Identifying who benefits most from treatments: estimating interactions and subgroup effects in aggregate data meta-analysis

Peter Godolphin

Meta-analysis programme, MRC Clinical Trials Unit at UCL

Cochrane Learning Live webinar

29 January 2024

Celebrating – 25 years – | smarter studies, global impact and better health

Outline

- Subgroups and interactions in a single trial
- Subgroups and interactions in meta-analysis: Aggregation bias
- Our new approach: A within-trial framework
- Example: STOPCAP Docetaxel meta-analysis
- Example: PORT meta-analysis
- What's next?

MRC Clinical Trials Unit

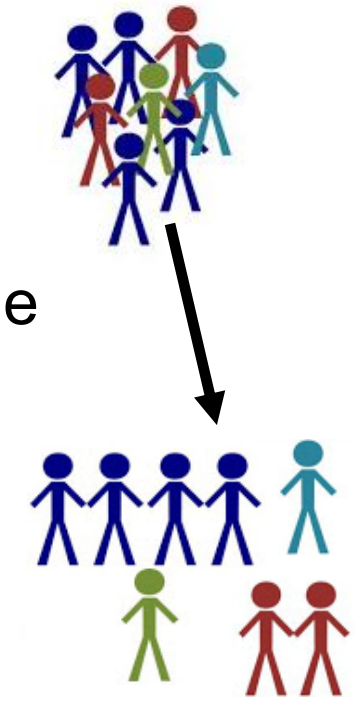
UCL

Subgroups and interactions in a single trial

Celebrating – 25 years –

smarter studies, global impact and better health

Interactions and subgroup effects



- The aim of a clinical trial is to estimate an *overall* treatment effect comparing intervention to control
- Trials recruit a diverse population → we also want to know whether the overall effect varies due to patient covariates (**interaction**)
- Often it is important to know the *subgroup effects* as well as the interactions
- Focus today is on **participant-level** factors:
  - **Participant characteristics:** Age, Sex, BMI, Smoking status, Comorbidities etc.
  - **Disease characteristics:** Disease severity, tumour mutations etc.
  - **Treatment characteristics:** E.g., Some patients got additional treatments as part of Standard of Care (SoC)

Interpreting subgroups in the STAMPEDE trial

Population: People with locally advanced or metastatic prostate cancer

Intervention: Abiraterone + Standard of care (SoC)

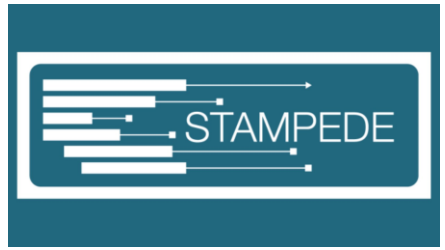
Comparator: Standard of care

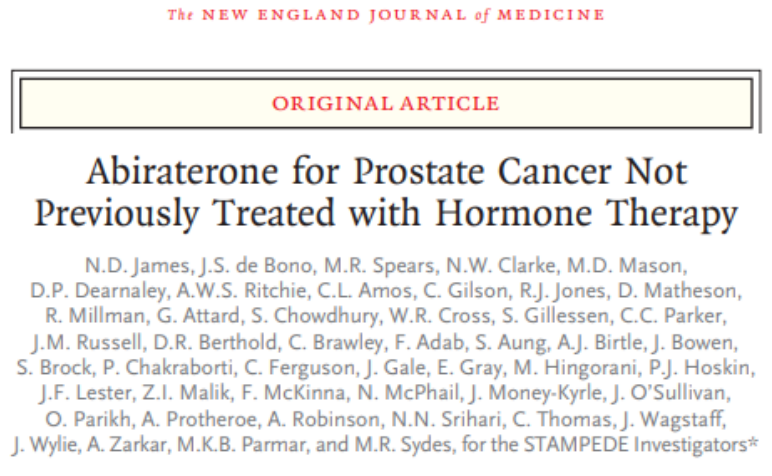
Outcome: Overall survival (HR)

Subgroup: Metastatic status at randomisation (M0, M1)

1917 patients randomised: 915 M0, 1002 M1

Overall survival (All patients): HR 0.63, CI:(0.52, 0.76)




The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy

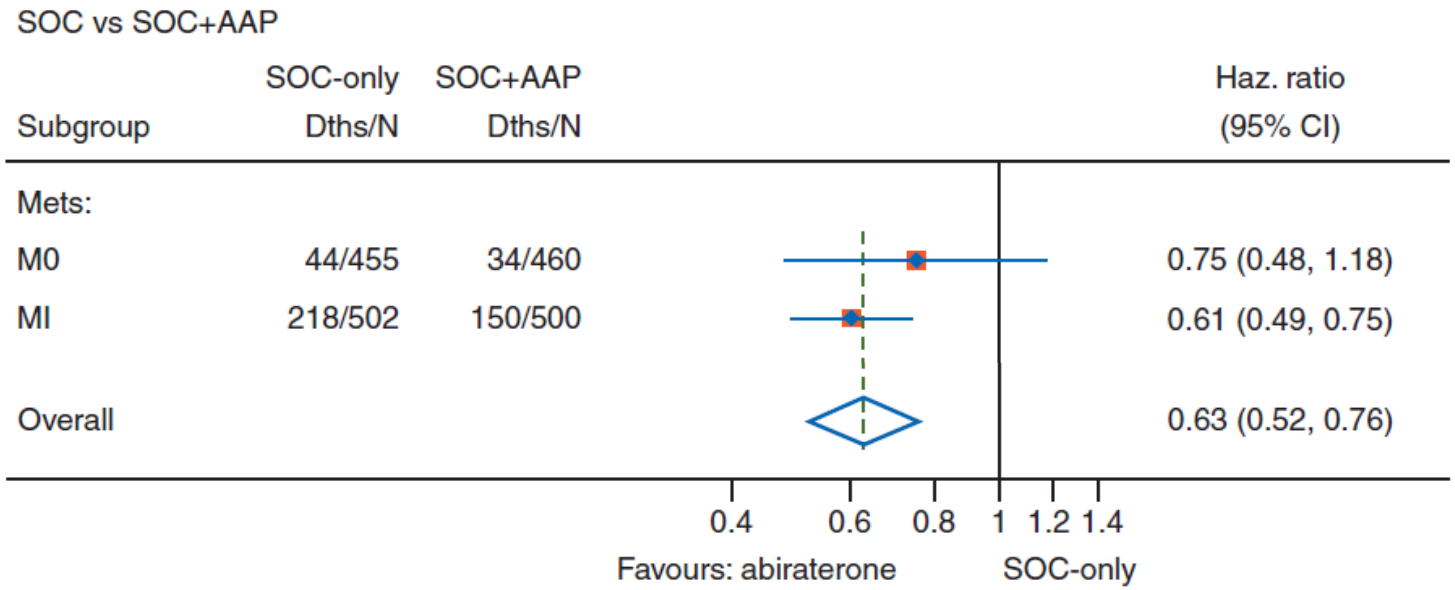
N.D. James, J.S. de Bono, M.R. Spears, N.W. Clarke, M.D. Mason, D.P. Dearnaley, A.W.S. Ritchie, C.L. Amos, C. Gilson, R.J. Jones, D. Matheson, R. Millman, G. Attard, S. Chowdhury, W.R. Cross, S. Gillessen, C.C. Parker, J.M. Russell, D.R. Berthold, C. Brawley, F. Adab, S. Aung, A.J. Birtle, J. Bowen, S. Brock, P. Chakraborti, C. Ferguson, J. Gale, E. Gray, M. Hingorani, P.J. Hoskin, J.F. Lester, Z.I. Malik, F. McKinna, N. McPhail, J. Money-Kyrle, J. O'Sullivan, O. Parikh, A. Protheroe, A. Robinson, N.N. Srihari, C. Thomas, J. Wagstaff, J. Wylie, A. Zarkar, M.K.B. Parmar, and M.R. Sydes, for the STAMPEDE Investigators*

Celebrating – 25 years – | smarter studies, global impact and better health

UKRI MRC Clinical Trials Unit

UCL

Does effect of Abiraterone vary based on metastatic status?



HR<1 favours abiraterone

Time for a poll…

Celebrating – 25 years – | smarter studies, global impact and better health

UKRI MRC Clinical Trials Unit

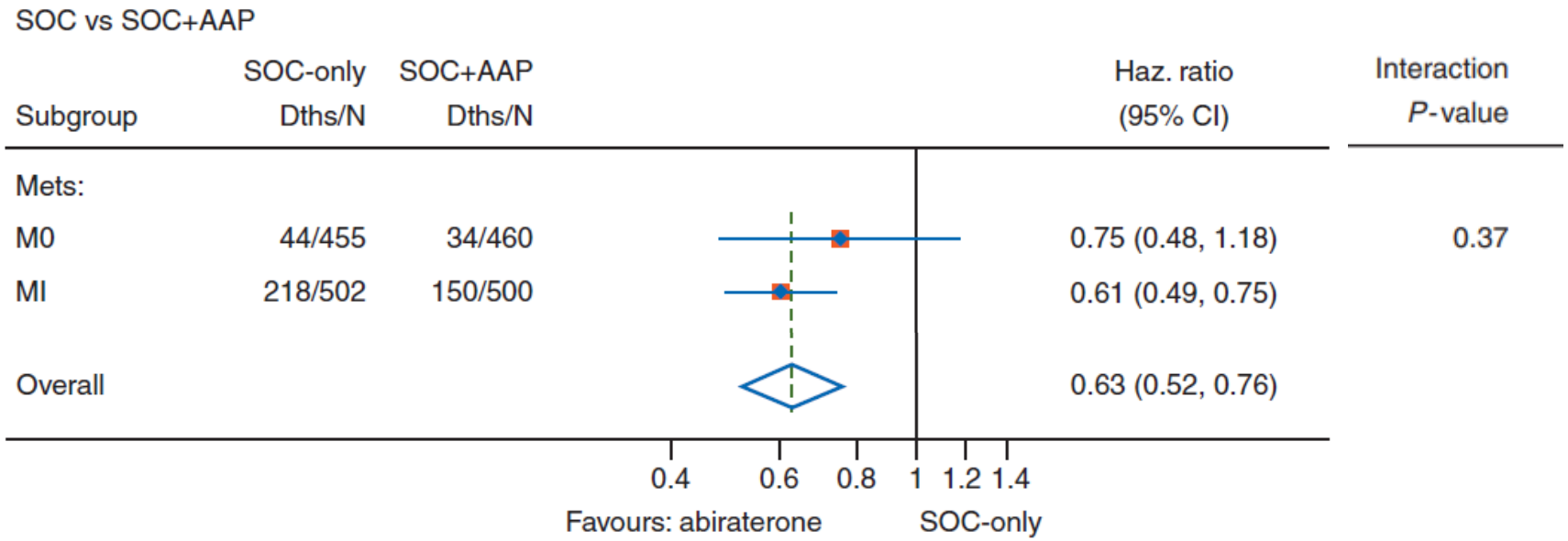
UCL

Annals of Oncology

'Thursday's child has far to go'—interpreting subgroups and the STAMPEDE trial

M. R. Spears[1], N. D. James[2] & M. R. Sydes[1*]
[1]MRC Clinical Trials Unit at UCL, Institute of Clinical Trials and Methodology, University College London, London; [2]Institute of Cancer and Genomic Sciences, University of Birmingham, Birmingham, UK

Does effect of Abiraterone vary based on metastatic status?



