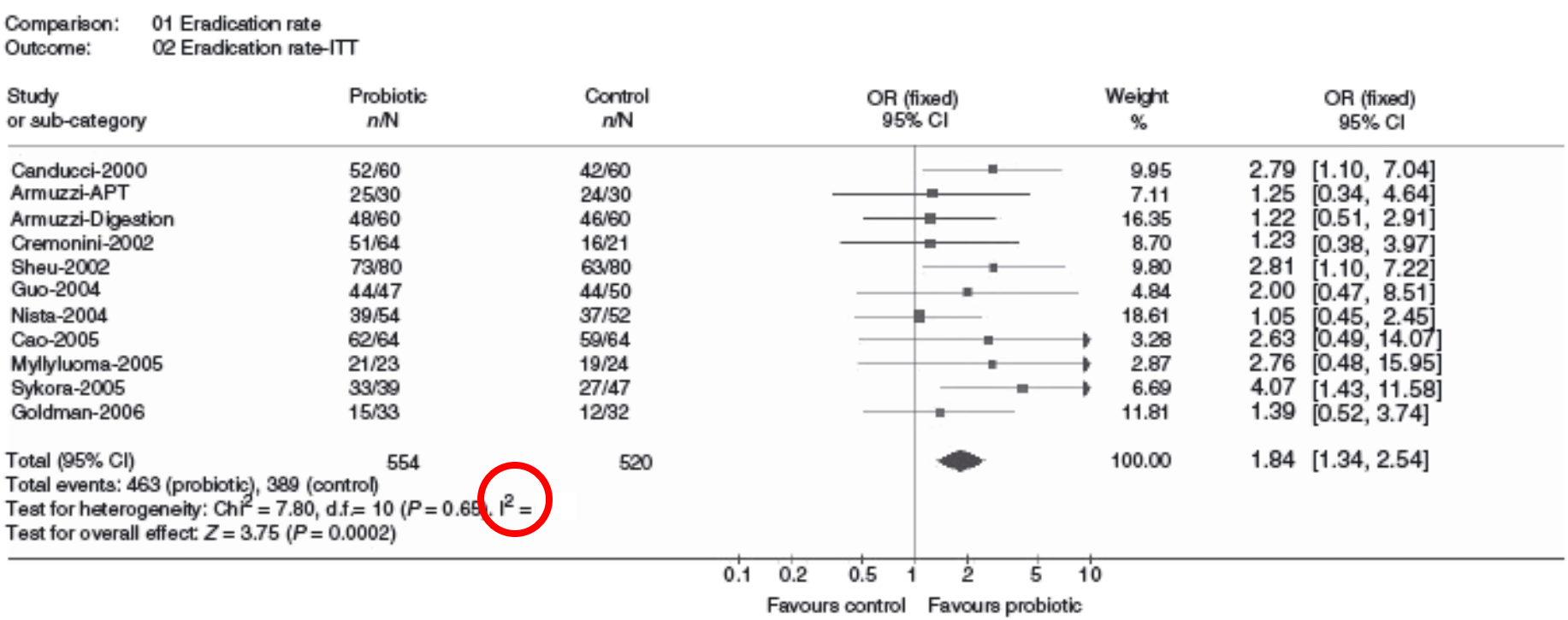


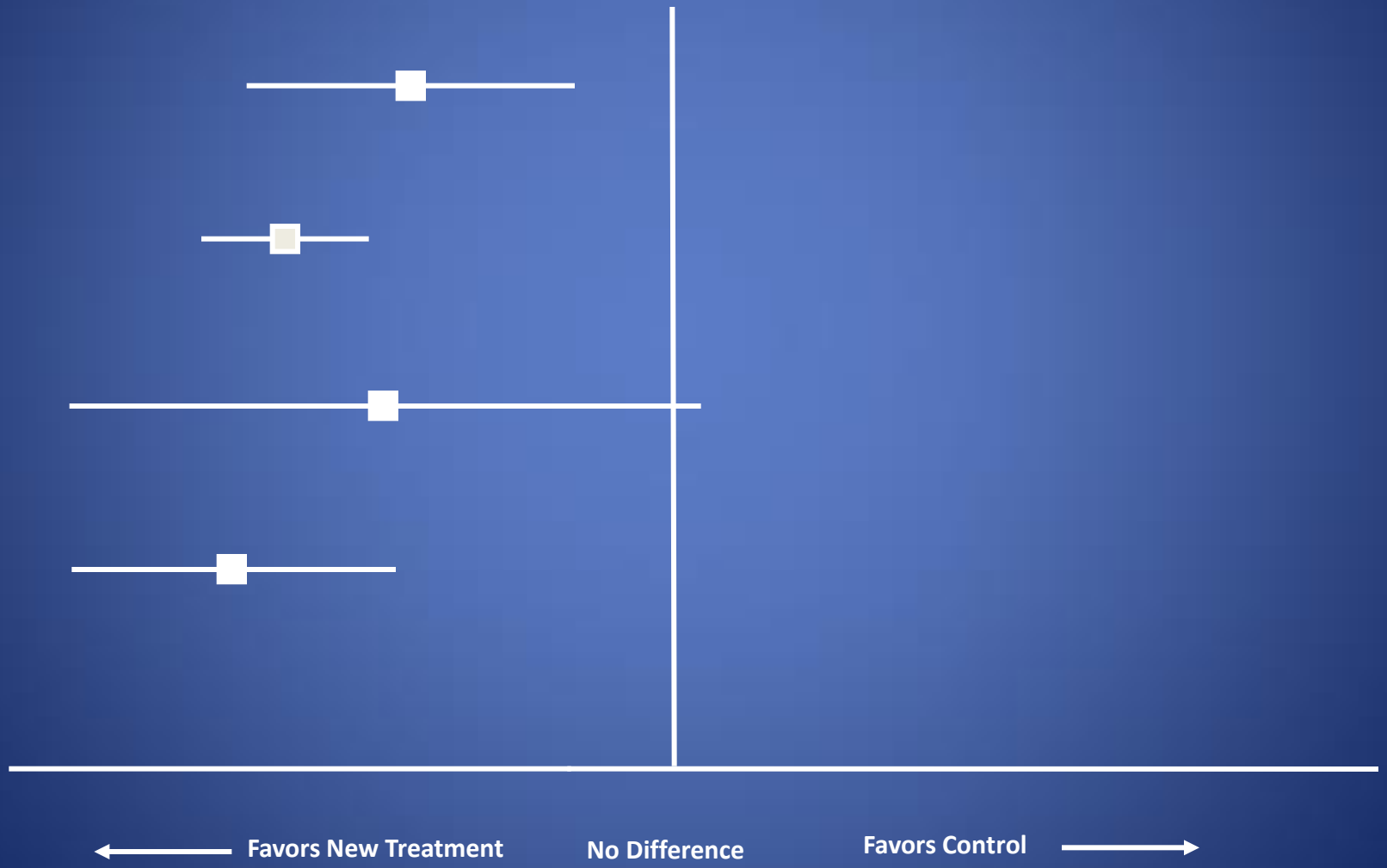
Figure 2. The effect of probiotics supplementation vs. without probiotics on eradication rates by intention-to-treat analysis. (n = number of successful eradication; N = number of participants).

I^2 what?

