A re-appraisal of fixed effect(s) meta-analysis

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tl;dr

- Fixed-effect**S** meta-analysis answers a sensible question **regardless of heterogeneity**
- Other questions can also be sensible
- Fixed-effect**S** methods extend to useful measures of heterogeneity and meta-regression, small-sample corrections and Bayesian inference
- Knowing **what question you're answering** helps determine **whether** it's sensible

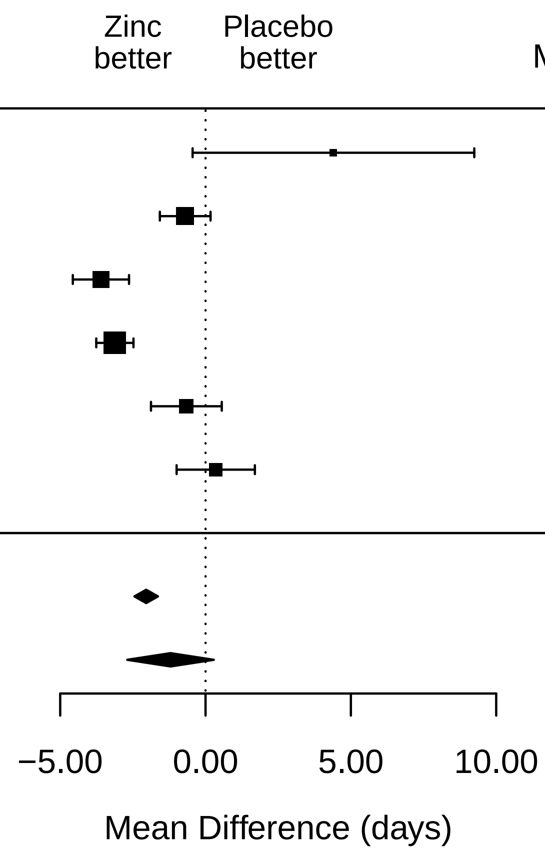
http://tinyurl.com/fixef

has these slides and more.

Generic example

Meta-analyzing trials* to estimate some overall effect;

Study	Zinc N	Zinc Mean	Zinc SD	Placebo N	Placebo Mean	Placebo SD	Mean Difference, 95% CI
Douglas 1987	33	12.1	9.8	30	7.7	9.8	4.40 [−0.45 , 9.25]
Petrus 1998	52	4.4	1.4	49	5.1	2.8	−0.70 [−1.57 , 0.17]
Prasad 2000	25	4.5	1.6	23	8.1	1.8	−3.60 [−4.57 , −2.63]
Prasad 2008	25	4	1.04	25	7.12	1.26	−3.12 [−3.76 , −2.48]
Turner 2000b	68	6.89	3.35	71	7.55	3.96	−0.66 [−1.88 , 0.56]
Turner 2000c	72	7.9	4.25	71	7.55	3.96	0.35 [−1.00 , 1.70]
Fixed effects, precision−weighted average (PWA) estimator							−2.04 [−2.45 , −1.64]
Random effects, DerSimonian−Laird estimator							−1.21 [−2.69 , 0.28]



- Generic Q: **Which average?** Why?

* from Zinc for the Common Cold (2011) – Cochrane review of zinc acetate lozenges for reducing duration of cold symptoms (days)

Fixed effect (singular)

... based on the assumption that the results of each trial represents a statistical fluctuation around some common effect

Steve Goodman

Controlled Clinical Trials, 1989

In the *fixed effect* model for k studies we assume

$$\begin{aligned} \widehat{\beta}_i &\sim N(\beta_i, \sigma_i^2),\ 1 \leq i \leq k, \text{ by the CLT,} \\ \text{where } \beta_i &= \beta_0, \qquad\qquad 1 \leq i \leq k \end{aligned}$$

and noise in σ_i is negligible. Obvious (and optimal) estimate is the *inverse variance-weighted* or *precision-weighted* average:

$$\widehat{\beta}_F = \sum_{i=1}^{k} \frac{\frac{1}{\sigma_i^2}}{\sum_{i=1}^{k} \frac{1}{\sigma_i^2}} \widehat{\beta}_i, \qquad \text{with } \mathrm{Var}[\,\widehat{\beta}_F\,] = \frac{1}{\sum_{i=1}^{k} \frac{1}{\sigma_i^2}}.$$

Fixed effectS (plural)

But assuming β_i exactly homogeneous is **silly** in (most) practice, as effects are **not identical**

- Environments & adherence differ (and much else)
- In my applied work, genetic ancestry differs

But but but note that if

$$\hat{\beta}_i \ \sim \ N(\beta_i, \sigma_i^2), \ 1 \leq i \leq k, \ \text{by the CLT},$$

