

**Relative efficiency of treatment effect estimates
from unadjusted and adjusted analyses with
missing data at baseline**

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ISCB Prague, 2009

Should we use adjusted estimates of treatment effect?

- Potential differences exist at baseline
 - Randomised trials
 - Observational studies
- Consider adjustment for baseline covariates...

Should we use adjusted estimates of treatment effect?

Unadjusted estimate
e.g. using
ANOVA

vs.

Adjusted estimate
e.g. using
ANCOVA

Should we use adjusted estimates of treatment effect?

- Adjustment can reduce bias
- Adjustment may improve efficiency
- But...baseline data may be partially missing
 - problems identifying relevant patients before treatment starts
 - missing responses
- Today...main focus on efficiency in trials.

Example

- Trial of elective surgery for torn meniscus
- Outcome = quality of life (QL)
- Ideal covariate = QL several weeks before surgery
- Identification and accessing patients before surgery may be difficult or costly
 - missing data
- Some patients observed early may be ineligible for trial
 - wasted resources

Objectives

- Compare ANOVA vs. ANCOVA
 - Relative efficiency
- Identify the preferred approach for various scenarios, characterised by:
 - Proportion of missing baseline data (η)
 - Correlation of baseline variable to outcome (ρ)
 - Expected baseline imbalance (δ)
 - Sample size (N)
 - (Cost of obtaining data)

ANOVA model

$$Y_{ij} = \mu + \tau_i + \varepsilon_{ij}$$

where $i = 1, 2, \dots, f$; $j = 1, 2, \dots, n_i$, $\mu = \text{mean}$;
 $\tau_i = \text{effect of treatment } i$; $\varepsilon_{ij} = \text{experiment error}$.

Treatment effect $D = \tau_1 - \tau_2$

$$\text{var}(\hat{D}) = 4\sigma^2/N$$

($N = \text{total sample size}$; assume $f = 2$ groups, $n_1 = n_2$)

ANCOVA model

$$Y_{ij} = \mu + \tau_i + \beta(X_{ij} - \bar{X}_{..}) + \varepsilon_{ij}$$

Adjusted treatment means – $\bar{Y}_i^* = \bar{Y}_i - \hat{\beta}(\bar{X}_i - \bar{X})$

- adjusted means are estimates of $\mu + \tau_i$

Variance of treatment effect:

$$\text{var}(\hat{D}^*) = \sigma^2 (1 - \rho^2) \left(\frac{N-2}{N-3} \right) \frac{4}{N} \left(1 + \frac{1 + N\delta^2/4}{N-4} \right)$$

where $\delta = (\mu_{X1} - \mu_{X2})/\sigma_x$

Relative efficiency

- Variance of ANCOVA treatment effect with proportion η of missing data:

$$\text{var}(\hat{D}^*) = \sigma^2 (1 - \rho^2) \frac{N' - 2}{N' - 3} \frac{4}{N'} \left(1 + \frac{N' \delta^2 / 4}{N' - 4} \right)$$

where $N' = N(1 - \eta)$

- Relative efficiency

$$\phi = \frac{\text{var}(\hat{D}^*)}{\text{var}(\hat{D})} = \frac{(1 - \rho^2) N' - 2}{(1 - \eta) N' - 3} \left(1 + \frac{1 + N' \delta^2 / 4}{N' - 4} \right)$$

Relative efficiency

$$\phi = \frac{\text{var}(\hat{D}^*)}{\text{var}(\hat{D})} = \frac{(1-\rho^2)}{(1-\eta)} \frac{N'-2}{N'-3} \left(1 + \frac{1+N'\delta^2/4}{N'-4} \right)$$

Large N'