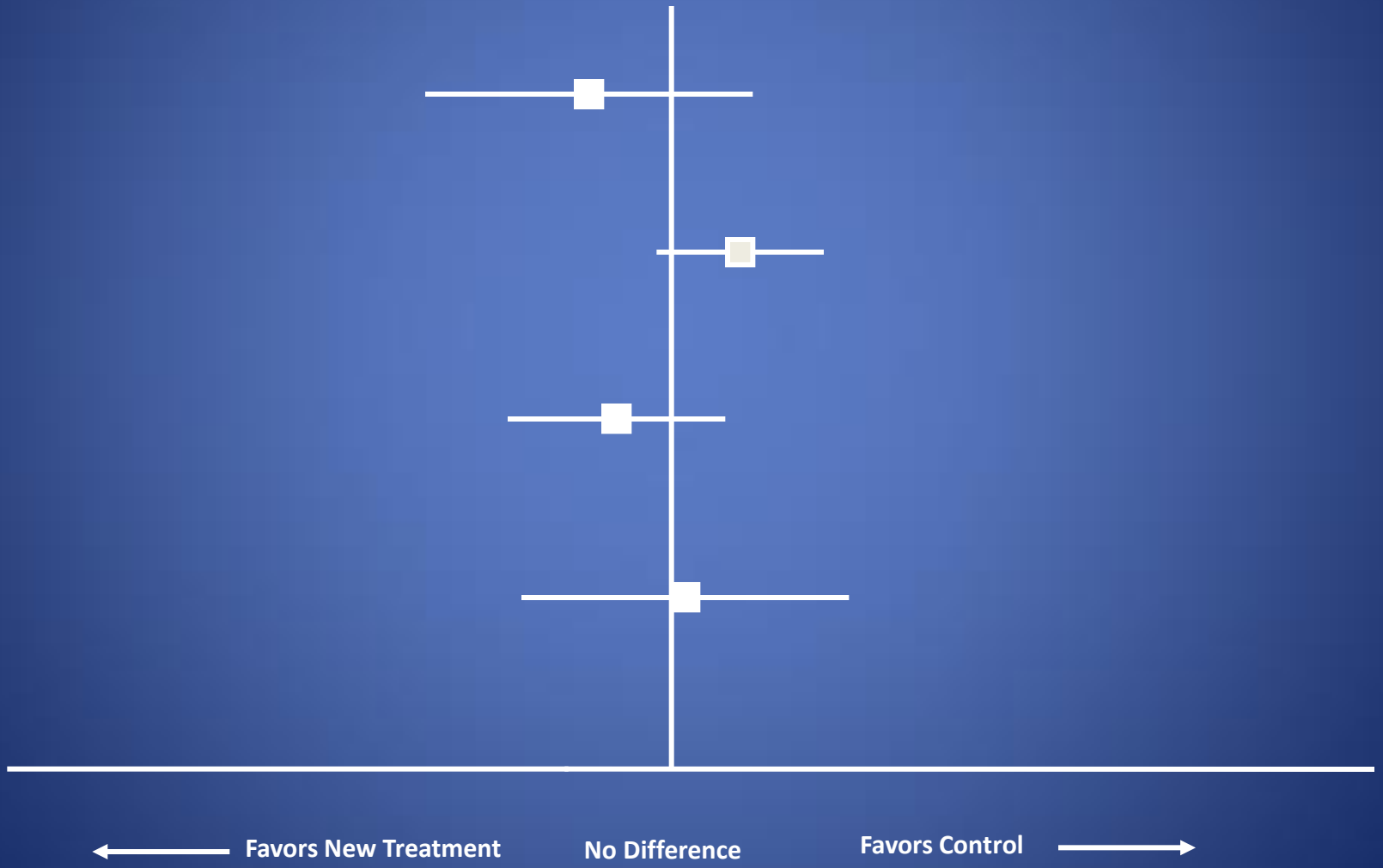
- What is the range of possible values for I^2
- From 0 to 100
- Explain in a sentence?
- The variability that is due to a real difference
- Is the variability between studies due ONLY to chance?
- $I^2 = 0$

- Is the variability between studies due ONLY to a real difference in treatment?
- $I^2 = 100$

