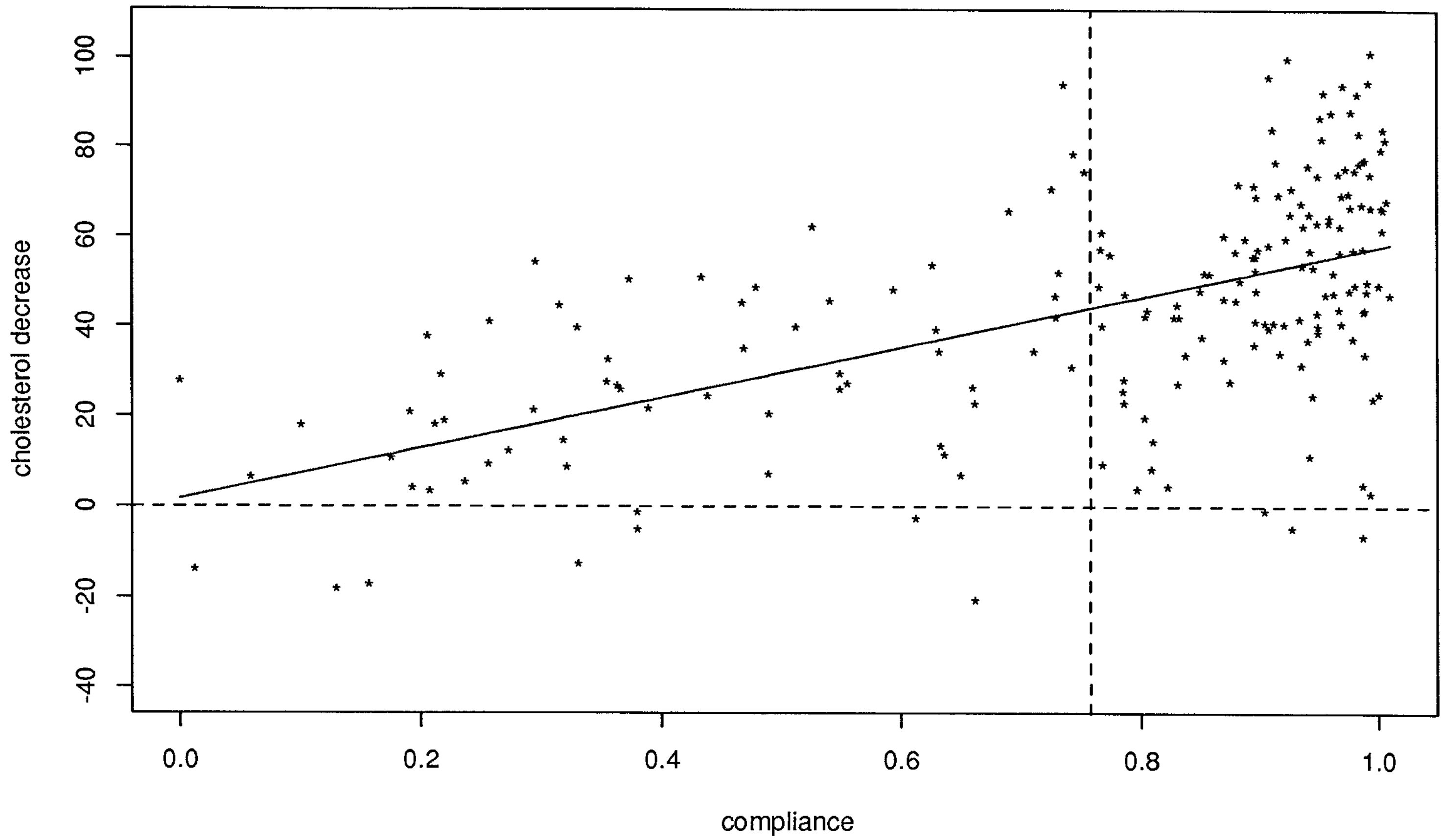
Compliance Analysis in Randomized Trials

