Diagnostics for Confounding in a PK/PD Model

Jerry Nedelman, Don Rubin, Lewis Sheiner

ECPAG,

April 27, 2004

NOVARTIS

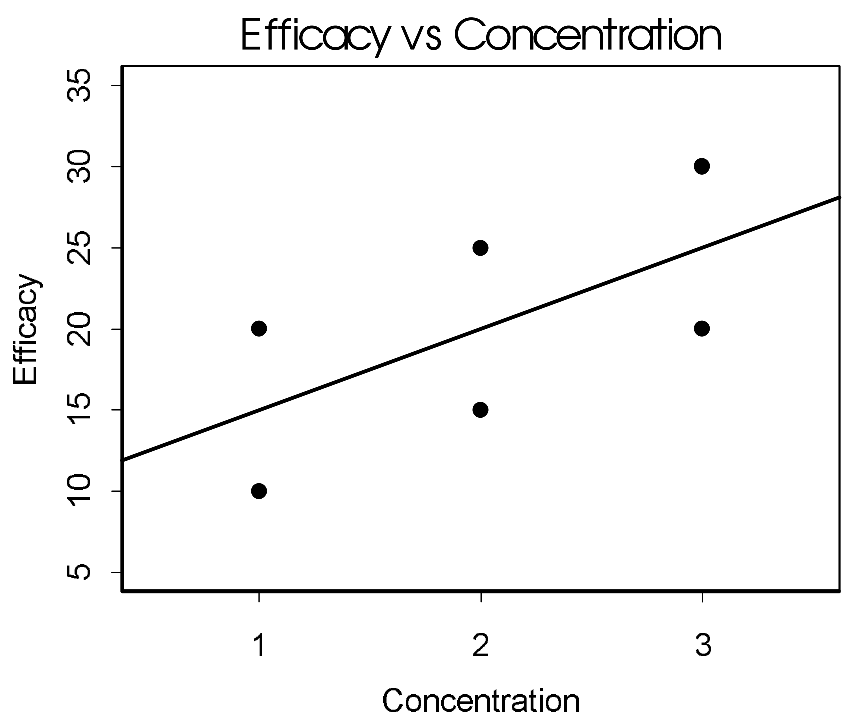
Outline

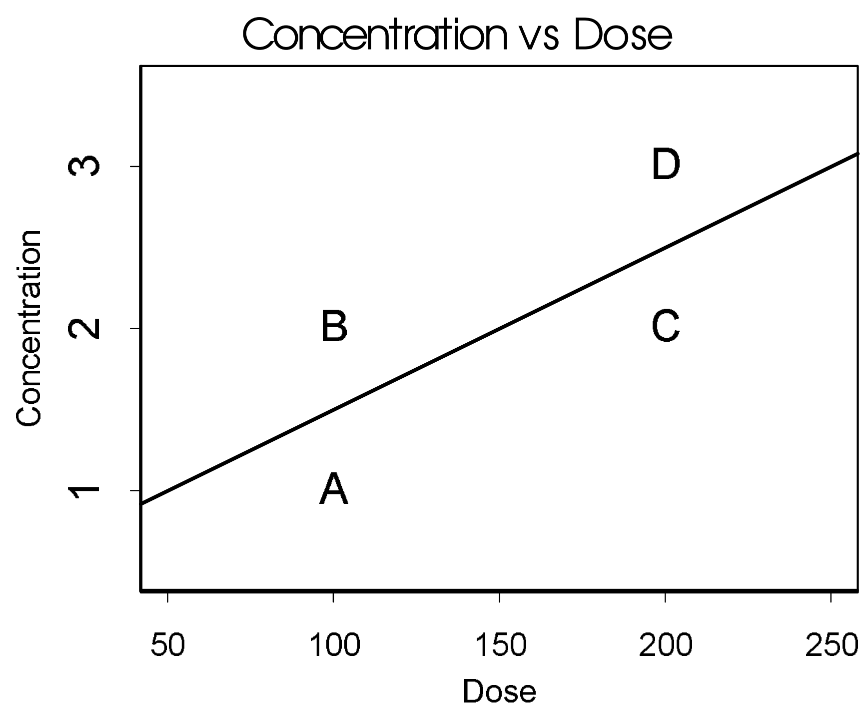
- PK/PD and confounding
- A heuristic example
- A (nearly) real example
- A model
- Model-implied diagnostics
- Conclusions

PK/PD and confounding

- PK/PD Relationship:
  - Plasma drug concentration
  - versus expected clinical response
  - when patients are randomly assigned to concentrations.
- In parallel-group, dose-controlled trials, concentration is an outcome.
  - Observed concentration versus mean response may be different.
  - Call such a difference confounding.

