



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

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Cochrane Learning Live webinar

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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?













Subgroups and interactions in a single trial



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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)

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*

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

1917 patients randomised: 915 M0, 1002 M1









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Does effect of Abiraterone vary based on metastatic status?

SOC vs SOC+AAP



HR<1 favours abiraterone

Time for a poll...







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Annals of Oncology

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

> M. R. Spears¹, N. D. James² & M. R. Sydes^{1*} ¹MRC Clinical Trials Unit at UCL, Institute of Clinical Trials and Methodology, University College London, London; ²Institute of Cancer and Genomic Sciences, University of Birmingham, Birmingham, UK

Does effect of Abiraterone vary based on metastatic status?

SOC vs SOC+AAP



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)









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

> M. R. Spears¹, N. D. James² & M. R. Sydes^{1*} ¹MRC Clinical Trials Unit at UCL, Institute of Clinical Trials and Methodology, University College London, London; ²Institute of Cancer and Genomic Sciences, University of Birmingham, Birmingham, UK





Subgroups and interactions in meta-analysis: Aggregation bias



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Convalescent plasma for people with COVID-19

28-day mortality: Antibodies detected at baseline subgroup analysis

		Convalescen	Convalescent plasma Pla		d care alone		Risk Ratio	Risk Ratio	Risk of Bias
	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI	ABCDEF
	6.1.1 Antibodies detect	ed at baseline							
S	Avendano-Sola 2021	0	48	3	61	0.1%	0.18 [0.01 , 3.42]	← →	$\bullet \bullet \bullet \bullet \bullet \bullet$
σ	Bar 2021	0	17	2	15	0.1%	0.18 [0.01 , 3.43]	← →	? • • • • ?
Ę	Estcourt 2021	190	599	135	409	25.4%	0.96 [0.80 , 1.15]		$\bullet \bullet \bullet \bullet \bullet \bullet$
S	Horby 2021b	575	3078	501	2810	71.1%	1.05 [0.94 , 1.17]		$\bullet \bullet \bullet \bullet \bullet \bullet$
_	Ortigoza 2022	28	228	26	258	3.3%	1.22 [0.74 , 2.02]		
Г	Subtotal (95% CI)		3970		3553	100.0%	1.03 [0.94 , 1.12]	•	1
	Total events:	793		007					1
	Heterogeneity: Tau ² = 0.	.00; Chi ² = 3.78, d	df = 4 (P = 0.4	44); I ² = 0%					
	Test for overall effect: Z	z = 0.56 (P = 0.57))						
	6.1.2 No antibodies det	tected at baseline							
6	Avendano-Sola 2021	7	130	11	107	2.1%	0.52 [0.21 , 1.30]	←	$\bullet \bullet \bullet \bullet \bullet \bullet$
	Bar 2021	2	23	8	24	0.8%	0.26 [0.06 , 1.10]	←───────────	? • • • ?
Ž	Estcourt 2021	130	271	78	148	30.1%	0.91 [0.75 , 1.11]	_ _	$\bullet \bullet \bullet \bullet \bullet \bullet$
P	Horby 2021b	642	2016	558	1660	62.1%	0.95 [0.86 , 1.04]		$\bullet \bullet \bullet \bullet \bullet \bullet$
ר_ ת	Ortigoza 2022	18	125	21	117	5.0%	0.80 [0.45 , 1.43]		_ • • • • • • •
	Subtotal (95% CI)		2565		2056	100.0%	0.91 [0.79 , 1.04]	•	
	Total events:	/99		0/0					
	Heterogeneity: Tau ² = 0.	.01; Chi ² = 4.98, d	df = 4 (P = 0.2	29); I ² = 20%					
	Test for overall effect: Z	z = 1.44 (P = 0.15))						Cochrane
Г									Library
	Test for subgroup differer	nces: Chi ² = 2.27,	, df = 1 (P =	0.13), I ² = 56.0%					Cochrane Database of Systematic Res
							Favours con	nvalescent plasma Favours placebo	Cochiane Database of Systematic Rev
				_					
(elebratin	smart	er studie l impact	es, and UK	MR	C nical			Convalescent plasma for people review (Review)
	– 25 years – 4	5 better	health	RL	Tria	ls Unit			

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



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 withintrial 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



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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







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Within-trial framework: Subgroup effects

Meta-analysis with *n* trials (i = 1, ..., n)