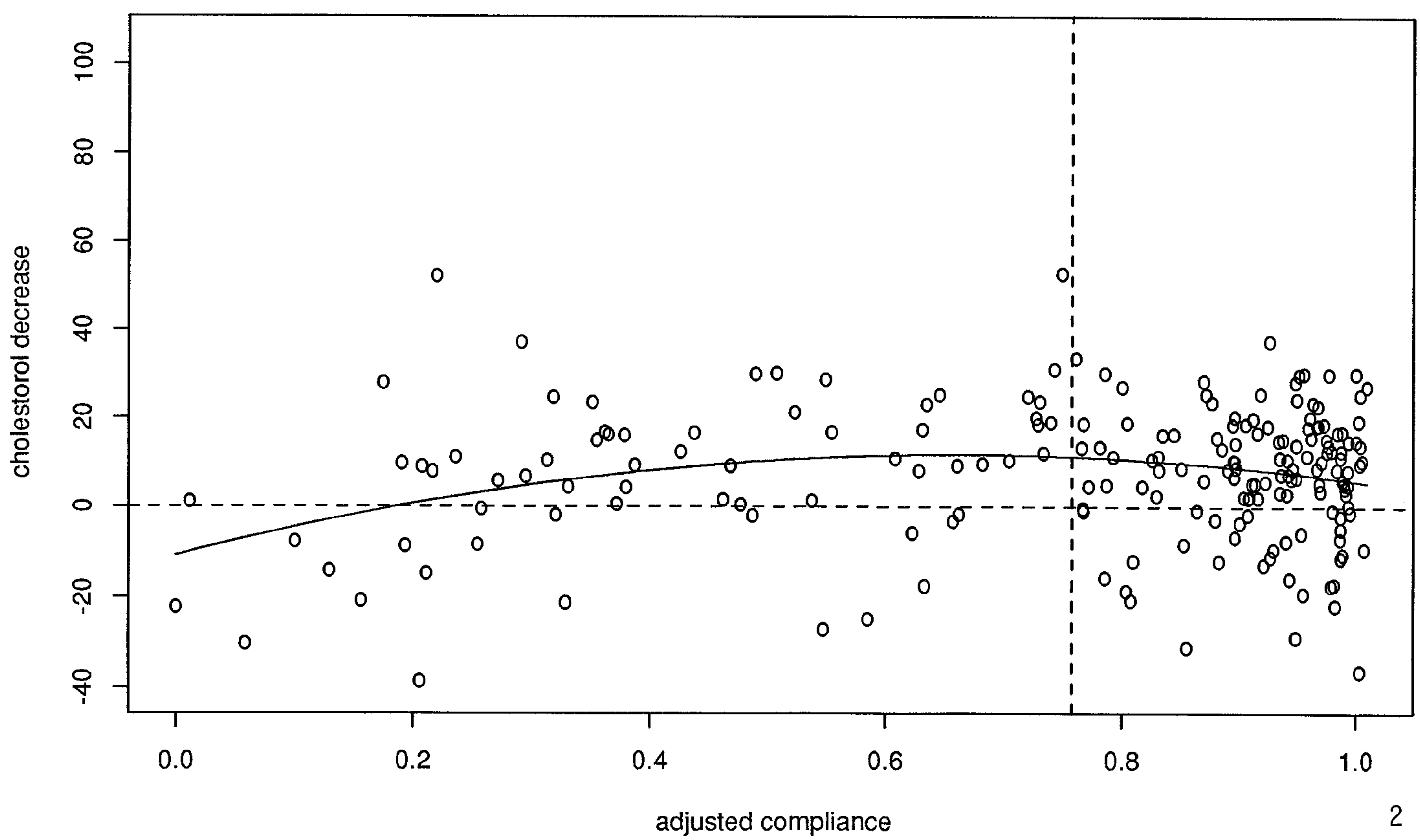
Bradley Efron

Stanford University

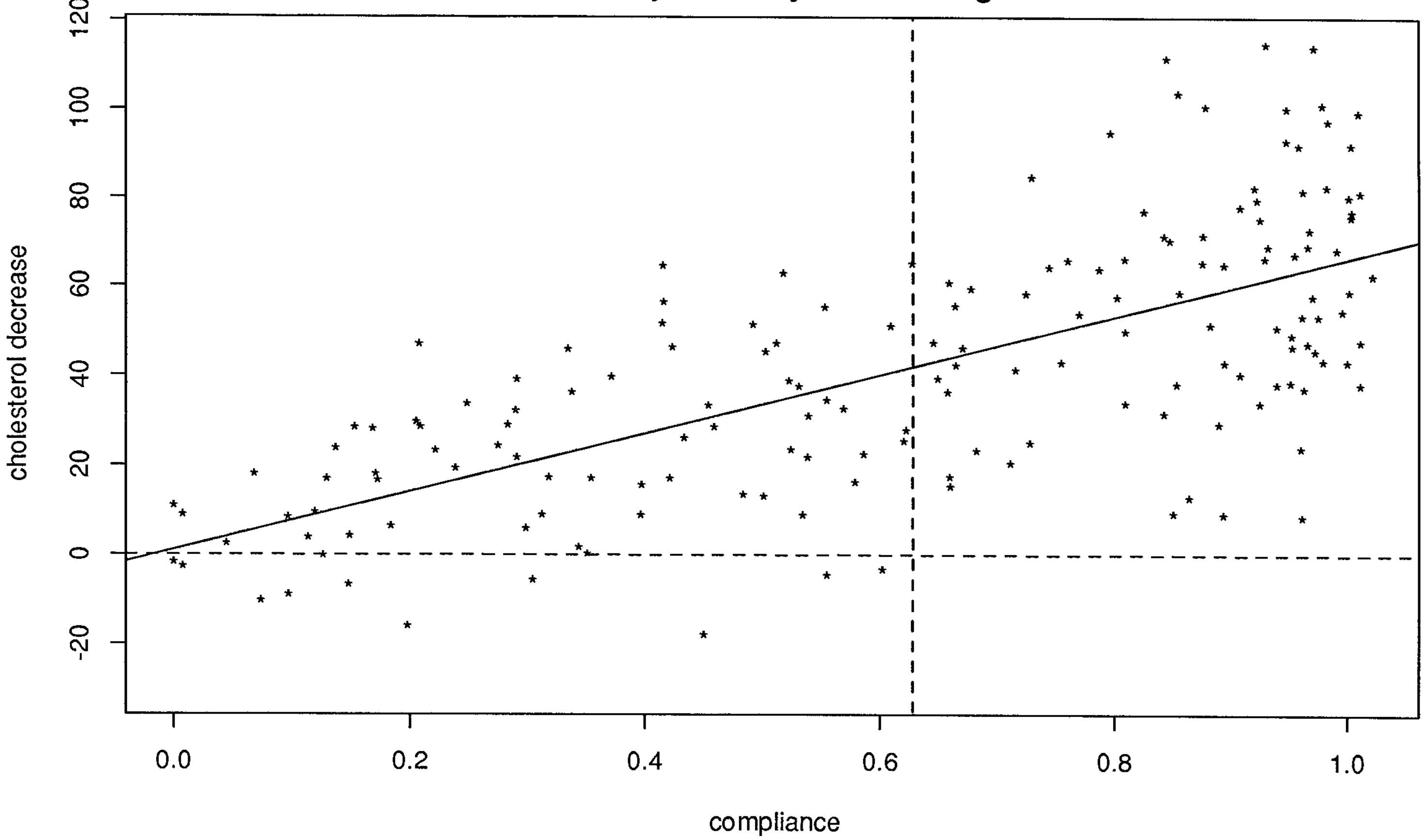
Minnesota Treatment Group: Cholestyramine, 200 subjects, 2yr averages



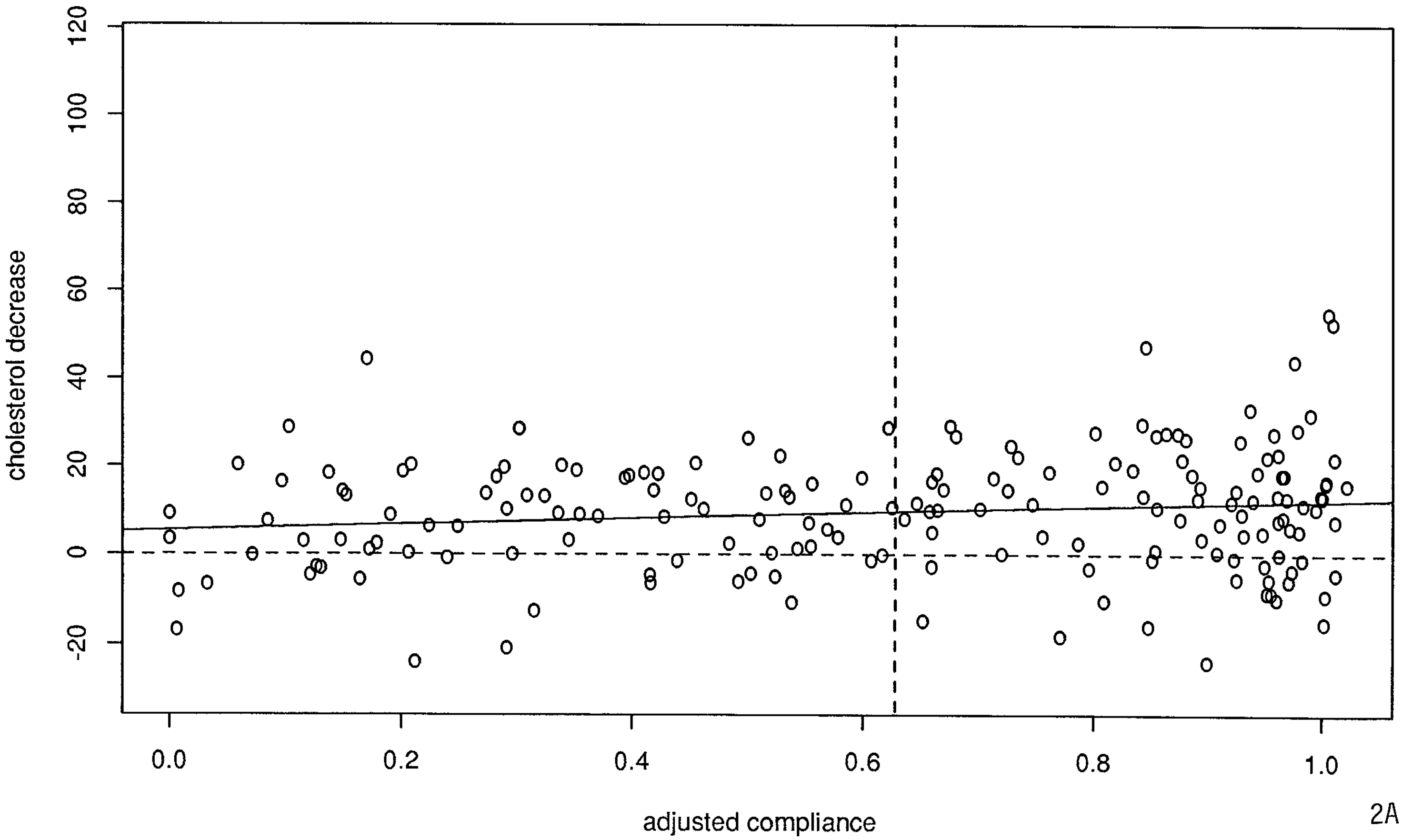
Control group: 201 subjects



Stanford Treatment Group: Cholestyramine, 168 subjects, 2 year averages



Stanford Control Group 180 Subjects



2A

Model (Efron and Feldman, 1991, JASA, p. 9-26)

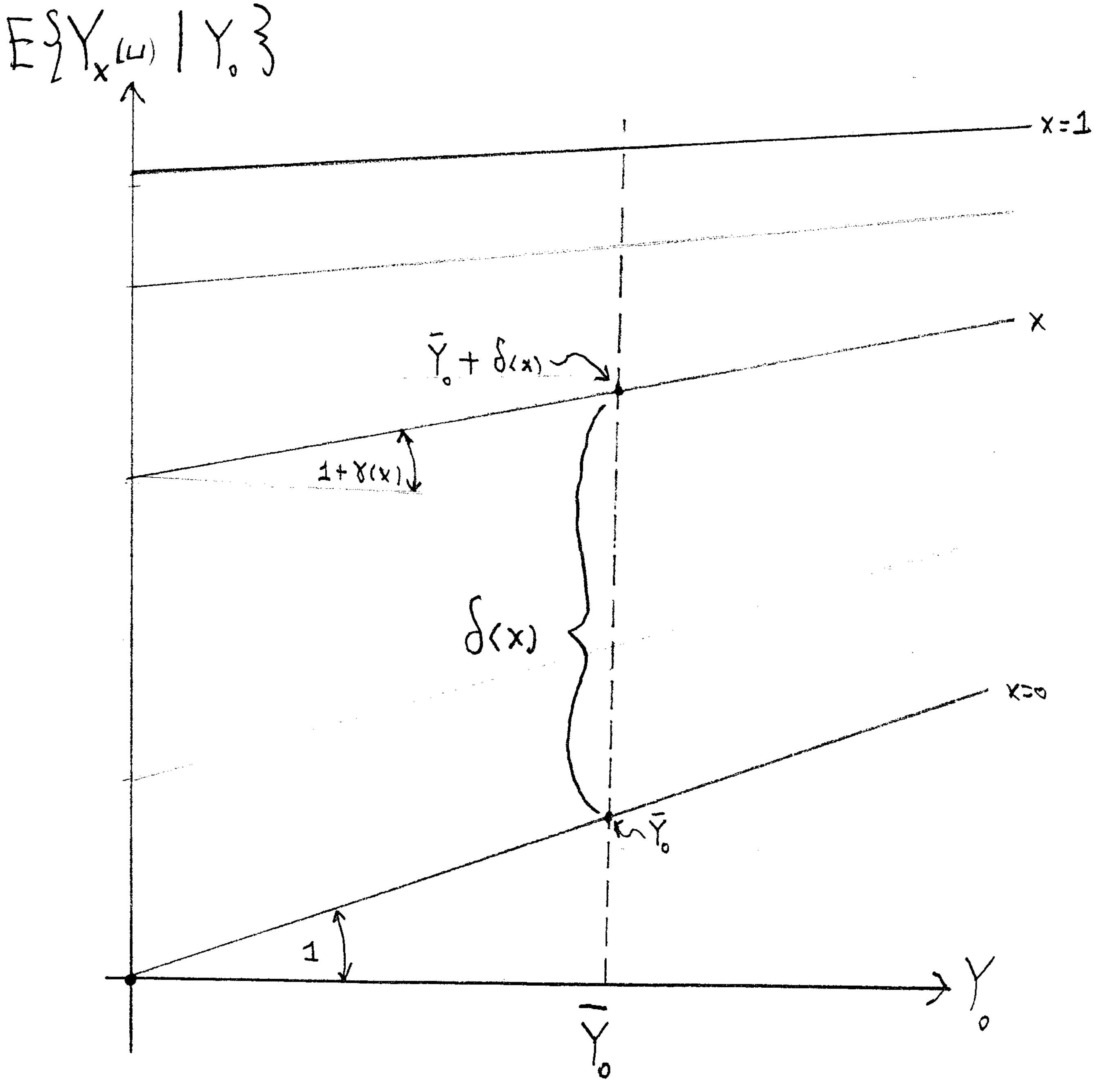
- $$Y_x(u) = Y_0(u) + \delta(x) + \gamma(x)[Y_0(u) - \bar{Y}_0] + e_x(u)$$