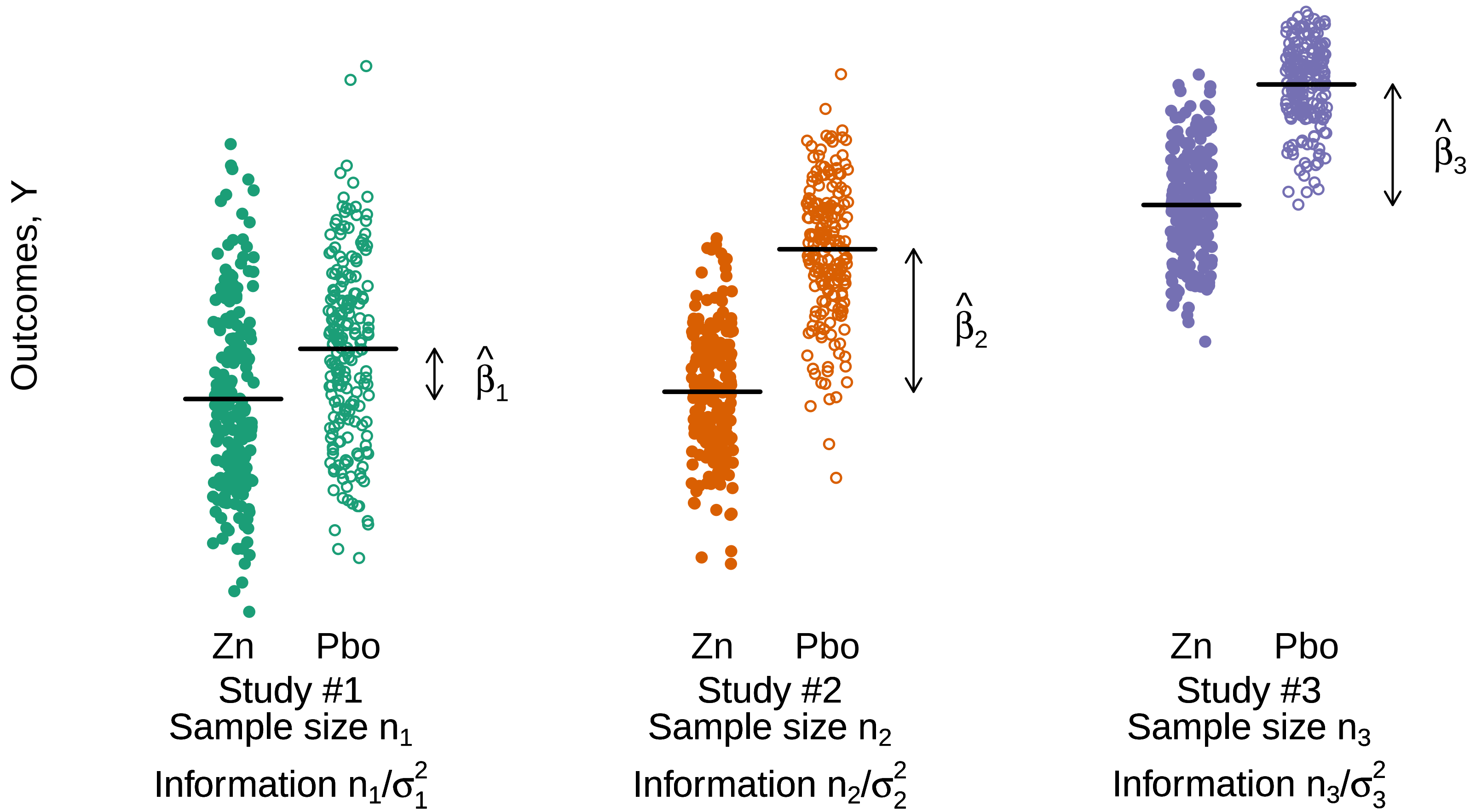
and noise in σ_i is negligible, then **can still define**

$$\hat{\beta}_F = \sum_{i=1}^{k} \frac{\frac{1}{\sigma_i^2}}{\sum_{i=1}^{k} \frac{1}{\sigma_i^2}} \hat{\beta}_i, \qquad \text{with Var}[\,\hat{\beta}_F\,] = \frac{1}{\sum_{i=1}^{k} \frac{1}{\sigma_i^2}}.$$

The *fixed effect***S** estimate provides **valid** statistical inference on an 'average' of the β_i, **regardless** of their homogeneity/heterogeneity

Fixed effectS: what average?