A heuristic example: setup





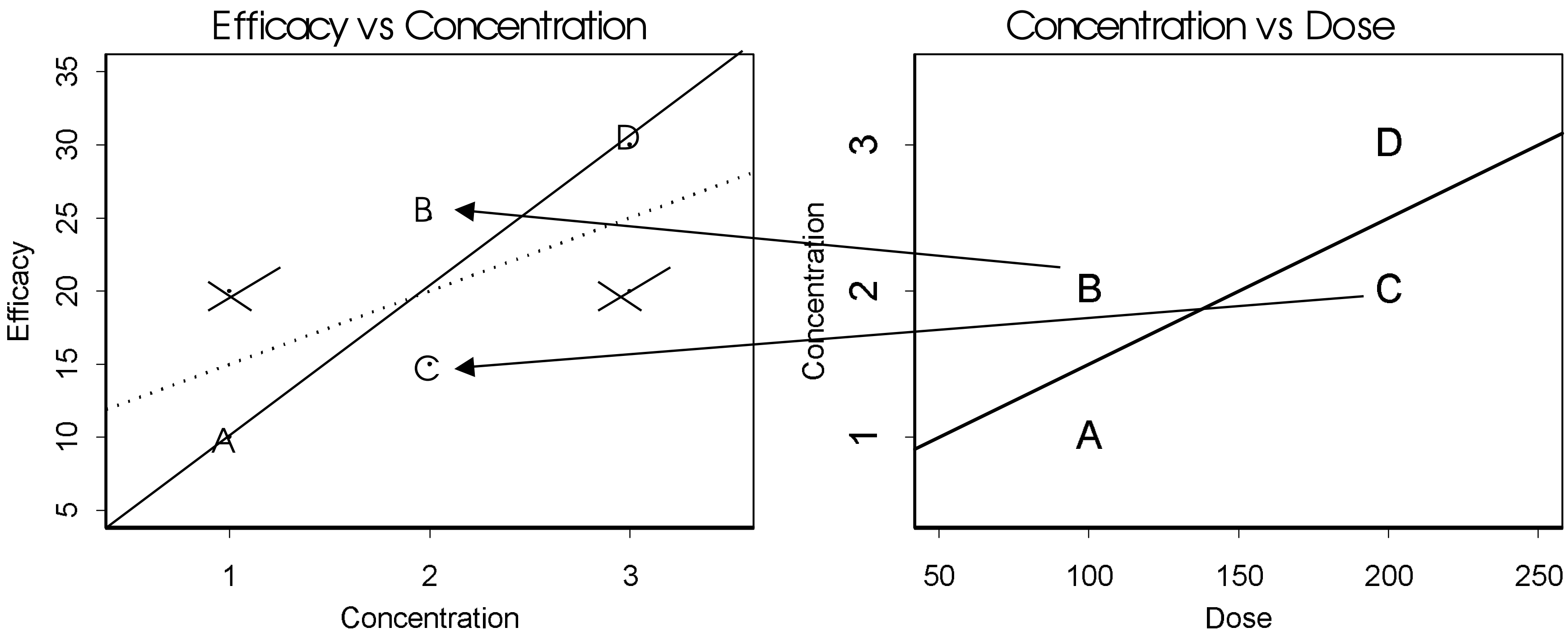
- PK/PD relationship, **concentration controlled trial**

- Dose/concentration relationship, **fixed-dose trial**

- Note correspondence of concentrations in the two plots.