where

$$\begin{aligned}
Y_x(u) &= \text{Response to dose } x \text{ for subject } u \\
Y_0(u) &= \text{Placebo response} \\
\delta(x) &= E\{Y_x(u) - Y_0(u)\} \\
&= \text{true dose-response curve} \\
\gamma(x) &= \text{interaction term} \\
\bar{Y}_0 &= E\{Y_0(u)\} \\
&= \text{average placebo response} \\
E\{e_x(u)\} &= 0
\end{aligned}$$

- $\delta(0) = 0,\ \ \gamma(0) = 0,\ \ e_0(u) = 0$

- $x = 1$ is "full dose"



Linear Regression of Y_x on Y_0

Compliance – Response Regressions

- $z(u)$ = compliance of subject u
  ($z = 1$ is full compliance)

- $C(z) = E\{y_c(u)|z(u) = z\}$
  $= E\{Y_0(u)|z(u) = z\}$

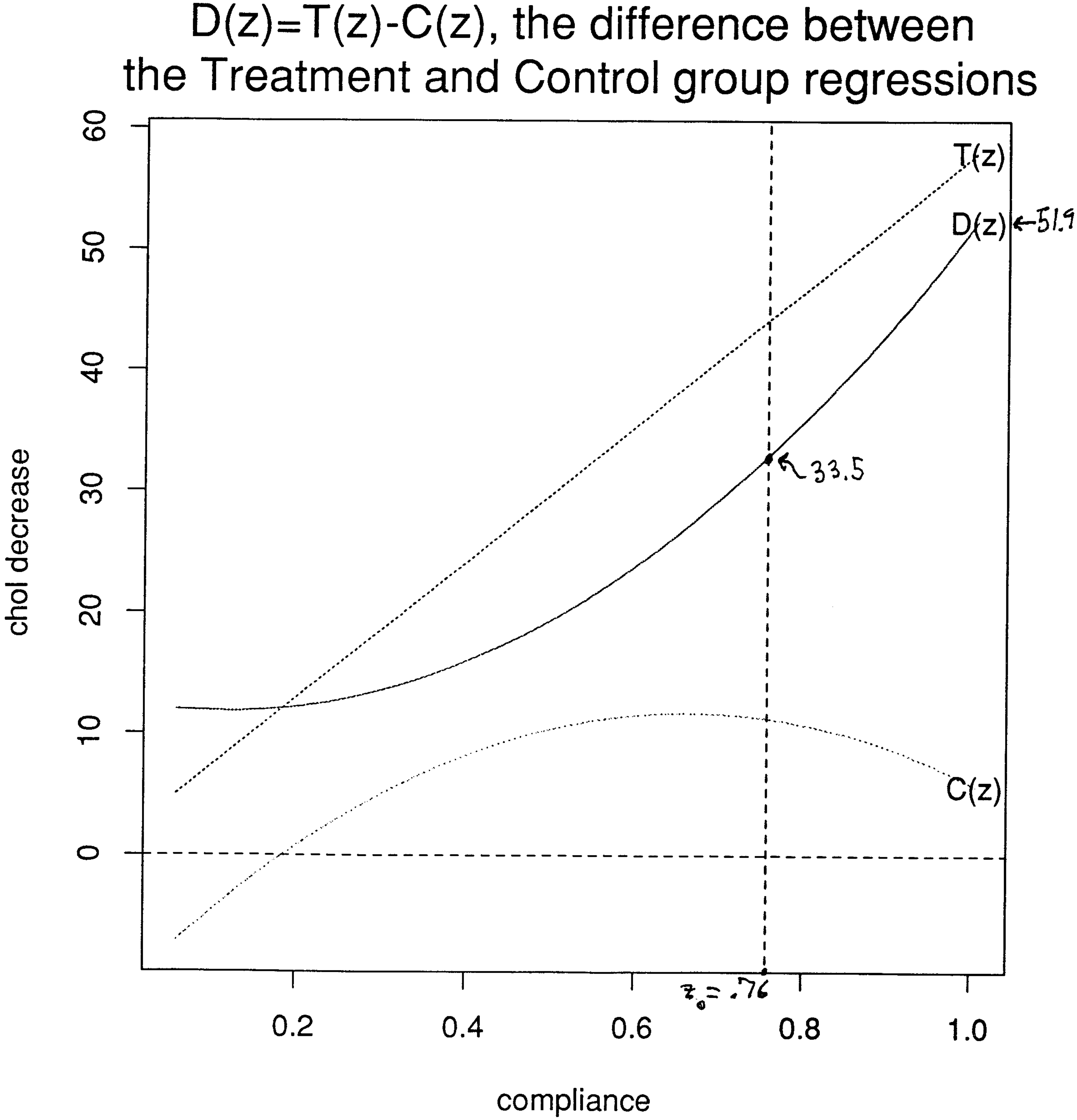
- $T(z) \;\; = E\{y_T(u)|z(u) = z\}$

$$= \; E\{Y_0 + \delta(x) + \gamma(x)[Y_0 - \bar{Y}_0] + e_x|z\}$$

$$= \; C(z) + \delta(z) + \gamma(z)[C(z) - \bar{Y}_0]$$

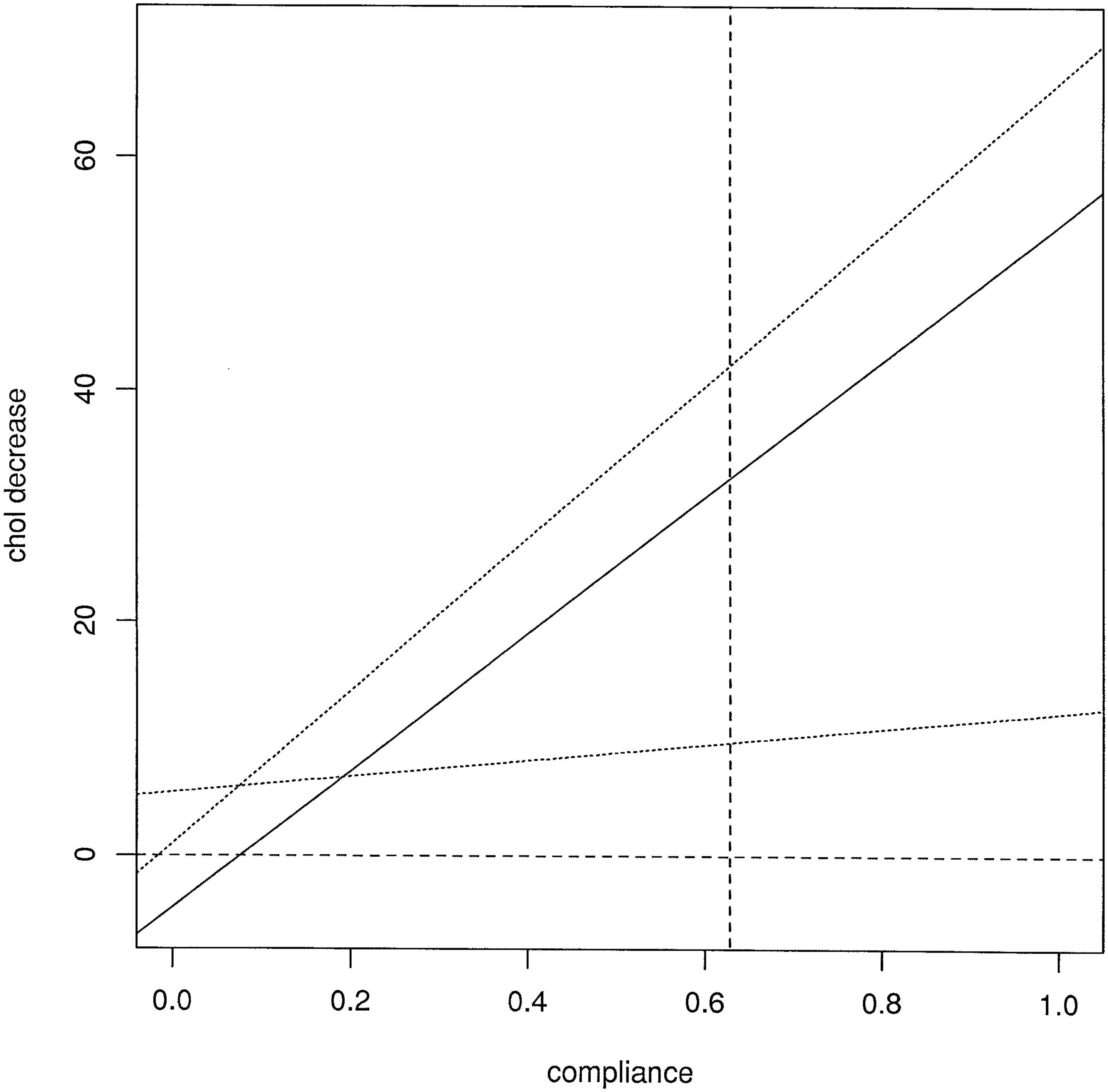
$$\boxed{\begin{aligned} D(z) &= T(z) - C(z) \\ &= \delta(z) + \gamma(z)[C(z) - \bar{Y}_0] \end{aligned}}$$