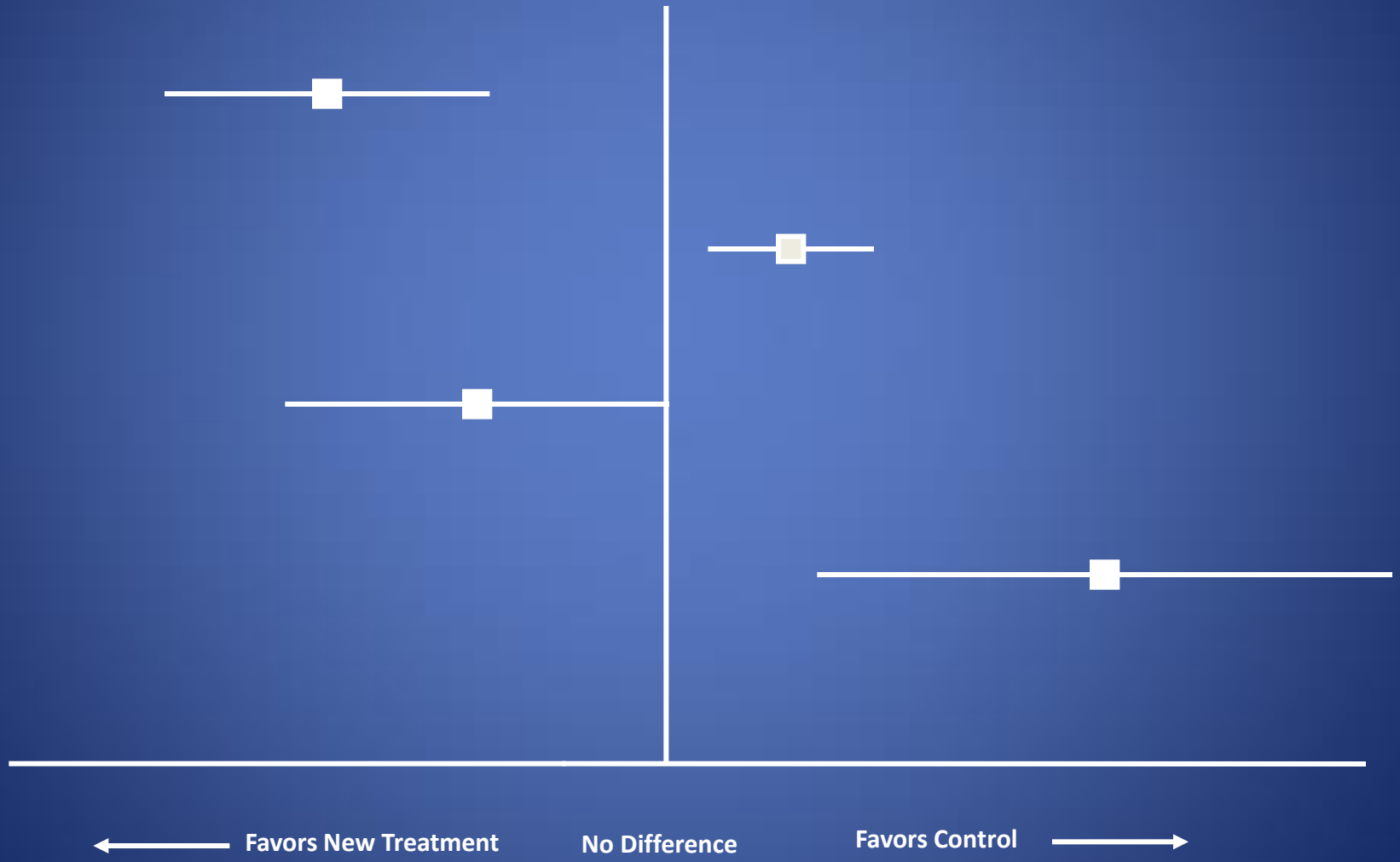
Result 1: what is I^2



Result 2: what is I^2



Result 3: what is I^2



Eradication Rate

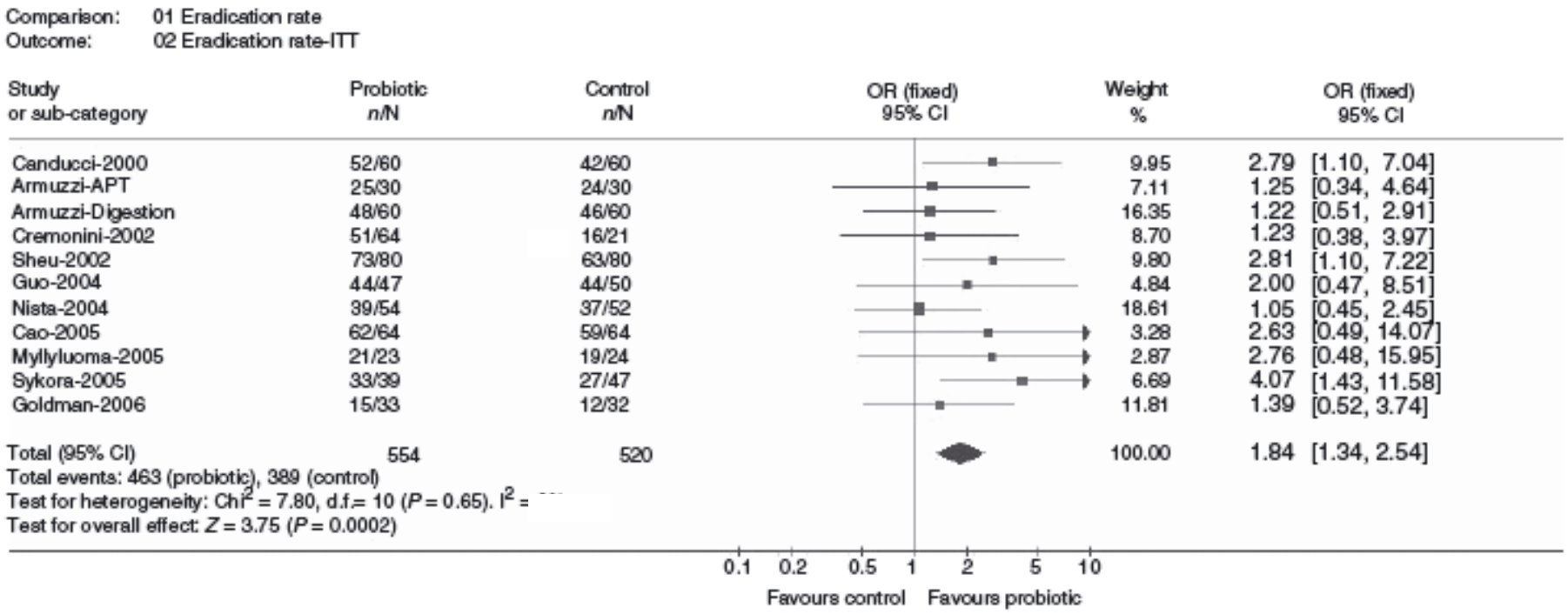


Figure 2. The effect of probiotics supplementation vs. without probiotics on eradication rates by intention-to-treat analysis. (n = number