

Accumulation Bias in meta-analysis

How to handle it ALL-IN
(and maybe subjective Bayesian)

Judith ter Schure
CWI, Machine Learning group

What's to come

Accumulation Bias

- The assumption of random sampling in a typical meta-analysis
- The assumption of fixed-series-size in a typical meta-analysis

Handling it ALL-IN

- Taking a random approach to series size
- Martingales

Empirical evidence for Accumulation Bias

What's to come

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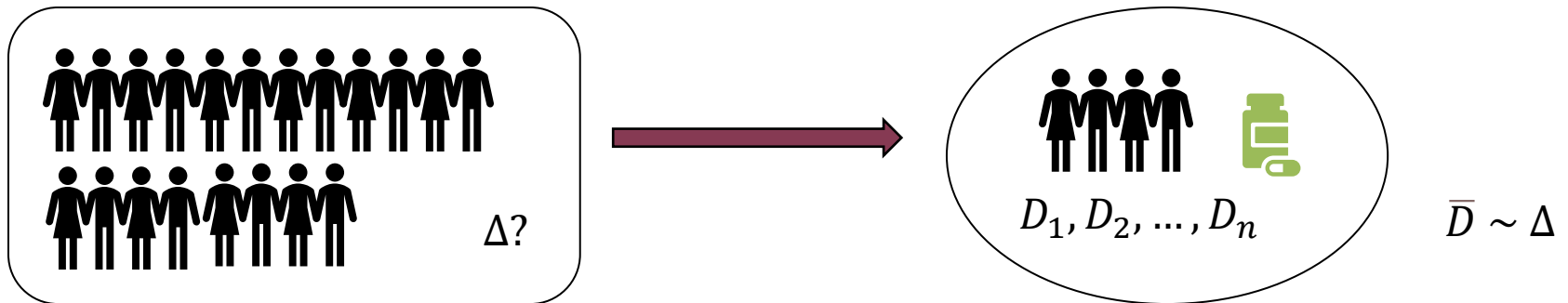
Empirical evidence for Accumulation Bias

(maybe) Handling it subjective Bayesian

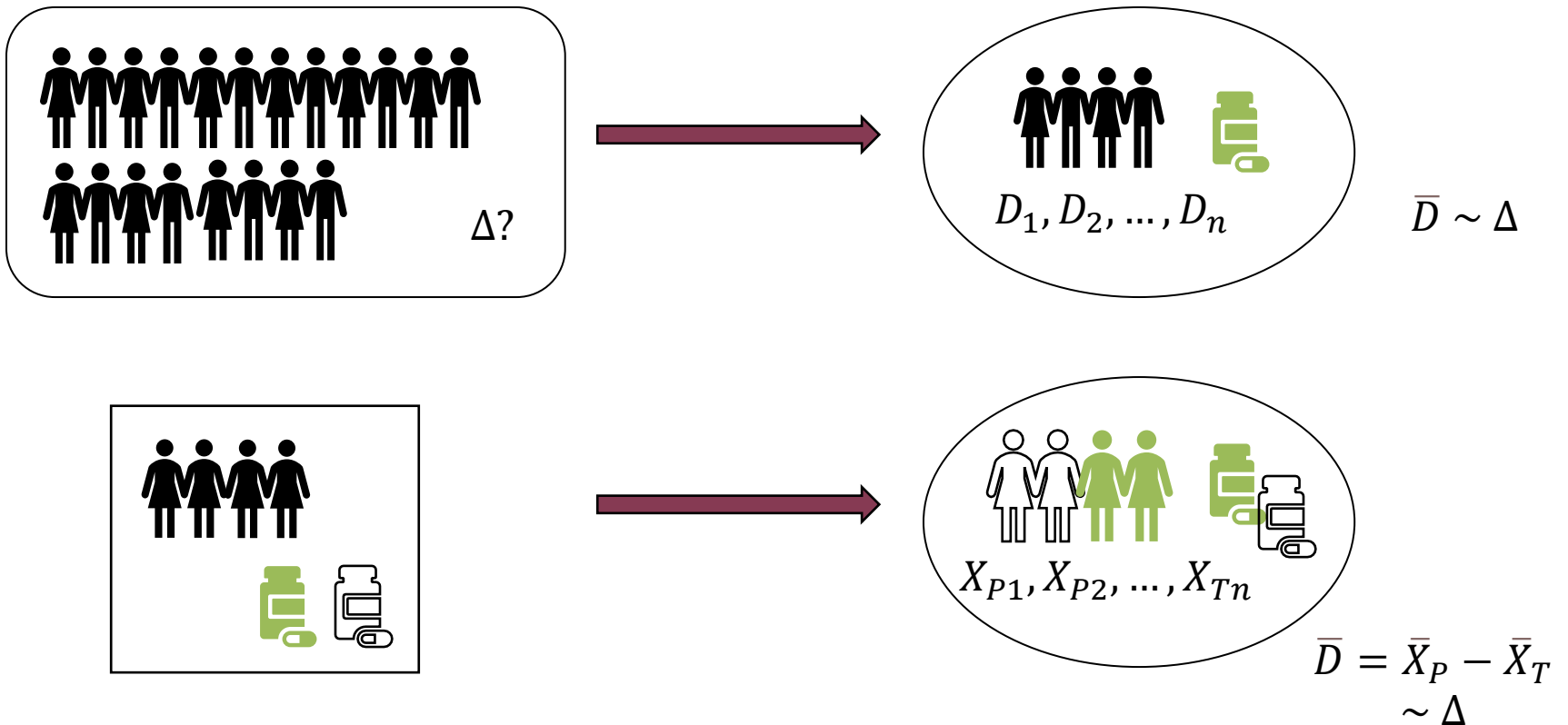
- Mixing a fixed-series-size approach with a prior

Random sampling in science

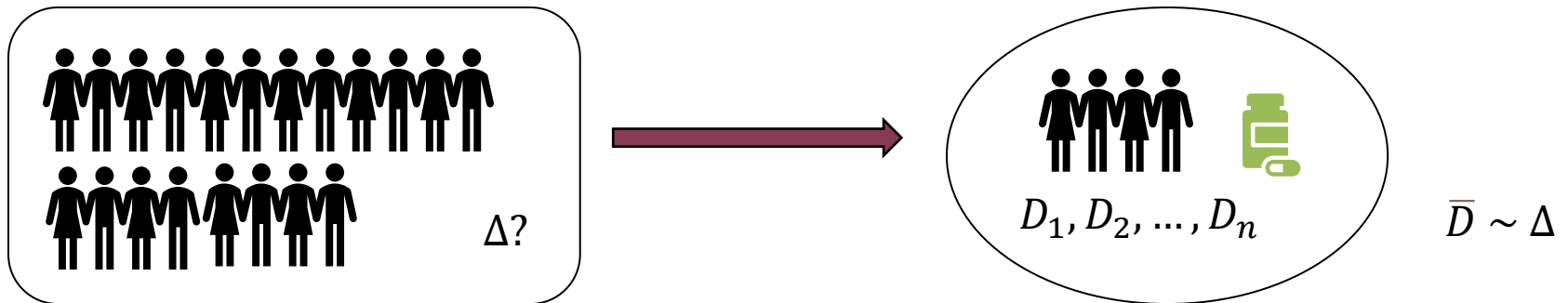
Random sampling of participants



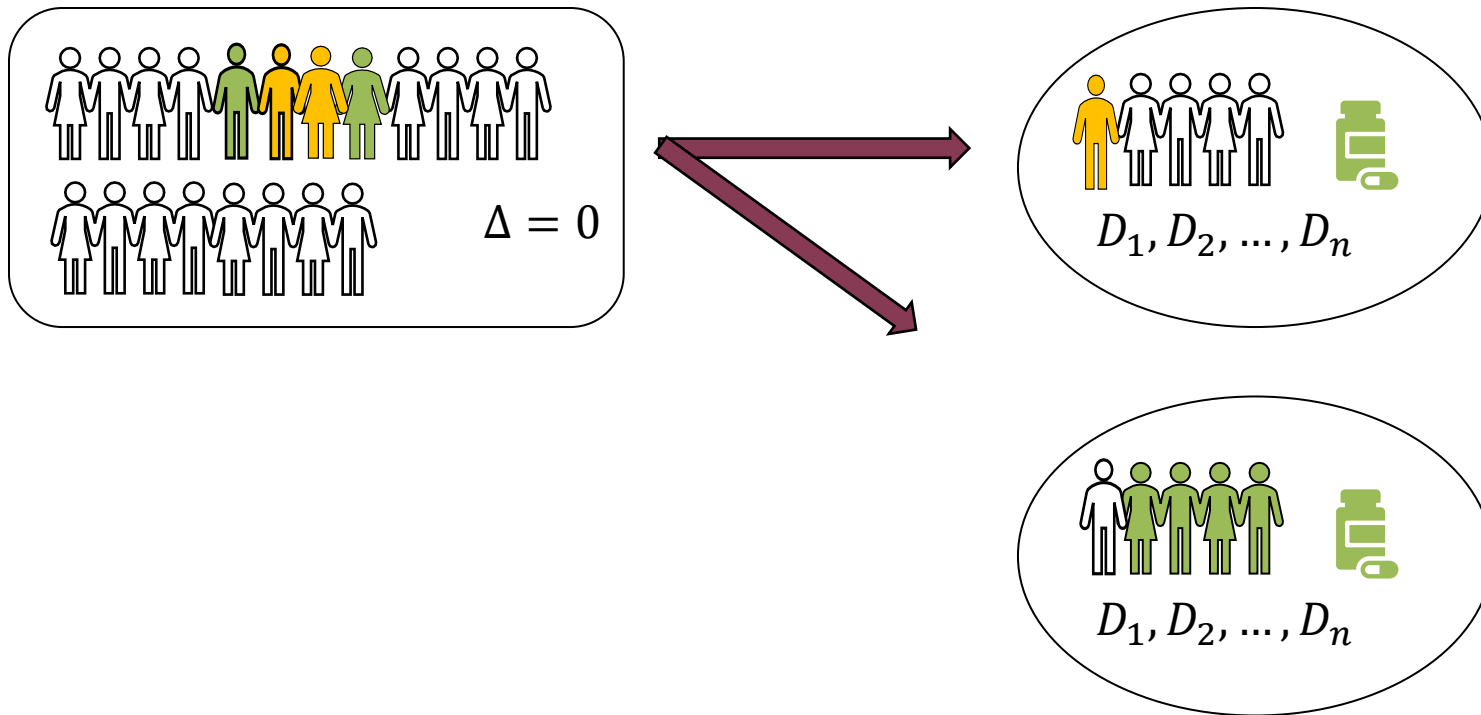
Random sampling of participants



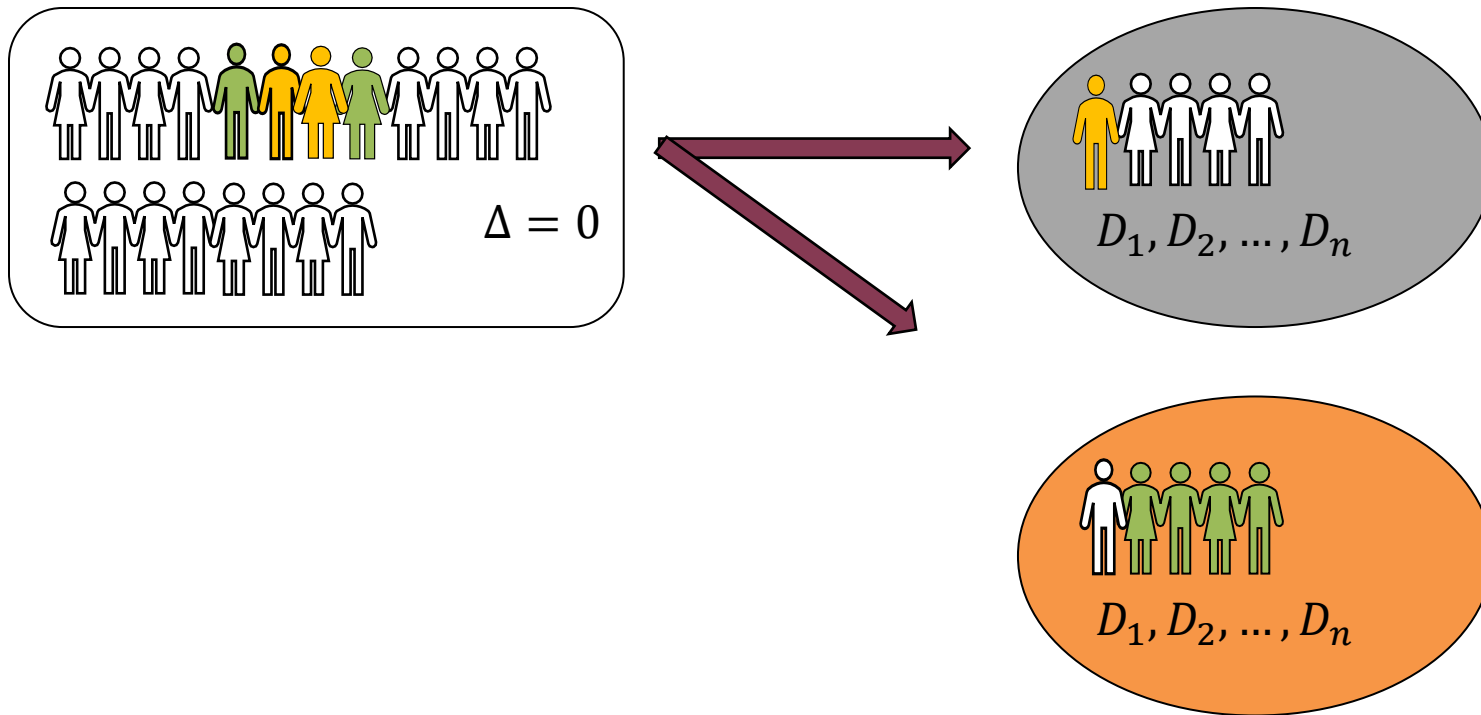
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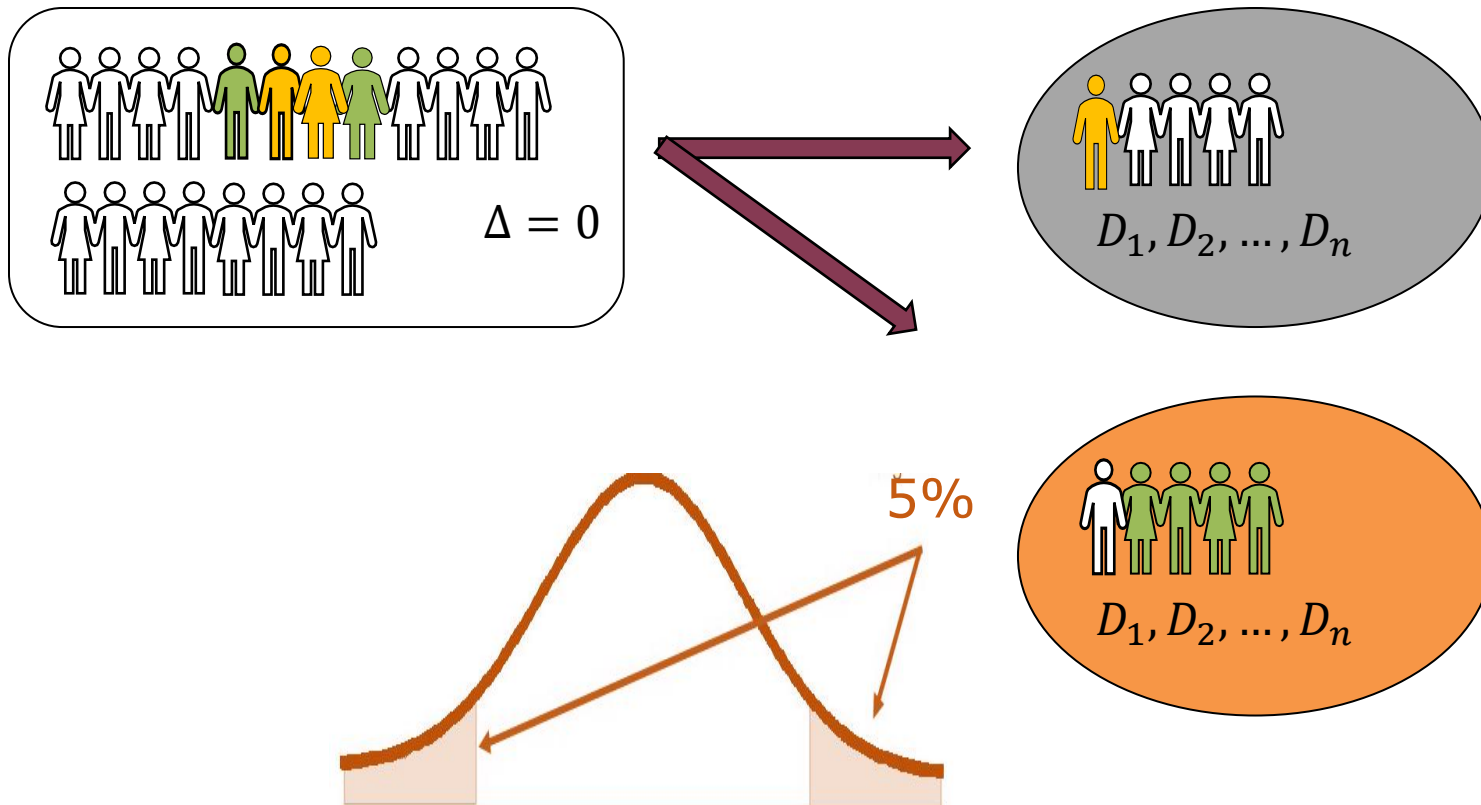
Random sampling of participants