Covariate with k subgroups (j = 1, ..., k)Disease severity, k=2

 $\hat{\beta}_{ii}$ = observed trt. effect in subgroup *j* of trial *i* $\hat{\beta}_{11}$ is effect for low severity in trial 1 $\hat{\beta}_{21}$ is effect for high severity in trial 1 $\hat{\beta}_i = vector \text{ of effects } \hat{\beta}_{ii}$ for trial *i* $\widehat{\boldsymbol{\beta}}_{1} = \begin{vmatrix} \widehat{\beta}_{11} \\ \widehat{\beta}_{21} \end{vmatrix} \quad \widehat{\boldsymbol{\beta}}_{22} = \begin{vmatrix} \widehat{\beta}_{12} \\ \widehat{\beta}_{22} \end{vmatrix} \quad \widehat{\boldsymbol{\beta}}_{n1} = \begin{vmatrix} \widehat{\beta}_{1n} \\ \widehat{\beta}_{2n} \end{vmatrix}$ Standard MV-MA model: $\widehat{\boldsymbol{\beta}}_i \sim MVN(\boldsymbol{\beta}, \boldsymbol{S}_i + \boldsymbol{\Sigma}_{\boldsymbol{\beta}})$ Subgroup effects in each trial **Between-trial heterogeneity matrix** Pooled subgroup effects Covariance matrix smarter studies, MRC Clinical 15 Trials Unit

Within-trial framework: Interactions

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

Standard MV-MA model:

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

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

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

$\widehat{\gamma}_{i} \sim MVN(\gamma, V_{i} + \Sigma_{\gamma})$ Interactions within each trial Pooled interaction effect(s) Between-trial heterogeneity matrix Covariance matrix Celebrating Summer studies, Summer studie

Within-trial framework: Compatibility

We wish to link the model for the subgroup effects (β) with the model for the interactions (γ)

Define a **compatibility** relationship:

"Floating" subgroup effects $\beta = \beta_1 \mathbf{1} + \begin{bmatrix} 0 \\ \mathbf{v} \end{bmatrix}$ Pooled effect in reference subgroup

Relationship ensures that:

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

Subgroup effect for high severity is effect for low severity + interaction Interaction: [effect for high] – [effect for low] Pooled within-trial interaction(s)

Vector of 1's, length k

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







Random-effects considerations

Three basic forms for heterogeneity covariance matrices Σ_{γ} and Σ_{β} :

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 (γ) and its variance

Step 2: Estimate "floating" subgroup-specific treatment effects (β), constrained by γ ; and their "apparent" variances

Step 3: Correct the variance of the floating subgroup-specific treatment effects to incorporate error in γ







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Setup, 3 different trials in meta-analysis



Step 1: Estimate within-trial interaction



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



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



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



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













Example: STOPCAP Docetaxel meta-analysis



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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





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Which patients with metastatic hormone-sensitive prostate \rightarrow 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



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Subgroup 1: Volume of disease



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Subgroup 2: Clinical tumour stage







Example: PORT metaanalysis



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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)

Cochrane Library

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







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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?



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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







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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

JAMA | Original Investigation

Research

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

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

Ratio of odds ratios (95% CI)

			No. of events	/total patients	Odds ratio	Favors	Favors	Ratio of odds		Favors anti-IL-6 with	Favors anti-IL-6 without	
	Outcome and treatment	I ² ,%	Control	Anti-IL-6	(95% CI)	anti-IL-6	control	ratios (95% CI)	l ² ,%	corticosteroids	corticosteroids	P value
1	28-d mortality											
•	AII anti-lL-6						_					
	No corticosteroid use	0	293/1280	537/2357	1.09 (0.91-1.30)			0.72 (0.56-0.92)	0	—o—		.008
0	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	—o—		.008
	Corticosteroid use	0	793/2585	693/2815	0.77 (0.68-0.87)							
3	Sarilumab											
U	No corticosteroid use	0	83/384	283/1134	1.18 (0.88-1.58)			0.77 (0.44-1.33)	0	O		.34
	Corticosteroid use	0	48/281	124/607	0.92 (0.61-1.38)							
4	Progression to IMV, ECMO, or death at 28 d											
4	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	—-o—		.07
	Corticosteroid use	0	893/2496	822/2986	0.71 (0.63-0.80)							
5	Tocilizumab											
U	No corticosteroid use	0	250/791	266/1016	0.95 (0.76-1.20)			0.70 (0.52-0.94)	0	——O——		.02
	Corticosteroid use	0	859/2283	729/2518	0.69 (0.61-0. 78)	-						
~	Sarilumab					_						
6	No corticosteroid use	0	59/214	126/498	0.98 (0.67-1.44)			1.41 (0.65-3.07)	0		0	.38
	Corticosteroid use	0	38/227	75/423	1.08 (0.67-1.75)							
	28-d secondary infections ^a											
7	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	C)	.85
	Corticosteroid use	1	160/798	310/1378	1.04 (0.82-1.31)							
0	Tocilizumab											
8	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)							
	Sarilumab											
Q	No corticosteroid use	8	79/373	285/1130	1.03 (0. 77-1.38)			0.94 (0.52-1.72)	6	0		.85
0	Corticosteroid use	0	28/225	92/560	0.94 (0.58-1.52)		<u> </u>					
												_
						0.5	1	2		0.4	1	4