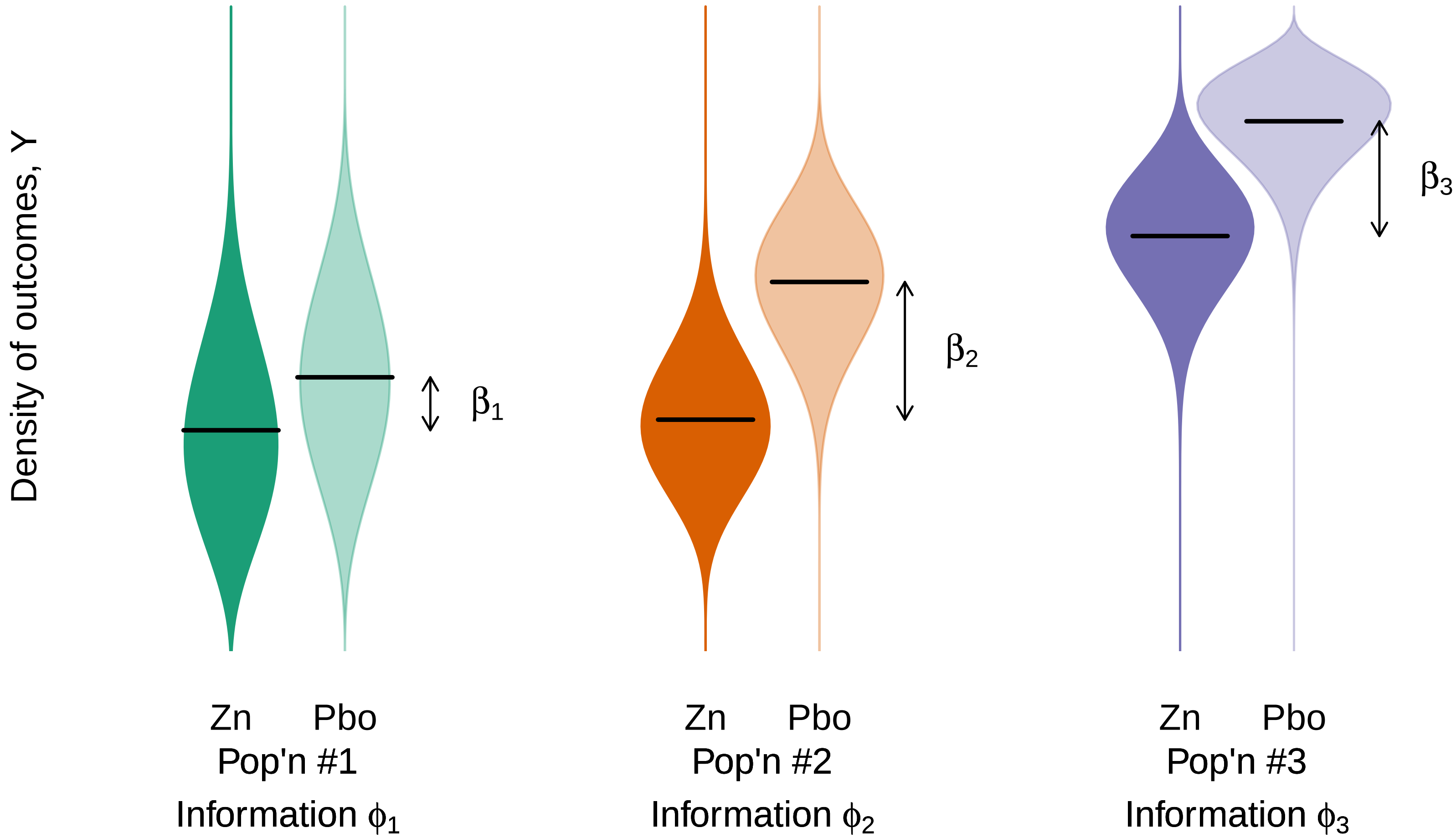
First, consider possible data from three studies;



Each $n_i = 200$ here. We assume all σ_i^2 known, for simplicity.

Fixed effectS: what average?

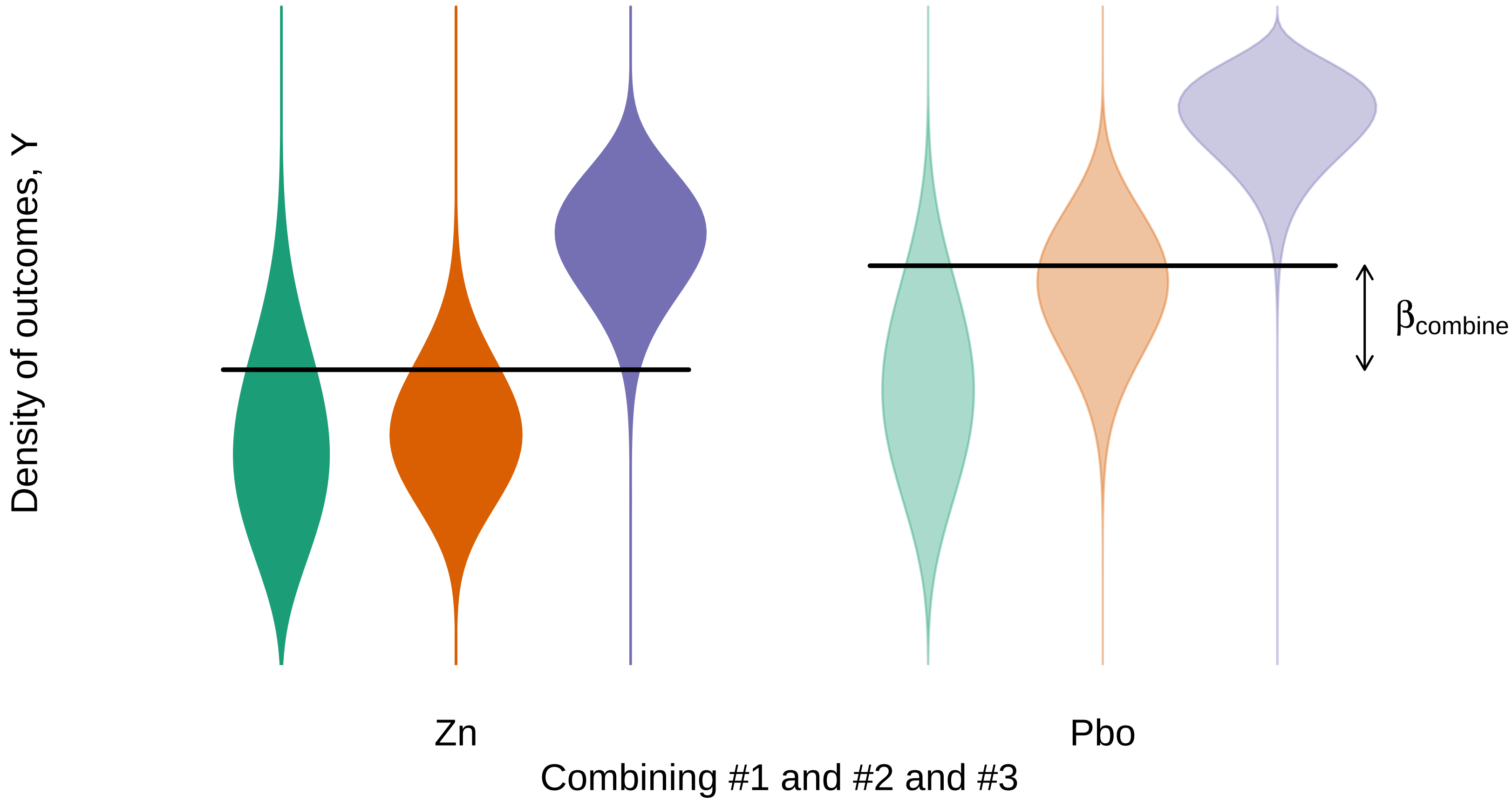
Population parameters those 3 studies are estimating;



Parameters are differences in means (β_i) **and** information per observation (ϕ_i).