Random sampling of participants

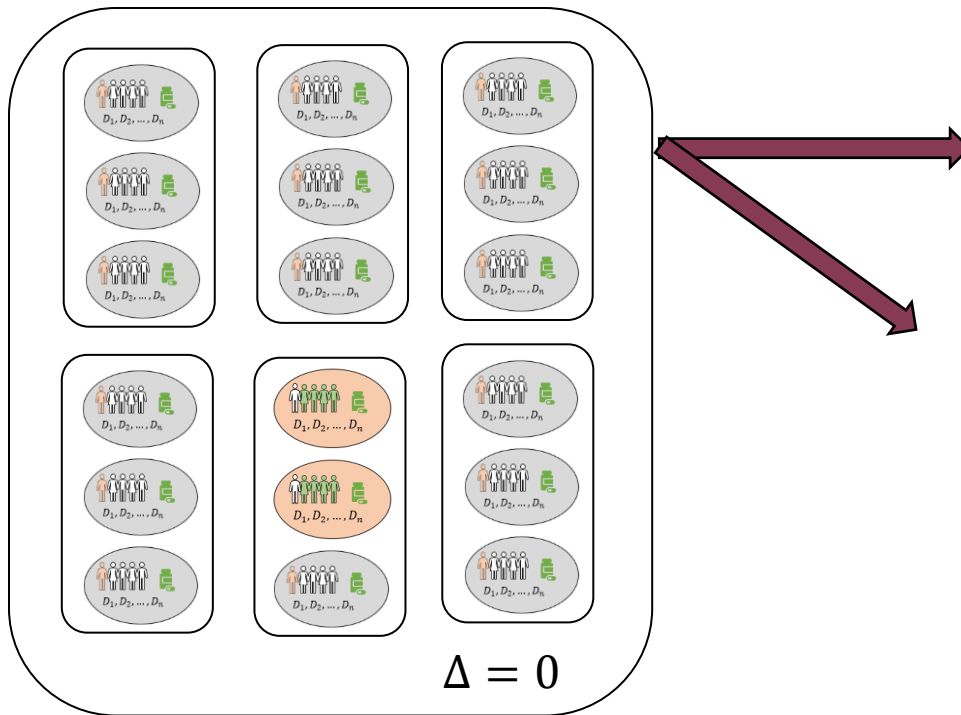


Random sampling of participants

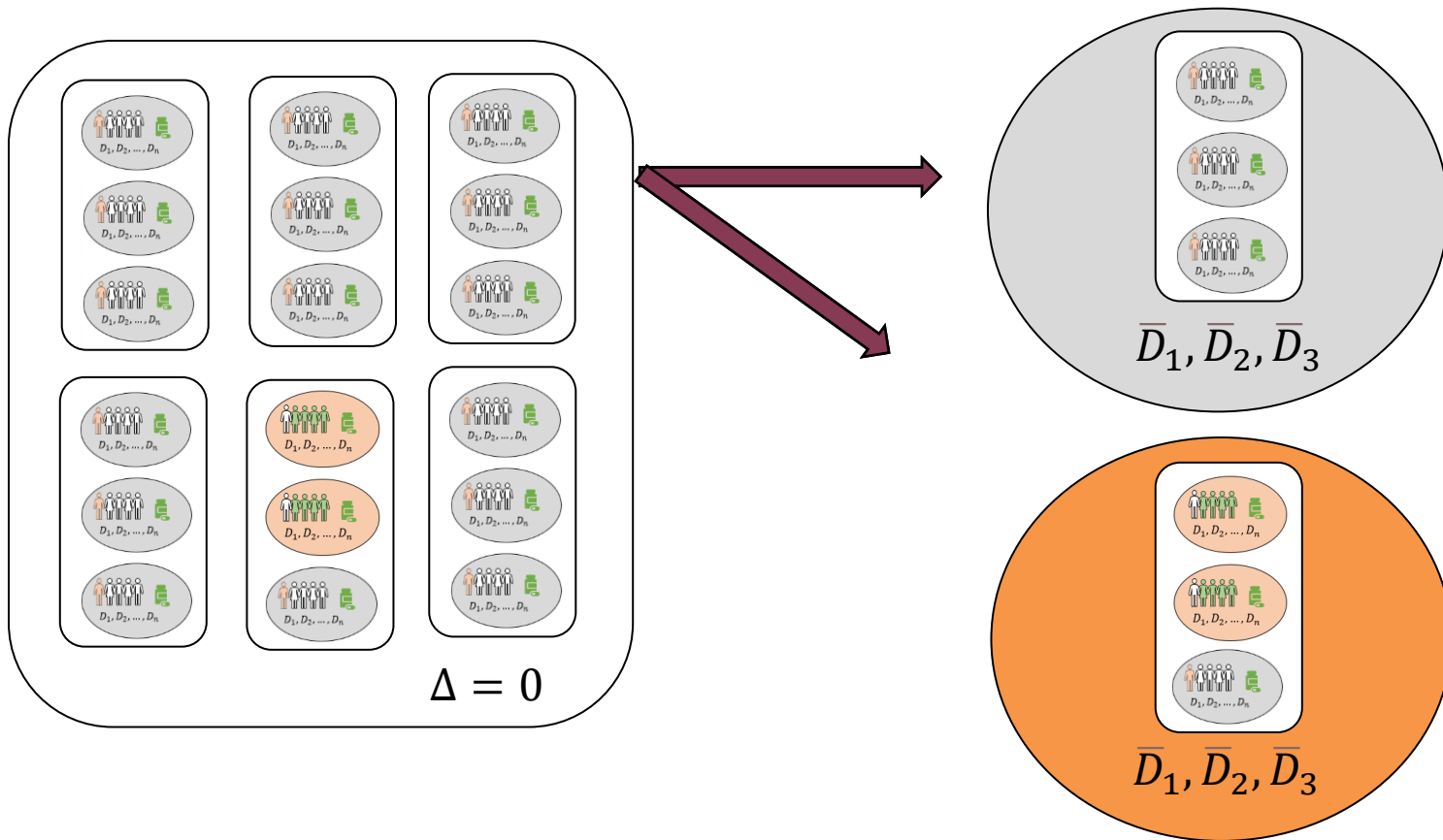


Random sampling of study series

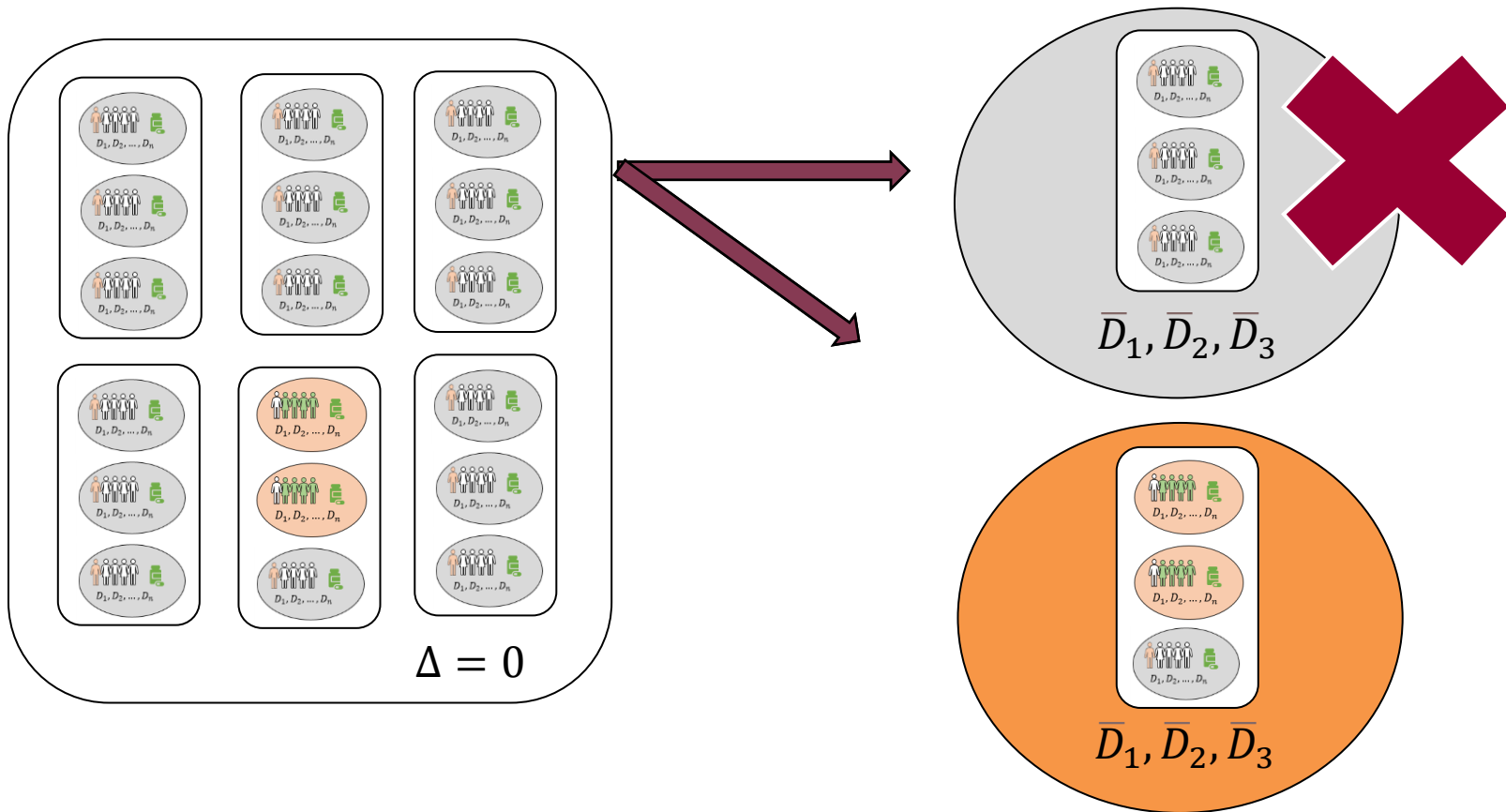
Random sampling of study series



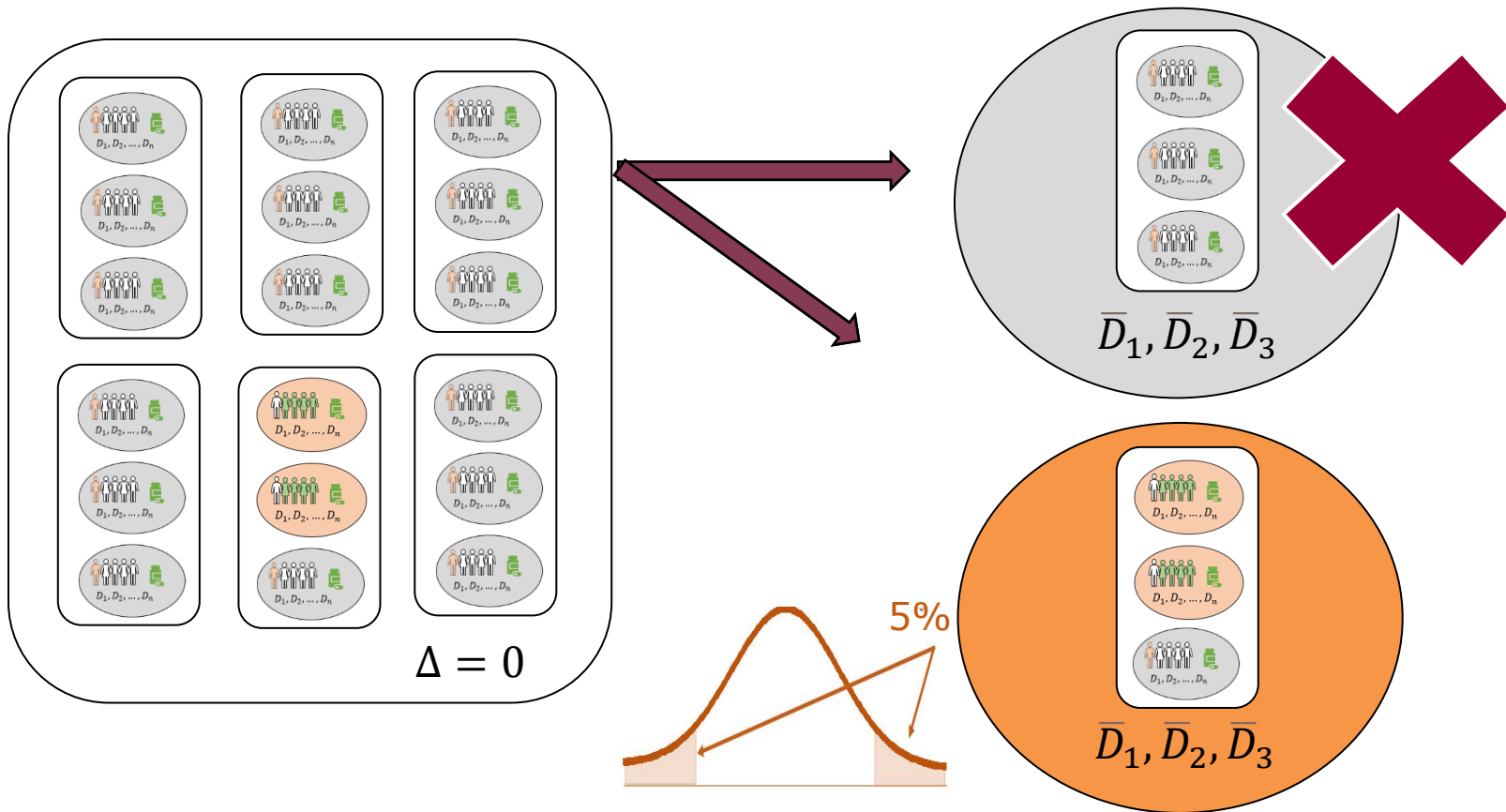
Random sampling of study series



Random sampling of study series



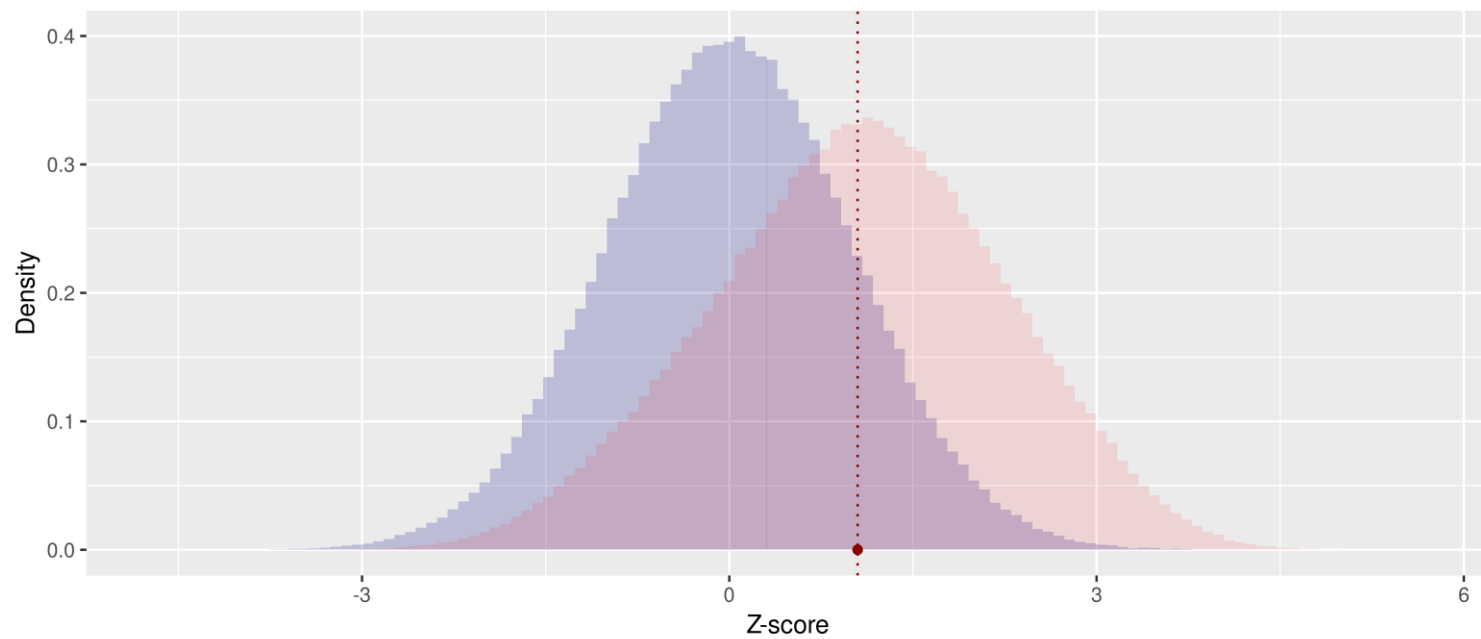
Random sampling of study series



Accumulation Bias arises if

whether or not a series of studies accumulates
is dependent on the results within

Accumulation Bias



Questions?