Interaction HR (ratio of HRs):

0.81 (0.50, 1.33)

Interaction P-value=0.37

- Test for effect *between subgroups* "interaction p=0.37 shows *no good evidence of heterogeneity of treatment effect* across these subgroups"
- Can also calculate Interaction HR (or ratio of HRs)

Celebrating – 25 years – | smarter studies, global impact and better health

UKRI MRC Clinical Trials Unit

UCL

Annals of Oncology

'Thursday's child has far to go'—interpreting subgroups and the STAMPEDE trial

M. R. Spears[1], N. D. James[2] & M. R. Sydes[1*]
[1]MRC Clinical Trials Unit at UCL, Institute of Clinical Trials and Methodology, University College London, London; [2]Institute of Cancer and Genomic Sciences, University of Birmingham, Birmingham, UK

MRC Clinical Trials Unit

UCL

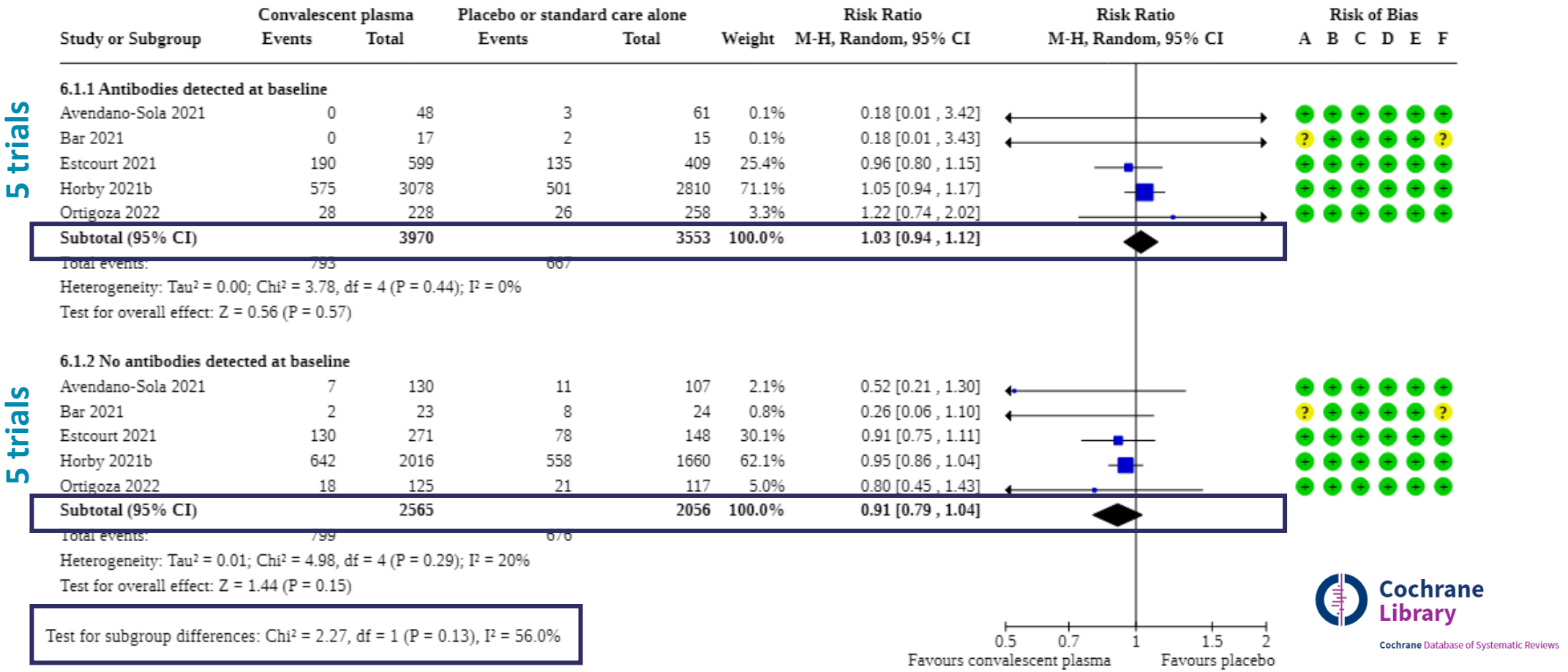
Subgroups and interactions in meta-analysis: Aggregation bias

Celebrating – 25 years –

smarter studies, global impact and better health

Convalescent plasma for people with COVID-19

28-day mortality: Antibodies detected at baseline subgroup analysis



Cochrane Library

Cochrane Database of Systematic Reviews

Celebrating – 25 years – | smarter studies, global impact and better health

UKRI MRC Clinical Trials Unit

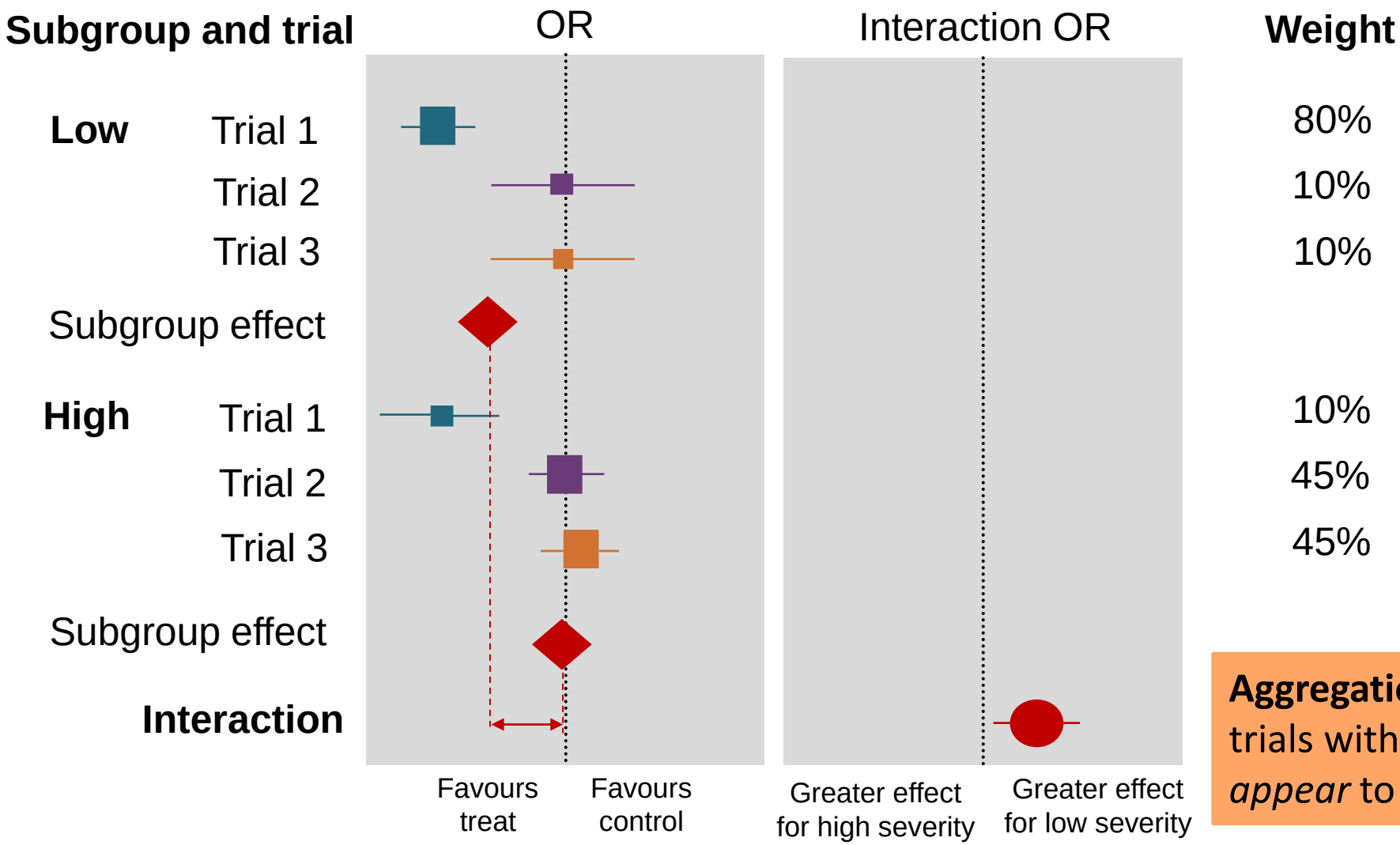
UCL

Convalescent plasma for people with COVID-19: a living systematic review (Review)

Iannizzi C, Chai KL, Piechotta V, Valk SJ, Kimber C, Monsef I, Wood EM, Lamikanra AA, Roberts DJ, McQuilten Z, So-Osman C, Jindal A, Cryns N, Estcourt LJ, Kreuzberger N, Skoetz N

What could go wrong with this approach?

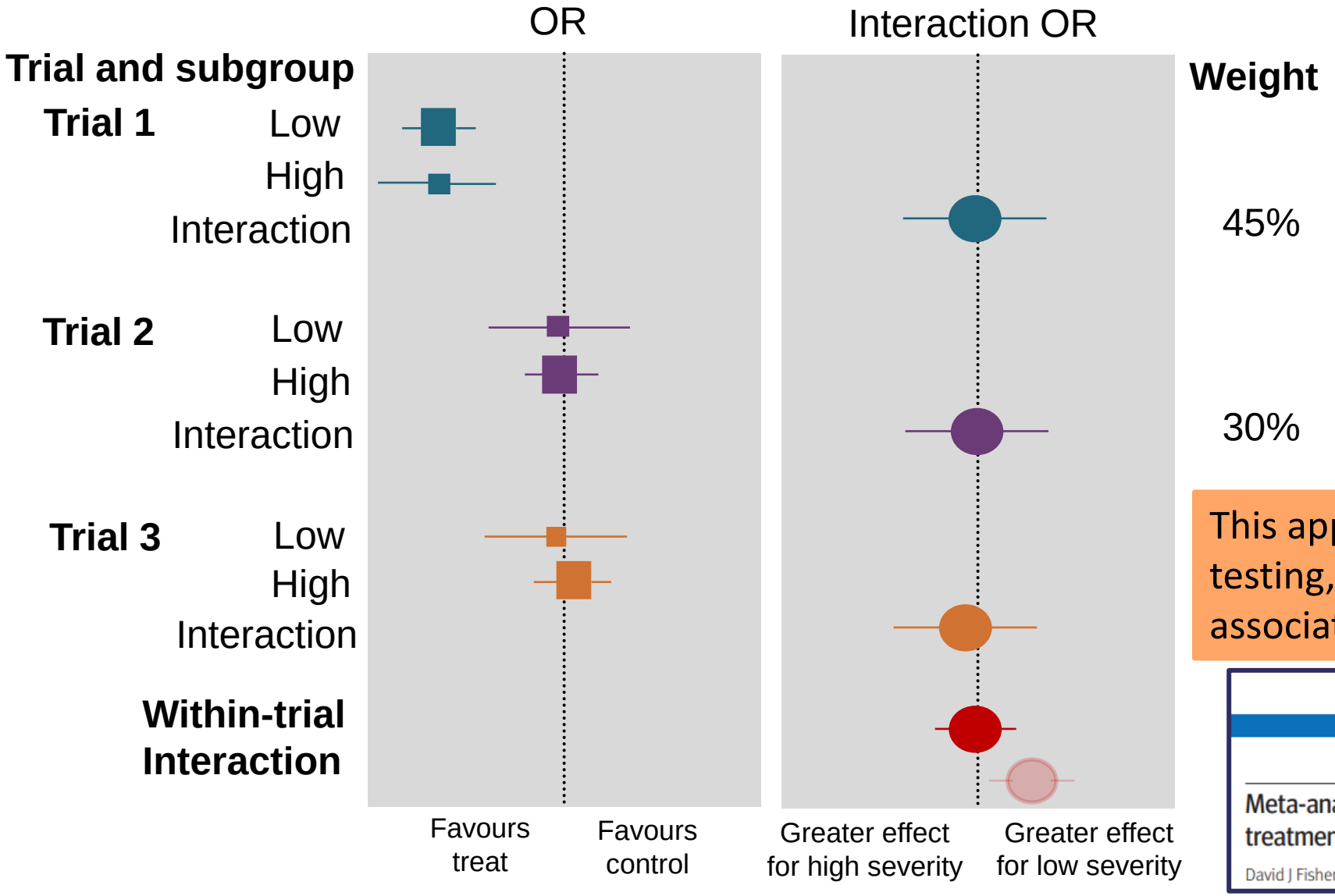
Example: Disease severity; “Subgroup-first” approach



Aggregation bias: Treatment effects for trials with covariate ratio imbalances may *appear* to be different from each other

Alternative approach to estimate interactions

Example: Disease severity; "Trial-first" approach



This approach gives *bias-free* interaction testing, but doesn't naturally produce associated **subgroup effects**

RESEARCH METHODS AND REPORTING

Meta-analytical methods to identify who benefits most from treatments: daft, deluded, or deft approach?

David J Fisher,[1] James R Carpenter,[1,2] Tim P Morris,[1] Suzanne C Freeman,[1] Jayne F Tierney[1]

What subgroup effects to use?

- The **"subgroup-first"** approach uses both ***across- and within-trial information*** so is at risk of aggregation bias
- The **"trial-first"** approach gives bias-free interaction testing: ***only uses within-trial information***
- BUT… "trial-first" approach doesn't produce associate subgroup effects. The "subgroup-first" approach does. Should we use these subgroup effects?
  - These are valid estimates of effect for patients in specific subgroups, but if we compare subgroup effects *then* the issue of aggregation bias comes in
  - Also, these "naïve" subgroup effects are not necessarily compatible with the within-trial interaction free of aggregation bias

So we needed a new approach!