Fixed effectS: what average?

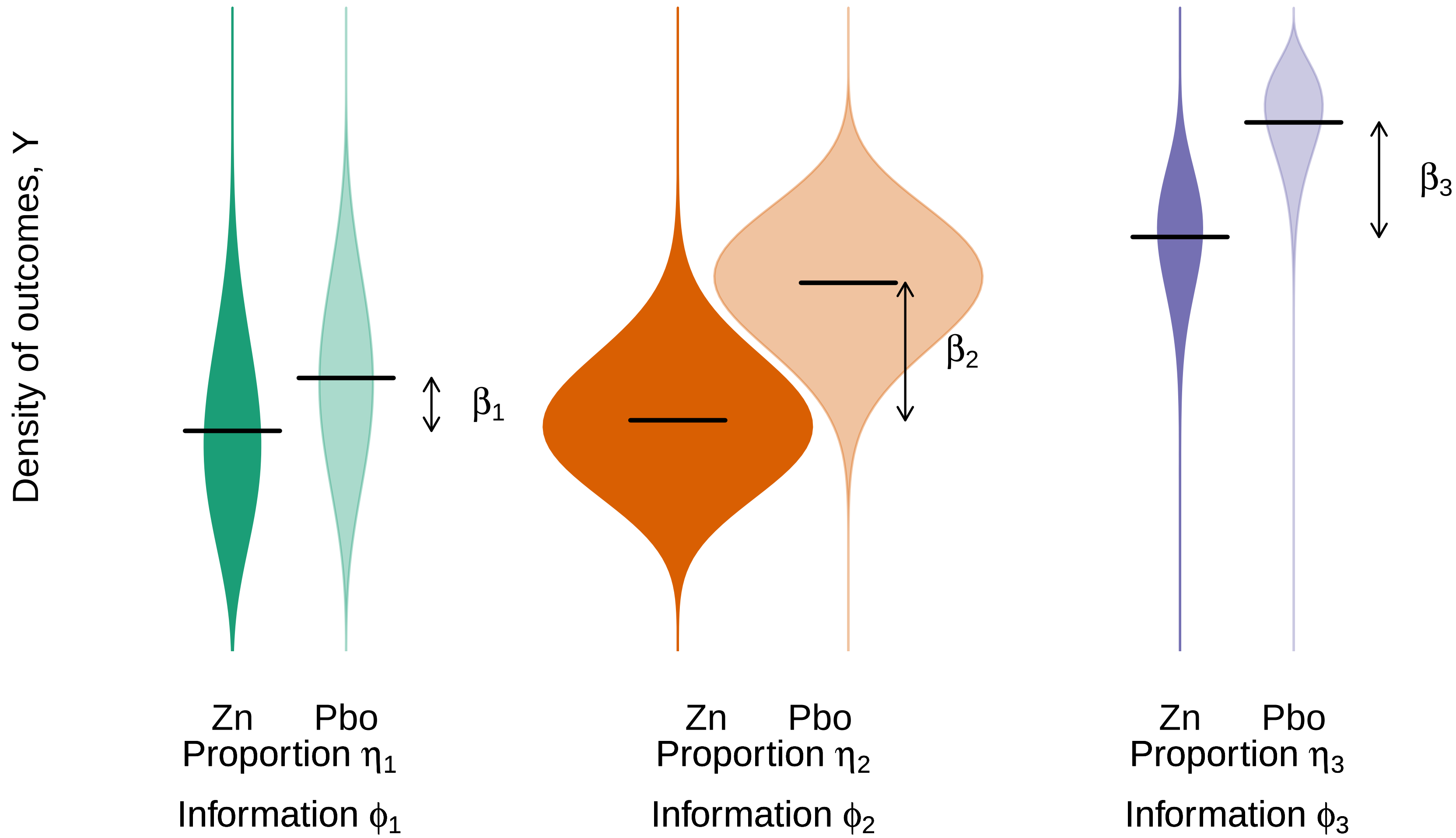
One overall population we might learn about;



β_{combine} is the mean difference (zinc vs placebo) with each sub-population represented equally, i.e. weighted 1/1/1.

Fixed effectS: what average?