- Assumes $E\{e_x(u)|z(u) = z\} = 0$.



D(z)=T(z)-C(z), the difference between
the Treatment and Control group regressions
T(z)
D(z)
←51.9
33.5
C(z)
z_0 = .76
0
10
20
30
40
50
60
chol decrease
0.2
0.4
0.6
0.8
1.0
compliance

D(z)=T(z)-C(z) for the Stanford Data



QUESTION How well does $D(z)$ approximate $\delta(z)$?

$$\boxed{\delta(z) = D(z) - \gamma(z)[C(z) - \bar{Y}_0]}$$

- $\delta(z) = D(z)$ if $C(z) = \bar{Y}_0$

- If $C(z)$ linear then $C(z_0) = \bar{Y}_0$

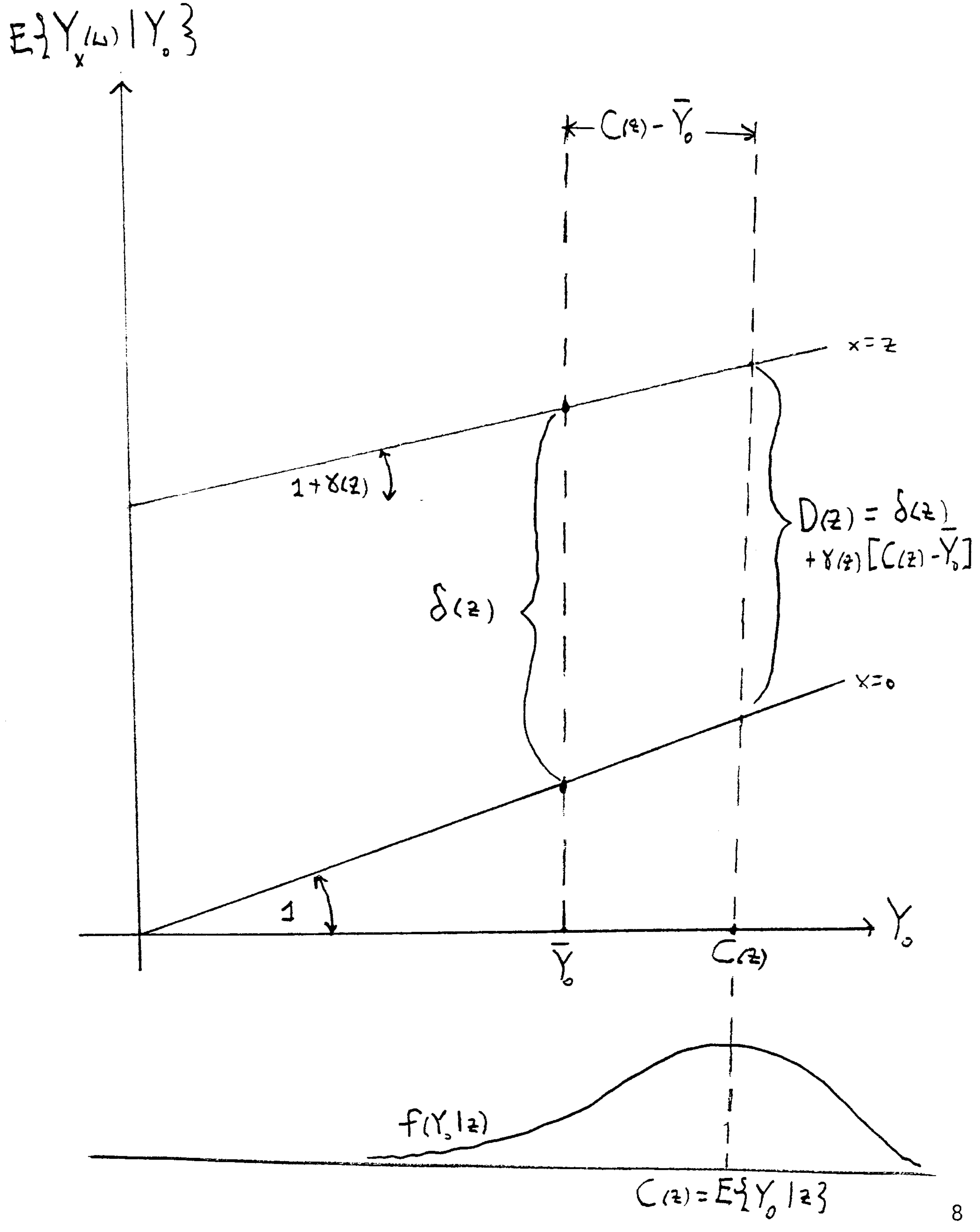
- Could define "z_0" by $C(z_0) = \bar{Y}_0$
  ($z_0 = .38$ and $.94$ for Minnesota data)

- For Minnesota data $D(1) = 51.9$ and

$$C(1) - \bar{Y}_0 = -1.4$$

so if $|\gamma(1)| \leq 1$ then

$$|\delta(1) - 51.9| \leq 1.4$$



E{Y_x(u) | Y_0}
C(z) - Ȳ_0
x = z
1 + γ(z)
D(z) = δ(z) + γ(z) [C(z) - Ȳ_0]
δ(z)
x = 0
1
Y_0
Ȳ_0
C(z)
f(Y_0 | z)
C(z) = E{Y_0 | z}