Our new approach: A within trial framework

Within-trial framework: Aims

We developed a new framework to:

1. Estimate **within-trial interactions** across two or more subgroups, ordered or unordered, for categorical covariates
2. Estimate **subgroup effects** that make maximum use of available data and are compatible with the within-trial interactions
3. Clearly **present** this data using novel implementations of forest plots

Within-trial framework: Subgroup effects

Meta-analysis with n trials $(i = 1, \ldots, n)$

Covariate with k subgroups $(j = 1, \ldots, k)$

Disease severity, $k=2$

$\hat{\beta}_{ji}$ = observed trt. effect in subgroup j of trial i

$\hat{\boldsymbol{\beta}}_i$ = *vector* of effects $\hat{\beta}_{ji}$ for trial i

$\hat{\beta}_{11}$ is effect for low severity in trial 1

$\hat{\beta}_{21}$ is effect for high severity in trial 1

$$\hat{\boldsymbol{\beta}}_1 = \begin{bmatrix} \hat{\beta}_{11} \\ \hat{\beta}_{21} \end{bmatrix} \quad \hat{\boldsymbol{\beta}}_2 = \begin{bmatrix} \hat{\beta}_{12} \\ \hat{\beta}_{22} \end{bmatrix} \quad \hat{\boldsymbol{\beta}}_n = \begin{bmatrix} \hat{\beta}_{1n} \\ \hat{\beta}_{2n} \end{bmatrix}$$

Standard MV-MA model:

$$\hat{\boldsymbol{\beta}}_i \sim MVN(\boldsymbol{\beta}, \boldsymbol{S}_i + \boldsymbol{\Sigma}_\beta)$$

Subgroup effects in each trial

Pooled subgroup effects

Covariance matrix

Between-trial heterogeneity matrix

Within-trial framework: Interactions

$$\hat{\boldsymbol{\gamma}}_i = \begin{bmatrix} \hat{\gamma}_{2i} \\ \vdots \\ \hat{\gamma}_{ki} \end{bmatrix} = \begin{bmatrix} \hat{\beta}_{2i} - \hat{\beta}_{1i} \\ \vdots \\ \hat{\beta}_{ki} - \hat{\beta}_{1i} \end{bmatrix}$$

k=2, so: $\hat{\boldsymbol{\gamma}}_i = \hat{\gamma}_{2i} = \hat{\beta}_{2i} - \hat{\beta}_{1i}$

In each trial i, the within-trial interaction is:

[effect for high severity] – [effect for low severity]

Standard MV-MA model:

$$\hat{\boldsymbol{\gamma}}_i \sim MVN\left(\boldsymbol{\gamma}, \boldsymbol{V}_i + \boldsymbol{\Sigma}_\gamma\right)$$

Interactions within each trial

Pooled interaction effect(s)

Covariance matrix

Between-trial heterogeneity matrix

Within-trial framework: Compatibility

We wish to link the model for the subgroup effects ($\boldsymbol{\beta}$) with the model for the interactions ($\boldsymbol{\gamma}$)

Define a **compatibility** relationship:

$$\boldsymbol{\beta} = \begin{bmatrix} \beta_1 \\ \beta_2 \end{bmatrix} = \begin{bmatrix} \beta_1 \\ \beta_1 + \gamma_2 \end{bmatrix}$$

Subgroup effect for high severity is effect for low severity + interaction

Interaction: [effect for high] – [effect for low]

"Floating" subgroup effects

$$\boldsymbol{\beta} = \beta_1 \mathbf{1} + \begin{bmatrix} 0 \\ \boldsymbol{\gamma} \end{bmatrix}$$

Pooled effect in reference subgroup

Pooled within-trial interaction(s)

Vector of 1's, length *k*

Relationship ensures that:

[difference between subgroup effects] = [within-trial interaction(s)]

Random-effects considerations

Three basic forms for heterogeneity covariance matrices $\boldsymbol{\Sigma_\gamma}$ and $\boldsymbol{\Sigma_\beta}$:

Common-effect: No heterogeneity variance for interactions and no heterogeneity variance for subgroups-specific treatment effects

Exchangeable random-effects: Single heterogeneity parameter for subgroup effects (τ_β^2) and single heterogeneity parameter for interactions (τ_γ^2), which may be set to 0.

Unstructured random-effects: This allows a different heterogeneity variance to be estimated within each subgroup

Within-trial framework: Implementation

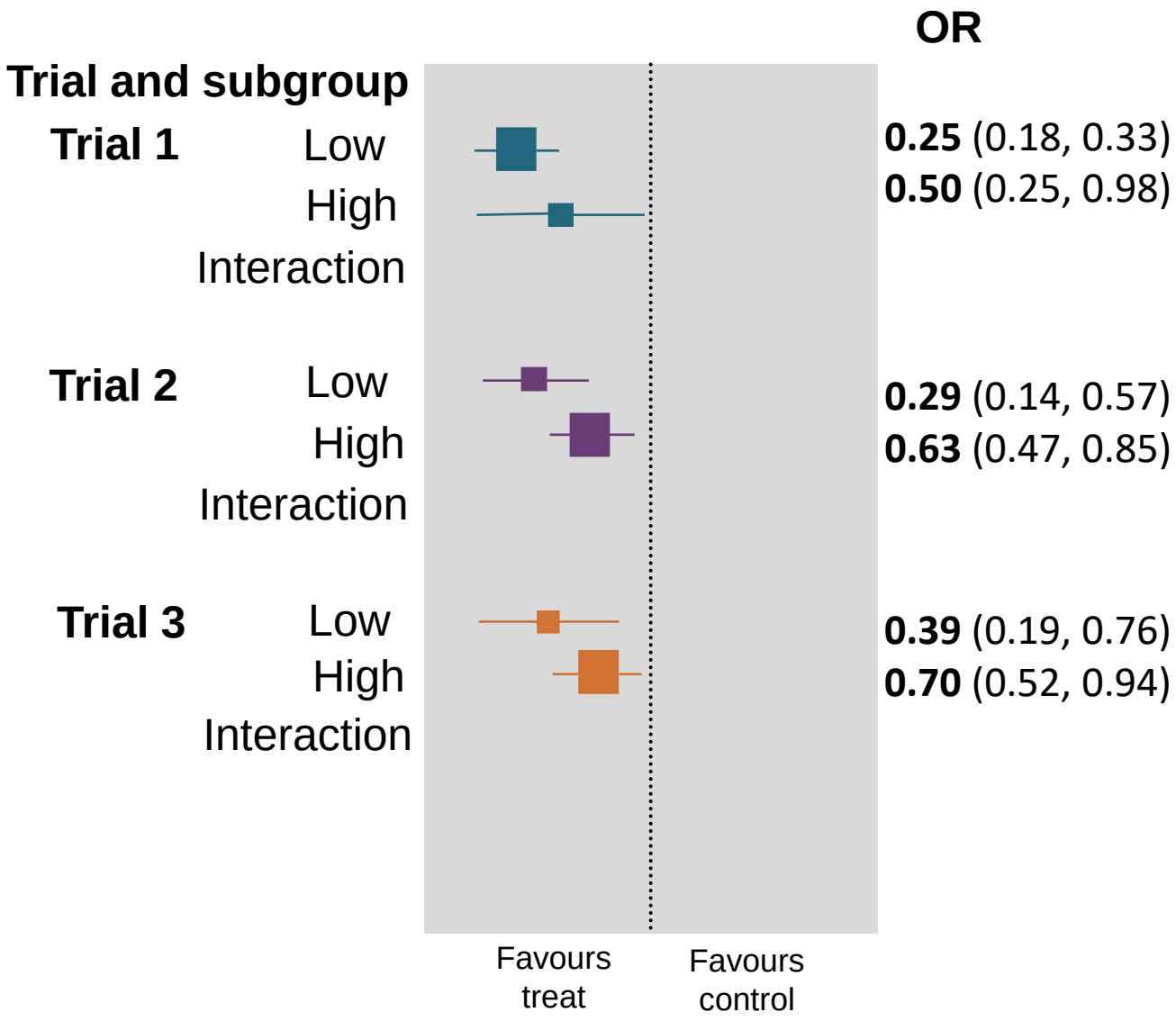
Step 1: Estimate the within-trial interaction ($\boldsymbol{\gamma}$) and its variance

Step 2: Estimate "floating" subgroup-specific treatment effects ($\boldsymbol{\beta}$), constrained by $\boldsymbol{\gamma}$; and their "apparent" variances

Step 3: Correct the variance of the floating subgroup-specific treatment effects to incorporate error in $\boldsymbol{\gamma}$

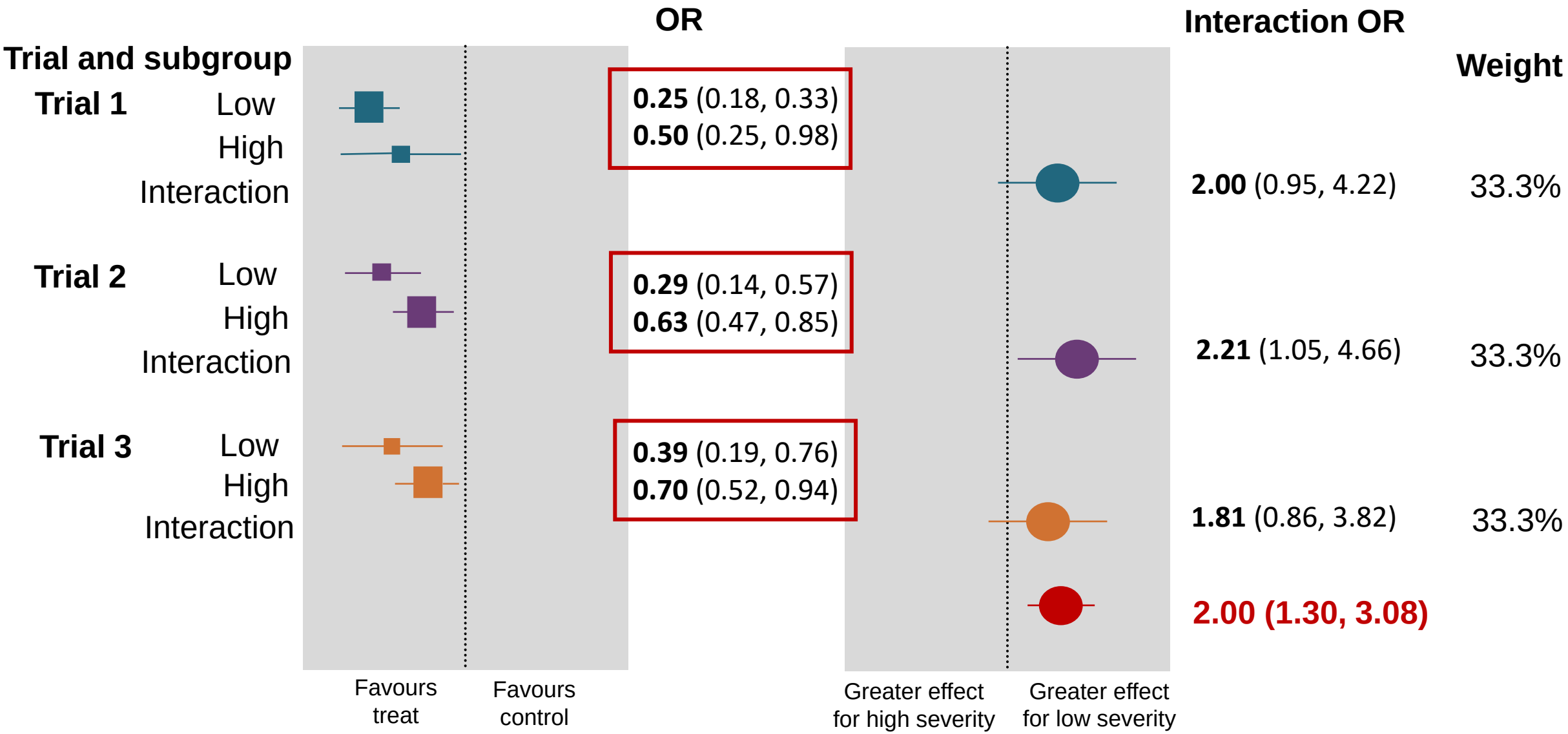
New example: Interaction by disease severity

Setup, 3 different trials in meta-analysis



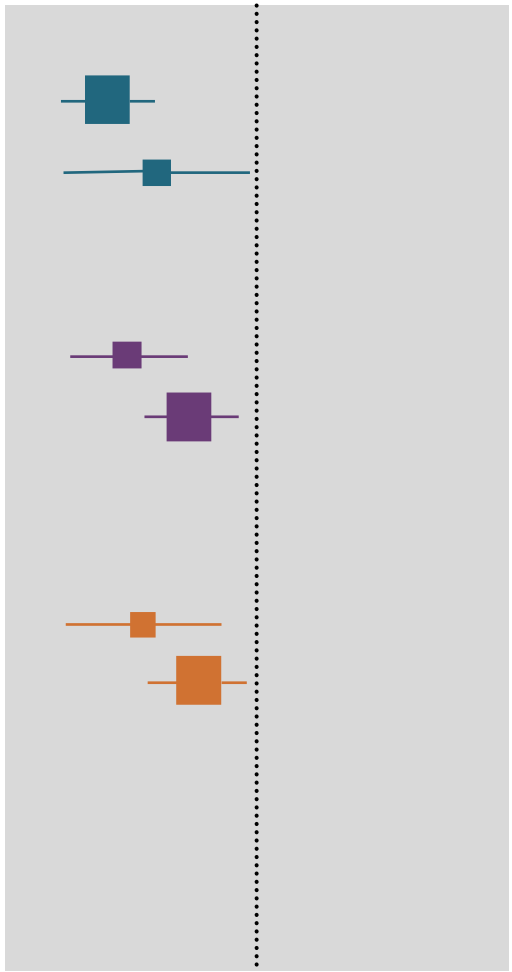
New example: Interaction by disease severity