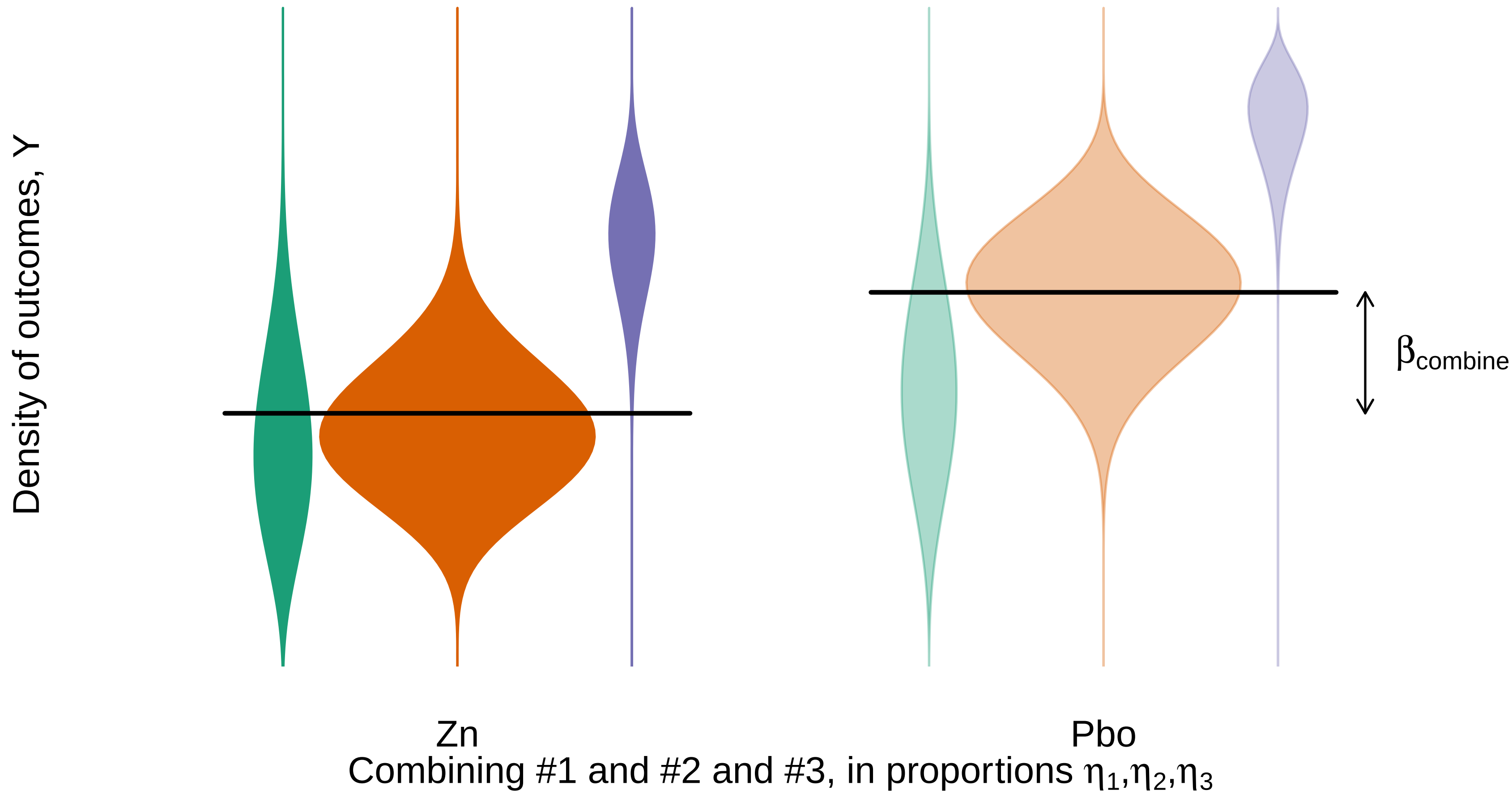
Another overall population we might learn about;



Weights here are 2/7/1, not 1/1/1 as before.

Fixed effectS: what average?

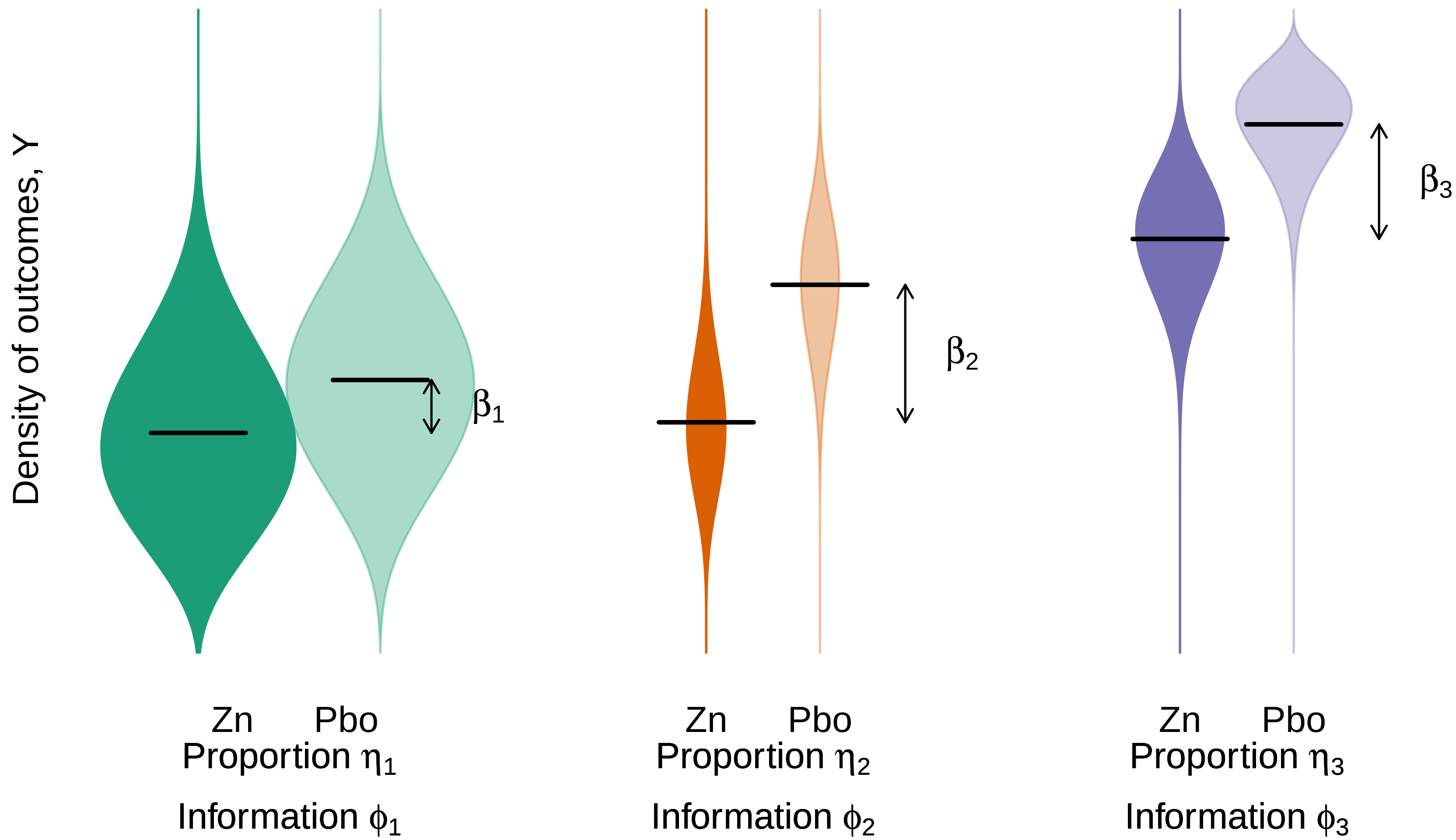
Another overall population we might learn about;