Odds ratio (95% CI)

Multiple subgroups and outcomes

	Treatme	ent Control	Odds ratio		Odds ratio
Outcome and Subgroup	n/N	n/N	(95% CI)		(95% CI)
Outcome 1					
Covariate 1 Subgr	oup 1 xxx/xxx	2000/2000	0.67 (0.31, 1.47)		0.83 (0.34, 2.02
Subgr	oup 2 xxx/xxx	χοος/χοος	0.91 (0.70, 1.18)		1.22 (0.75, 2.00
Subgr	oup 3 xxx/xxx	3000/3000	1.06 (0.80, 1.40)		1.31 (0.81, 2.12
Subgr	oup 4 xxx/xxx	xoox/xoox	0.81 (0.57, 1.16)	Ŷ	(Reference)
Covariate 2 Subgr	oup 1		1.13 (0.81, 1.56)	¢	(Reference)
Subgr	oup 2 xxx/xxx	χοοκ/χοοκ	- 0.91 (0.76, 1.10)		0.69 (0.44, 1.08
Covariate 3 Subgr	oup 1 xxx/xxx	xox/xox -	0.81 (0.65, 1.00)	•	(Reference)
Subgr	oup 2 xxx/xxx	x00x/x00x	1.16 (0.90, 1.50)		1.53 (1.09, 2.17
Outcome 2					
Covariate 1 Subgr	oup 1 xxx/xxx	x00X/X00X	0.80 (0.40, 1.60)		0.81 (0.38, 1.70
Subgr	oup 2 xxx/xxx	x00X/X00X	0.83 (0.67, 1.02)	-0-	0.83 (0.59, 1.17
Subgr	oup 3 xxx/xxx	x00x/x00x	1.13 (0.89, 1.44)	φ	(Reference)
Covariate 2 Subgr	oup 1		0.91 (0.68, 1.21)	•	(Reference)
Subgr	oup 2 xxx/xxx	x00x/x00x	0.93 (0.77, 1.12)		0.92 (0.60, 1.40
Covariate 3 Subgr	oup1 xxx/xxx	xoox/xoox -	0.79 (0.64, 0.97)	•	(Reference)
Subgr	oup 2 xxx/xxx	x00x/x00x	1.14 (0.89, 1.48)	-0	1.54 (1.11, 2.14
Outcome 3					
Covariate 1 Subgr	oup 1 xxx/xxx	xxx/xxxx <	0.39 (0.13, 1.20)	← •	0.60 (0.16, 2.24
Subgr	oup 2 xxx/xxx	x00x/x00x	- 0.47 (0.30, 0.74)		0.71 (0.32, 1.57
Subgr	oup 3 xxx/xxx	xxx/xxxx	0.54 (0.35, 0.84)		0.69 (0.33, 1.42
Subgr	oup 4 xxx/xxx	xox/xox	0.84 (0.50, 1.39)	¢	(Reference)
Covariate 2 Subgr	oup 1		0.67 (0.41, 1.08)	•	(Reference)
Subgr	oup 2 xxx/xxx	xxx/xxx —	0.51 (0.37, 0.69)		0.95 (0.49, 1.87
Covariate 3 Subgr	oup 1 xxx/xxx		0.57 (0.40, 0.82)	φ	(Reference)
<u> </u>	-		0.50(0.40,0.97)		1 02 (0 80 1 77

Favors higher dose Favors lower dose anticoagulant anticoagulant Favors lesser effect of higher dose Favors greater effect of higher dose anticoagulantwith reference subgroup nticoagulant with reference subgroup

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 >2subgroups

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







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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

Research Synthesis Methods	

RESEARCH ARTICLE 🖻 Open Access 🛛 😨 💽

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

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



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TUTORIAL IN BIOSTATISTICS 🛛 🔂 Open Access 🛛 🕲 🛈

Individual participant data meta-analysis to examine interactions between treatment effect and participant-level covariates: Statistical recommendations for conduct and planning

Richard D. Riley 🗙 Thomas P.A. Debray, David Fisher, Miriam Hattle, Nadine Marlin, Jeroen Hoogland, Francois Gueyffier, Jan A. Staessen, Jiguang Wang, Karel G.M. Moons, Johannes B. Reitsma, Joie Ensor







Individual Participant Data Meta-Analysis

A Handbook for Healthcare Research

STATISTICS IN PRACTICE

What's next?