- Want $C(z) = E\{Y_0(u)|z_T(u) = z\}$

  Compliance for Treatment subject

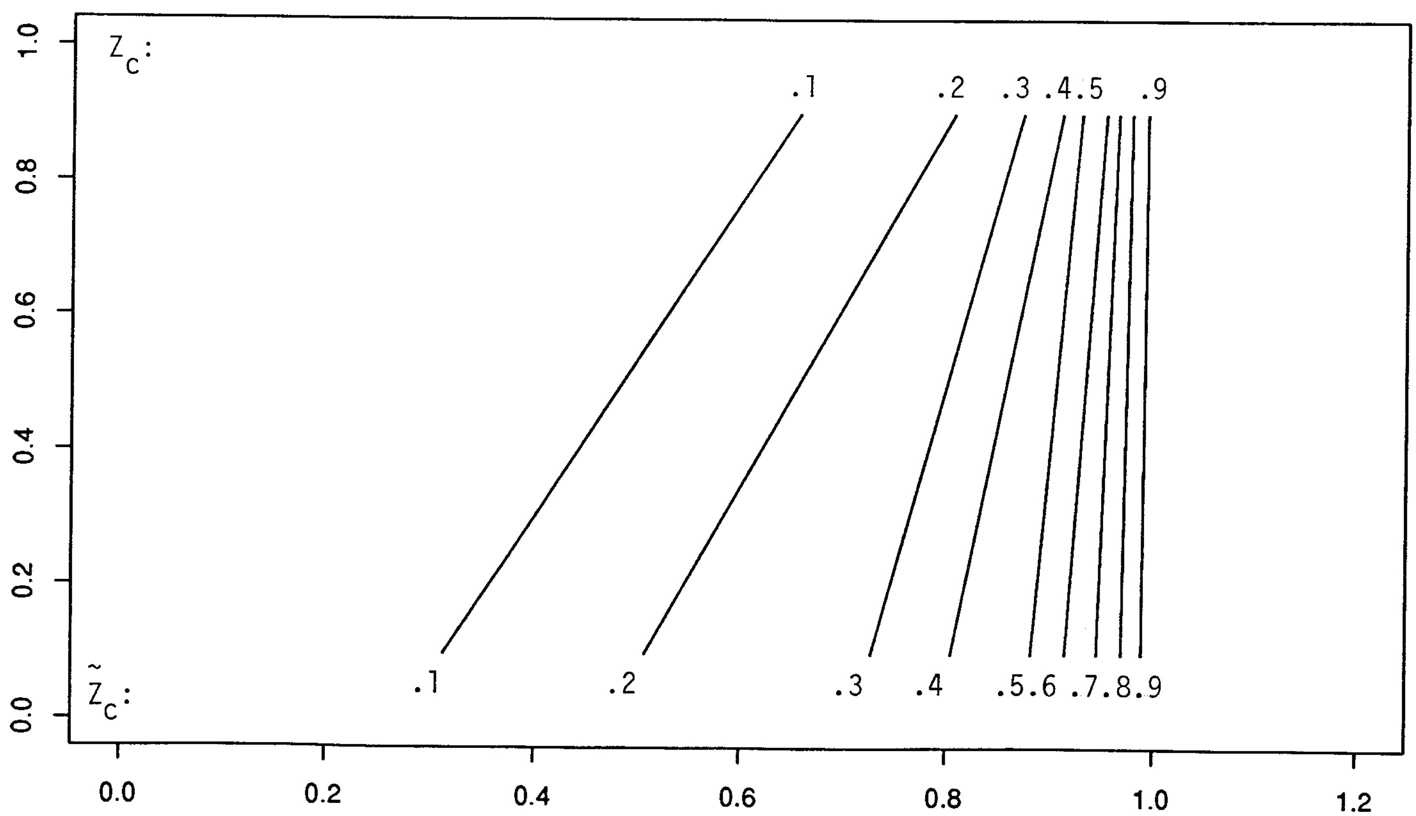
- Can estimate $E\{Y_0(u)|z_C(u) = z\}$

  Compliance for Control subject

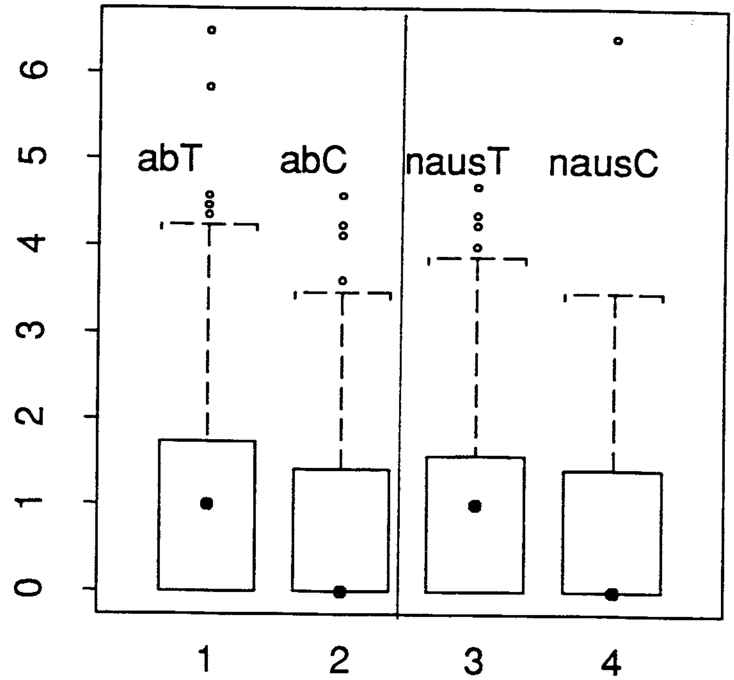
- Perfect Blind: $z_T(u) = z_C(u)$
  [sufficient: $z_T(u) = M(z_C(u))$ for monotone M]

- Percentile Matching: map $z_c \rightarrow \tilde{z}_c$
  ("Adjusted Compliance") so that

$$\tilde{z}_C^{(\alpha)} = z_T^{(\alpha)} \text{ for } 0 < \alpha < 1$$

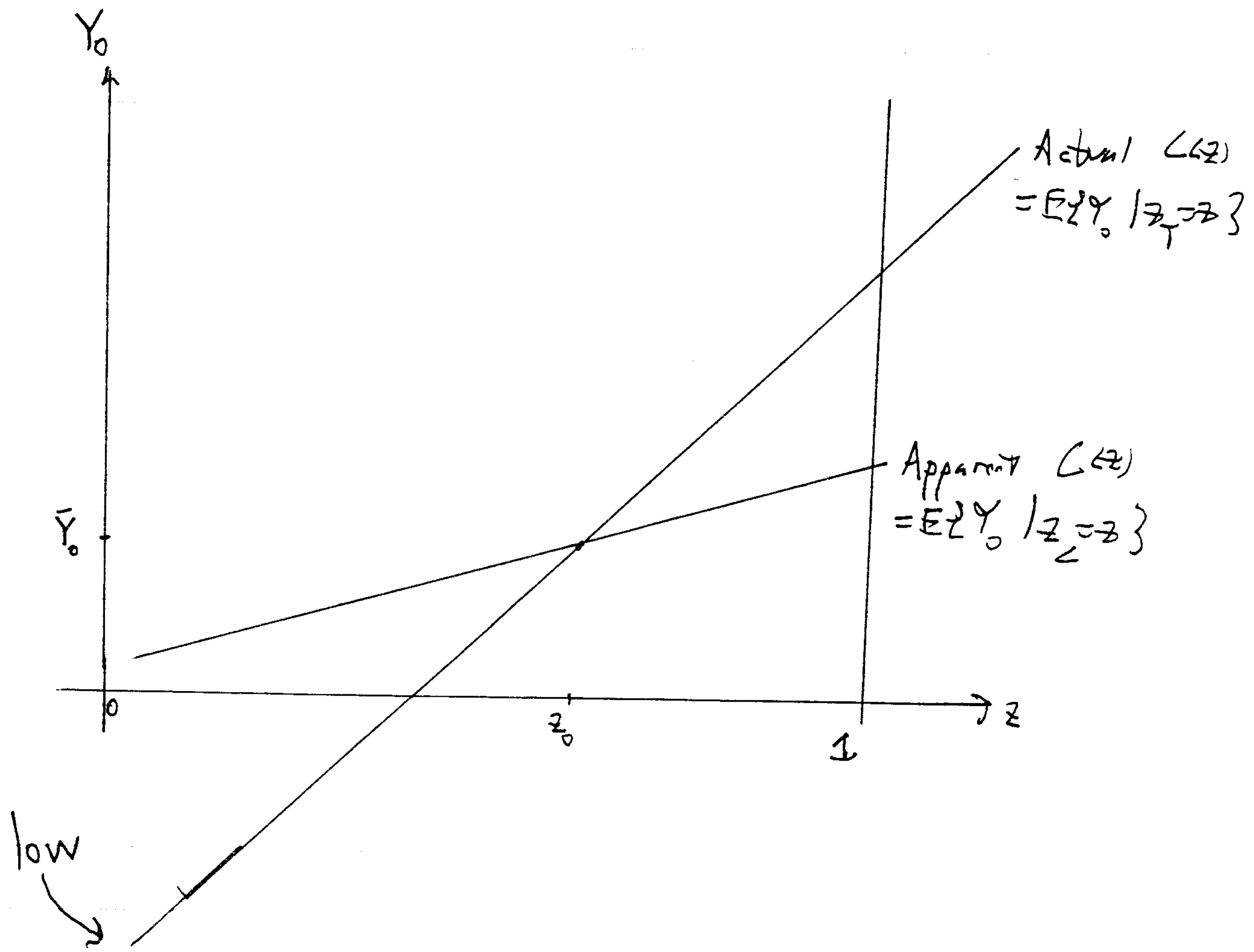


Abdominal Pain and Nausea, Comparing Treatment and Control Groups



tvalues of compliance on
eight separate adverse reactions
Minnesota Treatment group:

ab	bel	cons	diar	gas	hrt	naus	vom
-3.39	-2.74	-2.92	-2.56	-2.3	-2.42	-4.46	-2.78

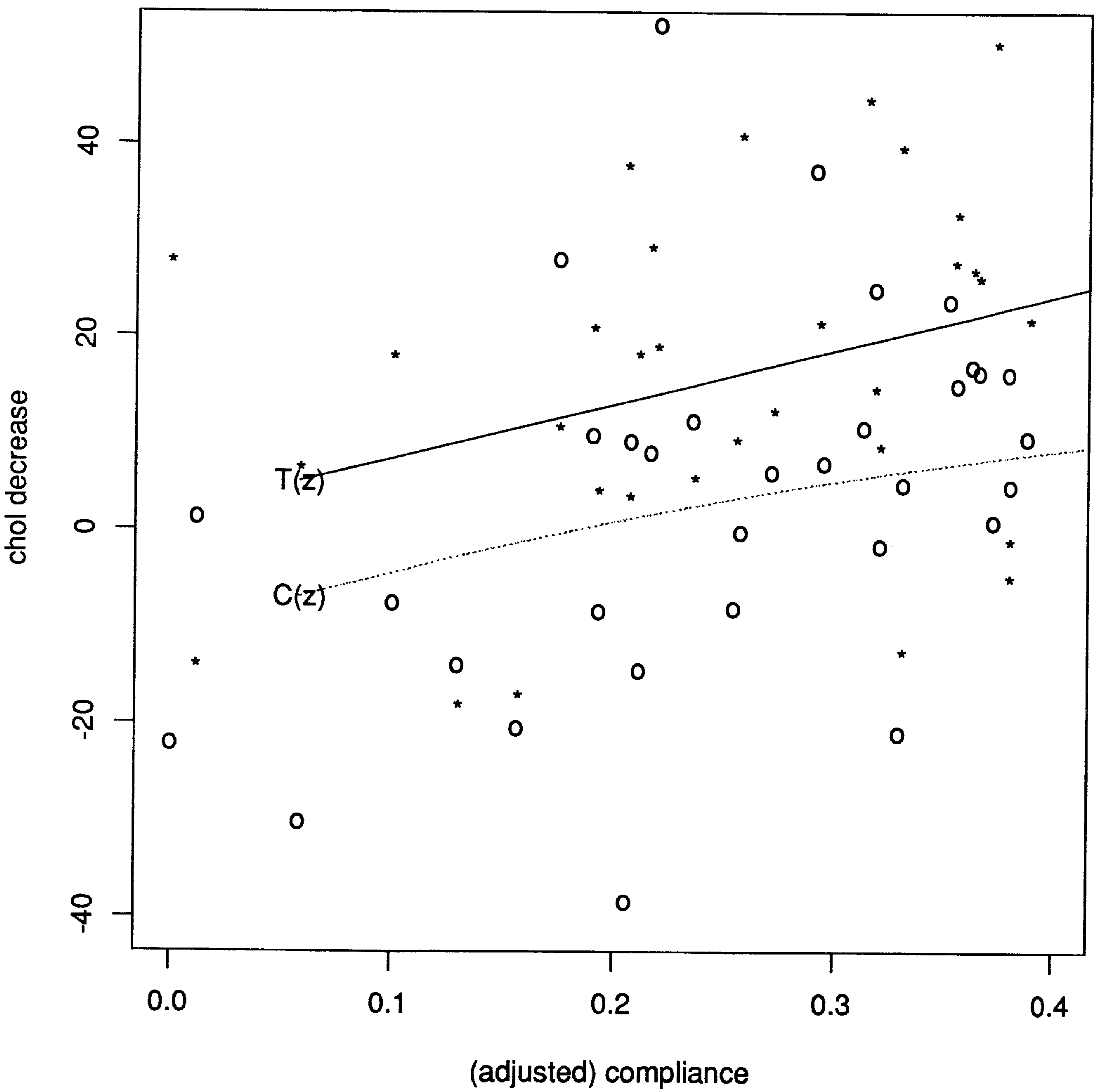


- BAD CASE: Actual $C(z)$ much steeper than Apparent $C(z)$

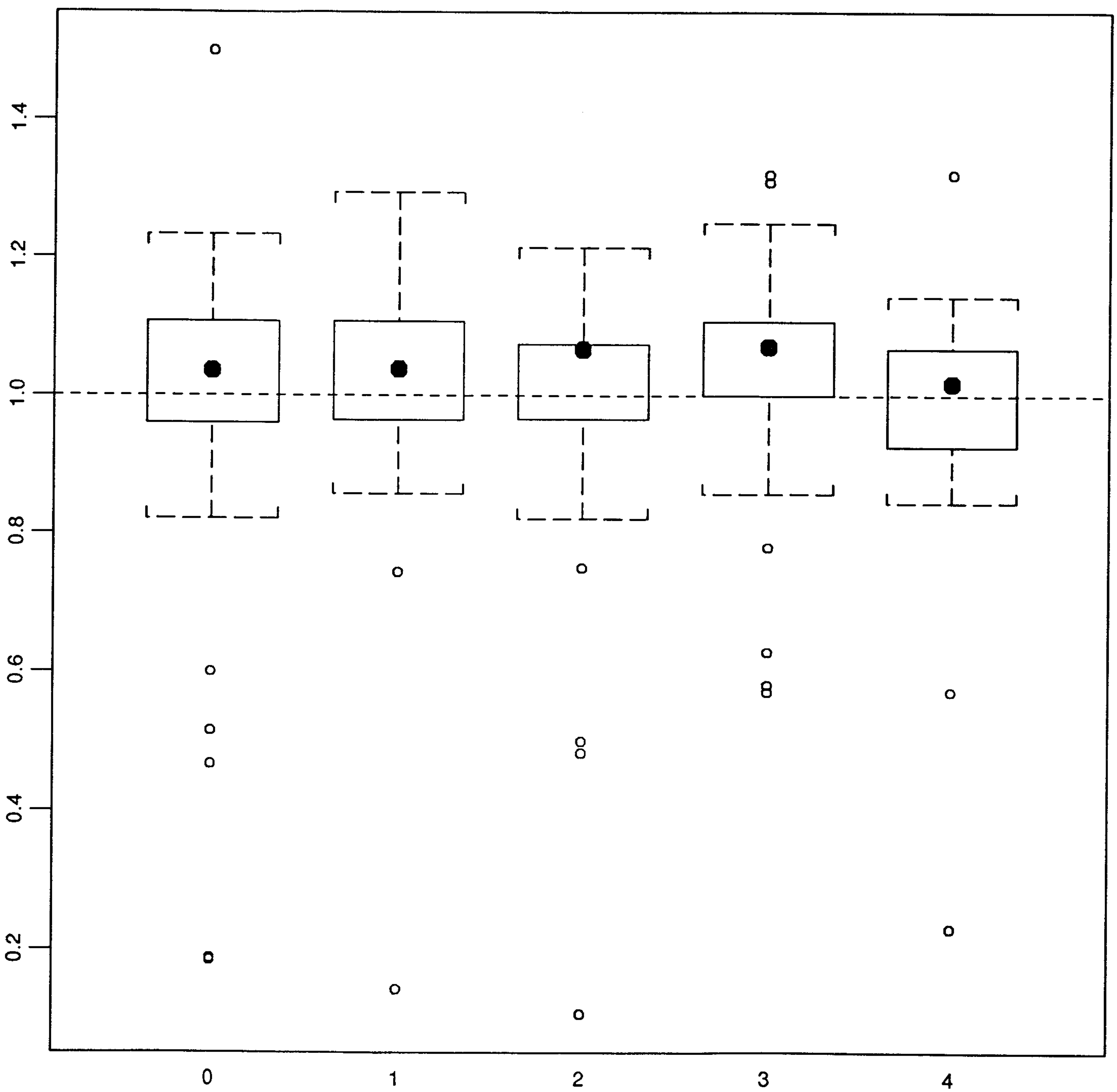
- Makes $D(1) = T(1) - C(1)$ look too big