Still an average effect, but closer to β_2 than before.

Fixed effectS: what average?

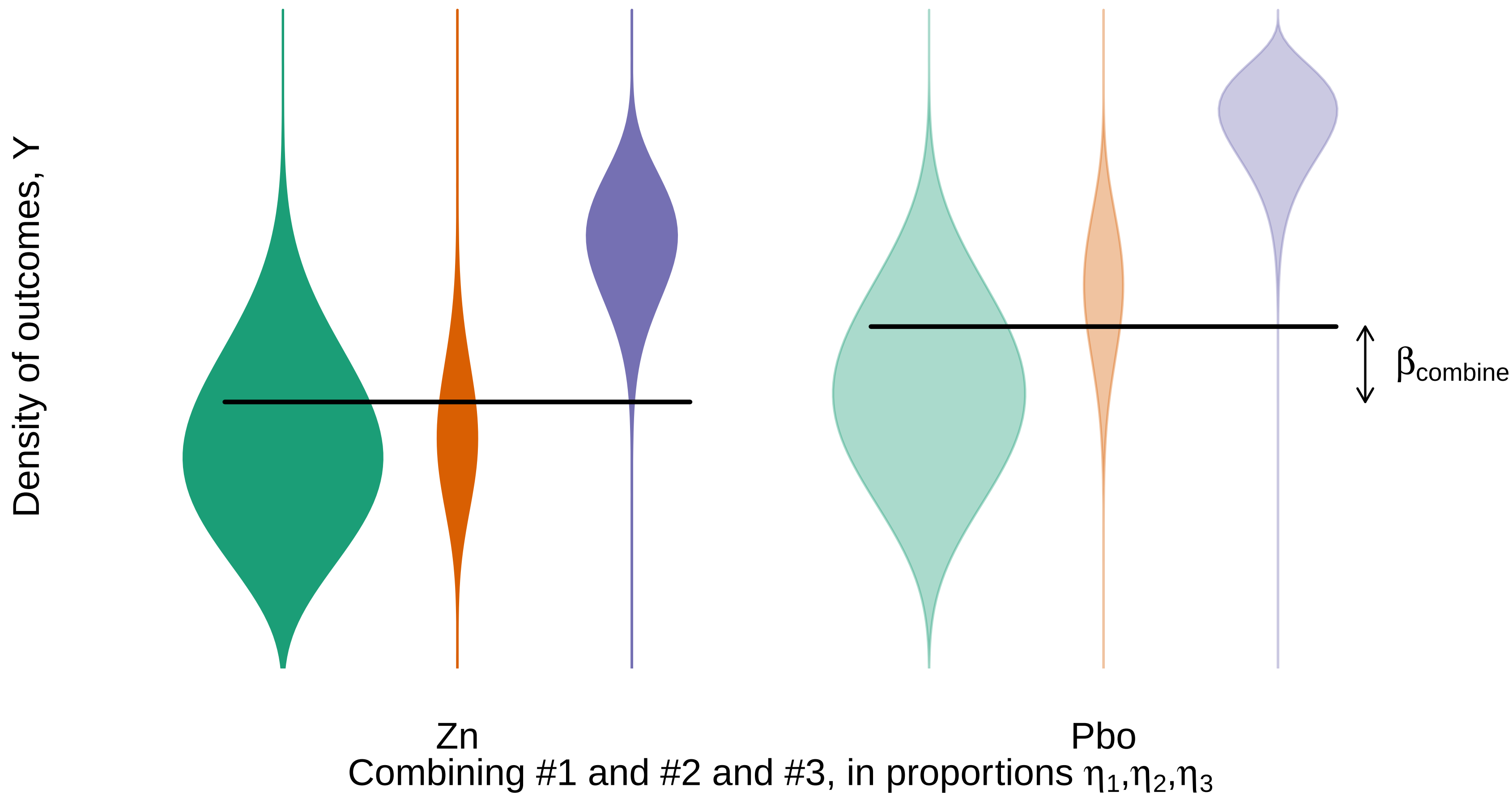
And another; (obviously, there are unlimited possibilities)



Weights here are 7/1/2.