NOVARTIS

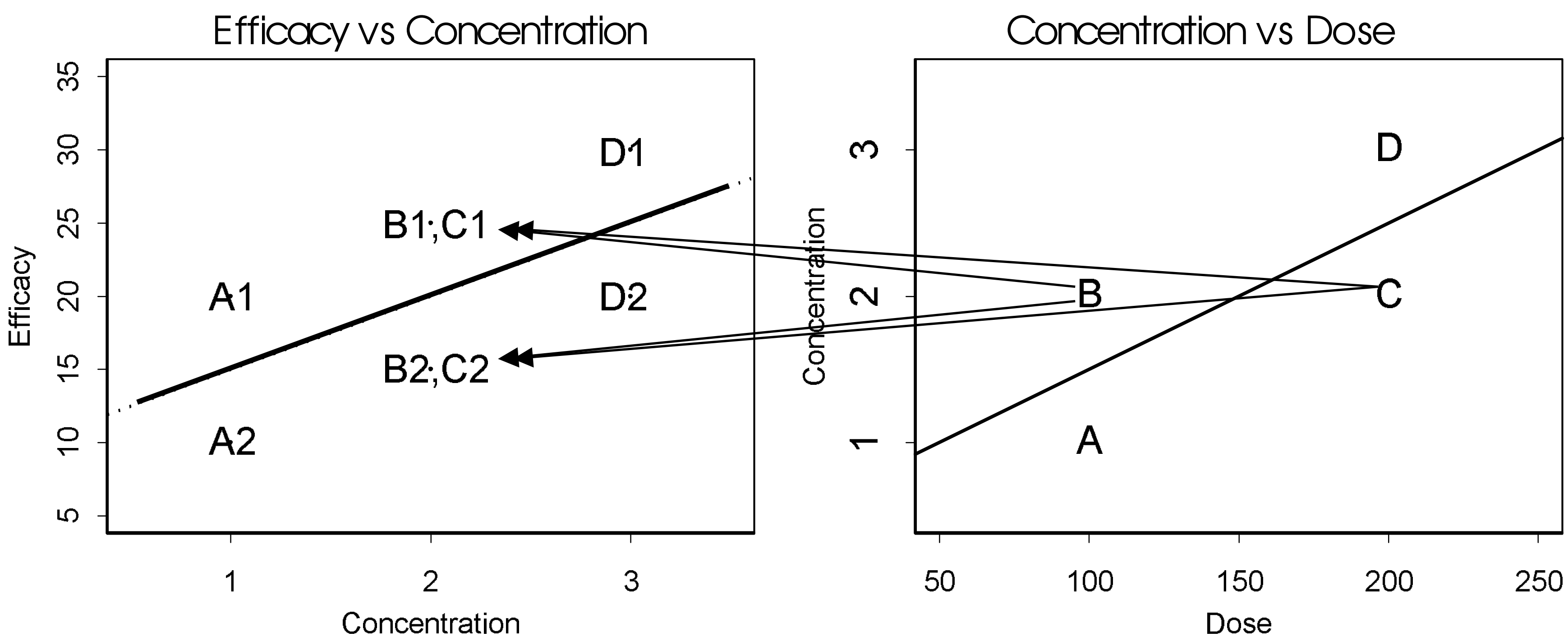
A heuristic example: confounding



- Suppose that in the fixed-dose trial, patients who have **higher concentrations at a given dose** also have **higher efficacy at a given concentration**
- The solid line is the least-squares fit to the resulting data
- It is a **biased** estimate of the true PK/PD relationship, the dotted line