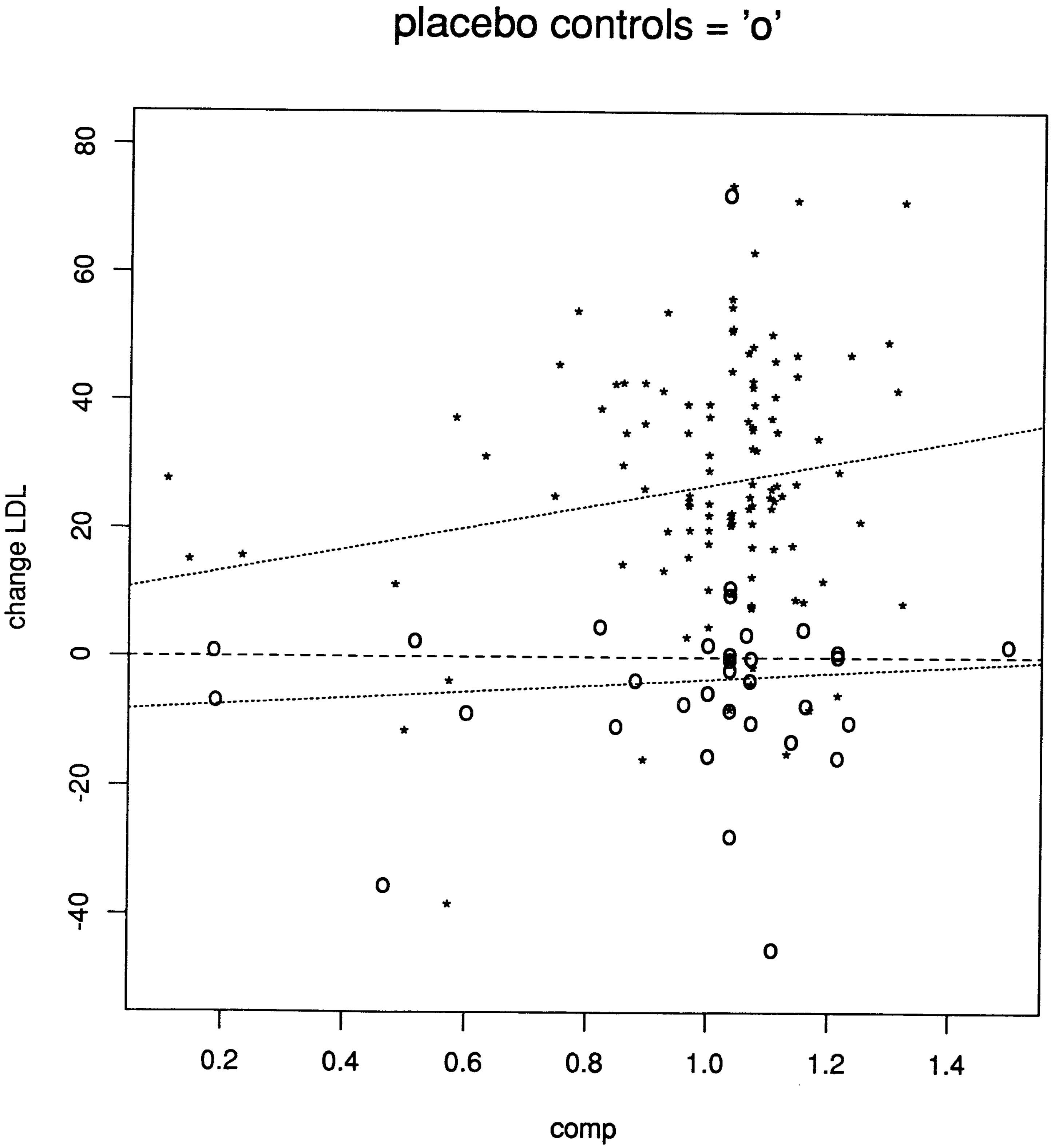
- But then the y_T values for z_T near 0 should be less than y_C values for z_C near 0.

Minnesota data for low compliances

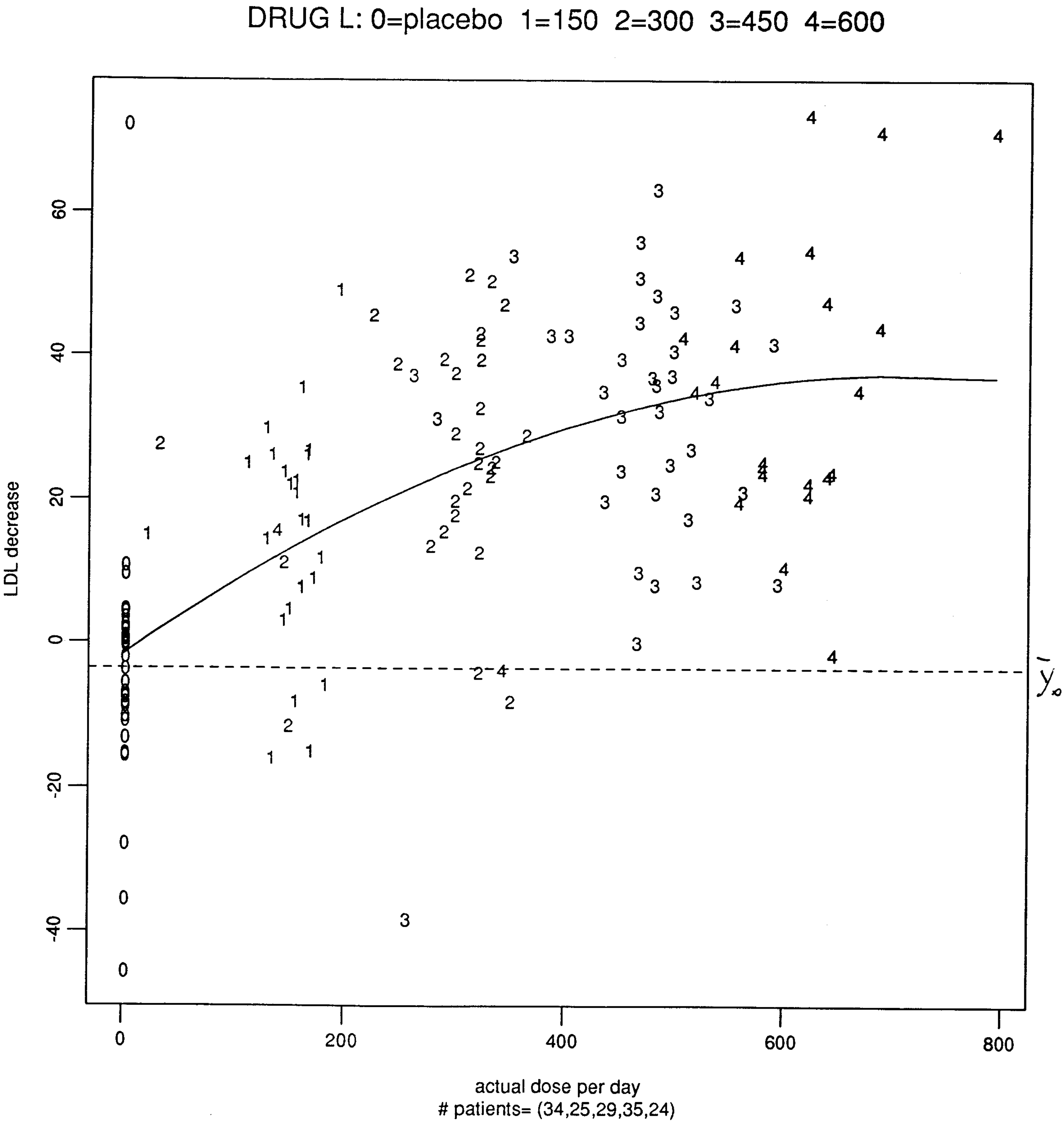


compliance by group for Drug L





placebo controls = 'o'
change LDL
80
60
40
20
0
-20
-40
0.2
0.4
0.6
0.8
1.0
1.2
1.4
comp


DRUG L: 0=placebo 1=150 2=300 3=450 4=600
LDL decrease
actual dose per day
patients= (34,25,29,35,24)

THREE-DOSE EXPERIMENT

- Besides Treatment (full dose) and Control (zero dose) have a Fractional Dose group (fraction f of full dose).

- Let $T_1(z) = E\{y_T|z\}$ and $T_f(z) = E\{y_F(z)|z\}$

- Assume $C(z)$ linear, then EF model gives

$$\delta(z) = \frac{z_0/z - 1/f}{1 - 1/f} T_1(z) + \frac{1 - z_0/z}{1 - 1/f} T_f(z) - \bar{Y}_0$$

- Can estimate $\delta(z)$ for any value of z.

- Interaction $\gamma(x)$ disappears.

- Control group needed only to estimate $\bar{Y}_0$.