Fixed effectS: what average?

And another; (obviously, there are unlimited possibilities)



Weights here are 7/1/2 – smaller average effect, closer to β_1

Fixed effectS: general case

Upweighting studies which are larger **and** more informative about their corresponding β_i, we can estimate population parameter

$$\beta_F = \frac{\sum_{i=1}^k \eta_i \phi_i \beta_i}{\sum_{i=1}^k \eta_i \phi_i} = \frac{\sum_{i=1}^k \frac{1}{\sigma_i^2}\beta_i}{\sum_{i=1}^k \frac{1}{\sigma_i^2}},$$

$$\text{by } \hat{\beta}_F = \frac{\sum_{i=1}^k \frac{1}{\sigma_i^2}\hat{\beta}_i}{\sum_{i=1}^k \frac{1}{\sigma_i^2}}, \quad \text{with } \mathrm{Var}[\hat{\beta}_F] = \frac{1}{\sum_{i=1}^k \frac{1}{\sigma_i^2}}.$$

- $\hat{\beta}_F$ is the *precision-weighted* average, a.k.a. *inverse-variance weighted* average a.k.a. fixed effect**S** estimator – **note the plural!**
- $\hat{\beta}_F$ is consistent for average effect β_F under regime where all $n_i \to \infty$ in fixed proportion
- Homogeneity, or tests for heterogeneity are **not required** to use $\hat{\beta}_F$ and its inference

Fixed effectS: general case

Homogeneity, or tests for heterogeneity are **not required** *to use $\widehat{\beta}_F$ and its inference*

Users who have **only** seen the fixed effect (singular) motivation tend to view it as the **only** reason for ever using $\widehat{\beta}_F$.

This is **specious**...

If I see you buy eggs, should I think the **only** reason is that you're making an omelet?

Fixed effectS: general case

The basic ideas here are **not new**:

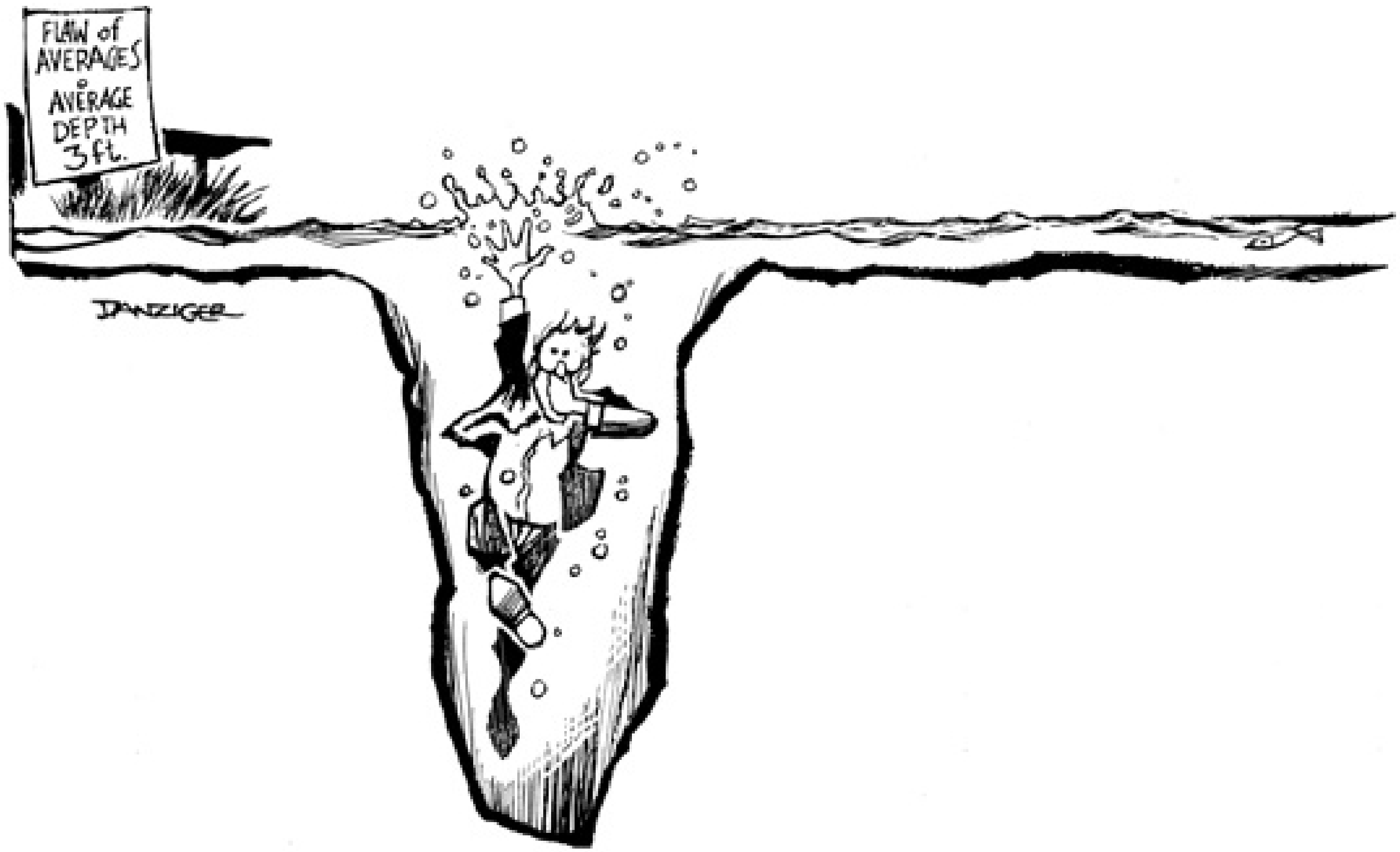
- Same average-effect argument already supports e.g. the Mantel-Haenszel estimate
- Fixed effect**S** arguments presented by e.g. Peto (1987), Fleiss (1993) and Hedges (various, e.g. Handbook of Research Synthesis), all noting the validity of β_F and inference using $\widehat{\beta}_F$ under heterogeneity