NOVARTIS

A heuristic example: no confounding

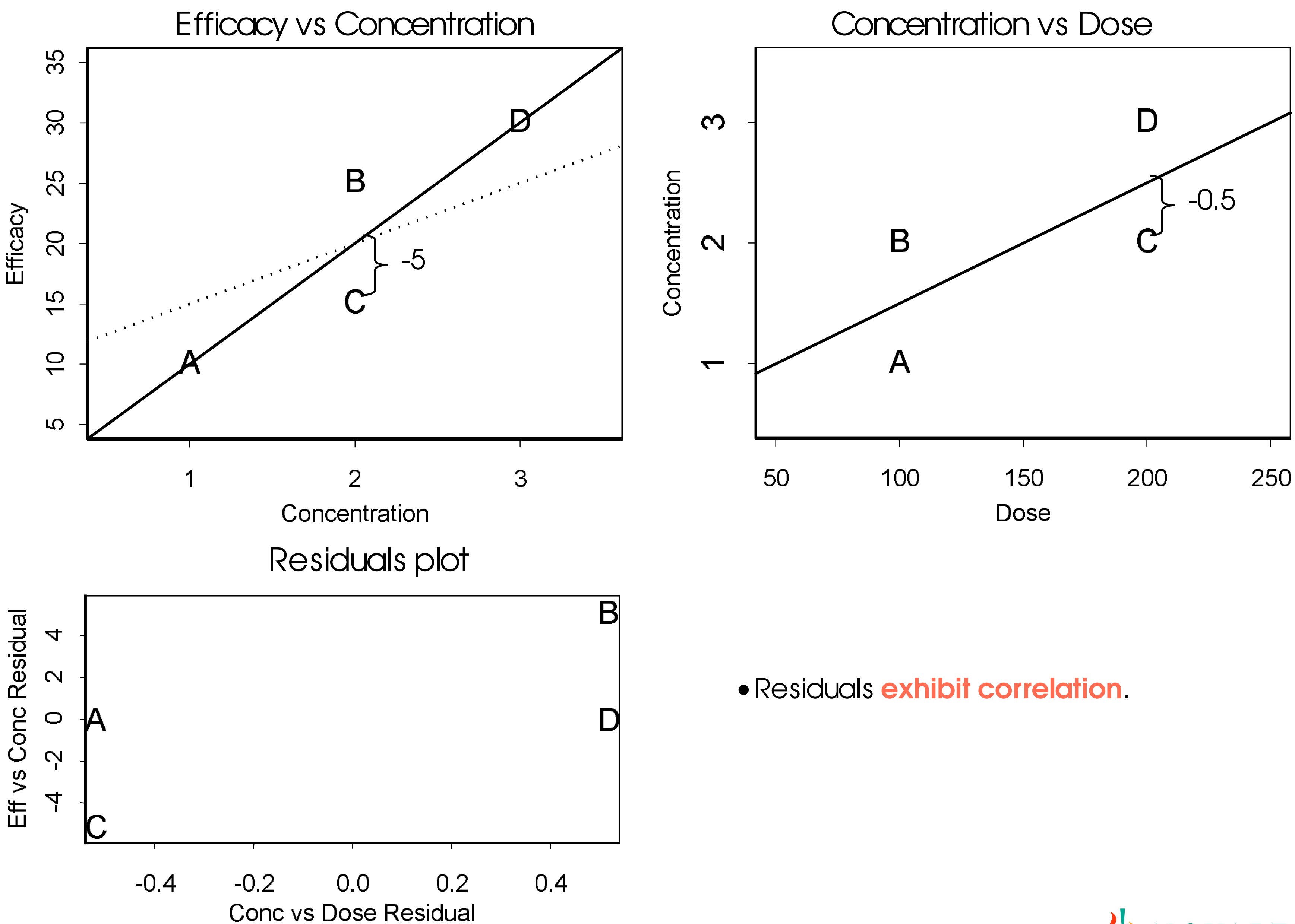


- Suppose that patients who have higher concentrations at a given dose are **equally likely to have high or low efficacy at a given concentration**, and the same for lower concentrations.

- The solid line is an **unbiased estimate** of the true PK/PD relationship

NOVARTIS

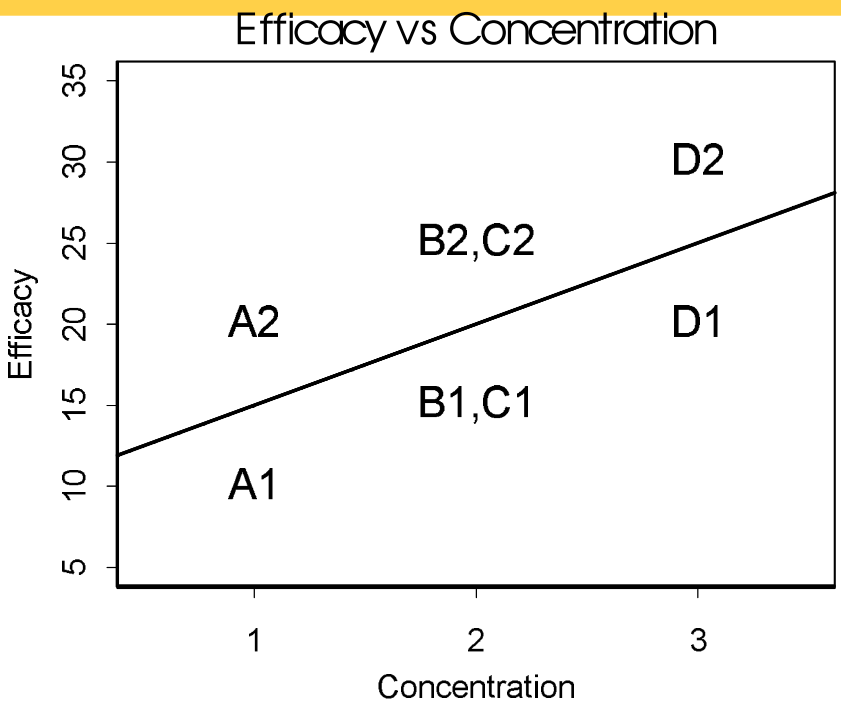
A heuristic example: residuals under confounding