Step 1: Estimate within-trial interaction



New example: Interaction by disease severity

Step 2a: Scale the non-reference data by the pooled interaction



Trial and subgroup		OR	Interaction OR	Weight
Trial 1	Low	**0.25** (0.18, 0.33)		
	High	**0.50** (0.25, 0.98)		
	Interaction	**Scaled: 0.25**	**2.00** (0.95, 4.22)	33.3%
Trial 2	Low	**0.29** (0.14, 0.57)		
	High	**0.63** (0.47, 0.85)		
	Interaction	**Scaled: 0.32**	**2.21** (1.05, 4.66)	33.3%
Trial 3	Low	**0.39** (0.19, 0.76)		
	High	**0.70** (0.52, 0.94)		
	Interaction	**Scaled: 0.35**	**1.81** (0.86, 3.82)	33.3%
			2.00 (1.30, 3.08)	

Favours treat

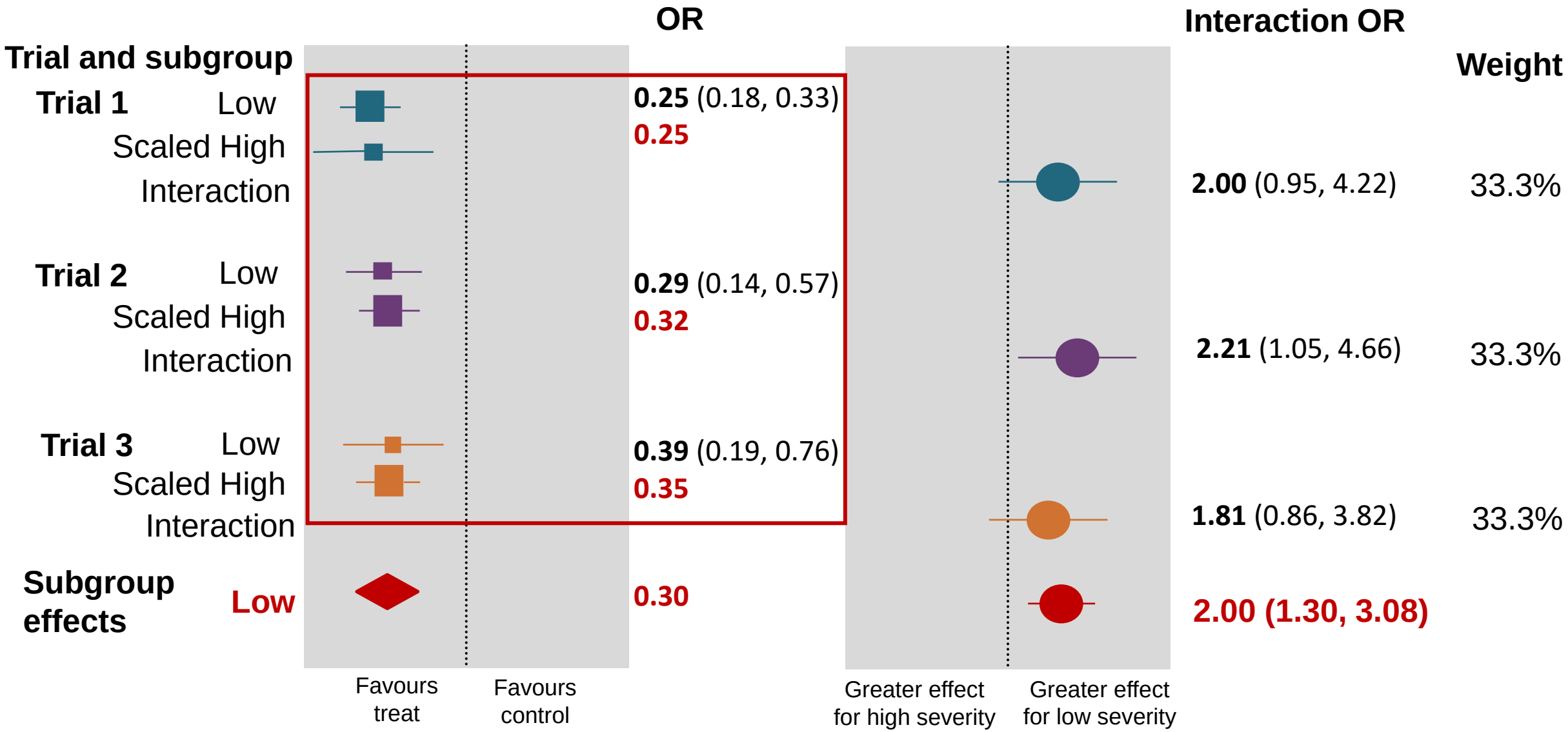
Favours control

Greater effect for high severity

Greater effect for low severity

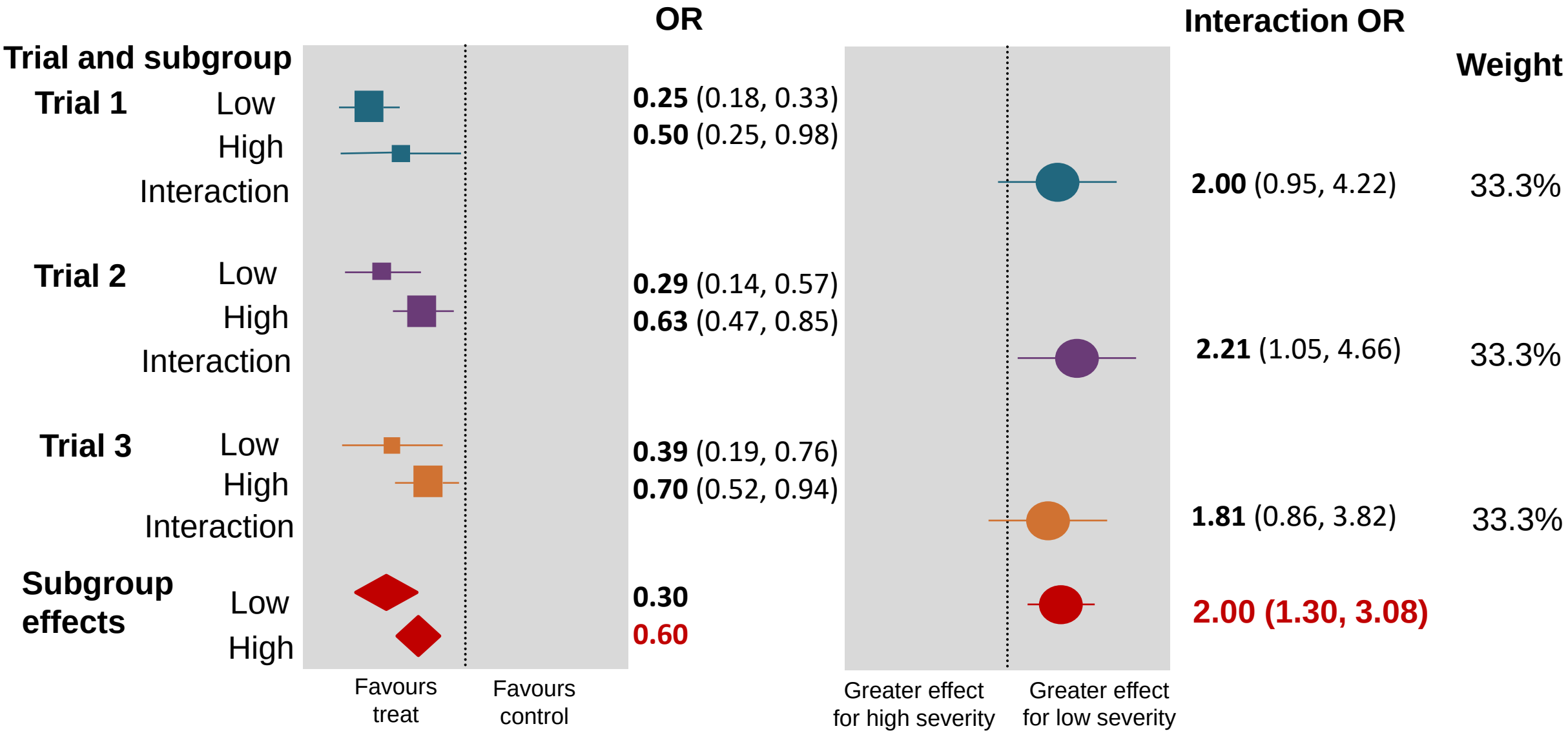
New example: Interaction by disease severity

Step 2b: Pool the reference subgroup and scaled non-reference to estimate reference



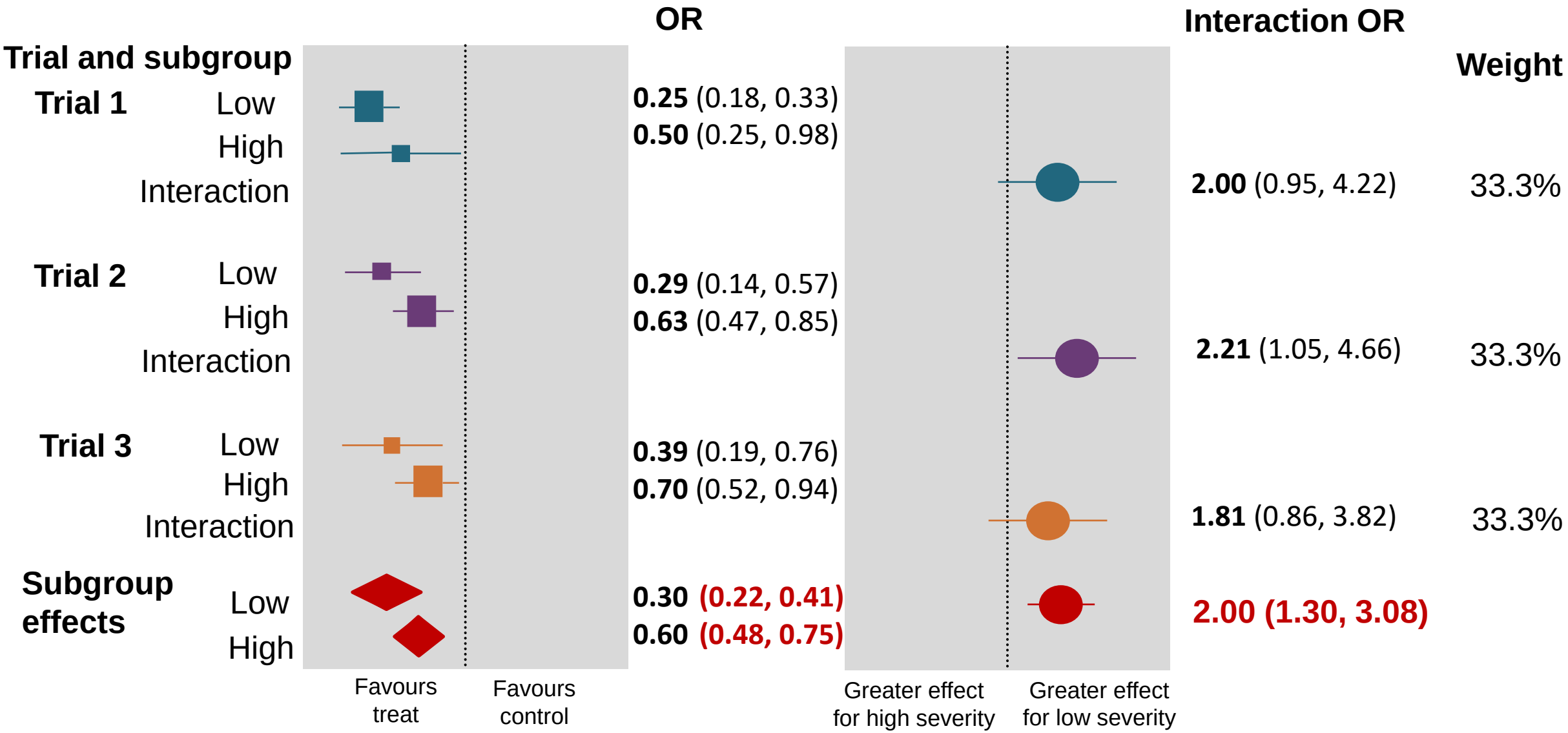
New example: Interaction by disease severity

Step 2c: Estimate non-reference subgroup using compatibility relationship



New example: Interaction by disease severity

Step 3: Correct the variance of the floating subgroup effects



Key features

- Within-trial framework gives bias-free interaction(s) and compatible subgroup effects for any categorical covariate
- Importantly, designed to be used with **aggregate data** as well as with IPD
- Uses **all the available data** when estimating subgroup effects
  - "Single-subgroup" trials can be incorporated
  - Requires an assumption about that the pooled interaction would still apply to this trial
- Heterogeneity can be incorporated in estimation of interaction(s) and subgroup effects
- Software available in Stata