<u>Ideal Choice of Third Dose "f"</u>

<u>Theorem</u> Suppose $T_1(z), T_f(z)$, and $C(z)$ are linear, and that

$$z(u) \sim (z_0, \sigma_z^2).$$

Then the choice of f that minimizes the variance of $\hat{\delta}(z)$ is

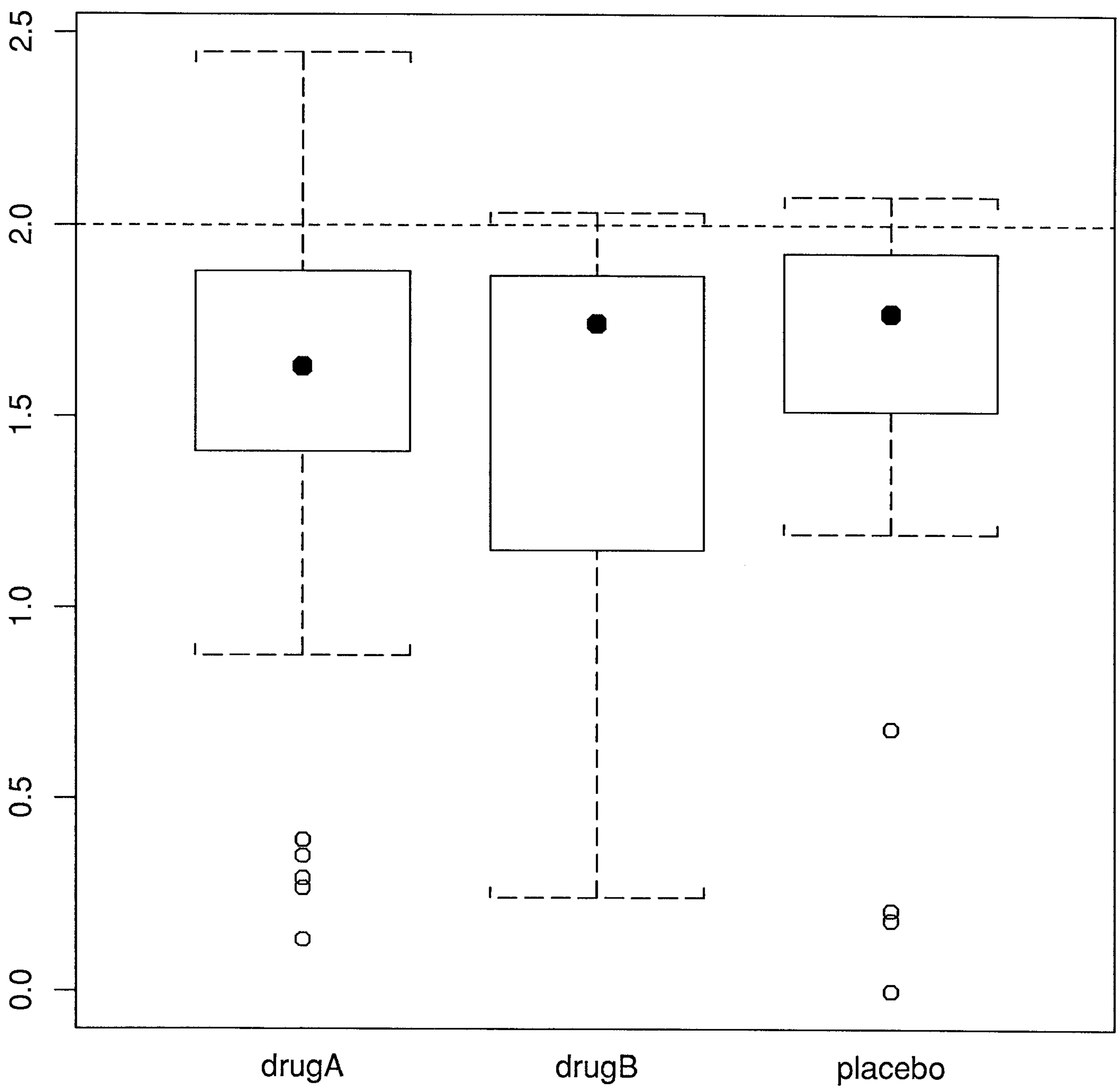
$$\boxed{\frac{1}{\hat{f}} = z_0 - \frac{1 - z_0}{1 + 2(1 - z_0)^2/\sigma_z^2}}$$

- <u>Minnesota</u> $z_0 = .758$ $\hat{\sigma}_z = .266$ gives

$$\hat{f} = 1.50$$

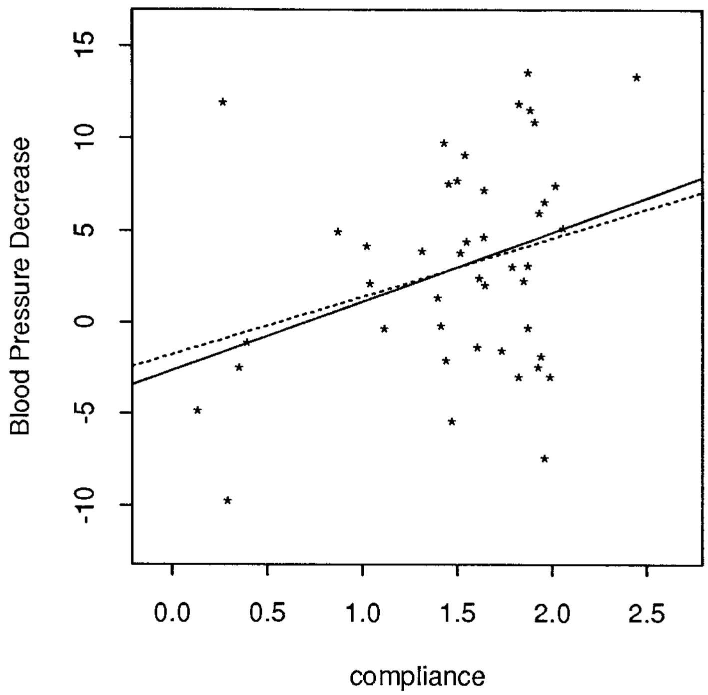
- Always have $\frac{1}{z_0} \leq \hat{f} \leq \frac{1}{2z_0 - 1}$ for $z_0 > \frac{1}{2}$.

COMPLIANCE IN 3-ARM BLOOD PRESSURE STUDY

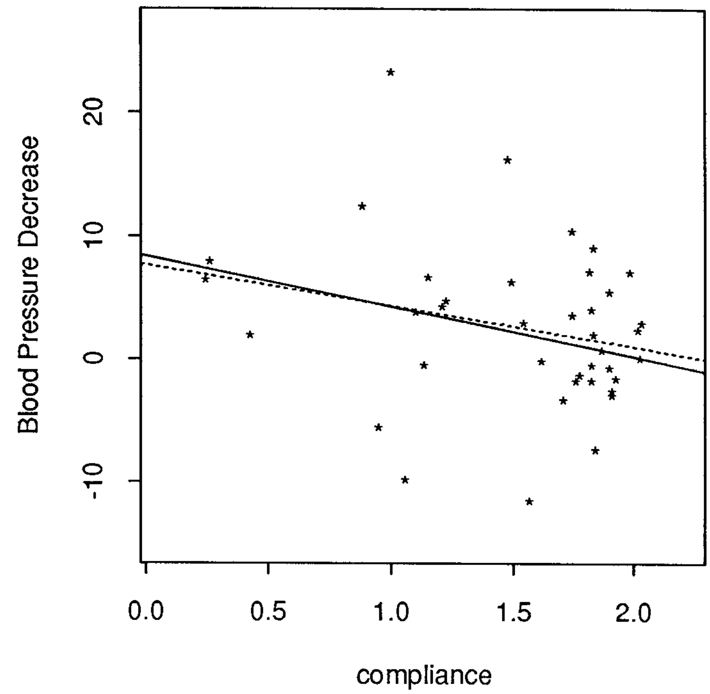


average compliance z0=.75

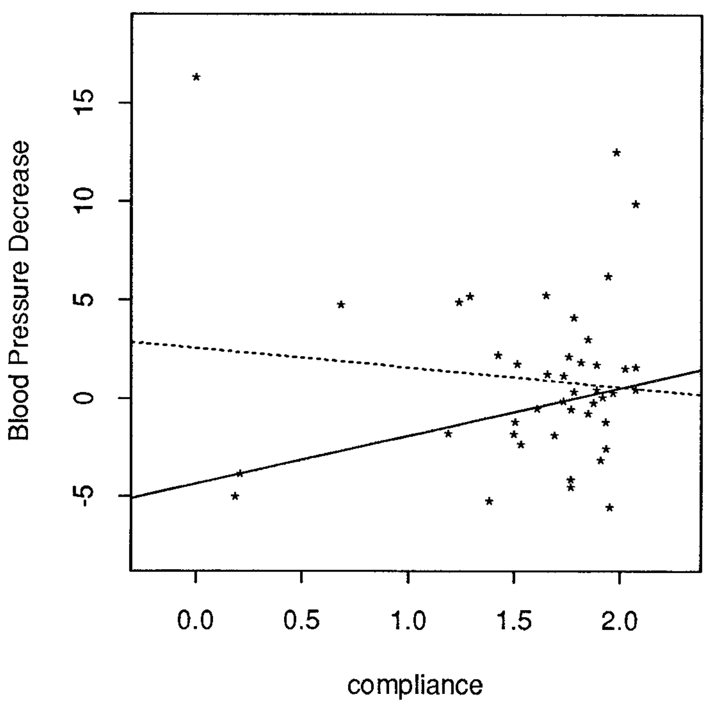
DRUG A



DRUG B



PLACEBO



dashed line is Least Squares
solid line is Least Abs Devs

THE DATA FOR THE FIRST SUBJECT:

week	sys	dia	d1	d2	d3	d4	d5	d6	d7	d8	d9	d10
0	140	94.5	0	0	0	0	0	0	0	0	0	0
2	142	94.0	2	1	2	2	2	2	2	2	2	2
4	143	91.0	2	2	2	1	2	2	2	2	2	2
6	142	90.0	2	1	1	2	2	2	2	2	2	1
8	146	105.0	3	2	2	1	2	1	2	2	2	2
10	148	89.0	3	1	2	2	2	2	2	2	2	2
12	148	90.0	2	1	2	2	2	2	2	2	2	2
14	151	100.0	1	1	1	1	1	2	2	2	1	2
16	133	90.0	1	1	2	1	0	1	2	2	2	1

[Drug A]

Thanks to

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