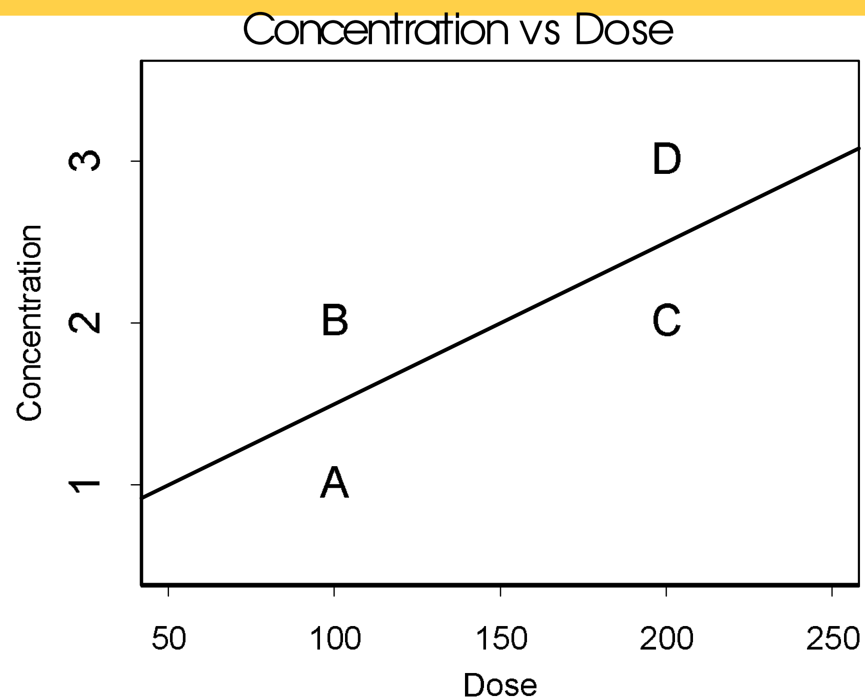


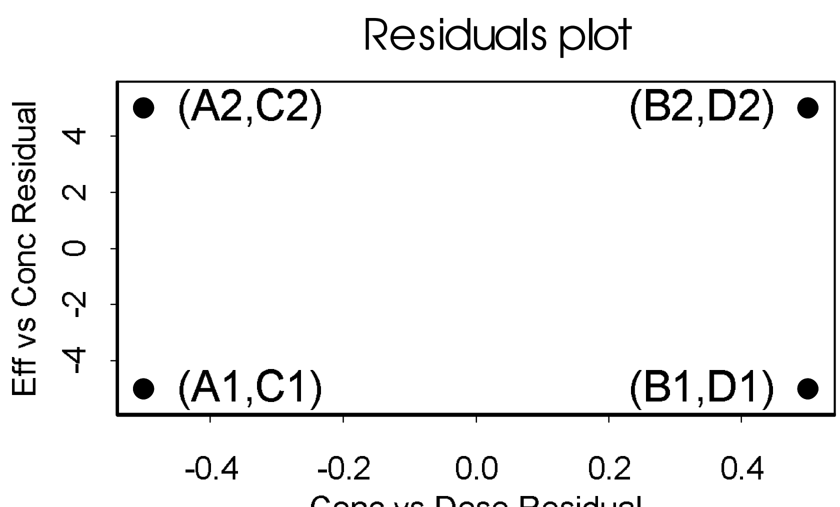
- Residuals **exhibit correlation**.

NOVARTIS

A heuristic example: Residuals, no confounding







- Residuals **do not** exhibit correlation.