of successful eradication; N = number of participants).

$I^2 = 0\%$

Side Effect - Overall

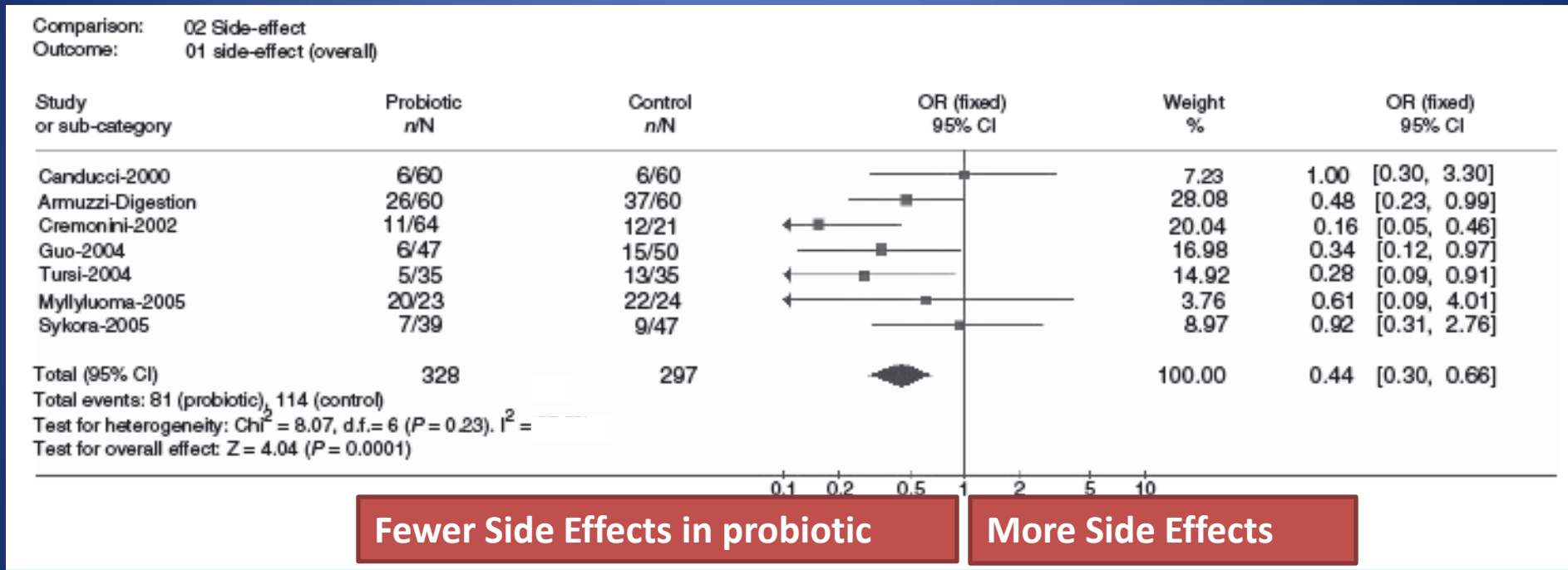


Figure 4. The effect of probiotics supplementation vs. without probiotics on the incidence of total side effects. (n = number of side effects; N = number of participants).