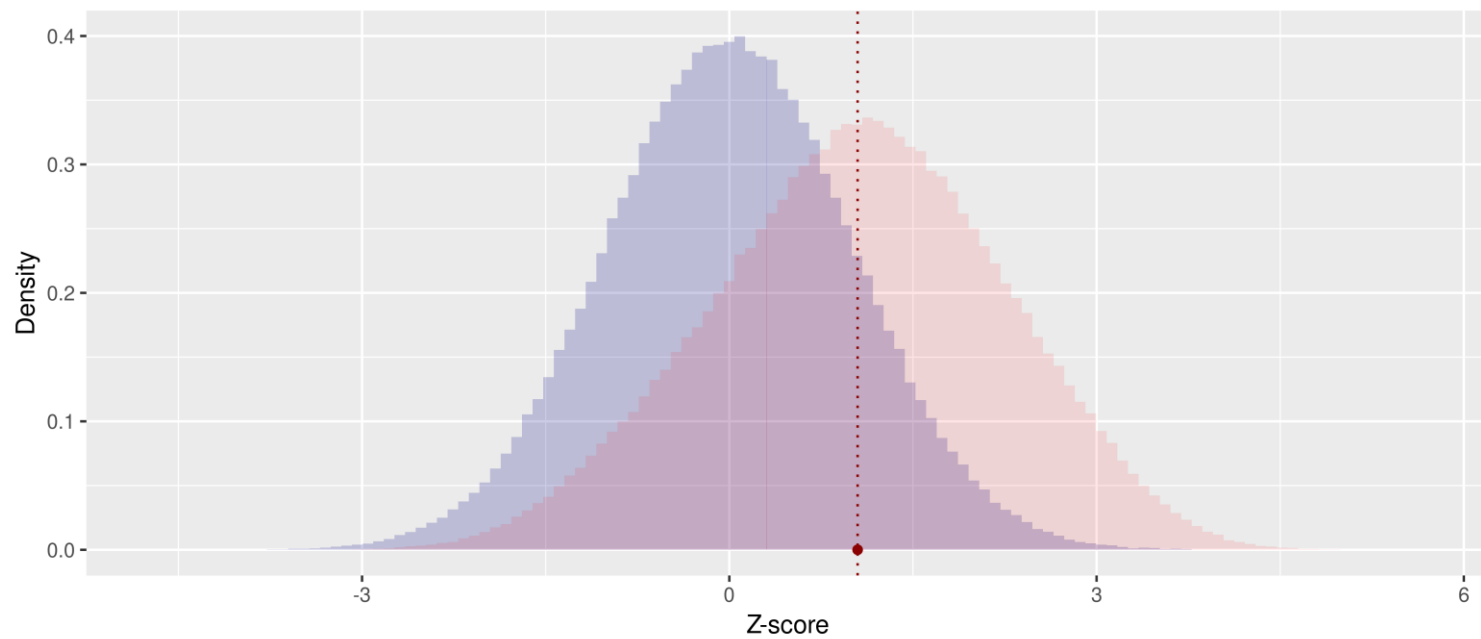
Questions?

1. Why do you think statisticians argue against meta-analyzing **replication studies** with their **original studies**?
2. How does **accumulation bias** relate to **publication bias**?

Accumulation Bias arises if

whether or not a series of studies accumulates
is dependent on the results within

Accumulation Bias



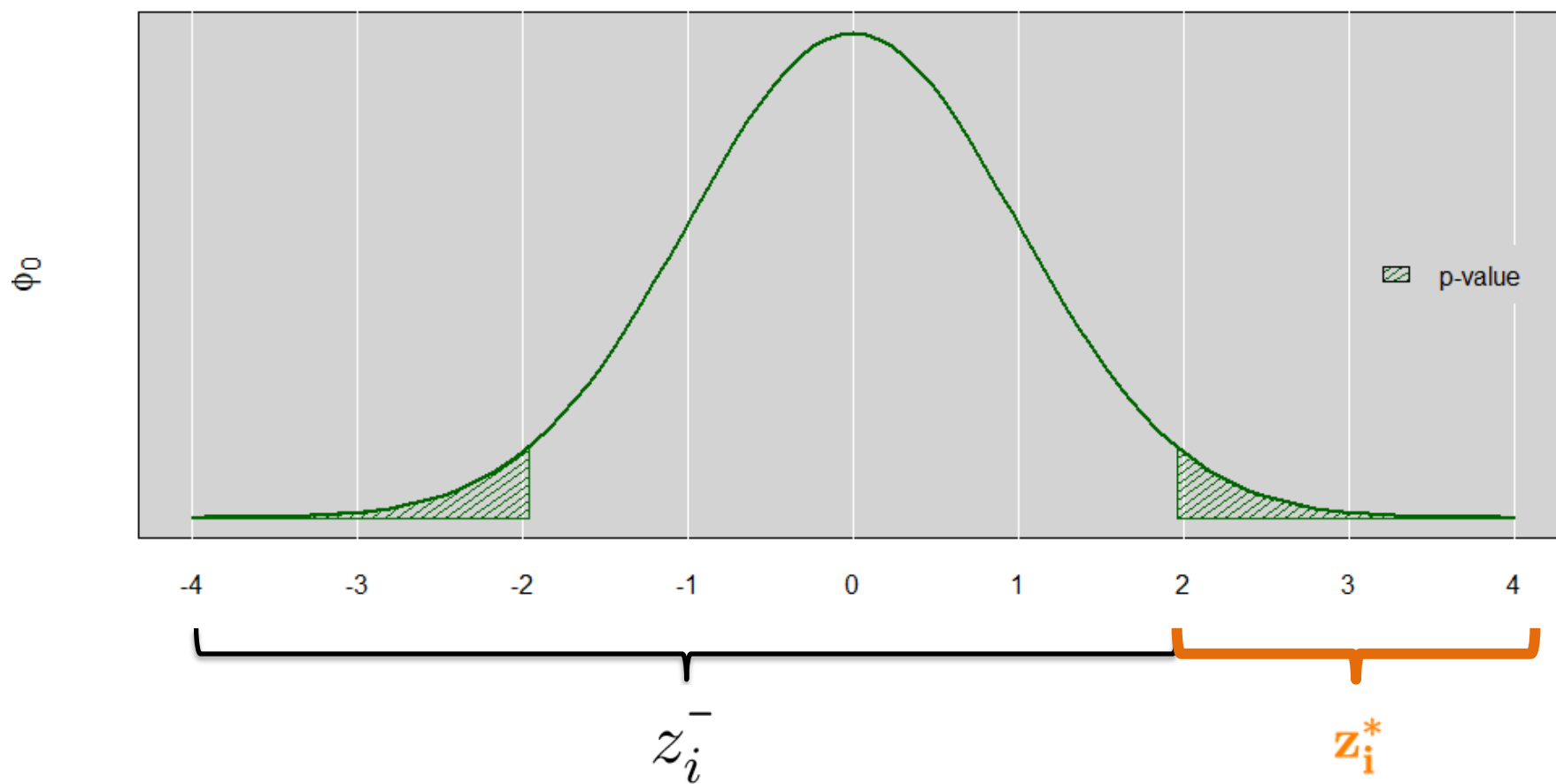
Accumulation Bias framework

$$A(t)$$

Gold Rush example

$$z_1, z_2, z_3, \dots, z_t$$

Gold Rush example



Gold Rush example

$$z_1, z_2, z_3, \dots, z_t$$

Gold Rush example

$$z_1, z_2, z_3, \dots, z_t$$

$$A(t \mid z_1, \dots, z_{t-1}) = \begin{cases} 1, & \text{if } t = 1 \quad \text{or} \quad \text{for all } i < t : z_i = \mathbf{z_i^*}. \\ 0, & \text{otherwise.} \end{cases}$$

Gold Rush example

$$z_1^-$$

$$z_1^*$$

$$z_1^*, z_2^-$$

$$z_1^*, z_2^*$$

$$z_1^*, z_2^*, z_3^-$$

$$z_1^*, z_2^*, z_3^*$$

Gold Rush example

$$z_1^- \rightarrow z^{(1)}$$

$$\mathbf{z}_1^* \rightarrow z^{(1)}$$

$$\mathbf{z}_1^*, z_2^- \rightarrow z^{(2)}$$

$$\mathbf{z}_1^*, \mathbf{z}_2^* \rightarrow z^{(2)}$$

$$\mathbf{z}_1^*, \mathbf{z}_2^*, z_3^- \rightarrow z^{(3)}$$

$$\mathbf{z}_1^*, \mathbf{z}_2^*, \mathbf{z}_3^* \rightarrow z^{(3)}$$

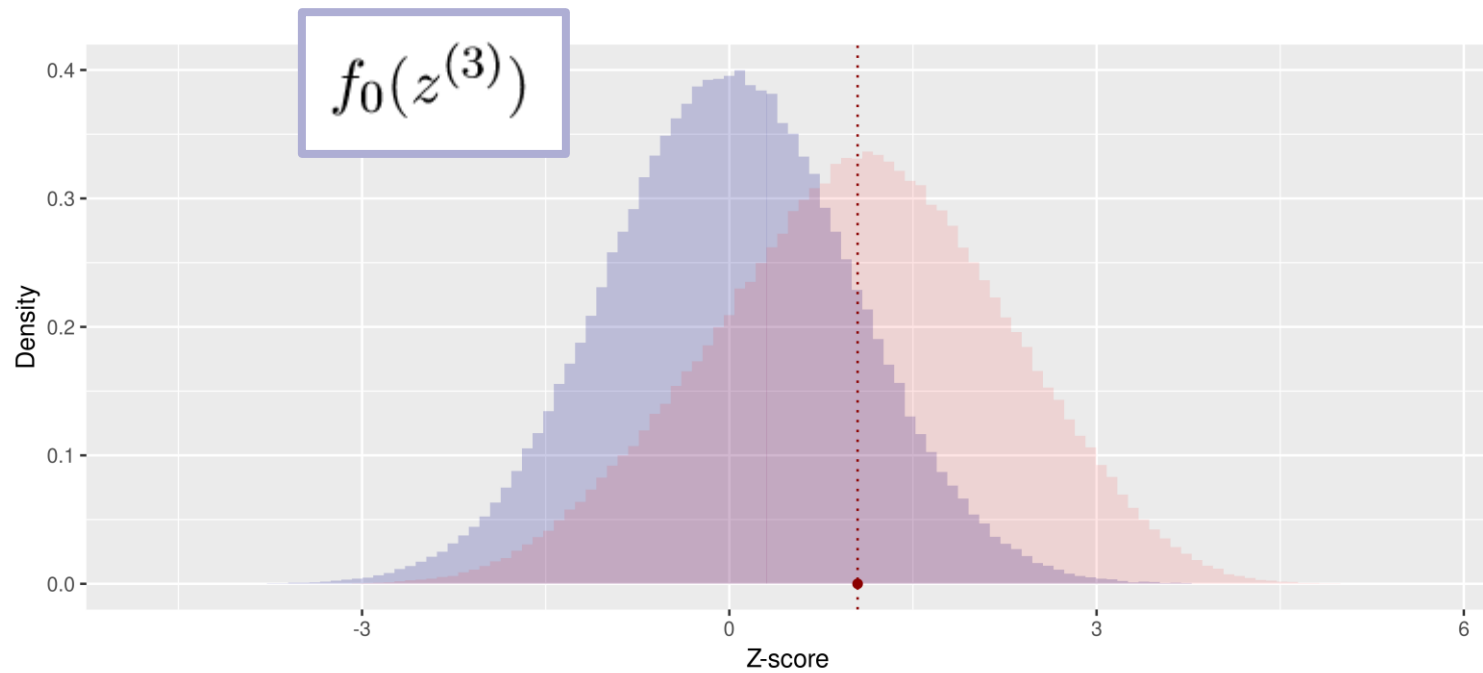
Gold Rush example

$$\begin{array}{lcl}
 z_1^- & & \\
 z_1^* & & \\
 z_1^*, z_2^- & & \\
 z_1^*, z_2^* & & \\
 z_1^*, z_2^*, z_3^- & \rightarrow & z^{(3)} \\
 z_1^*, z_2^*, z_3^* & \rightarrow & z^{(3)}
 \end{array}
 \quad T \geq 3$$