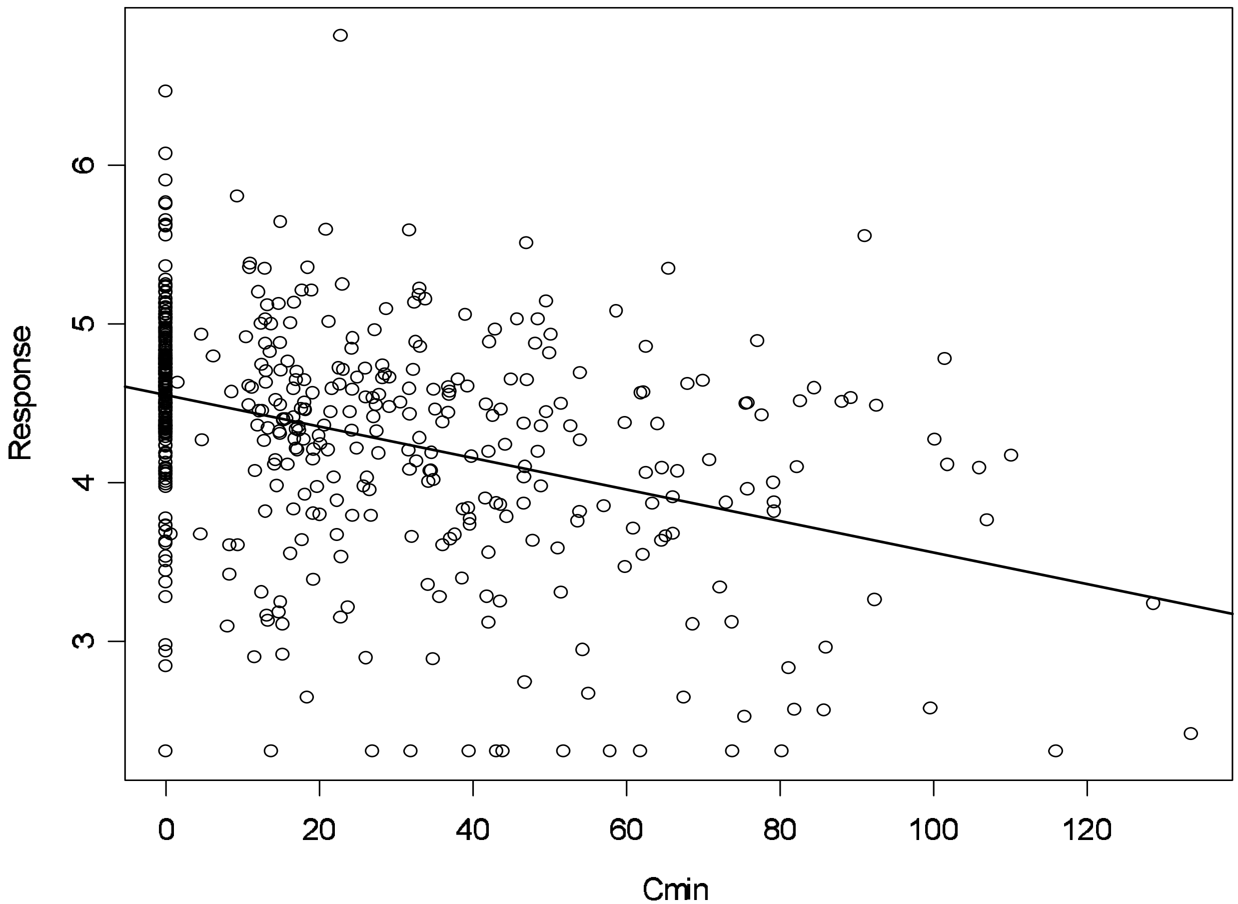
NOVARTIS

PK/PD and confounding, reprise

- A cause: patients differ with respect to confounders, covariates that affect both PK and PD.
- Confounders may not be observed.
- We'll assume such a cause.

A (nearly) real example

- Real drug, some details changed
- PD = quantitative clinical outcome
- Trough concentrations observed in parallel-group, dose-controlled study



A model to examine possible confounding

D_i = randomized maintenance dose for the i'th patient

c_i = steady-state trough concentration, C_{min}

y_i = efficacy response

$\eta_{1i}, \eta_{2i}, \ldots$ = **unobserved covariates**, which will be handled in modeling as independent random variables with mean zero

$\varepsilon_{ci}, \varepsilon_{yi}$ = random variables with mean zero, independent of each other and of $\eta_{1i}, \eta_{2i}, \ldots$

$$\log(c_i) = \alpha_0 + \alpha_1 \log(D_i) + \alpha_2\eta_{1i} + \alpha_3\eta_{2i} + \varepsilon_{ci} \qquad \text{(A2.1)}$$

$$y_i = \beta_0 + \beta_1 c_i + \beta_2\eta_{1i} + \beta_3\eta_{3i} + \varepsilon_{yi} \qquad \text{(A2.2)}$$

$$\log(c_i) = \alpha_0 + \alpha_1 \log(D_i) + \varepsilon'_{ci} \qquad \text{(A2.3)}$$

$$y_i = \beta_0 + \beta_1 c_i + \varepsilon'_{yi} \qquad \text{(A2.4)}$$

A model to examine possible confounding: 2

$$\log(c_i) = \alpha_0 + \alpha_1 \log(D_i) + \alpha_2 \eta_{1i} + \alpha_3 \eta_{2i} + \varepsilon_{ci} \quad \text{(A2.1)}$$

$$y_i = \beta_0 + \beta_1 c_i + \beta_2 \eta_{1i} + \beta_3 \eta_{3i} + \varepsilon_{yi} \quad \text{(A2.2)}$$

$$\log(c_i) = \alpha_0 + \alpha_1 \log(D_i) + \acute{\varepsilon}_{ci} \quad \text{(A2.3)}$$

$$y_i = \beta_0 + \beta_1 c_i + \acute{\varepsilon}_{yi} \quad \text{(A2.4)}$$

- η_1 contributes to both models
  - In (A.2.4) c_i is correlated with $\acute{\varepsilon}_{yi}$.
  - The least-squares estimates of β_0 and β_1 are biased.
  - **This bias is due to the confounder η_1.**
- (A.2.1) arises because patients were randomized to dose, not concentration
- If they were randomized to concentration, then in (A2.4) c_i would be independent of $\acute{\varepsilon}_{yi}$. The least squares estimates would be unbiased.

A model to examine possible confounding: 3

$$\log(c_i) = \alpha_0 + \alpha_1 \log(D_i) + \alpha_2 \eta_{1i} + \alpha_3 \eta_{2i} + \varepsilon_{ci} \quad \text{(A2.1)}$$

$$y_i = \beta_0 + \beta_1 c_i + \beta_2 \eta_{1i} + \beta_3 \eta_{3i} + \varepsilon_{yi} \quad \text{(A2.2)}$$

$$\log(c_i) = \alpha_0 + \alpha_1 \log(D_i) + \acute{\varepsilon}_{ci} \quad \text{(A2.3)}$$

$$y_i = \beta_0 + \beta_1 c_i + \acute{\varepsilon}_{yi} \quad \text{(A2.4)}$$

- But randomization to concentration is not necessary.
  - It suffices that **$\alpha_2 = 0$ and/or $\beta_2 = 0$ and/or $\mathrm{var}(\eta_1) = 0$**;
  - that is, no nontrivial covariate simultaneously influences both concentration and efficacy response.