$I^2 = 25\%$

Diarrhea

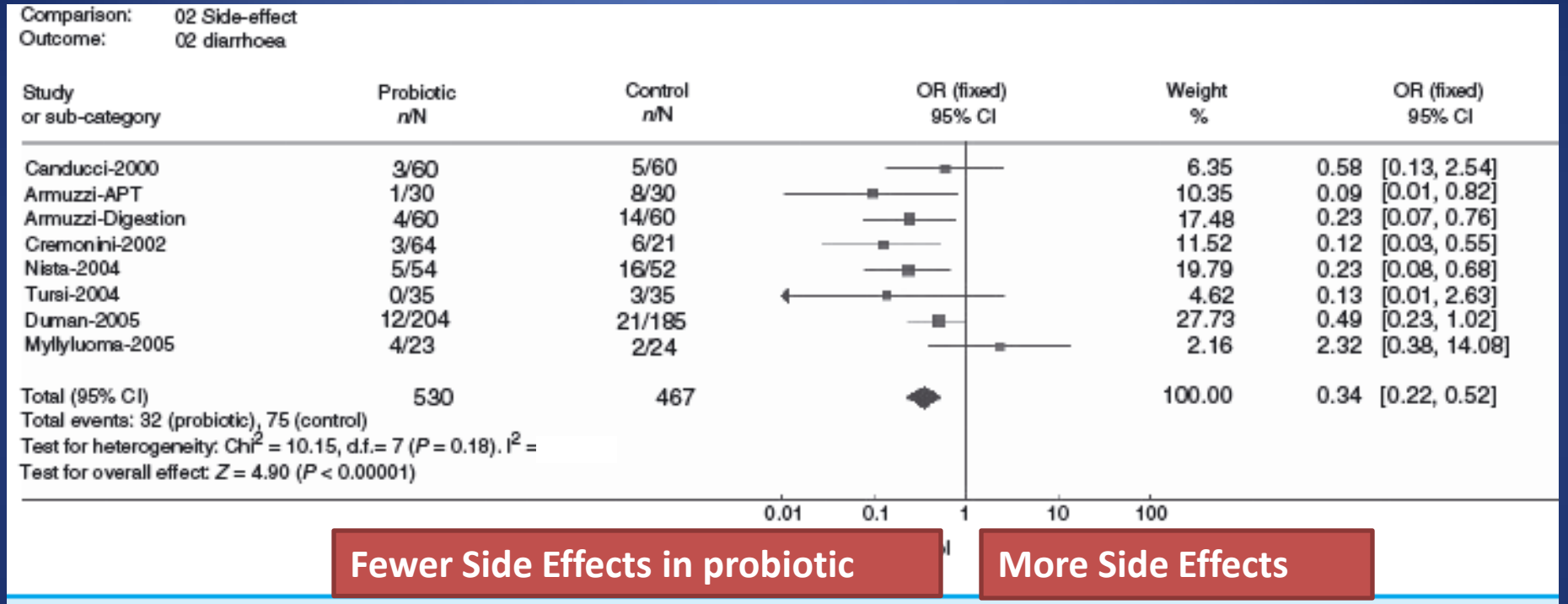


Figure 5. The effect of probiotics supplementation vs. without probiotics on the incidence of diarrhoea. (n = number of diarrhoea; N = number of participants).