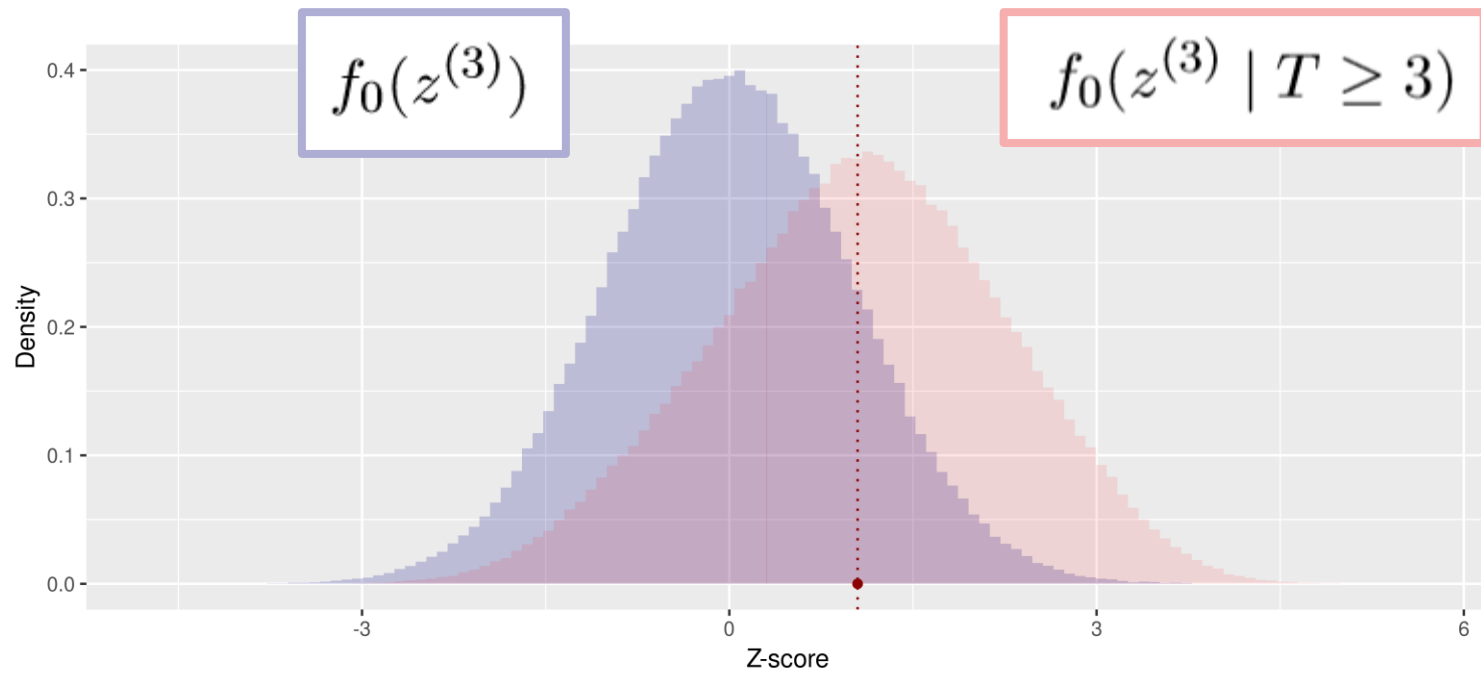
Accumulation Bias



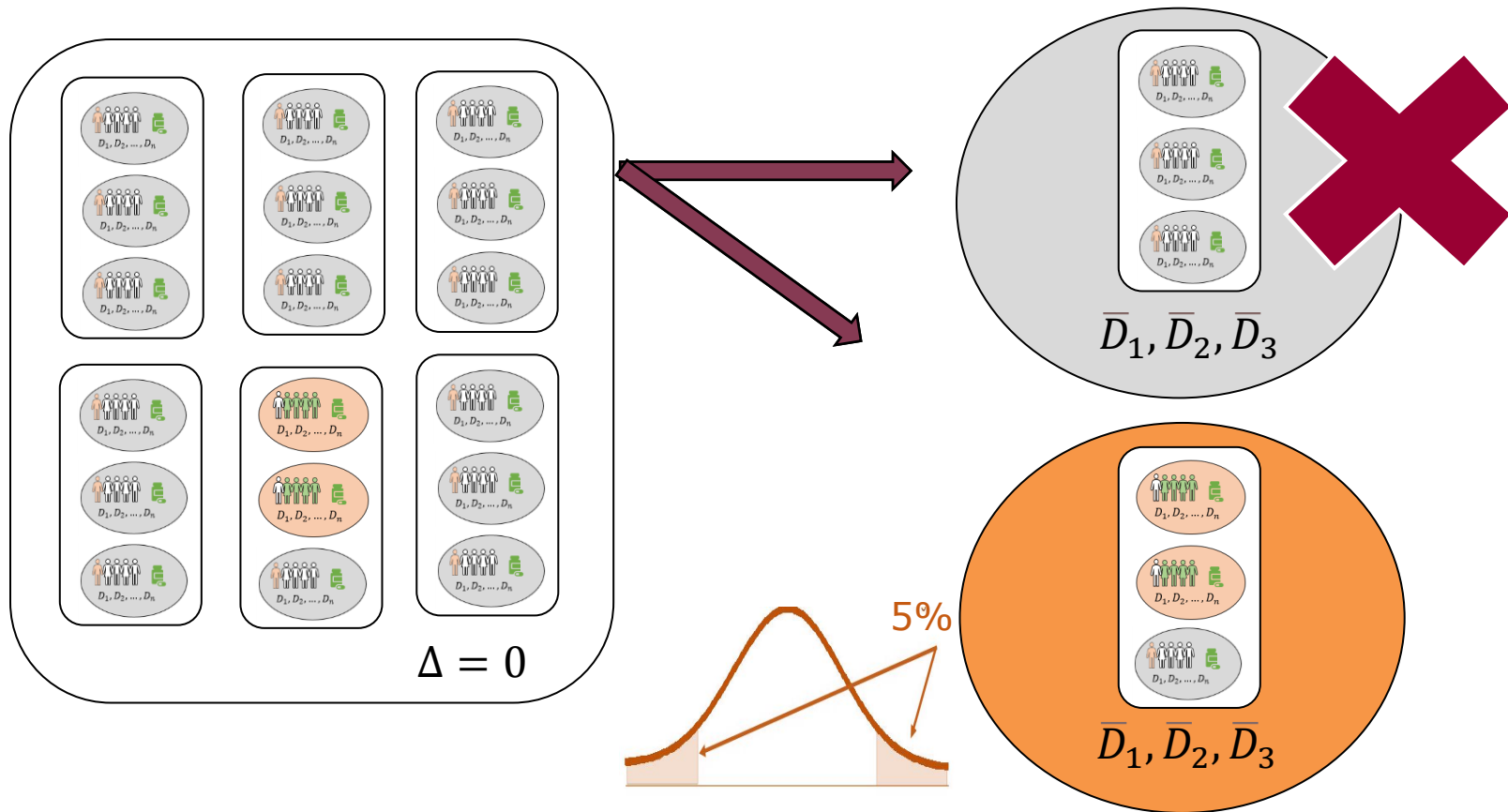
Accumulation Bias



Accumulation Bias



Random sampling of study series of fixed size



A typical meta-analysis is a

conditional analysis:

given the available number of studies

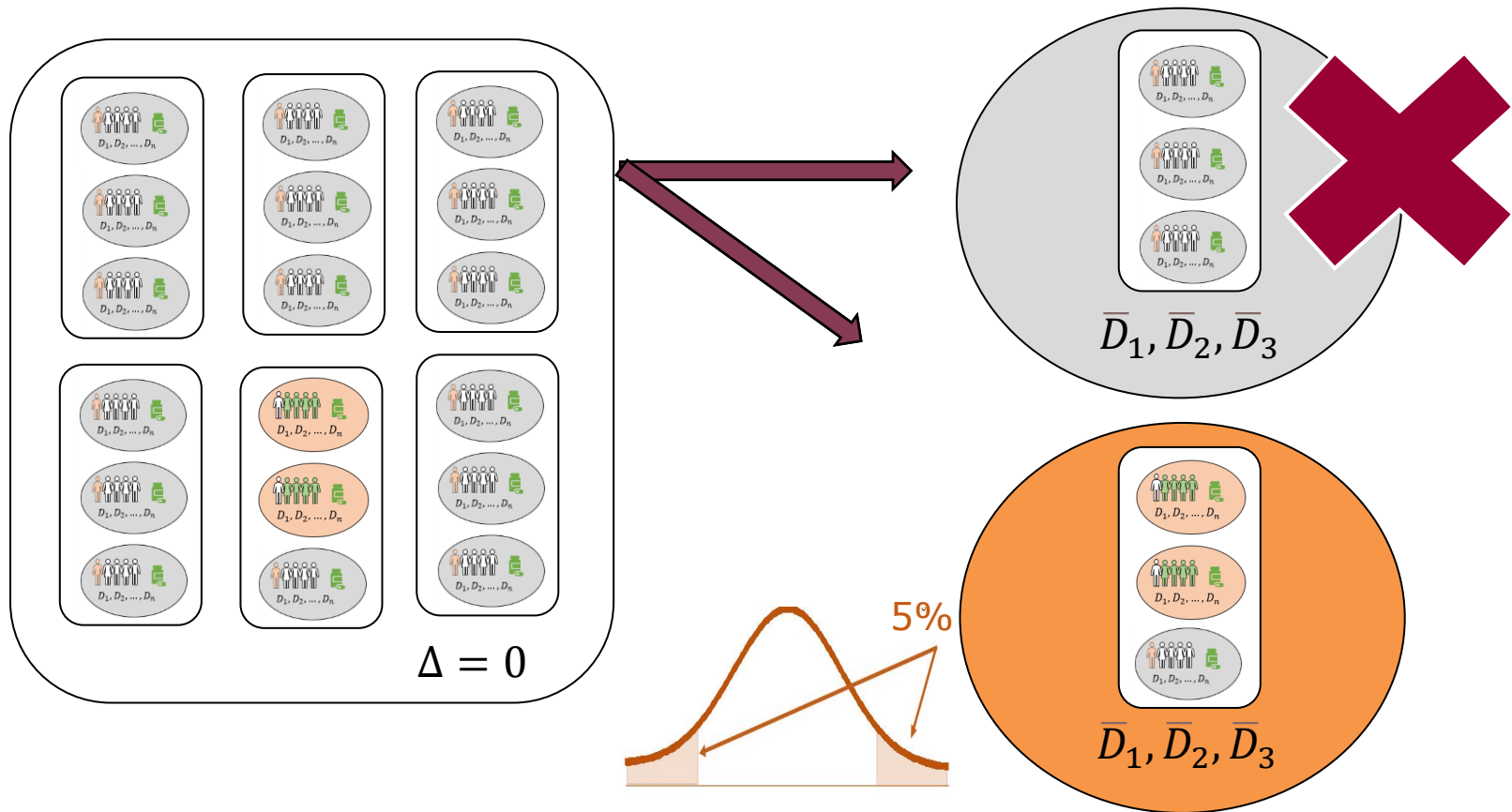
Accumulation Bias **invalidates**

the assumed conditional sampling distribution

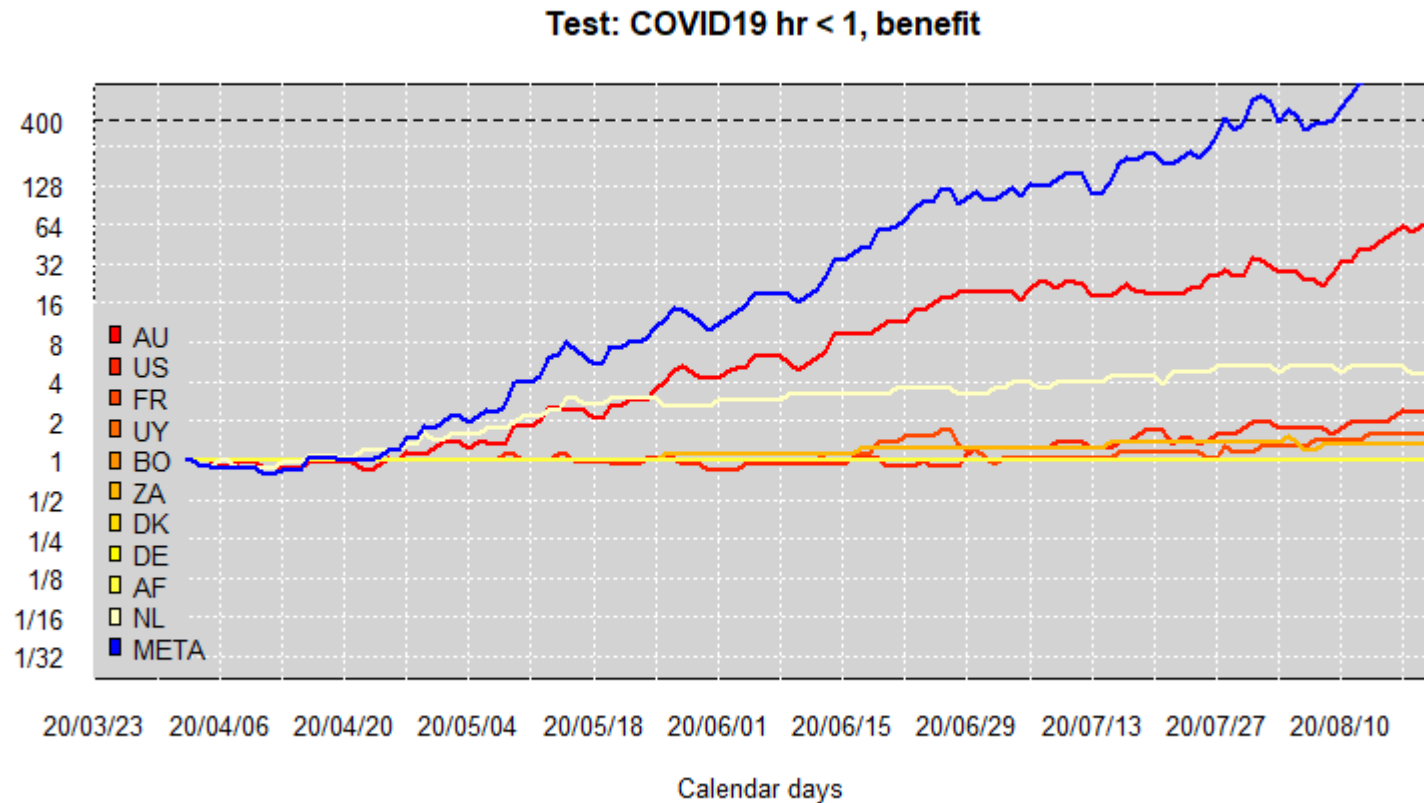
inflating type-I errors

Questions?

Random sampling of study series of fixed size



ALL-IN meta-analysis



ALL-IN meta-analysis

Anytime

Live and

Leading

INTERim meta-analysis

ALL-IN meta-analysis is an

unconditional analysis:

assuming random number of studies

Gold Rush example

$$z_1^-$$

$$z_1^*$$

$$z_1^*, z_2^-$$

$$z_1^*, z_2^*$$

$$z_1^*, z_2^*, z_3^- \rightarrow z^{(3)}$$

$$z_1^*, z_2^*, z_3^* \rightarrow z^{(3)}$$

$$T \geq 3$$

Gold Rush example

$$z_1^- \rightarrow z^{(1)}$$

$$\mathbf{z}_1^* \rightarrow z^{(1)}$$

$$\mathbf{z}_1^*, z_2^- \rightarrow z^{(2)}$$

$$\mathbf{z}_1^*, \mathbf{z}_2^* \rightarrow z^{(2)}$$

$$\mathbf{z}_1^*, \mathbf{z}_2^*, z_3^- \rightarrow z^{(3)}$$

$$\mathbf{z}_1^*, \mathbf{z}_2^*, \mathbf{z}_3^* \rightarrow z^{(3)}$$

Gold Rush example

$$\begin{array}{ll}
 z_1^- & \rightarrow z^{(1)} \\
 \cancel{z_1^*} & \rightarrow z^{(1)} \\
 z_1^*, z_2^- & \rightarrow z^{(2)} \\
 \cancel{z_1^*}, z_2^* & \rightarrow z^{(2)} \\
 z_1^*, z_2^*, z_3^- & \rightarrow z^{(3)} \\
 z_1^*, z_2^*, z_3^* & \rightarrow z^{(3)}
 \end{array}$$

Gold Rush example

ALL-IN solution

t		$*$
1	z_1^-	0
2	z_1^*, z_2^-	1
3	z_1^*, z_2^*, z_3^-	2
3	z_1^*, z_2^*, z_3^*	3
Σ		

Gold Rush example

ALL-IN solution

t		*
1	z_1^-	0
2	z_1^*, z_2^-	1
3	z_1^*, z_2^*, z_3^-	2
3	z_1^*, z_2^*, z_3^*	3
Σ		

P_0

Gold Rush example

ALL-IN solution

t		*
1	z_1^-	0
2	z_1^*, z_2^-	1
3	z_1^*, z_2^*, z_3^-	2
3	z_1^*, z_2^*, z_3^*	3
Σ		

$$\frac{P_0}{1 - \alpha}$$

Gold Rush example

ALL-IN solution

t		*
1	z_1^-	0
2	z_1^*, z_2^-	1
3	z_1^*, z_2^*, z_3^-	2
3	z_1^*, z_2^*, z_3^*	3
Σ		

P_0
$1 - \alpha$
$\alpha(1 - \alpha)$

Gold Rush example

ALL-IN solution

t		*
1	z_1^-	0
2	z_1^*, z_2^-	1
3	z_1^*, z_2^*, z_3^-	2
3	z_1^*, z_2^*, z_3^*	3
Σ		