Diagnostic #1

$$\log(c_i) = \alpha_0 + \alpha_1 \log(D_i) + \alpha_2 \eta_{1i} + \alpha_3 \eta_{2i} + \varepsilon_{ci} \qquad \text{(A2.1)}$$

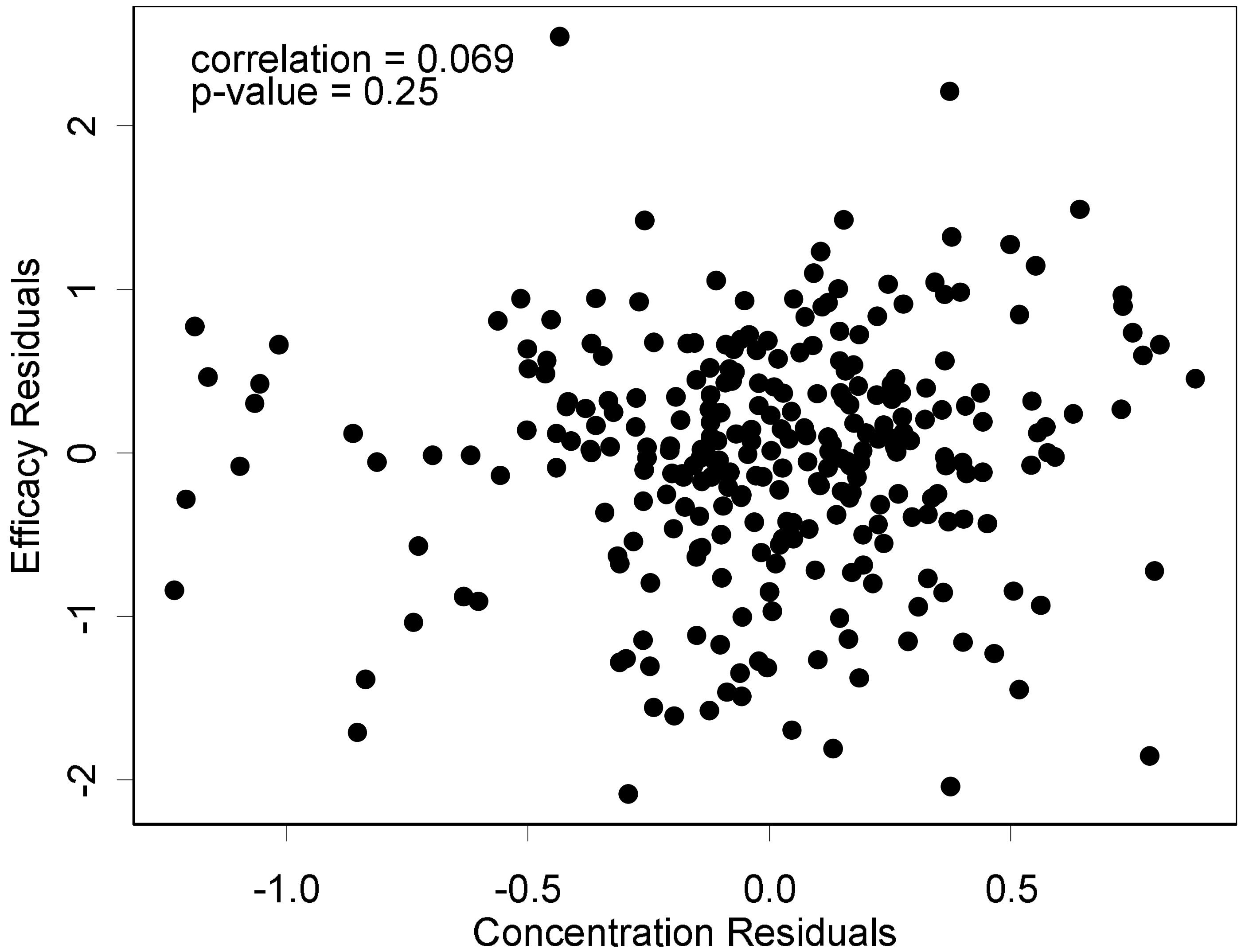
$$y_i = \beta_0 + \beta_1 c_i + \beta_2 \eta_{1i} + \beta_3 \eta_{3i} + \varepsilon_{yi} \qquad \text{(A2.2)}$$