$$\phi = \frac{1-\rho^2}{1-\eta} \left(1 + \frac{\delta^2}{4} \right)$$

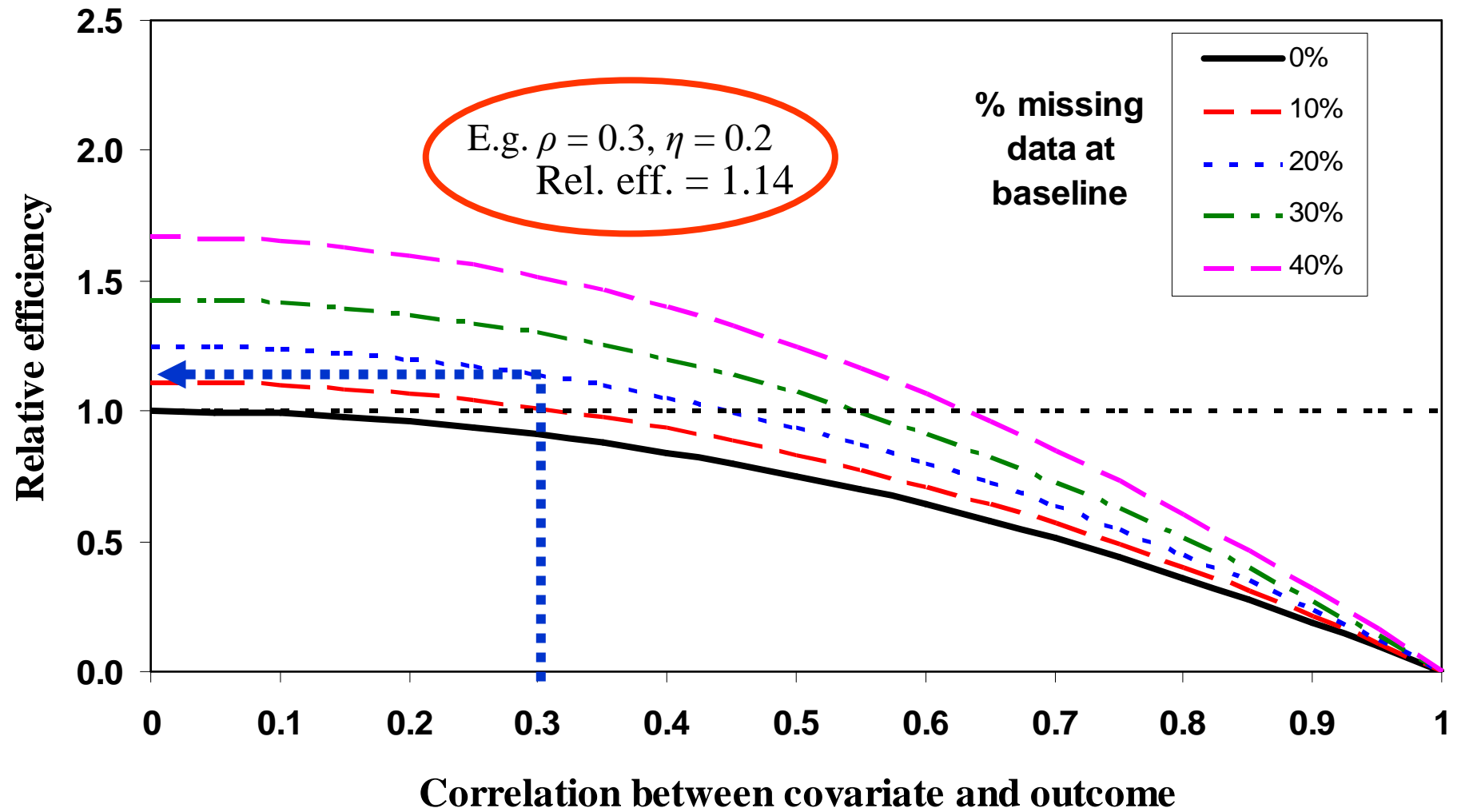
RCTs [$\delta = 0$]