P_0
$1 - \alpha$
$\alpha(1 - \alpha)$
$\alpha^2(1 - \alpha)$

Gold Rush example

ALL-IN solution

t		*
1	z_1^-	0
2	z_1^*, z_2^-	1
3	z_1^*, z_2^*, z_3^-	2
3	z_1^*, z_2^*, z_3^*	3
Σ		

P_0
$1 - \alpha$
$\alpha(1 - \alpha)$
$\alpha^2(1 - \alpha)$
α^3
1

Gold Rush example

ALL-IN solution

t		*
1	z_1^-	0
2	z_1^*, z_2^-	1
3	z_1^*, z_2^*, z_3^-	2
3	z_1^*, z_2^*, z_3^*	3
Σ		

P_0	$* \cdot P_0$
$1 - \alpha$	0
$\alpha(1 - \alpha)$	$\alpha(1 - \alpha)$
$\alpha^2(1 - \alpha)$	$2\alpha^2(1 - \alpha)$
α^3	$3\alpha^3$
1	$\alpha + \alpha^2 + \alpha^3$

Gold Rush example

ALL-IN solution

t		*
1	z_1^-	0
2	z_1^*, z_2^-	1
3	z_1^*, z_2^*, z_3^-	2
3	z_1^*, z_2^*, z_3^*	3
Σ		

P_0	$* \cdot P_0$	$t \cdot P_0$
$1 - \alpha$	0	$1 - \alpha$
$\alpha(1 - \alpha)$	$\alpha(1 - \alpha)$	$2\alpha(1 - \alpha)$
$\alpha^2(1 - \alpha)$	$2\alpha^2(1 - \alpha)$	$3\alpha^2(1 - \alpha)$
α^3	$3\alpha^3$	$3\alpha^3$
1	$\alpha + \alpha^2 + \alpha^3$	$1 + \alpha + \alpha^2$

Gold Rush example

ALL-IN solution

t	*
1	z_1^- 0
2	z_1^*, z_2^- 1
3	z_1^*, z_2^*, z_3^- 2
3	z_1^*, z_2^*, z_3^* 3
Σ	

P_0	$* \cdot P_0$	$t \cdot P_0$
$1 - \alpha$	0	$1 - \alpha$
$\alpha(1 - \alpha)$	$\alpha(1 - \alpha)$	$2\alpha(1 - \alpha)$
$\alpha^2(1 - \alpha)$	$2\alpha^2(1 - \alpha)$	$3\alpha^2(1 - \alpha)$
α^3	$3\alpha^3$	$3\alpha^3$
1	$\alpha + \alpha^2 + \alpha^3$	$1 + \alpha + \alpha^2$

$$\frac{E_0[*]}{E_0[t]} =$$

Gold Rush example

ALL-IN solution

t		*
1	z_1^-	0
2	z_1^*, z_2^-	1
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3	z_1^*, z_2^*, z_3^*	3
Σ		

P_0	$* \cdot P_0$	$t \cdot P_0$
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$\alpha(1 - \alpha)$	$\alpha(1 - \alpha)$	$2\alpha(1 - \alpha)$
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α^3	$3\alpha^3$	$3\alpha^3$
1	$\alpha + \alpha^2 + \alpha^3$	$1 + \alpha + \alpha^2$

$$\frac{E_0[*]}{E_0[t]} = \frac{\alpha(1 + \alpha + \alpha^2)}{1 + \alpha + \alpha^2}$$

Gold Rush example

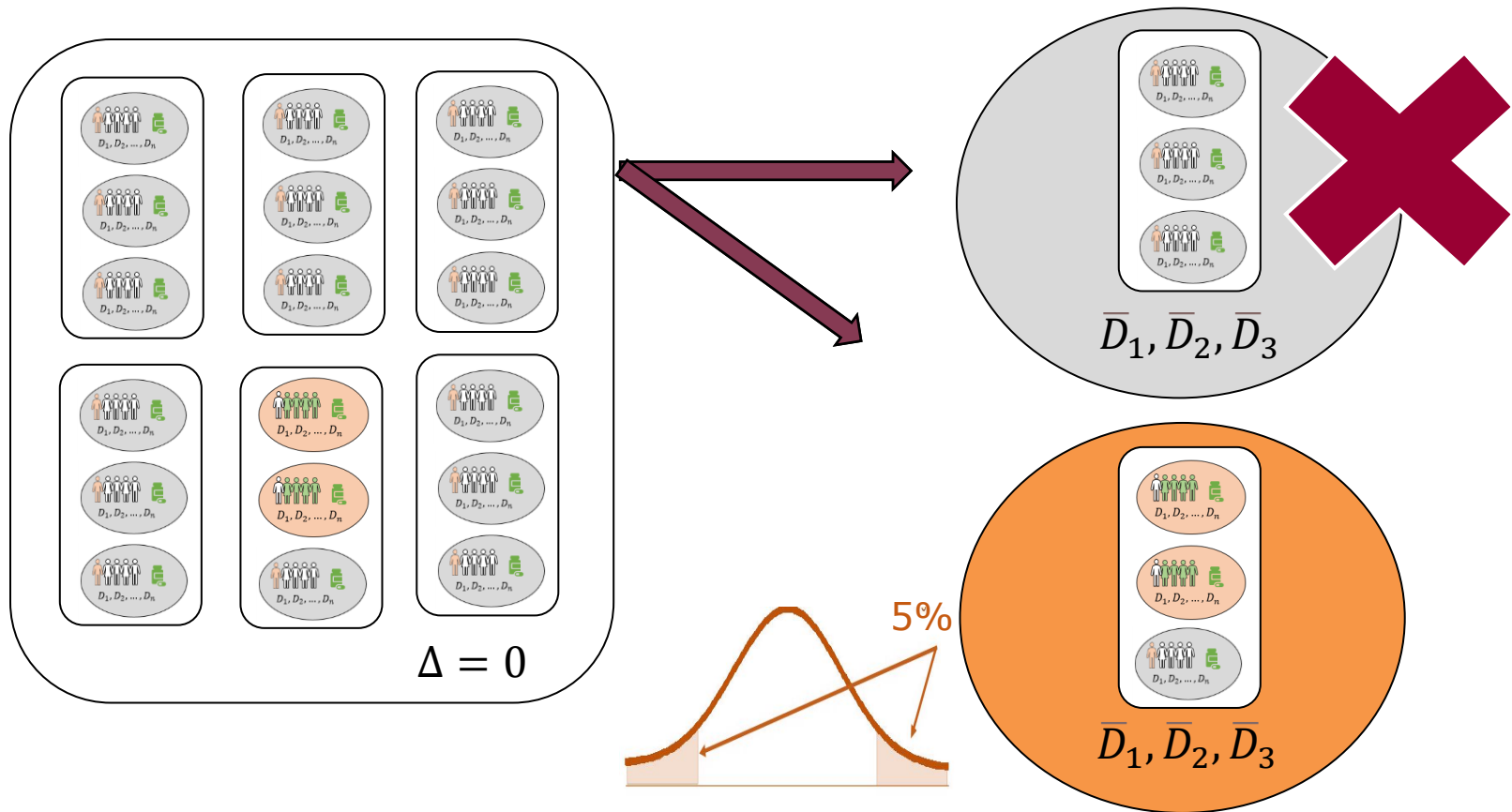
ALL-IN solution

t		*
1	z_1^-	0
2	$\mathbf{z}_1^*, z_2^-$	1
3	$\mathbf{z}_1^*, \mathbf{z}_2^*, z_3^-$	2
3	$\mathbf{z}_1^*, \mathbf{z}_2^*, \mathbf{z}_3^*$	3
Σ		

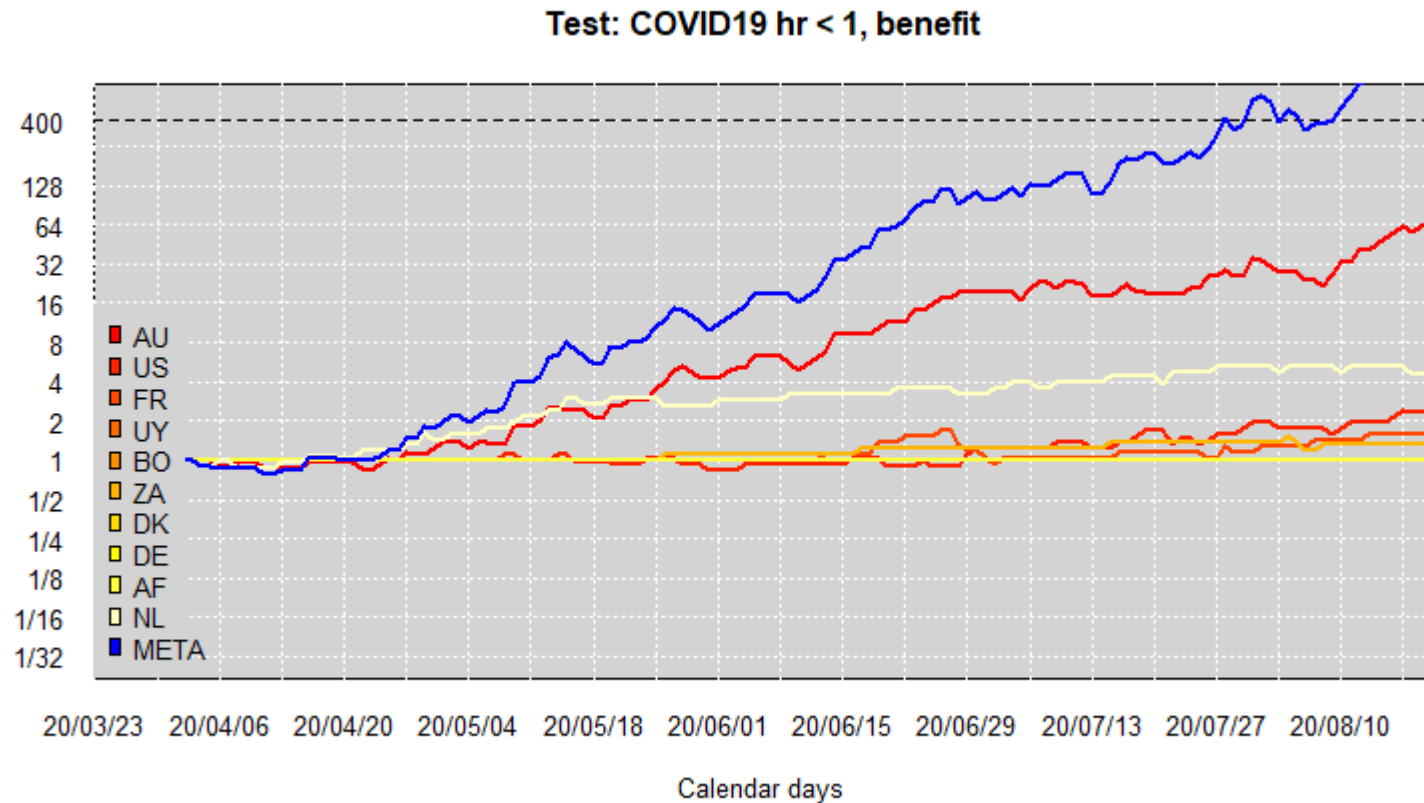
P_0	$* \cdot P_0$	$t \cdot P_0$
$1 - \alpha$	0	$1 - \alpha$
$\alpha(1 - \alpha)$	$\alpha(1 - \alpha)$	$2\alpha(1 - \alpha)$
$\alpha^2(1 - \alpha)$	$2\alpha^2(1 - \alpha)$	$3\alpha^2(1 - \alpha)$
α^3	$3\alpha^3$	$3\alpha^3$
1	$\alpha + \alpha^2 + \alpha^3$	$1 + \alpha + \alpha^2$

$$\frac{\mathbf{E}_0[*]}{\mathbf{E}_0[t]} = \frac{\alpha(1 + \alpha + \alpha^2)}{1 + \alpha + \alpha^2} = \alpha$$

Random sampling of study series of fixed size



ALL-IN meta-analysis



ALL-IN meta-analysis uses

a stochastic process

instead of a probability density function

to control type-I errors

Questions?

A test martingale

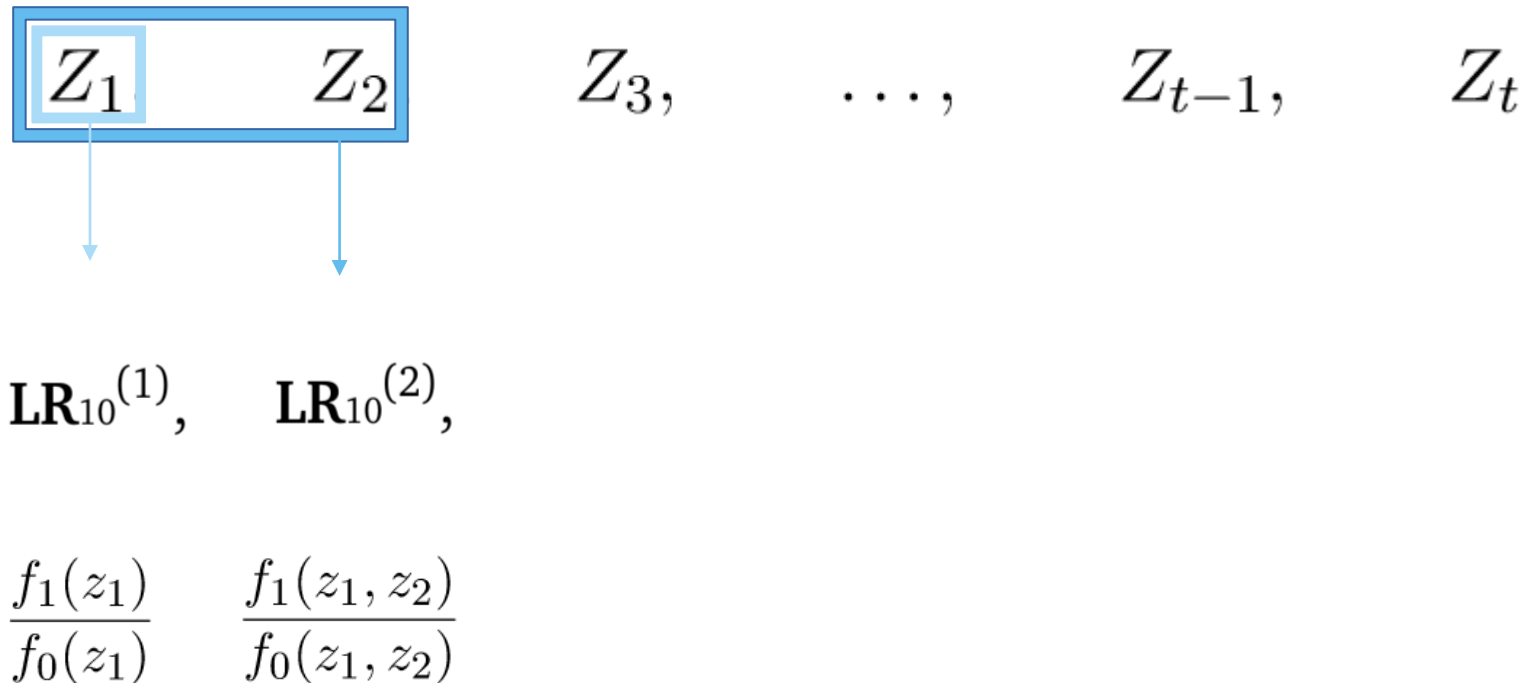
$$Z_1, \quad Z_2, \quad Z_3, \quad \dots, \quad Z_{t-1}, \quad Z_t$$