Also

- Can still motivate $\widehat{\beta}_F$ when σ_i are estimated, though Var[$\widehat{\beta}_F$] requires more care (Domínguez-Islas & Rice 2018)
- Can use them in Bayesian work, with exchangeable priors (Domínguez-Islas & Rice, under review) – much less sensitive than default methods

But what about heterogeneity?

We all know the '*flaw* of averages';



- Average effect β_F answers one question
- This does not mean other questions aren't interesting!

But what about heterogeneity?

A weighted variance of effects:

$$\zeta^2 = \frac{1}{\sum_{i=1}^k \eta_i \phi_i} \sum_{i=1}^k \eta_i \phi_i (\beta_i - \beta_F)^2.$$

And an empirical estimate of it:

$$\hat{\zeta}^2 = \frac{\sum_{i=1}^k \sigma_i^{-2} (\hat{\beta}_i - \hat{\beta}_F)^2 - (k-1)}{\sum_{i=1}^k \sigma_i^{-2}} = \frac{Q - (k-1)}{\sum_{i=1}^k \sigma_i^{-2}}$$

where Q is *Cochran's Q* and $I^2 = 1 - (k-1)/Q$ (truncated at zero) are standard statistics for assessing homogeneity.

- (Weighted) standard deviation ζ – measure on the β scale – is easier to interpret than Q or I^2
- Inference on ζ **far more stable** than mean of (hypothetical) random effects distributions

But what about heterogeneity?

Meta-regression – essentially weighted linear regression of the $\widehat{\beta}_i$ on known study-specific covariates x_i – also tells us about differences from zero, beyond the overall effect $\widehat{\beta}_F$.

Using extensions of the arguments for $\widehat{\beta}_F$, the standard linear meta-regression 'slope' estimate can be written

$$\widehat{\beta}_{MR} = \frac{\sum_{i=1}^k w_i(x_i - \widehat{x}_F)^2 \frac{\widehat{\beta}_i - \widehat{\beta}_F}{x_i - \widehat{x}_F}}{\sum_{i'=1}^k w_{i'}(x_{i'} - \widehat{x}_F)^2}, \text{ where } \widehat{x}_F = \frac{\sum_{i=1}^k w_i x_i}{\sum_{i'=1}^k w_{i'}} \text{ and } w_i = \frac{1}{\sigma_i^2},$$

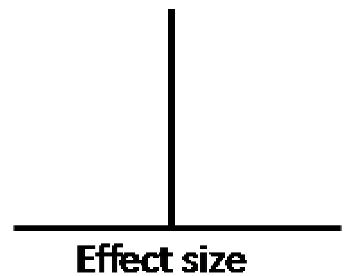
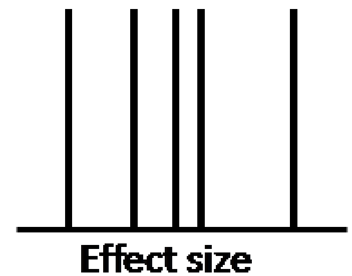
which **with no further assumptions** estimates

$$\beta_{MR} = \frac{\sum_{i=1}^k \eta_i \phi_i (x_i - x_F)^2 \frac{\beta_i - \beta}{x_i - x_F}}{\sum_{i'=1}^k \eta_{i'} \phi_{i'} (x_{i'} - x)^2}, \text{ where } x_F = \frac{\sum_{i=1}^k \eta_i \phi_i x_i}{\sum_{i'=1}^k \eta_{i'} \phi_{i'}}.$$

- Var[$\widehat{\beta}_{MR}$] also available
- ANOVA/ANCOVA breakdowns of total 'signal:noise' available to accompany ζ^2 and $\widehat{\beta}_{MR}$ analysis

Are you going to stop now?

Summary, under standard conditions;

Name:	Common effect	Fixed effect**S**
Assumptions:	 All $\beta_i = \beta_0$	 β_i unrestricted
Plausible?	**Rarely**	**Often!**
$\widehat{\beta}_F$ estimates:	Single β_0	Sensible average, β_F
Valid estimate?	Yes	Yes
StdErr[$\widehat{\beta}_F$] valid?	≈Yes*	≈Yes*
Estimate heterogeneity?	Makes no sense	Yes, via ζ^2, Q, I^2
Meta regression?	Makes no sense	Yes, via $\widehat{\beta}_{MR}$

* ... if we can ignore uncertainty about the σ_i^2

Acknowledgements

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Julian Higgins

Reminder: http://tinyurl.com/fixef for slides & more.