$I^2 = 31\%$

Epigastric Pain

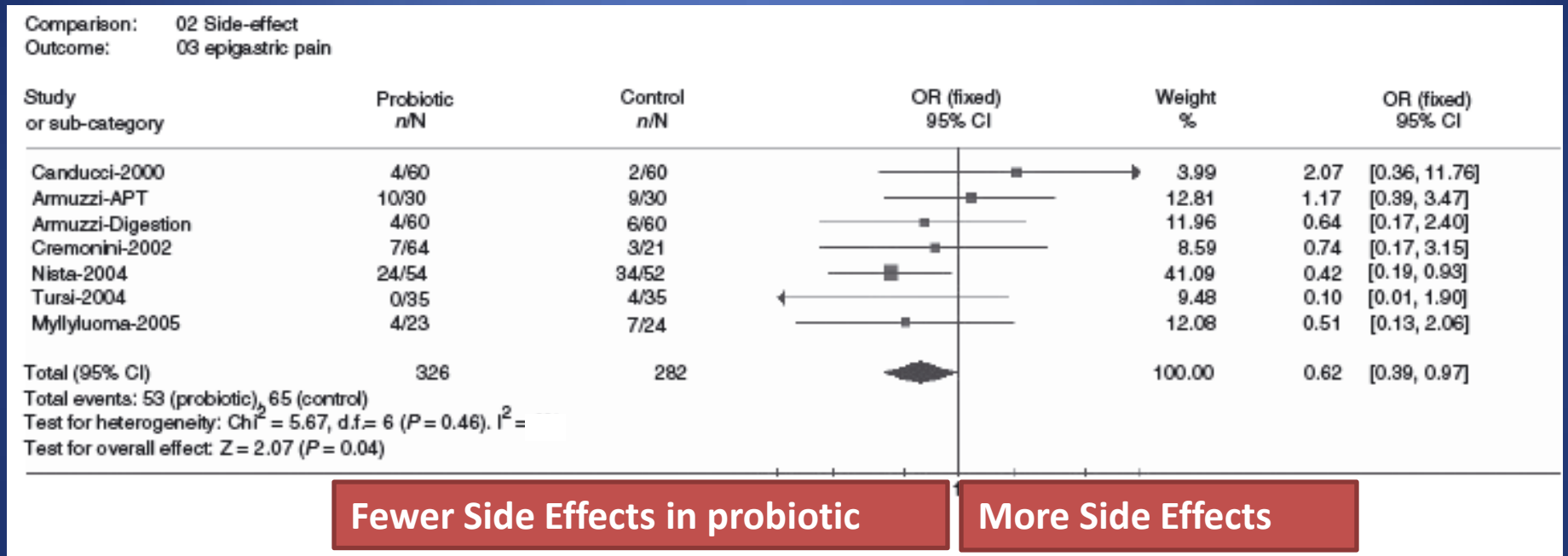


Figure 6. The effect of probiotics supplementation vs. without probiotics on the incidence of epigastic pain. (n = number of epigastic pain; N = number of participants).

$I^2 = 0\%$

Nausea

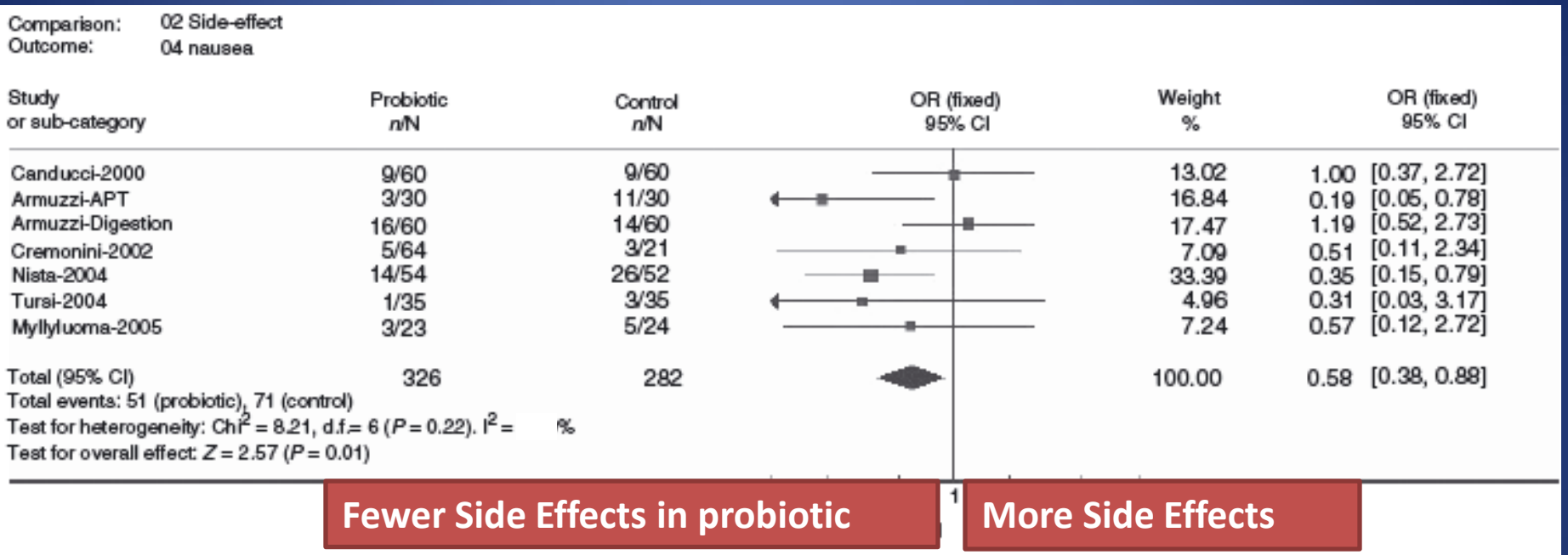


Figure 7. The effect of probiotics supplementation vs. without probiotics on the incidence of nausea. (n = number of nausea; N = number of participants).