The likelihood ratio as a test martingale

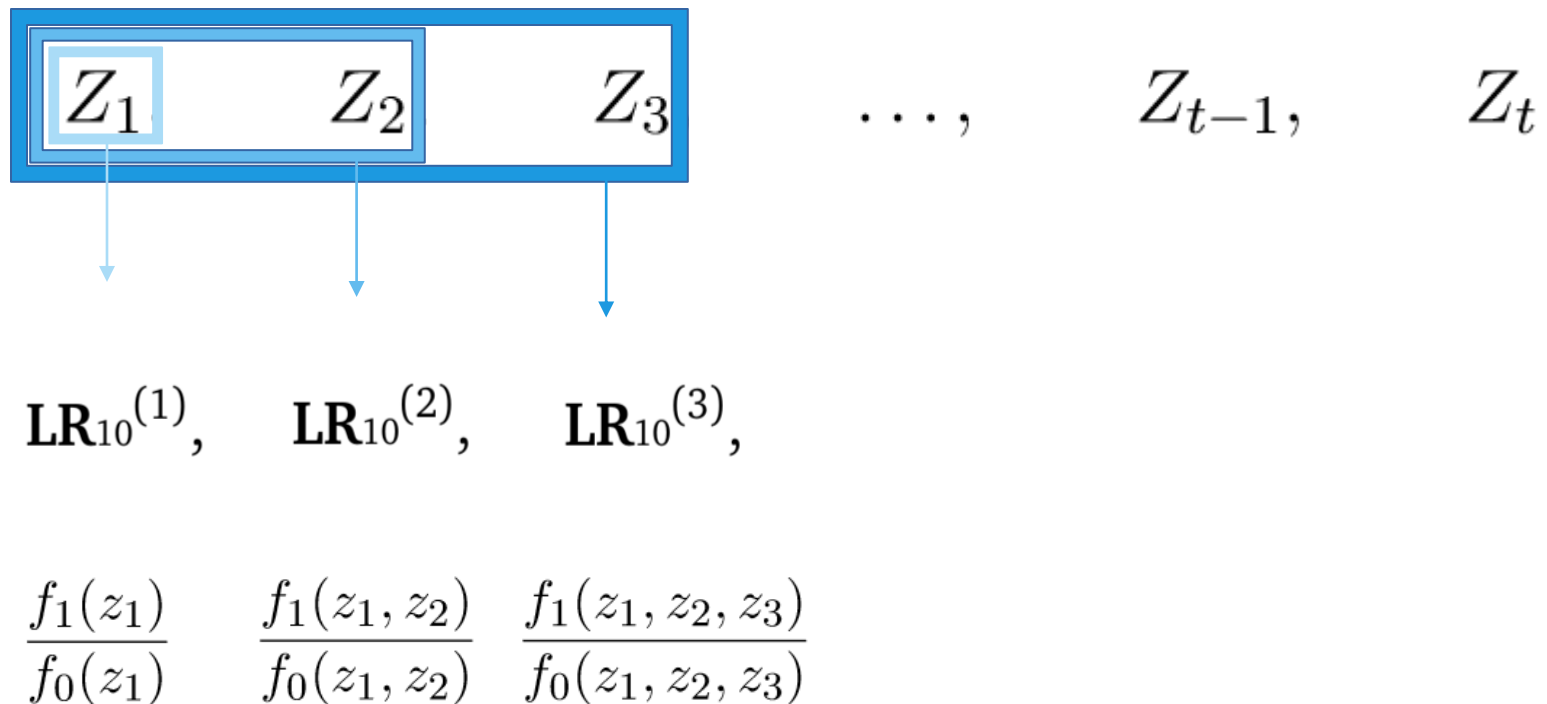
 Z_1  $Z_2,$ $Z_3,$ $\dots,$ $Z_{t-1},$ Z_t $\mathbf{LR}_{10}^{(1)},$

$$\frac{f_1(z_1)}{f_0(z_1)}$$

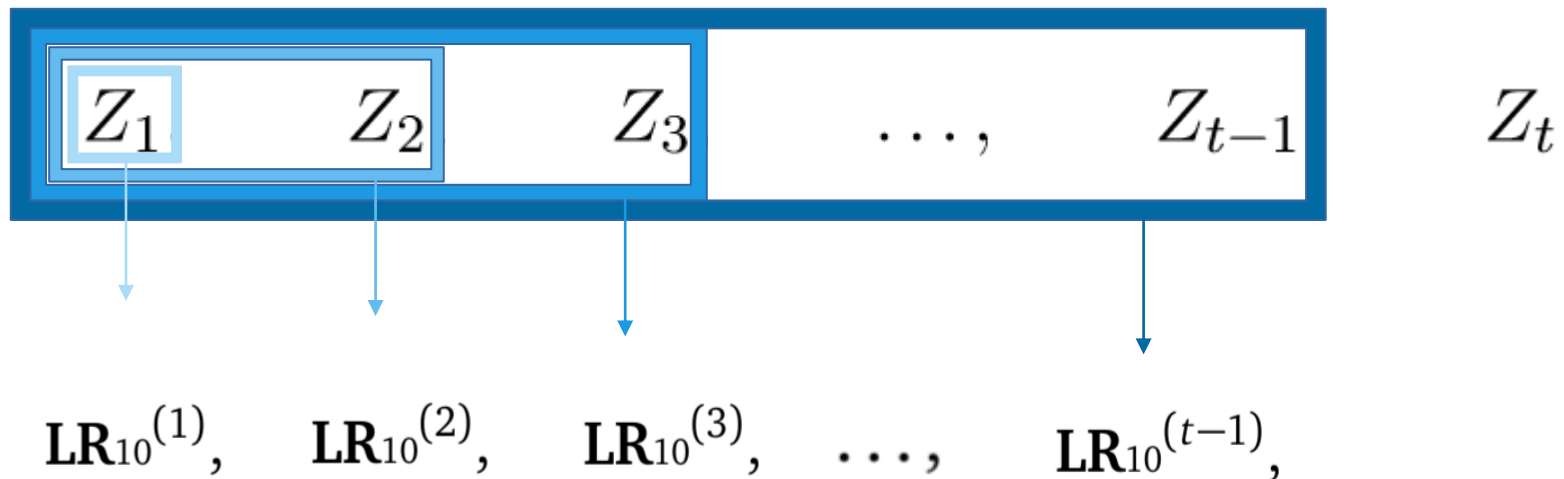
The likelihood ratio as a test martingale



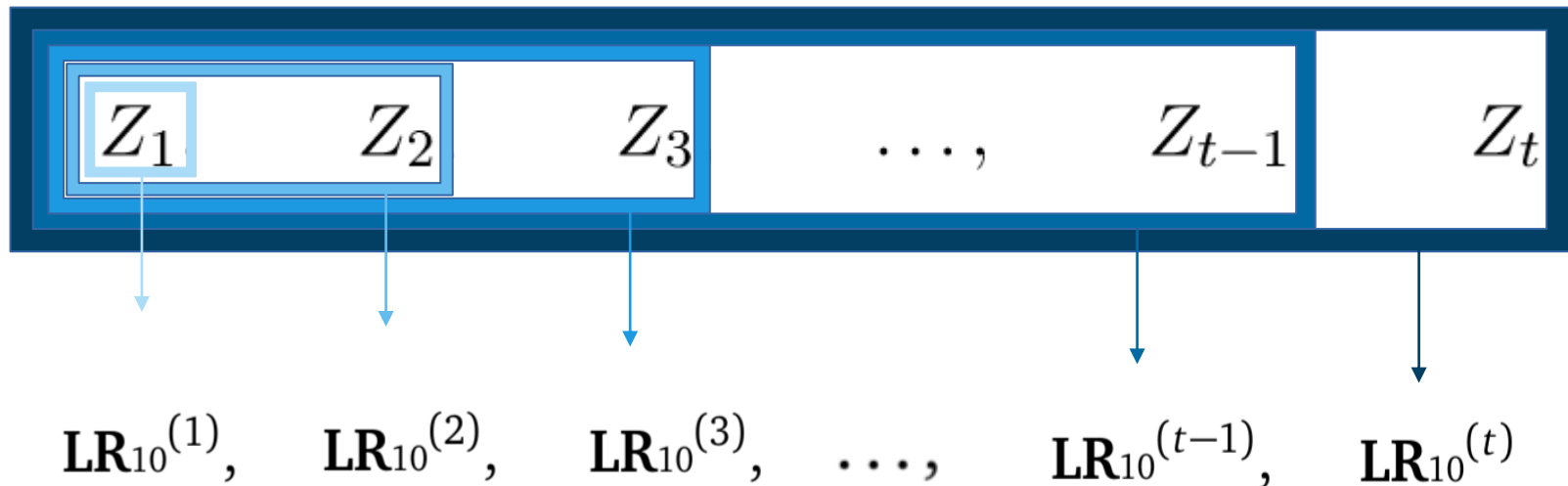
The likelihood ratio as a test martingale



The likelihood ratio as a test martingale



The likelihood ratio as a test martingale



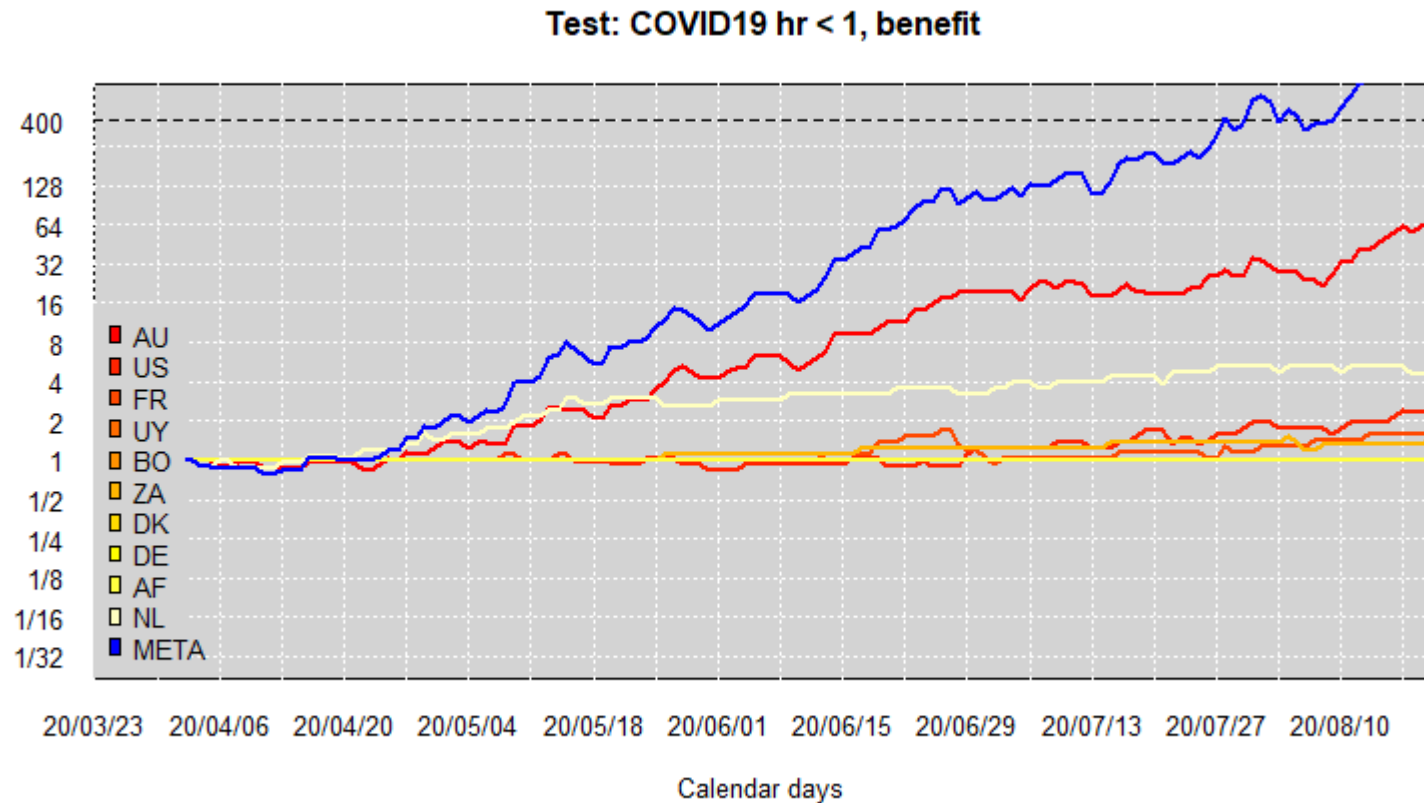
Test martingales: control type-I error

reject $\mathcal{H}_0$ if $\mathbf{LR}_{10}^{(t)} > 20$ for $\alpha = 0.05$ error control

Universal bound *over time* (Ville's inequality):

$$\mathbf{P}_0 \left[\mathbf{LR}_{10}^{(t)} \geq \frac{1}{\alpha} \text{ for some } t \right] \leq \alpha$$

ALL-IN meta-analysis



Questions?

Questions?