$$\log(c_i) = \alpha_0 + \alpha_1 \log(D_i) + \acute{\varepsilon}_{ci} \qquad \text{(A2.3)}$$

$$y_i = \beta_0 + \beta_1 c_i + \acute{\varepsilon}_{yi} \qquad \text{(A2.4)}$$

- But randomization to concentration is not necessary.
  - It suffices that **$\alpha_2 = 0$ and/or $\beta_2 = 0$ and/or var(η_1) = 0**;
  - that is, no nontrivial covariate simultaneously influences both concentration and efficacy response.
- **Then** $\acute{\varepsilon}_{ci}$ and $\acute{\varepsilon}_{yi}$ are independent.
  - Assess residuals for correlation.
  - Absence of correlation is consistent with absence of confounding.

Diagnostic #1, applied



Diagnostic #2: Sensitivity analysis

- Origins: Cornfield et al (1959) smoking and lung cancer
- Rosenbaum and Rubin (1983):
  - Assess the impact of putative confounders on estimated treatment differences
  - Show that to have a clinically relevant impact, a confounder would need to have unreasonably large correlations with **both** treatment **and** response
- Methodology:
  - Assume there is an unobserved confounder
  - Assume "large" correlations with both concentration and efficacy response, but zero correlation with observed covariates.
  - Treat assumed confounder as missing data
  - Estimate model parameters by multiple imputation.
  - Assess impact.

Diagnostic #2, Sensitivity Analysis, cont'd

- Step 1: **How large** is a large correlation of a covariate with concentration or response?

Covariates and their correlations with PK and Efficacy

	Correlation with:		
	C_{min}	Efficacy Response	
Covariate	Active Drug	Placebo	Active Drug
Age	-0.06	0.07	-0.03
Height	-0.00	-0.08	0.05
Weight	-0.10	-0.07	0.10
Body Surface Area	-0.09	-0.08	0.10
Creatinine Clearance	-0.02	-0.09	0.06
Gender (1=Female, 0=Male)	0.02	0.00	-0.08
Covariate X[a]	-0.11	0.15	0.06
Covariate Y	-0.05	0.01	0.02
Covariate Z	-0.07	0.04	-0.03

a) Covariates X, Y, and Z are masked to preserve drug anonymity

Diagnostic #2, Sensitivity Analysis, cont'd

- Step 2: Imputation results

Condition	$\hat{\beta}_0$	$\hat{\beta}_1$
1. Model (A2.4)	4.58 ± 0.04	-0.0098 ± 0.0011
2. To 1., add covariates and their interactions[a] with C_{min}	4.58 ± 0.04	-0.0103 ± 0.0012
3. To 2., add simulated confounder having correlation **0.15** with C_{min} and efficacy	4.60 ± 0.04	-0.0105 ± 0.0012
4. To 2., add simulated confounder having correlation **0.20** with C_{min} and efficacy	4.60 ± 0.04	-0.0110 ± 0.0012
5. To 2., add simulated confounder having correlation **0.25** with C_{min} and efficacy	4.62 ± 0.04	-0.0117 ± 0.0012
6. To 2., add simulated confounder having correlation **0.30** with C_{min} and efficacy	4.63 ± 0.04	-0.0124 ± 0.0013

a) Covariates are centered when multiplying C_{min} to create the interaction, so that $\hat{\beta}_1$ estimates the slope with respect to C_{min} for average values of the covariates

Note: For conditions 3-6, parameter estimates are means of 100 imputations.

NOVARTIS

Diagnostic #3: Instrumental variables

- Find covariates (instrumental variables) that are correlated with concentration variables but uncorrelated with residual error in the model relating efficacy response to concentration (A2.4)
- Regress concentration variables on the instrumental variables and then regress efficacy response on the predictions from the first regression
  - "Two-stage regression", available in SAS PROC MODEL (SAS/ETS)
  - Estimators are consistent
- Hausman's test compares the two-stage-regression result with the OLS result to assess H_0: the OLS estimators are consistent (e.g., there is no confounding)
  - Hausman's test also available in SAS PROC MODEL

NOVARTIS

Diagnostic #3: Instrumental variables, cont'd

Estimation method and data	$\hat{\beta}_0$	$\hat{\beta}_1$	Hausman p-value
Ordinary least squares	4.56 ± 0.04	-0.010 ± 0.001	
Two-stage regression	4.58 ± 0.04	-0.011 ± 0.001	0.47

Conclusions

- The true PK/PD relationship is defined in terms of randomized concentrations.
- But in dose-controlled studies, concentration is also an outcome.
- Such studies may permit only a biased estimate of the true PK/PD relationship.
- The existence of such confounding cannot be definitively disproven within the dose-controlled study itself.
- However, diagnostics may be derived that lend credence to an assumed absence of confounding.