$I^2 = 27\%$

Taste Disturbance

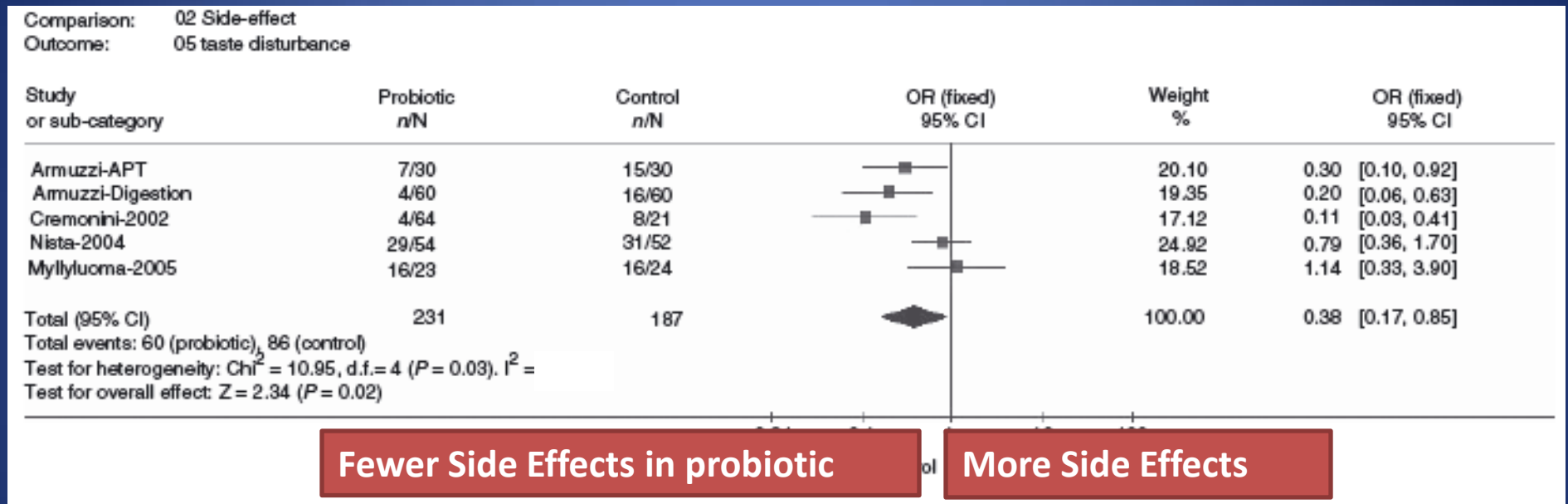


Figure 8. The effect of probiotics supplementation vs. without probiotics on the incidence of taste disturbance. (n = number of taste disturbance; N = number of participants).

$I^2 = 64\%$

Back to your best friend…

- In patients with H. pylori infection, probiotic supplementation improves eradication rates and reduces side effects of anti-H. pylori treatment.

What Systematic Reviews **Can** Do for You

- Save time
- Increase power to detect rare events
  - Obviate need for large, expensive trials
  - Detect harm
- Increase the precision of the estimate of effect
- Enhance generalizability of the results if samples from different populations are included

What Systematic Reviews **Can't** Do for You

- Allow you to determine "equivalency" of different interventions
- "Get rid of" bias from individual studies

Teaching Objectives

- To shun fear and learn to love forest plots
- Understand what systematic reviews can and cannot do for you
- To review principles of when it is appropriate to combine studies
- Interpret the results of a meta-analysis including forest plots
- Demonstrate teaching techniques and identify resources to assist

Extra-Special Teaching Objective

- JARGON FREE (at least for the first half…)
- Avoided words
  - Point Estimate
  - Confidence Interval
  - Summary Statistic
  - Heterogeneity
  - I^2

Take Home Points.

- A well done meta-analysis seeks to get us closer to the truth by combining results of well done individual trials.
- Sometimes it's okay to combine the results of different trials… sometimes it's not.
- Differences between trials can be assessed using different methods.
- $I^2 = 0$ is EXCELLENT.
- $I^2 = 100$ is AWFUL.
- We can all still learn a lot from Cookie Monster.

Gleeful to Grief-stricken Scale

- Validated instrument for assessing levels of comfort (glee) or fear (grief) in EBM workshop participants

We Hope It Wasn't So Scary After All.

Thank You.