MRC Clinical Trials Unit

UCL

Example: STOPCAP Docetaxel meta-analysis

Celebrating – 25 years –

smarter studies, global impact and better health

Example 1: STOPCAP Docetaxel MA

Population: People with metastatic hormone sensitive prostate cancer

Intervention: Docetaxel chemotherapy

Comparator: SoC (Androgen deprivation therapy, ADT)

Outcome: Progression free survival (HR)

Subgroup 1: Volume of disease (Low, High)

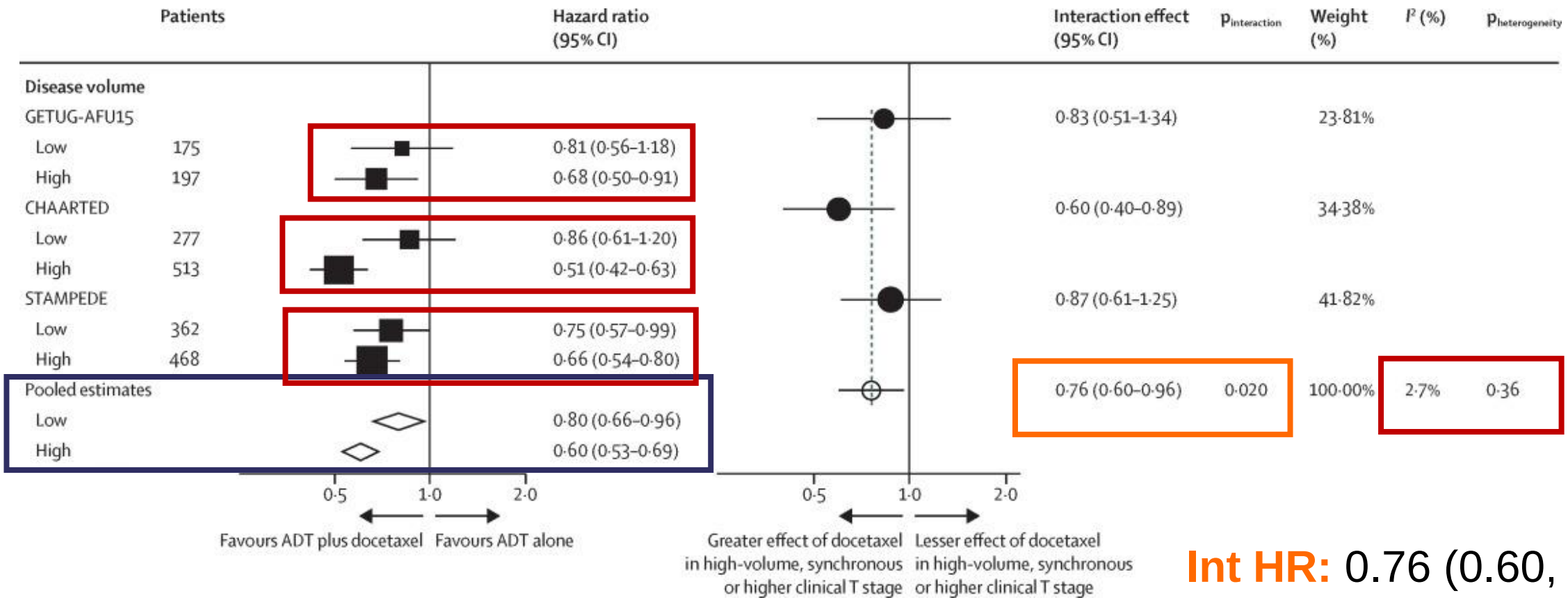
Subgroup 2: Clinical tumour stage (T1-2, T3, T4)

3 trials included, 2261 participants

Which patients with metastatic hormone-sensitive prostate cancer benefit from docetaxel: a systematic review and meta-analysis of individual participant data from randomised trials

Claire L Vale*, David J Fisher*, Peter J Godolphin, Larysa H Rydzewska, Jean-Marie Boher, Sarah Burdett, Yu-Hui Chen, Noel W Clarke, Karim Fizazi, Gwenaelle Gravis, Nicholas D James, Glenn Liu, David Matheson, Laura Murphy, Robert E Oldroyd, Mahesh K B Parmar, Ewelina Rogozinska, Patrick Sfumato, Christopher J Sweeney, Matthew R Sydes, Bertrand Tombal, Ian R White, Jayne F Tierney, on behalf of the STOPCAP Collaboration

Subgroup 1: Volume of disease



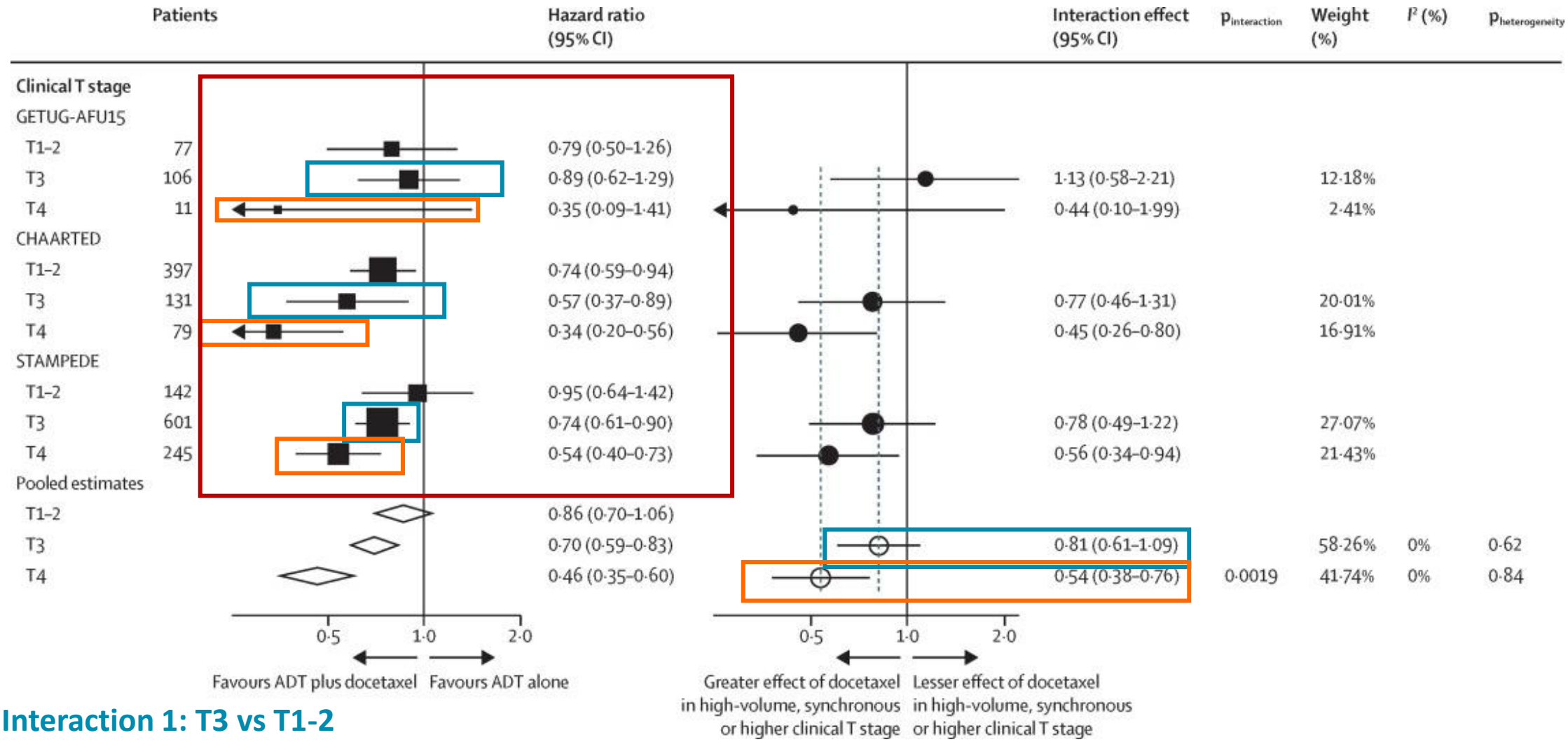
Low: 0.80 (0.66, 0.96)

High: 0.60 (0.53, 0.69)

Int HR: 0.76 (0.60, 0.96)

Int p-value: 0.020

Subgroup 2: Clinical tumour stage



Interaction 1: T3 vs T1-2

Interaction 2: T4 vs T1-2

MRC Clinical Trials Unit

UCL

Example: PORT meta-analysis

Celebrating – 25 years –

smarter studies, global impact and better health

Example 2: Nodal status in PORT MA

Population: Patients with non-small cell lung cancer

Intervention: Post operative radiotherapy (PORT)

Comparator: No PORT

Outcome: Overall survival (HR)

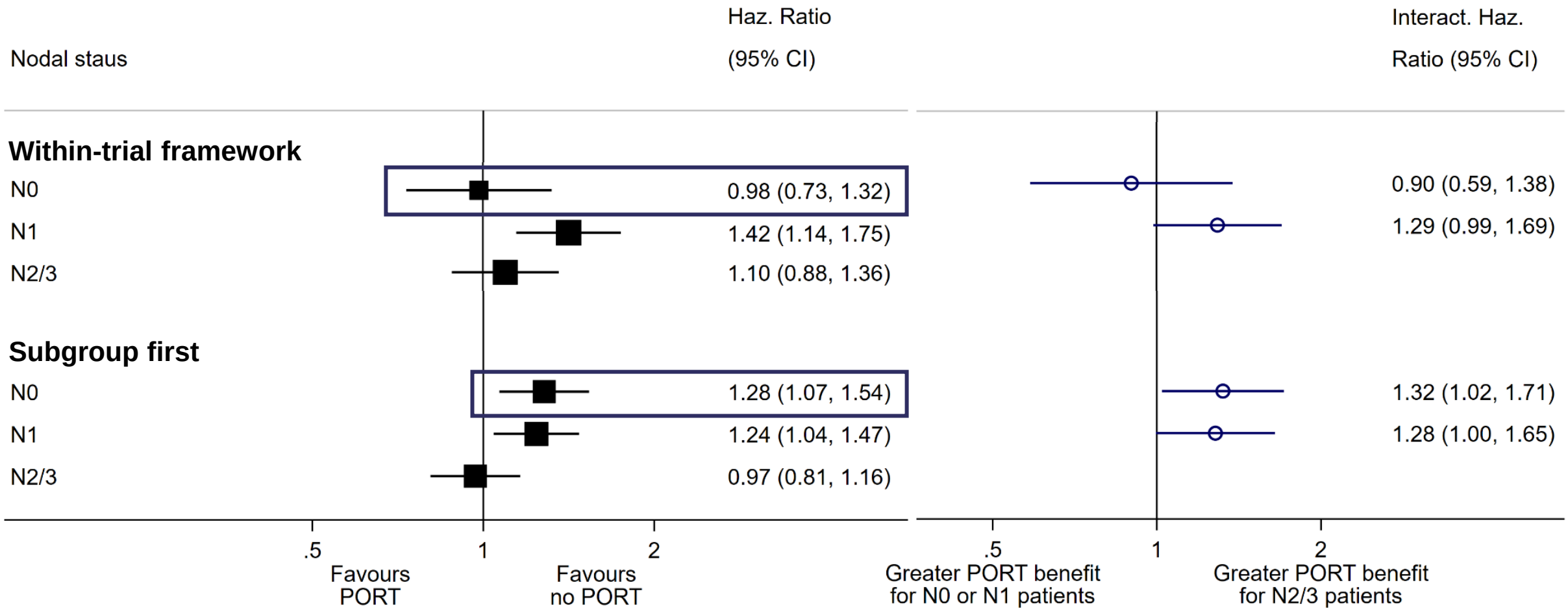
Subgroup: Nodal status (N0, N1, N2/3)

Reference group: N2/3

Postoperative radiotherapy for non-small cell lung cancer (Review)

Burdett S, Rydzewska L, Tierney J, Fisher D, Parmar MKB, Arriagada R, Pignon JP, Le Pechoux C, on behalf of the PORT Meta-analysis Trialists Group