1. Do you think accumulation bias actually affects real-life meta-analysis?



Viewpoint

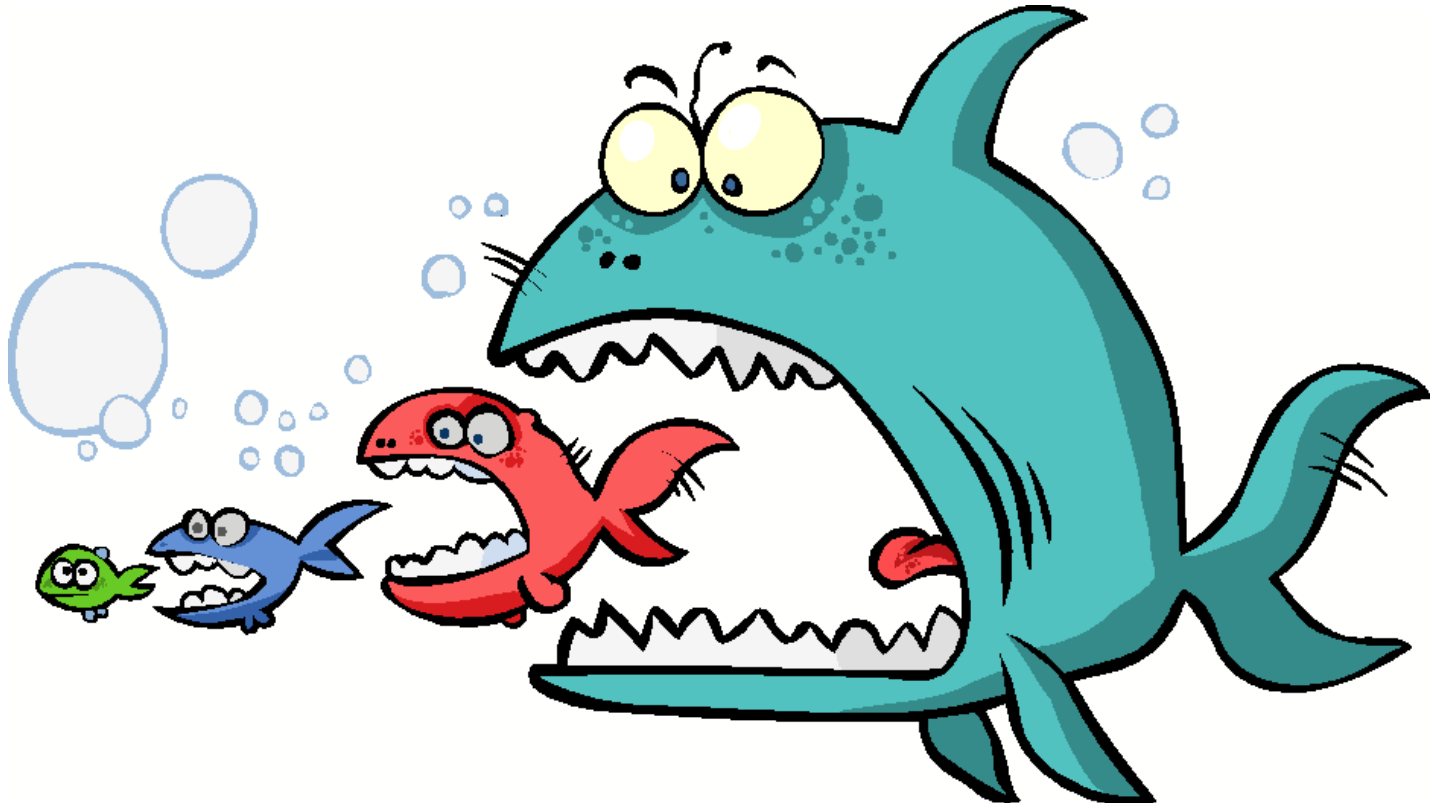


Avoidable waste in the production and reporting of research evidence

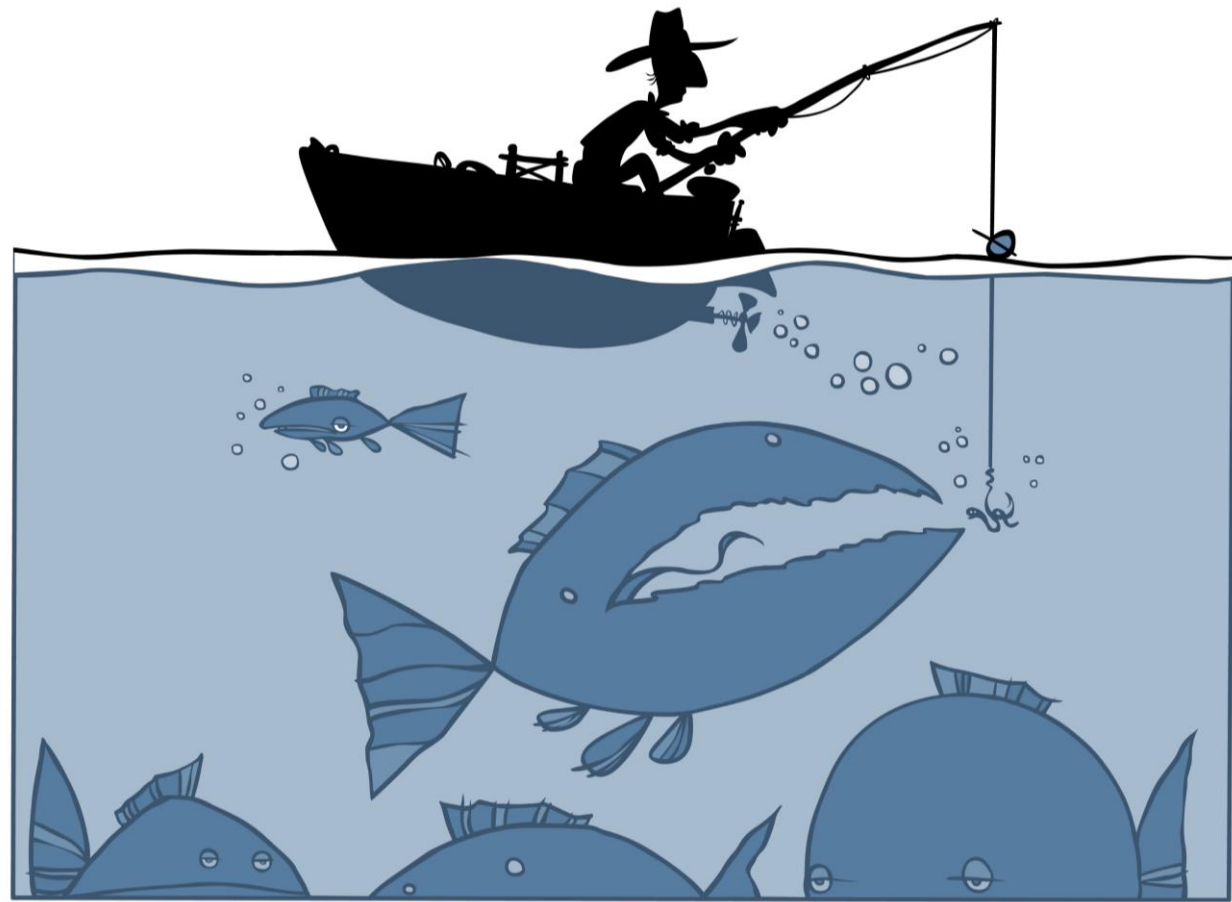
Iain Chalmers, Paul Glasziou

Lancet 2009; 374: 86-89

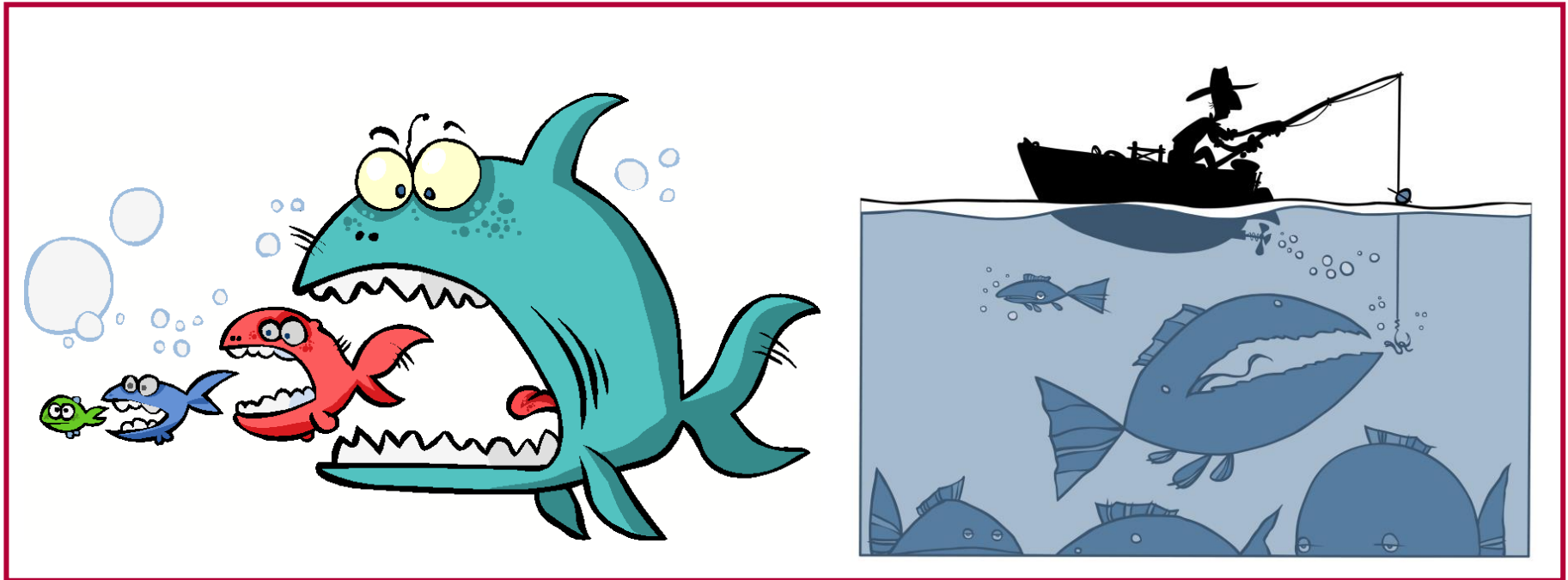
Accumulation Bias: introduced by the study series



Accumulation Bias: introduced by the meta-analysis



Accumulation Bias



dependency on series size

dependency on meta-analysis timing

Accumulation Bias framework

$$A(t)$$

BMC Medical Research Methodology



Research article

Open Access

The **fading** of reported effectiveness. A meta-analysis of randomised controlled trials

Bernhard T Gehr¹, Christel Weiss² and Franz Porzsolt^{*3}

fading

Correspondence

How systematic reviews cause research waste

fading

Systematic reviews of small trials increase waste by advertising to the scientific community **inflated**, often significant treatment effects that become smaller or absent when large, high-quality trials are done. Effect estimates from systematic reviews often inform sample size calculations.⁴ However, because most reviews provide **exaggerated estimates** of treatment effects due to inclusion

We declare no competing interests.

**Ian Roberts, Katharine Ker*
ian.roberts@lshtm.ac.uk

Clinical Trials Unit, London School of Hygiene & Tropical Medicine, London WC1E 7HT, UK

fading

inflated,

exaggerated estimates

Perspective

**Why do Phase III Trials of Promising Heart Failure Drugs
Often Fail? The Contribution of 'Regression to the Truth'**

HENRY KRUM, MBBS, PhD, FRACP, ANDREW TONKIN, MD, FRACP

Victoria, Australia

fading

inflated,

exaggerated estimates

Regression to the Truth

fading

inflated,

exaggerated estimates



ELSEVIER

Journal of Clinical Epidemiology 58 (2005) 543–549

**Journal of
Clinical
Epidemiology**

REVIEW ARTICLES

Early extreme contradictory estimates may appear in published research: The Proteus phenomenon in molecular genetics research and randomized trials

John P.A. Ioannidis^{a,b,c,*}, Thomas A. Trikalinos^{a,b}

fading

inflated,

exaggerated estimates

Correspondence

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Clinical Trials Unit, London School of Hygiene & Tropical Medicine, London WC1E 7HT, UK

Correspondence

Systematic reviews and research waste

We share Ian Roberts' and Katharine Ker's frustration with the poor quality of much research (Oct 17,

their suggestion scientifically flawed, it is also unrealistic. Funders and regulators cannot be expected to support and endorse large studies without some reassurance from the results of smaller existing studies that the substantial investment needed is justified. We hope that, instead of promoting their

**Iain Chalmers, Paul Glasziou
ichalmers@jameslind.net*

Correspondence

Early extreme contradictory estimates

The Proteus phenomenon

Regression to the Truth

fading

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rain Chalmers, Paul Glasziou

ichalmers@jameslind.net

$A(t)$

Early extreme contradictory estimates

The Proteus phenomenon

 $A(t)$

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Correspondence

$$A(t)$$

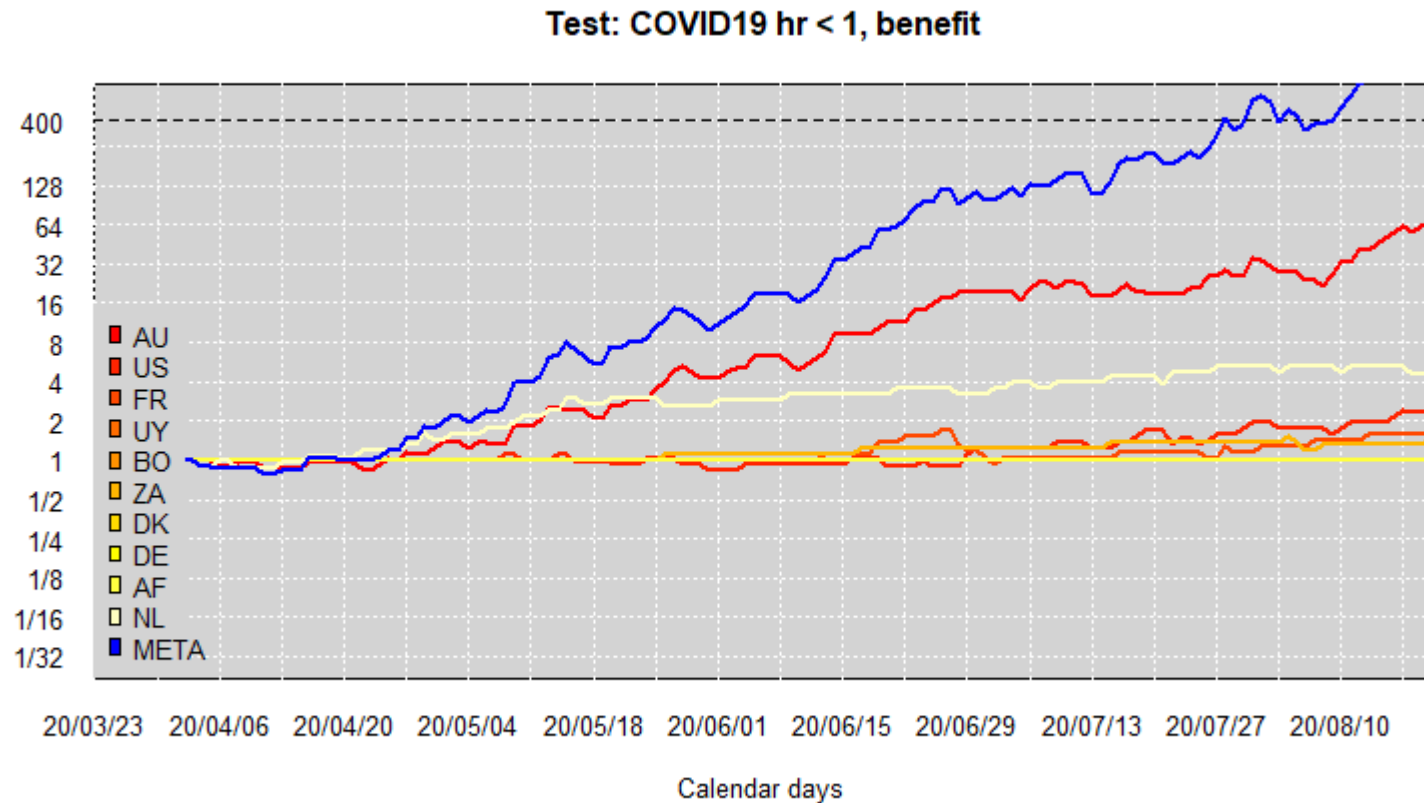
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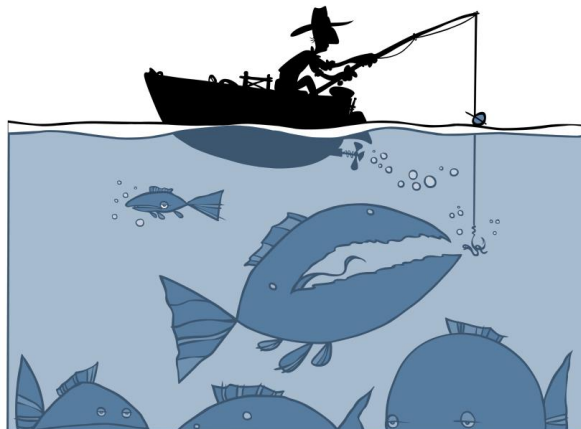
ALL-IN meta-analysis



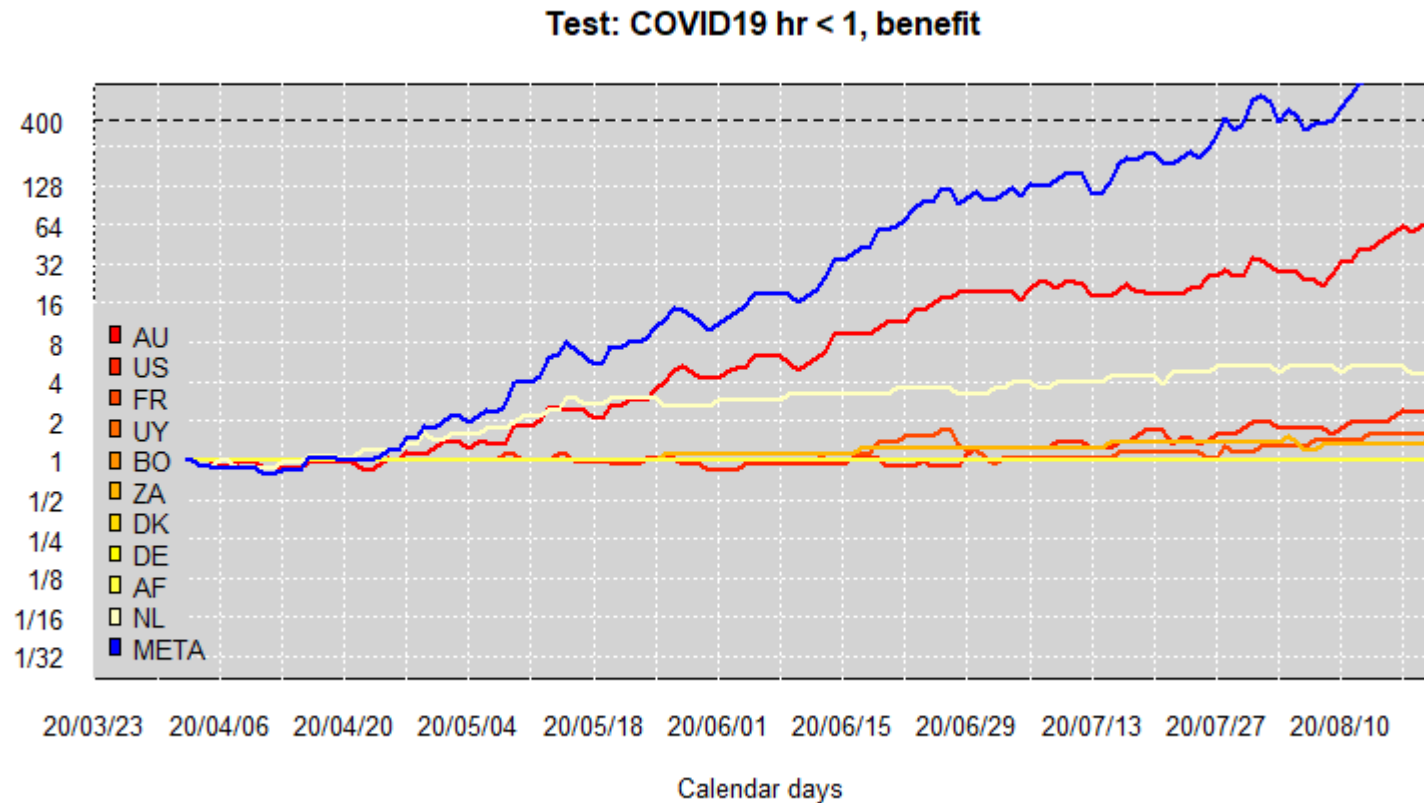
- ter Schure J and Grünwald P. (2019) Accumulation Bias in meta-analysis: the need to consider *time* in error control *F1000Research*, **8**:962.