$$\phi = \frac{(1-\rho^2)}{(1-\eta)} \frac{N'-2}{N'-4}$$

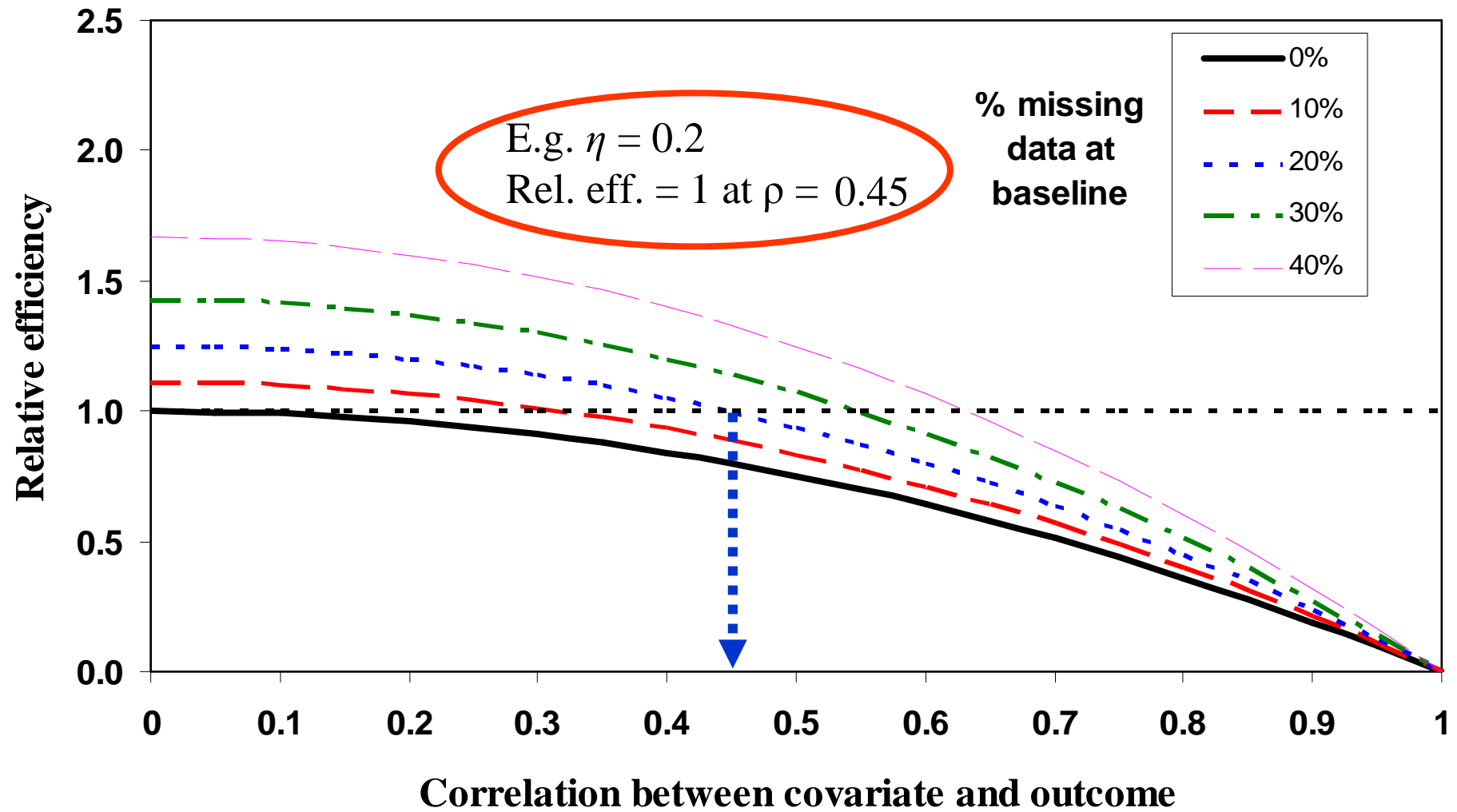
Large RCTs

$$\phi = \frac{1-\rho^2}{1-\eta}$$

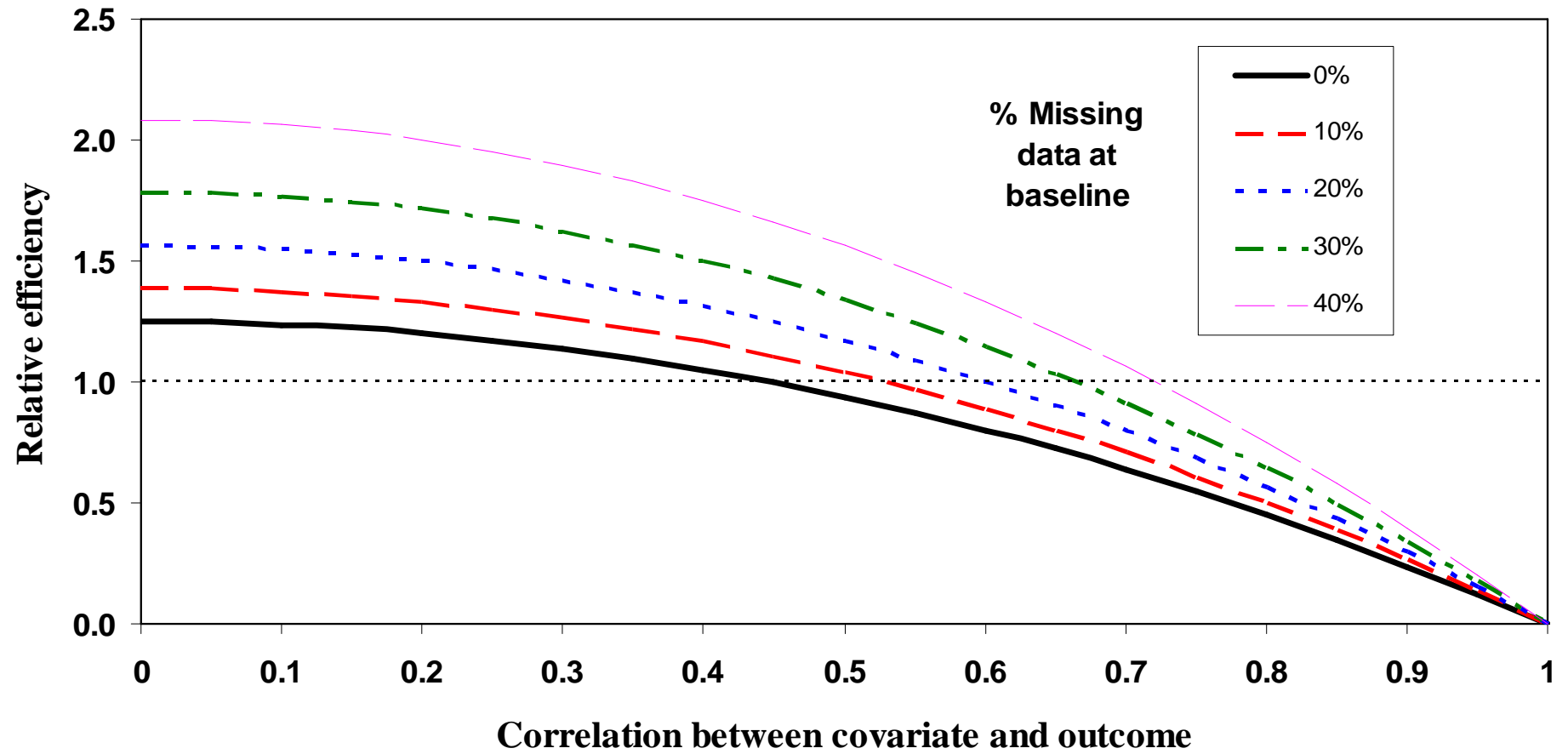
Asymptotic Relative Efficiency: ANOVA vs. ANCOVA, $\delta = 0$



Asymptotic Relative Efficiency: ANOVA vs. ANCOVA, $\delta = 0$



Asymptotic Relative Efficiency: ANOVA vs. ANCOVA, $\delta = 1$



Minimum correlation to justify adjusted analysis

$$\rho = \sqrt{1 - \frac{(1-\eta)(N'-3)(N'-4)}{(N'-2)(N'-3 + N'\delta^2/4)}}$$

Large N'