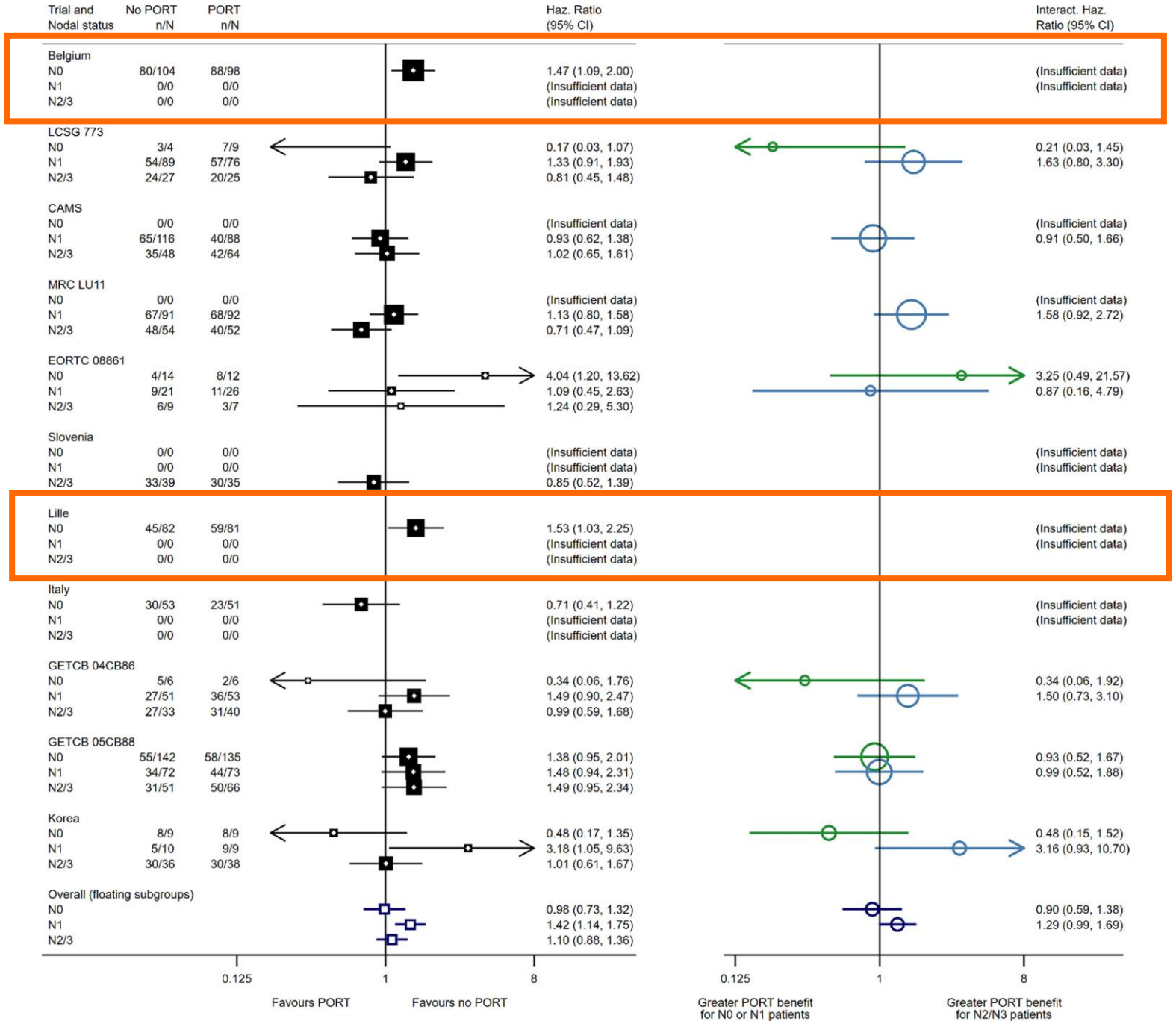
Example 2: Nodal status in PORT MA



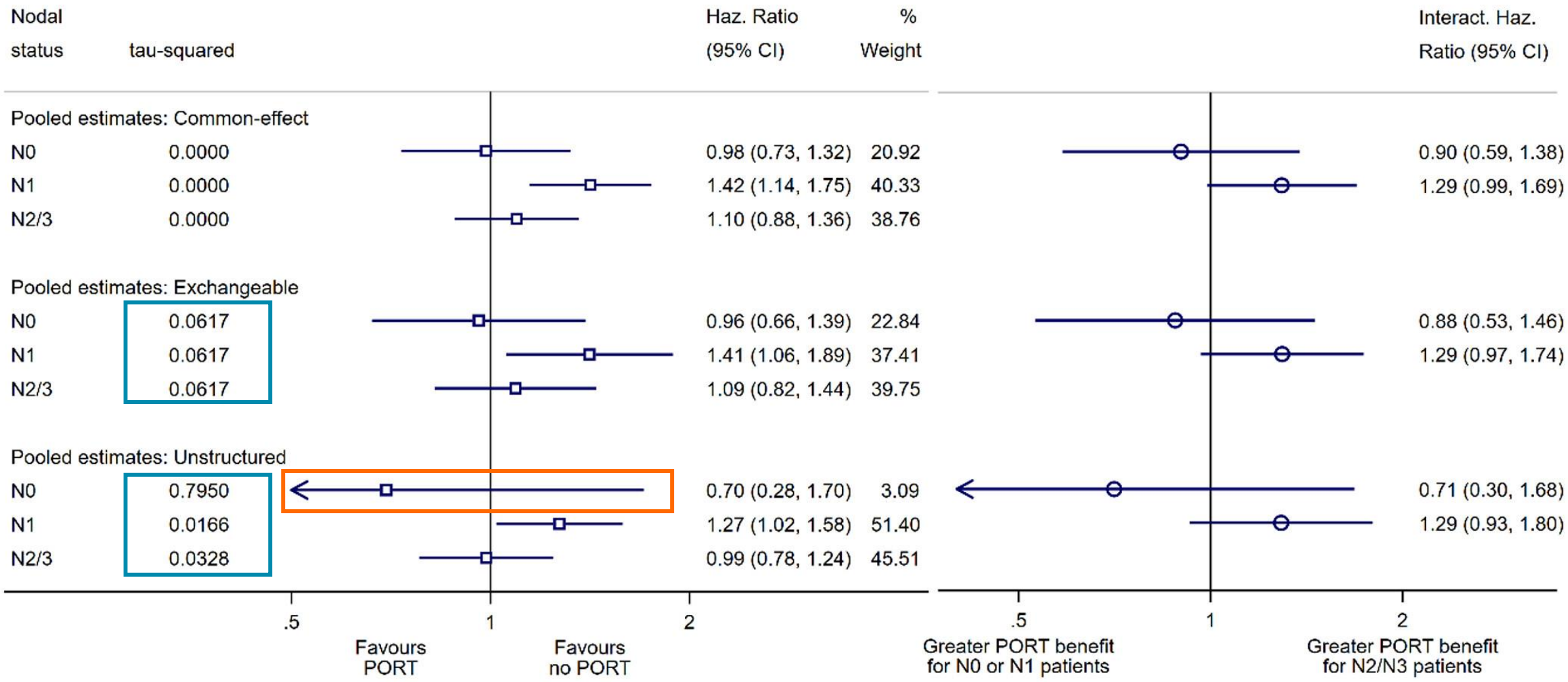
Nodal status in PORT MA

Green interaction: N2/3 vs N0

Blue interaction: N2/3 vs N1



Random-effects in PORT MA



What's next?

What's next?

What is the best way to present interactions and subgroup effects together?

Trial-level two-panel plots struggle with many trials and covariates with >2 subgroups

Can we incorporate continuous covariates without dichotomising?

Method can be generalised to continuous covariates, but would require IPD

How can we make the method more accessible?

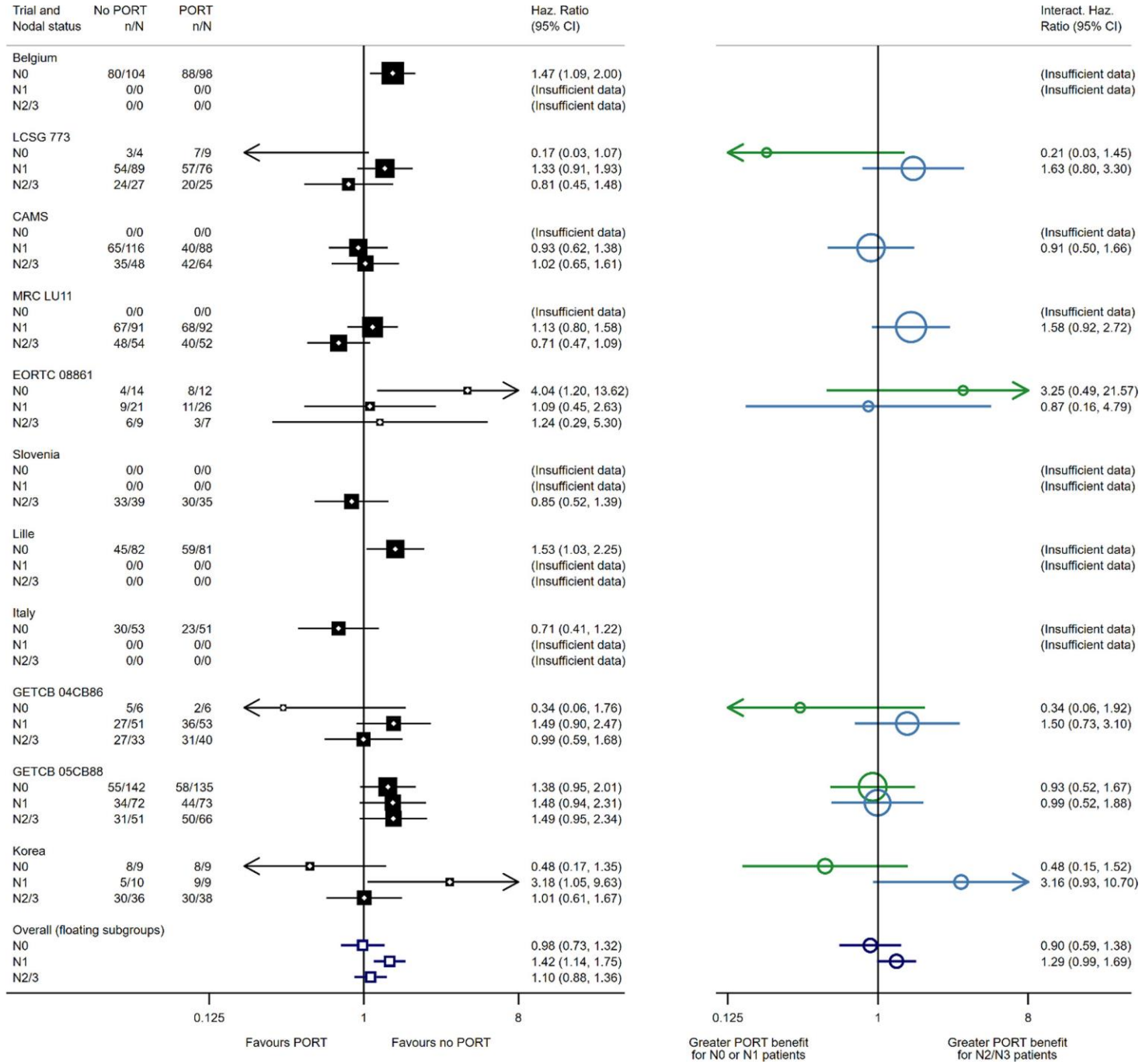
Software available in Stata, but ideally want to get this programmed in R

Subgroups with *three* categories

Choice of reference group

Colours for different interactions

11 trials and 3 categories, already this plot is quite complicated…



(Multiple) *summary* effects only

Research

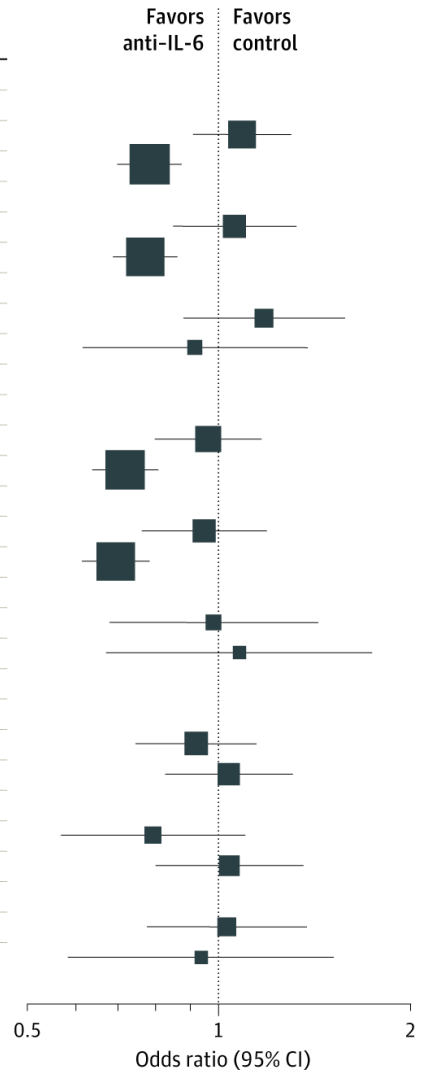
JAMA | Original Investigation

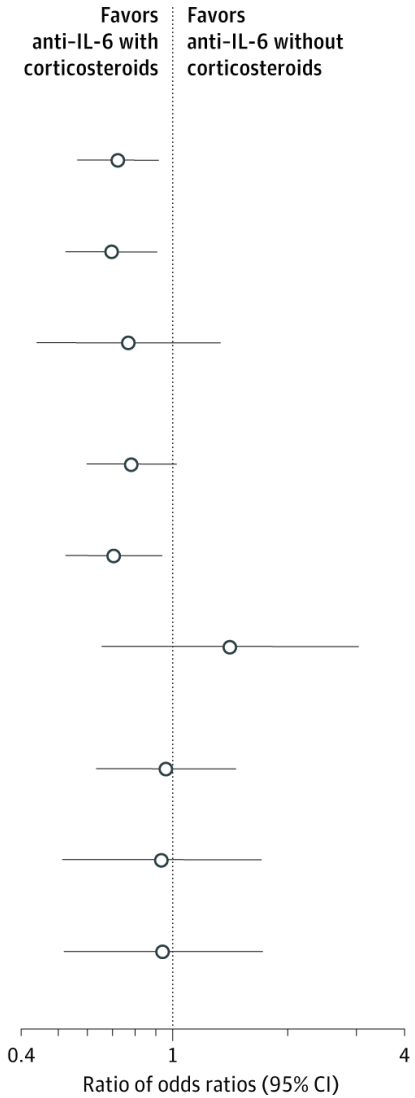
Association Between Administration of IL-6 Antagonists and Mortality Among Patients Hospitalized for COVID-19