Thank you!

Contact me on: schure@cw.nl

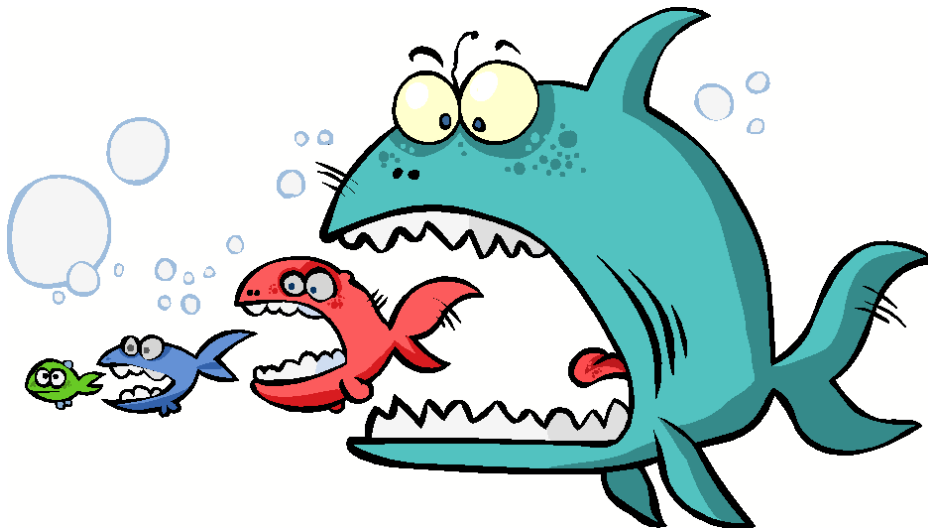


ALL-IN meta-analysis



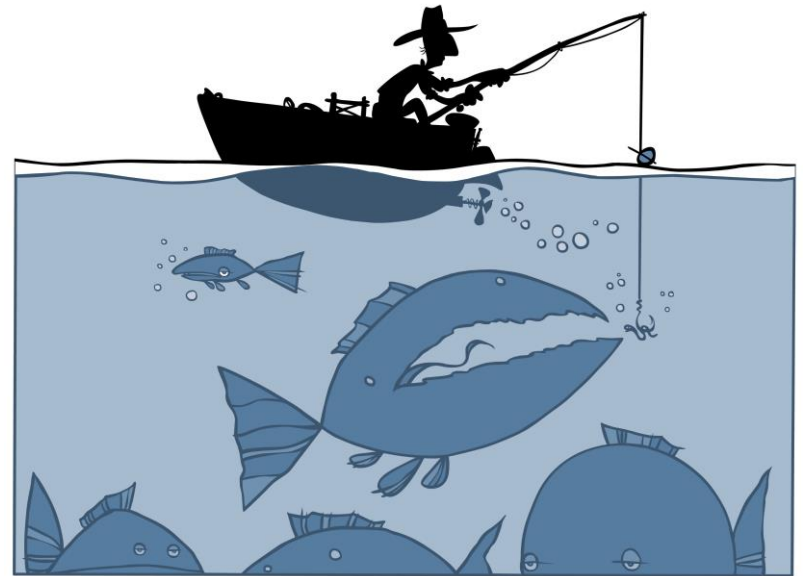
$$\mathbf{LR}_{10}^{(t)}(z_1, \dots, z_t, \mathcal{A}^{(t)}, T \geq t)$$

Accumulation Bias



dependency on series size

$$T \geq t$$



dependency on meta-analysis timing

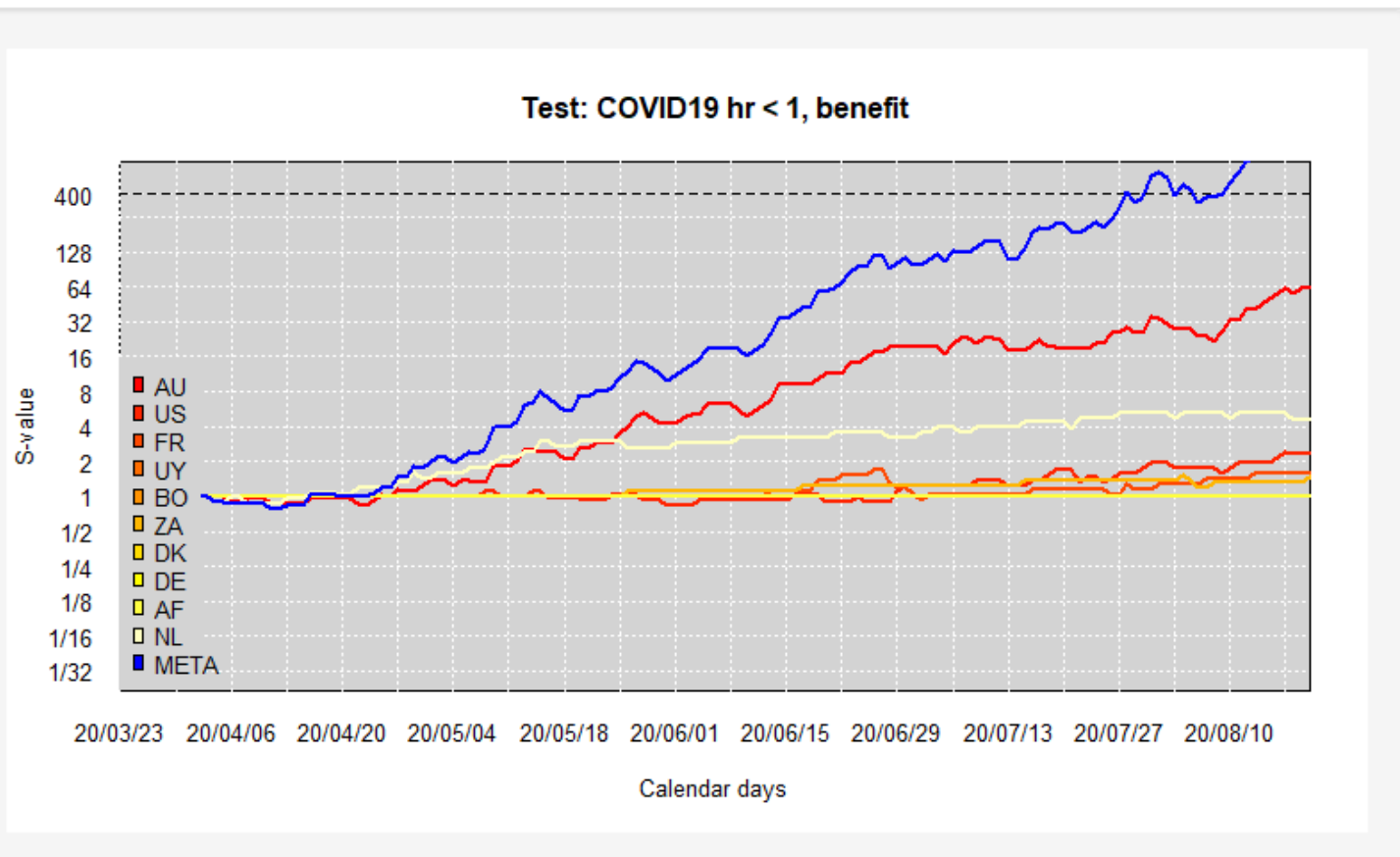
$$\mathcal{A}^{(t)}$$

$$\begin{aligned} & \mathbf{LR}_{10}^{(t)}(z_1, \dots, z_t, \mathcal{A}^{(t)}, T \geq t) \\ & \quad := \frac{f_1(z_1, \dots, z_t) \cdot \mathbf{P}_1(\mathcal{A}^{(t)}, T \geq t \mid z_1, \dots, z_t)}{f_0(z_1, \dots, z_t) \cdot \mathbf{P}_0(\mathcal{A}^{(t)}, T \geq t \mid z_1, \dots, z_t)} \end{aligned}$$

$$\begin{aligned} \mathbf{LR}_{10}^{(t)}(z_1, \dots, z_t, \mathcal{A}^{(t)}, T \geq t) \\ &:= \frac{f_1(z_1, \dots, z_t) \cdot \mathbf{P}_1(\mathcal{A}^{(t)}, T \geq t \mid z_1, \dots, z_t)}{f_0(z_1, \dots, z_t) \cdot \mathbf{P}_0(\mathcal{A}^{(t)}, T \geq t \mid z_1, \dots, z_t)} \\ &= \frac{f_1(z_1, \dots, z_t) \cdot A(t \mid z_1, \dots, z_t)}{f_0(z_1, \dots, z_t) \cdot A(t \mid z_1, \dots, z_t)} \end{aligned}$$

$$\begin{aligned} & \mathbf{LR}_{10}^{(t)}(z_1, \dots, z_t, \mathcal{A}^{(t)}, T \geq t) \\ & \quad := \frac{f_1(z_1, \dots, z_t) \cdot \mathbf{P}_1(\mathcal{A}^{(t)}, T \geq t \mid z_1, \dots, z_t)}{f_0(z_1, \dots, z_t) \cdot \mathbf{P}_0(\mathcal{A}^{(t)}, T \geq t \mid z_1, \dots, z_t)} \\ & \quad = \frac{f_1(z_1, \dots, z_t) \cdot A(t \mid z_1, \dots, z_t)}{f_0(z_1, \dots, z_t) \cdot A(t \mid z_1, \dots, z_t)} \\ & \quad = \frac{f_1(z_1, \dots, z_t)}{f_0(z_1, \dots, z_t)} \\ & \quad = \mathbf{LR}_{10}(z_1, \dots, z_t). \end{aligned}$$

ALL-IN meta-analysis



Subjective Bayesian analysis **uses**

the same likelihood to update the prior

with or without Accumulation Bias

$$\frac{\mathbf{P}[H_1 \mid z_1, \dots, z_t, \mathcal{A}^{(t)}, T \geq t]}{\mathbf{P}[H_0 \mid z_1, \dots, z_t, \mathcal{A}^{(t)}, T \geq t]}$$

$$\begin{aligned} & \frac{\mathbf{P}[H_1 \mid z_1, \dots, z_t, \mathcal{A}^{(t)}, T \geq t]}{\mathbf{P}[H_0 \mid z_1, \dots, z_t, \mathcal{A}^{(t)}, T \geq t]} \\ &= \frac{f_1(z_1, \dots, z_t, \mathcal{A}^{(t)}, T \geq t) \cdot \pi}{f_0(z_1, \dots, z_t, \mathcal{A}^{(t)}, T \geq t) \cdot (1 - \pi)} \\ &= \mathbf{LR}_{10}^{(t)}(z_1, \dots, z_t, \mathcal{A}^{(t)}, T \geq t) \cdot \frac{\pi_1}{\pi_0} \\ &= \mathbf{LR}_{10}(z_1, \dots, z_t) \cdot \frac{\pi_1}{\pi_0} \end{aligned}$$

Gold Rush example

ALL-IN solution

t		*
1	z_1	0
2	z_1^*, z_2	1
3	z_1^*, z_2^*, z_3	2
3	z_1^*, z_2^*, z_3^*	3
Σ		

P_0	$* \cdot P_0$	$t \cdot P_0$
$1 - \alpha$	0	$1 - \alpha$
$\alpha(1 - \alpha)$	$\alpha(1 - \alpha)$	$2\alpha(1 - \alpha)$
$\alpha^2(1 - \alpha)$	$2\alpha^2(1 - \alpha)$	$3\alpha^2(1 - \alpha)$
α^3	$3\alpha^3$	$3\alpha^3$
1	$\alpha + \alpha^2 + \alpha^3$	$1 + \alpha + \alpha^2$

Gold Rush example

ALL-IN solution

$$\pi_0 = 1$$

t		*
1	z_1	0
2	z_1^*, z_2	1
3	z_1^*, z_2^*, z_3	2
3	z_1^*, z_2^*, z_3^*	3
Σ		

P_0	$* \cdot P_0$	$t \cdot P_0$
$1 - \alpha$	0	$1 - \alpha$
$\alpha(1 - \alpha)$	$\alpha(1 - \alpha)$	$2\alpha(1 - \alpha)$
$\alpha^2(1 - \alpha)$	$2\alpha^2(1 - \alpha)$	$3\alpha^2(1 - \alpha)$
α^3	$3\alpha^3$	$3\alpha^3$
1	$\alpha + \alpha^2 + \alpha^3$	$1 + \alpha + \alpha^2$

Gold Rush example

Bayesian solution

$$z_1^-$$

$$z_1^*$$

$$z_1^*, z_2^-$$

$$z_1^*, z_2^*$$

$$z_1^*, z_2^*, z_3^-$$

$$z_1^*, z_2^*, z_3^*$$

$$\pi_1$$

Gold Rush example

Bayesian solution

z_1^-
 z_1^*
 z_1^*, z_2^-
 z_1^*, z_2^*
 z_1^*, z_2^*, z_3^-
 z_1^*, z_2^*, z_3^*

 π_1

$$\bar{A}_1(1) = 1 = 1$$

$$\bar{A}_1(2) = 0.8 = 0.8$$

$$\bar{A}_1(3) = 0.8 \cdot 0.8 = 0.65$$

Gold Rush example

Bayesian solution

z_1^-
 z_1^*
 z_1^*, z_2^-
 z_1^*, z_2^*
 z_1^*, z_2^*, z_3^-
 z_1^*, z_2^*, z_3^*

 π_0

$$\bar{A}_0(1) = 1 = 1$$

$$\bar{A}_0(2) = 0.05 = 0.05$$

$$\bar{A}_0(3) = 0.05 \cdot 0.05 = 0.0025$$

Gold Rush example

Bayesian solution

	π_1	π_0
z_1^-		
z_1^*		
z_1^*, z_2^-	$\bar{A}_1(1) = 1$	$\bar{A}_0(1) = 1$
z_1^*, z_2^*	$\bar{A}_1(2) = 0.8$	$\bar{A}_0(2) = 0.05$
z_1^*, z_2^*, z_3^-	$\bar{A}_1(3) = 0.65$	$\bar{A}_0(3) = 0.0025$
z_1^*, z_2^*, z_3^*		

Subjective Bayesian analysis **relies**

**on the prior so much that the same would hold
with or without *publication* bias**

Publication Bias

Bayesian solution

	π_1	π_0
z_1^-		
z_1^*		
z_1^*, z_2^-	$\bar{A}_1(1) = 1$	$\bar{A}_0(1) = 1$
z_1^*, z_2^*	$\bar{A}_1(2) = 0.8$	$\bar{A}_0(2) = 0.05$
z_1^*, z_2^*, z_3^-	$\bar{A}_1(3) = 0.65$	$\bar{A}_0(3) = 0.0025$
z_1^*, z_2^*, z_3^*		

Publication Bias

Bayesian solution

	π_1	π_0
z_1^-		
z_1^*		
z_1^*, z_2^-		
z_1^*, z_2^*	$\bar{A}_1(2) = 0.8$	$\bar{A}_0(2) = 0.05$
z_1^*, z_2^*, z_3^-	$\bar{A}_1(3) = 0.65$	$\bar{A}_0(3) = 0.0025$
z_1^*, z_2^*, z_3^*		