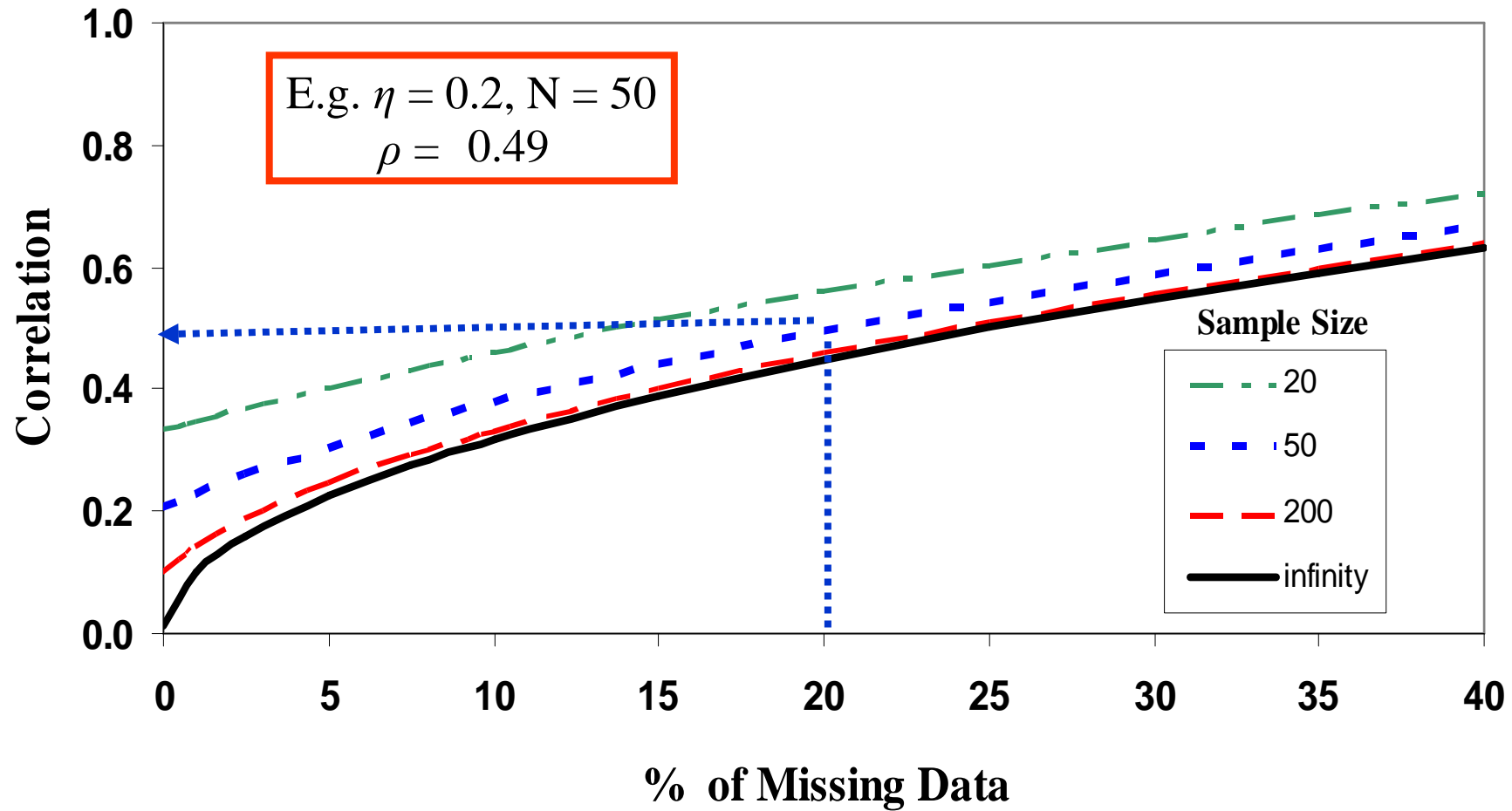
$$\rho = \sqrt{1 - \frac{1-\eta}{1+\delta^2/4}}$$

RCTs [$\delta = 0$]