A Meta-analysis

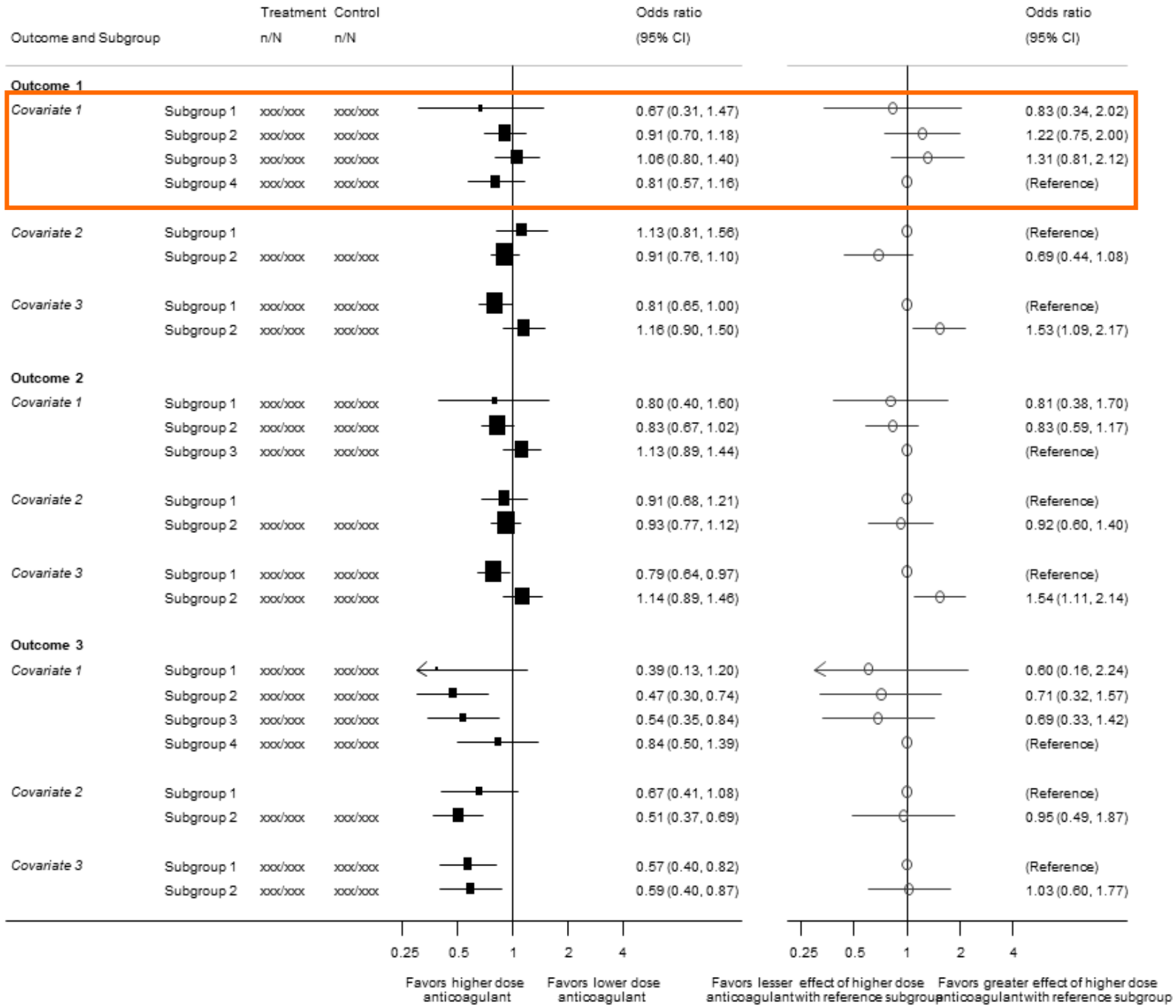
The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group

	Outcome and treatment	I^2, %	No. of events/total patients: Control	No. of events/total patients: Anti-IL-6	Odds ratio (95% CI)	Ratio of odds ratios (95% CI)	I^2, %	*P* value
1	28-d mortality							
	All anti-lL-6							
	No corticosteroid use	0	293/1280	537/2357	1.09 (0.91-1.30)	0.72 (0.56-0.92)	0	.008
	Corticosteroid use	0	838/2848	827/3468	0.78 (0.69-0.88)			
2	Tocilizumab							
	No corticosteroid use	0	211/898	254/1192	1.06 (0.85-1.33)	0.69 (0.52-0.91)	0	.008
	Corticosteroid use	0	793/2585	693/2815	0.77 (0.68-0.87)			
3	Sarilumab							
	No corticosteroid use	0	83/384	283/1134	1.18 (0.88-1.58)	0.77 (0.44-1.33)	0	.34
	Corticosteroid use	0	48/281	124/607	0.92 (0.61-1.38)			
4	Progression to IMV, ECMO, or death at 28 d							
	All anti-lL-6							
	No corticosteroid use	0	308/1004	399/1541	0.96 (0.79-1.17)	0.78 (0.59-1.02)	0	.07
	Corticosteroid use	0	893/2496	822/2986	0.71 (0.63-0.80)			
5	Tocilizumab							
	No corticosteroid use	0	250/791	266/1016	0.95 (0.76-1.20)	0.70 (0.52-0.94)	0	.02
	Corticosteroid use	0	859/2283	729/2518	0.69 (0.61-0. 78)			
6	Sarilumab							
	No corticosteroid use	0	59/214	126/498	0.98 (0.67-1.44)	1.41 (0.65-3.07)	0	.38
	Corticosteroid use	0	38/227	75/423	1.08 (0.67-1.75)			
7	28-d secondary infections[a]							
	All anti-lL-6							
	No corticosteroid use	3	165/758	434/1820	0.92 (0.74-1.15)	0.96 (0.63-1.46)	0	.85
	Corticosteroid use	1	160/798	310/1378	1.04 (0.82-1.31)			
8	Tocilizumab							
	No corticosteroid use	0	86/385	146/659	0.79 (0.57-1.10)	0.94 (0.51-1.71)	11	.83
	Corticosteroid use	16	132/573	210/772	1.04 (0.80-1.36)			
9	Sarilumab							
	No corticosteroid use	8	79/373	285/1130	1.03 (0. 77-1.38)	0.94 (0.52-1.72)	6	.85
	Corticosteroid use	0	28/225	92/560	0.94 (0.58-1.52)			





Multiple subgroups *and* outcomes



What's next?

What is the best way to present interactions and subgroup effects together?

Trial-level two-panel plots struggle with many trials and covariates with >2 subgroups

Can we incorporate continuous covariates without dichotomising?

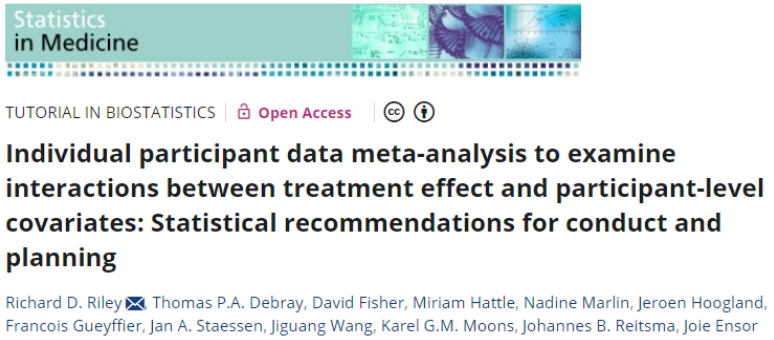
Method can be generalised to continuous covariates, but would require IPD

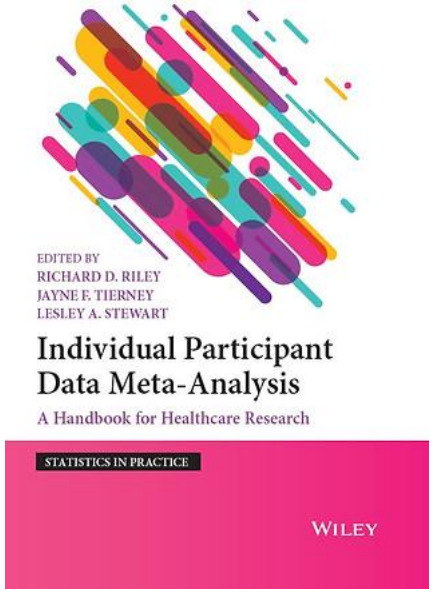
How can we make the method more accessible?

Software available in Stata, but ideally want to get this programmed in R

Continuous covariates

- We don't want to categorise (e.g., Age), want to be able to estimate personalised treatment effects **across the entire age spectrum**
  - May be non-linear relationships as well
- Work ongoing that builds on ideas from RSM paper (Godolphin et al. 2023), tutorial in Stat Med (Riley et al. 2020) and IPD Handbook (Riley, Tierney, Stewart. 2021)
  - Needs IPD – but also with IPD the method can be more powerful





Celebrating – 25 years – | smarter studies, global impact and better health

UKRI MRC Clinical Trials Unit

UCL

What's next?

What is the best way to present interactions and subgroup effects together?

Trial-level two-panel plots struggle with many trials and covariates with >2 subgroups

Can we incorporate continuous covariates without dichotomising?

Method can be generalised to continuous covariates, but would require IPD

How can we make the method more accessible?

Software available in Stata, but ideally want to get this programmed in R

Software

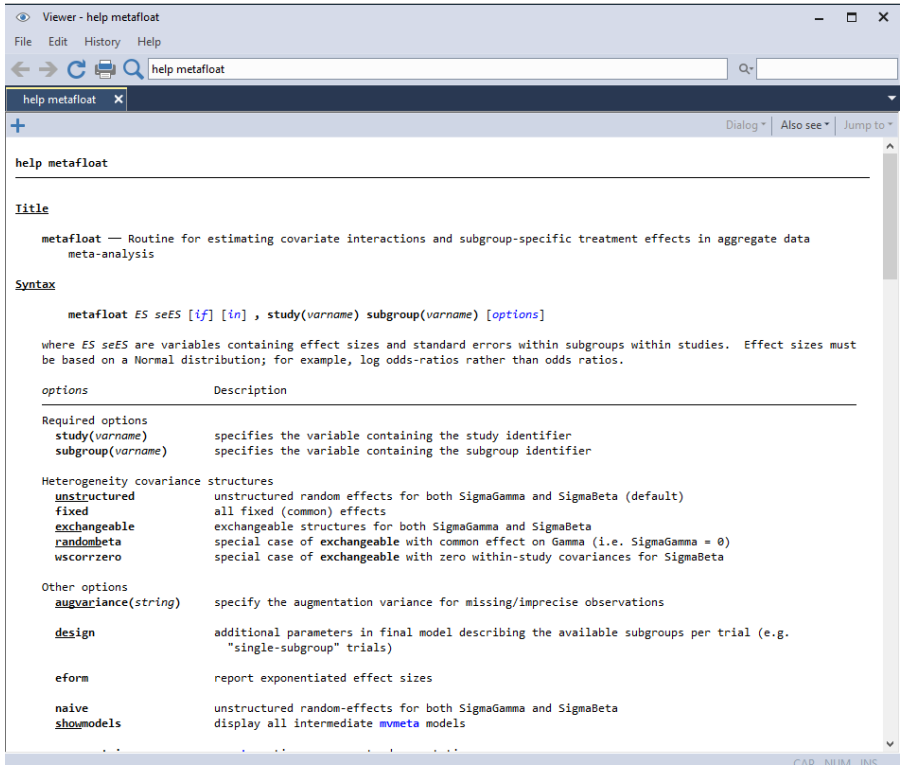
github.com/UCL/metafloat

- `metafloat` package in Stata, helpfiles and example available
- `ipdfloat` package in Stata under development

```
Test of interaction(s):

 ( 1)  [Overall_mean]y_Jnodal_1 = 0
 ( 2)  [Overall_mean]y_Jnodal_2 = 0

           chi2(  2) =    4.68
         Prob > chi2 =    0.0961

Test for trend:

 ( 1)  [y_Jnodal_1]_Trend_1 = 0

           chi2(  1) =    0.26
         Prob > chi2 =    0.6119
```

Floating subgroups:

Subgroup	exp(b)	Std. err.	z	P>|z|	[95% conf.	interval]
y_Inodal_0	.9818489	.1476356	-0.12	0.903	.7312297	1.318364
y_Inodal_1	1.411556	.1528087	3.18	0.001	1.141697	1.745201
y_Inodal_2	1.092993	.1210759	0.80	0.422	.8796822	1.358029



Conclusions

- Subgroup analyses are important in trials & meta-analysis to work out whether effects of treatments do vary → **impact clinical decision making**
- Trials lack power to look at subgroups, so meta-analysis is potentially the **most reliable** way to do this
- BUT… meta-analysis has additional issues that subgroup analysis in a single trial doesn't have → **aggregation bias**
- We proposed a novel approach to ensure you get compatible subgroup effects alongside the bias-free interaction
  - Can be implemented using aggregate data
- We suggest approaches to present interactions and subgroup effects together

Acknowledgments

Co-authors

David Fisher, Jayne Tierney, Ian White

Colleagues in meta-analysis programme at MRC CTU

Claire Vale, Sarah Burdett, Tim Morris, Becky Turner, Lara Rydzewska, Ewelina Rogozińska, Lily Nicholson

Collaborators in our meta-analysis projects

STOPCAP, WHO REACT

Funders UKRI Medical Research Council; PROSTATE CANCER UK; Prostate Cancer Foundation Curing Together.; NIHR | National Institute for Health Research

Are there any questions?