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Software



- 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



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help metafloat 🗙		5
+	Dialog * Also see * Jump	10 *
help metafloat		î
Title		
metafloat — Routine fo meta-analysis	or estimating covariate interactions and subgroup-specific treatment effects in aggregate data	
<u>Syntax</u>		ľ
metafloat ES seES [<pre>[if] [in] , study(varname) subgroup(varname) [options]</pre>	
where <i>ES seES</i> are varia be based on a Normal di	bles containing effect sizes and standard errors within subgroups within studies. Effect sizes must istribution; for example, log odds-ratios rather than odds ratios.	
options	Description	
Required options study(varname) subgroup(varname)	specifies the variable containing the study identifier specifies the variable containing the subgroup identifier	
Heterogeneity covarianc <u>unstr</u> uctured fixed <u>exch</u> angeable <u>randomb</u> eta wscorrzero	<pre>te structures unstructured random effects for both SigmaGamma and SigmaBeta (default) all fixed (common) effects exchangeable structures for both SigmaGamma and SigmaBeta special case of exchangeable with common effect on Gamma (i.e. SigmaGamma = 0) special case of exchangeable with zero within-study covariances for SigmaBeta</pre>	
Heterogeneity covarianc <u>unstr</u> uctured fixed <u>exchangeable</u> <u>randomb</u> eta wscorrzero Other options <u>augvar</u> iance(string)	<pre>se structures unstructured random effects for both SigmaGamma and SigmaBeta (default) all fixed (common) effects exchangeable structures for both SigmaGamma and SigmaBeta special case of exchangeable with common effect on Gamma (i.e. SigmaGamma = 0) special case of exchangeable with zero within-study covariances for SigmaBeta specify the augmentation variance for missing/imprecise observations</pre>	
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Conclusions

- Subgroup analyses are important in trials & meta-analysis to work out whether effects of treatments do vary \rightarrow 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 \rightarrow 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







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Prostate Cancer Foundation Curing Together.





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Are there any questions?

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Research Synthesis Methods

RESEARCH ARTICLE 🔂 Open Access

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

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











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Appendix slides



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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

$$\widehat{\boldsymbol{\beta}}_{SS} = \begin{bmatrix} \widehat{\beta}_{1SS} \\ \vdots \end{bmatrix} \quad \widehat{\gamma}_{2SS} = \begin{bmatrix} \vdots - \widehat{\beta}_{1SS} \end{bmatrix} = ne$$

 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)

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

- Similar approach to that used in network meta-analysis
- Important to check that alternative values of the assigned variance give nearidentical results
- 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

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Research

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



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





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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

SOC vs SOC+AAP

Subgroup	SOC-only Dths/N	SOC+AAP Dths/N	Interaction <i>P</i> -value						Haz. ratio (95% Cl)
Born on a:									
Sunday	36/144	29/148						+	0.68 (0.41, 1.12)
Monday	32/128	15/122	0.33	\leftarrow	+		-		0.37 (0.19, 0.73)
Tuesday	46/141	26/144			+	-	_		0.45 (0.28, 0.74)
Wednesday	33/132	26/135				•			0.50 (0.29, 0.86)
Thursday	40/137	25/127						<u> </u>	0.69 (0.42, 1.15)
Friday	34/135	34/153				÷	•	<u> </u>	0.95 (0.58, 1.54)
Saturday	41/140	29/131			_	-		-	0.69 (0.42, 1.14)
Diagnosed on a:									
Monday*	38/176	40/167	0.0021					\rightarrow	1.24 (0.78, 1.97)
Other day	224/781	144/793			-				0.55 (0.44, 0.68)
Overall						\langle	>		0.63 (0.52, 0.76)
			C).2	0.4	0.6	0.8	1 1.2 1.4	
					Favours: abi	raterone)	SOC-only	

Annals of Oncology

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

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