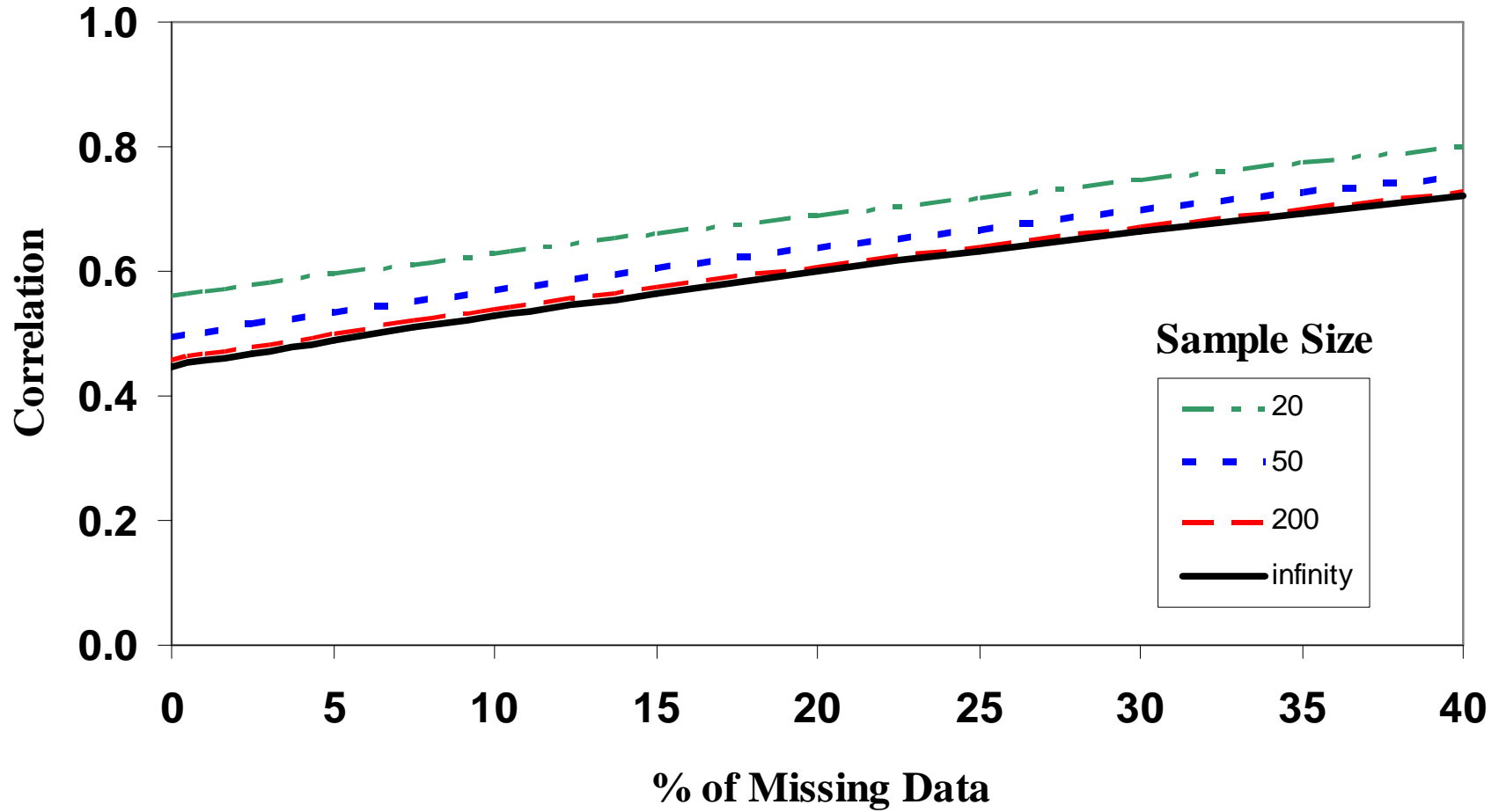
$$\rho = \sqrt{1 - \frac{(1-\eta)(N'-4)}{(N'-2)}}$$

Large RCTs $\rho = \sqrt{\eta}$

Minimum required correlation to justify adjusted analysis: $\delta = 0$



Minimum required correlation to justify adjusted analysis: $\delta = 1$



Example

Randomised trial of open vs. arthroscopic surgery
for torn meniscus

- suture vs. bio-absorbable implants

Outcome: QL [WOMET - Western Ontario
Meniscal Evaluation Tool]

$N = 77$ (38 suture, 39 implants) total

$N = 71$ (36 suture, 35 implants) with baseline data

Example: Mean QL scores

<u>Observation</u>	<u>Implant</u> <u>(n=35)</u>	<u>Suture</u> <u>(n=36)</u>	<u>Diff</u>
Pre-op	34.55	39.13	- 4.58
12 months post-op	66.75	65.95	0.81
Adjusted 12 months post-op	67.17	65.54	1.63

Example: efficiency

% missing data at baseline (η) = 8% (6/77)

$N = 77; N' = 71$

Correlation (ρ)

Threshold	0.33
Asymp. threshold	0.28
Actual	0.13

Efficiency, ANOVA vs. ANCOVA

Variance ratio = 0.91, $\varphi = 1.10$

Asymptotic var. ratio = 0.94, $\varphi = 1.07$

→ ANOVA preferred

Conclusions

- Efficiency (and cost-efficiency) results can guide choice of design and analysis
 - Calculate relative efficiency and threshold correlation
- ANCOVA is preferred if we have:
 - Small % of missing baseline data
 - Strong correlation of baseline variable to outcome
 - Low cost for observing baseline data
- Conclusions are only weakly dependent on N



Other points

- Measurement error in baseline variable is ignored in ANCOVA
- Can also include a cost framework
- Hybrid analysis (adjust where possible, otherwise don't adjust)?
- Imputation?

Example: ANOVA and ANCOVA Estimates

<u>Parameter</u>	<u>ANOVA</u>	<u>ANCOVA</u>
D	0.81	1.63
p	0.89	0.77