Contact details:

Dr Peter Godolphin

p.godolphin@ucl.ac.uk

@petegodolphin

Further details:

RESEARCH ARTICLE | Open Access

Estimating interactions and subgroup-specific treatment effects in meta-analysis without aggregation bias: A within-trial framework

Peter J. Godolphin, Ian R. White, Jayne F. Tierney, David J. Fisher

github.com/UCL/metafloat

References

James ND et al. Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy. NEJM. 2017

Spears MR et al. ‘Thursday’s child has far to go’—interpreting subgroups and the STAMPEDE trial. Ann Oncol. 2017

Iannizzi C et al. Convalescent plasma for people with COVID-19: a living systematic review. Cochrane Database Syst Rev. 2023

Fisher DJ et al. Meta-analytical methods to identify who benefits most from treatments: daft, deluded, or deft approach? BMJ. 2017

Godolphin PJ et al. Estimating interactions and subgroup-specific treatment effects in meta-analysis without aggregation bias: A within-trial framework. Res Syn Meth. 2023

Vale CL et al. Which patients with metastatic hormone-sensitive prostate cancer benefit from docetaxel: a systematic review and meta-analysis of individual participant data from randomised trials. Lancet Oncol. 2023

Burdett S et al. Postoperative radiotherapy for non-small cell lung cancer. Cochrane Database Syst Rev. 2016

WHO REACT Group. Association Between Administration of IL-6 Antagonists and Mortality Among Patients Hospitalized for COVID-19: A Meta-analysis. JAMA. 2021

Riley RD et al. Individual participant data meta-analysis to examine interactions between treatment effect and participant-level covariates: Statistical recommendations for conduct and planning. Stat Med. 2020

Riley RD, Tierney J, Stewart LA (Eds). Individual Participant Data Meta-Analysis: A Handbook for Healthcare Research. Wiley. 2021

MRC Clinical Trials Unit

UCL

Appendix slides

Celebrating – 25 years – | smarter studies, global impact and better health

Single-subgroup trials…

- Trials including only a single participant subgroup cannot contribute to the within-trial interaction
  - There is nothing to estimate here
  - We refer to these as **“single-subgroup”** trials

$$\widehat{\boldsymbol{\beta}}_{SS} = \begin{bmatrix} \hat{\beta}_{1SS} \\ . \end{bmatrix} \quad \hat{\gamma}_{2SS} = [. \; -\hat{\beta}_{1SS}] = ne$$

- But we can still use the information from this trial in the within-trial framework when estimating **subgroup-specific treatment effects** compatible with this interaction

Estimating subgroup-specific effects compatible with the interaction with single-subgroup trials

- The unobserved estimates may be considered to be very imprecisely estimated
  - Assign them a **value of zero** for the effect size
  - Assign them a **large variance** (e.g., 10,000)
  - Similar approach to that used in network meta-analysis
  - Important to check that alternative values of the assigned variance give near-identical results

$$\widehat{\boldsymbol{\beta}}_{SS} = \begin{bmatrix} \hat{\beta}_{1SS} \\ 0 \end{bmatrix}$$

- Then use all of the information from the trial (observed and ***augmented*** values)

Assumption of transitivity

- By using all of the trial's information, we are making a strong assumption:

Assumption of transitivity across subgroups

- This assumes that any **non-observed** subgroup-specific treatment effect could in principle have been
- And its true value would be **identical** to those of the remaining studies
- If such studies are assigned relatively large weights, then this assumption may have a substantial impact upon the subgroup estimates

An extreme example – WHO REACT Corticosteroids PMA

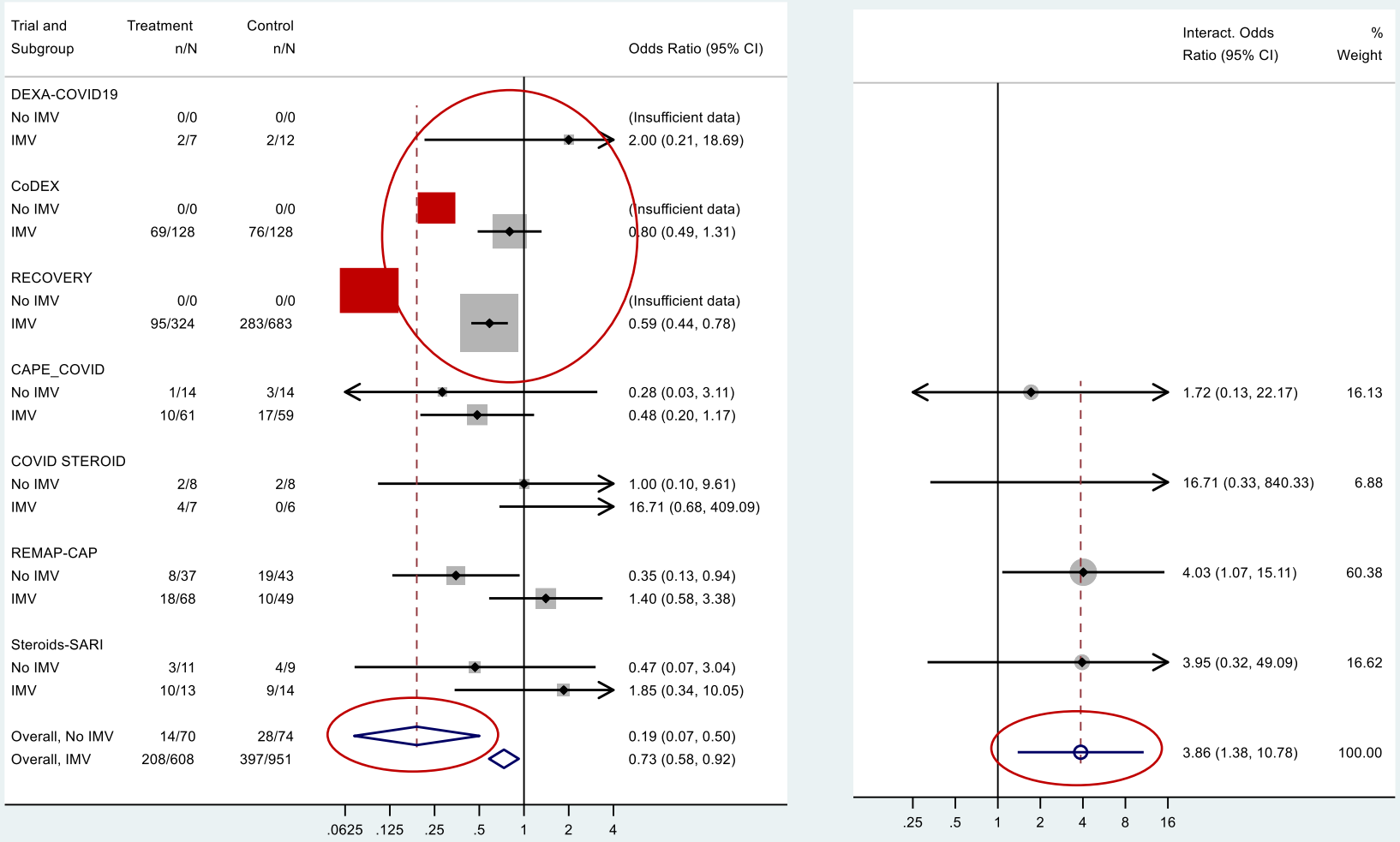
Population: Patients hospitalised with COVID-19

Intervention: Corticosteroids

Outcome: 28-day mortality

Study design: RCTs

Subgroup: invasive mechanical ventilation



Research

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19
A Meta-analysis

The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group

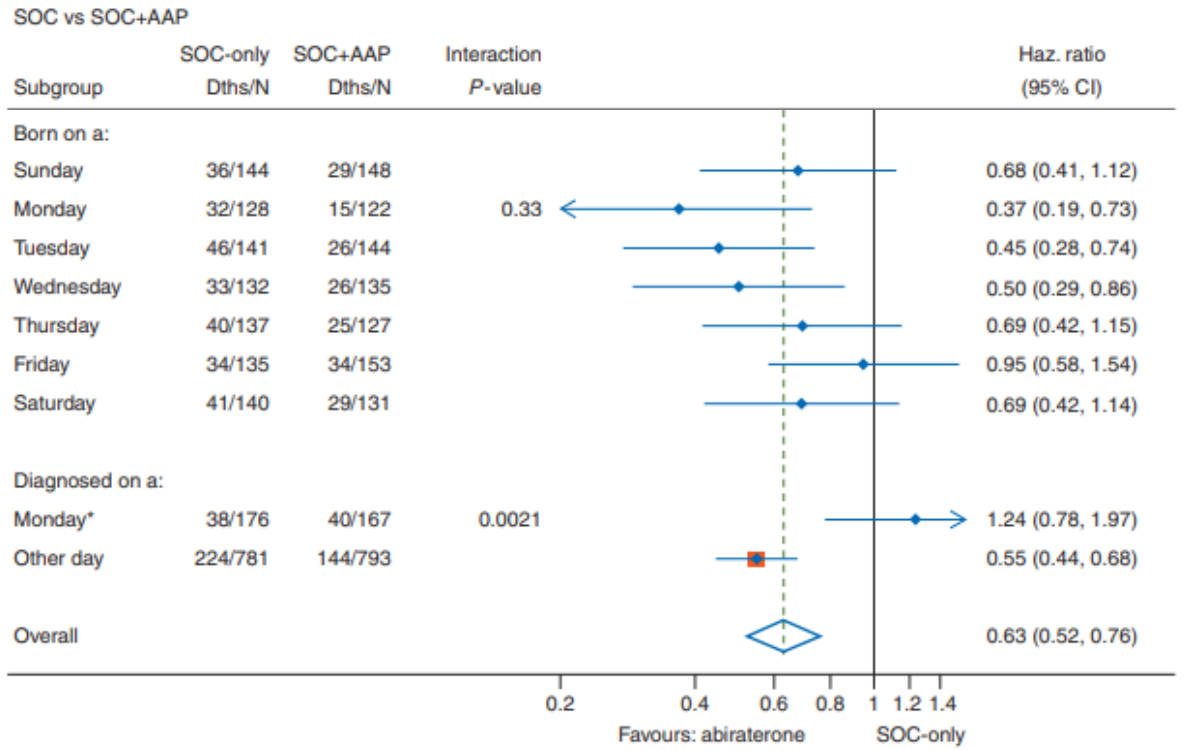
Dealing with single-subgroup trials

- If the estimate from a single-subgroup trial is extreme relative to the remaining data, then it may be questionable whether the **pooled interaction is applicable** to this trial
- We strongly recommend that reviewers **critically evaluate the design and setting** of “single-subgroup” trials to assess whether this assumption holds
- As a sensitivity analysis, it may be sensible to remove single-subgroup trials from estimation procedure to test the impact of this assumption on estimates

An aside: importance of pre-specification

Spears: If data is repeatedly trawled, a subgroup will likely be found which appears significant. To mitigate, only a small number of clinically plausible (or, ideally, hypothesized) subgroups should be tested

All of this remains true for meta-analysis



Annals of Oncology

'Thursday's child has far to go'—interpreting subgroups and the STAMPEDE trial

M. R. Spears[1], N. D. James[2] & M. R. Sydes[1*]
[1]MRC Clinical Trials Unit at UCL, Institute of Clinical Trials and Methodology, University College London, London; [2]Institute of Cancer and Genomic Sciences, University of Birmingham, Birmingham, UK