

Pre/Post data analysis – simple or is it?

SMAR 2011_1 – Mar 3, 2011

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Today: March 3, 2011

- Paradigm for pre/post data.
- How should we describe change?
- Common analysis methods for comparing post to pre results.
- What do we mean by “% change”?
- What are we testing when we compare % changes?
- Some simulation results
- Conclusions

Characteristics of Pre/Post data

repeated-measures design

<u>subject</u>	<u>pre</u>	<u>post</u>
1	36.4	31.5
2	48.8	40.1
3	25.9	25.6
etc

<u>subject</u>	<u>session</u>	<u>meas.</u>
1	L-60	50.3
1	L-10	48.6
1	R+0	35.7
1	R+3	39.4
1	R+10	46.0
2	L-60	75.0
2	L-10	78.5
2	R+0	69.6
2	R+3	73.5
2	R+10	77.9
etc

Characteristics of Pre/Post data (cont.)

partially repeated-measures design

<u>subject session meas. group</u>				<u>subject session meas. group</u>			
1	L-60	50.3	C	9	L-60	50.3	E
1	L-10	48.6	C	9	L-10	48.6	E
1	R+0	35.7	C	9	R+0	35.7	E
1	R+3	39.5	C	9	R+3	39.4	E
1	R+10	46.0	C	9	R+10	46.0	E
<hr/>				<hr/>			
2	L-60	75.0	C	10	L-60	75.0	E
2	L-10	78.5	C	10	L-10	78.5	E
2	R+0	69.6	C	10	R+0	69.6	E
2	R+3	73.5	C	10	R+3	73.5	E
2	R+10	77.9	C	10	R+10	77.9	E
<hr/>				<hr/>			
etc	C	etc	E

How should we express the effect of an intervention?

- mean change?
- % change?
- mean change in log measurements?

How should we express the effect of an intervention?

- mean change

pre	post	dif	% ch
75	85	10	13.3%
100	111	11	11.0%

How should we express the effect of an intervention?

- % change

pre	post	dif	% ch
10	18	8	80%
30	51	21	70%

How should we express the effect of an intervention?

- mean change in log measurements

pre	post	dif	% ch
10	18	8	80%
1000	1700	700	70%

How should we express the effect of an intervention?

- mean change in log measurements

pre	post	dif	% ch
10	18	8	80%
1000	1700	700	70%

- Observed outcome measurements are > 0
- They can range over one or more orders of magnitude

How should we express the effect of an intervention?

- mean change?
- % change?
- mean change in log measurements?

pre	post	dif	% ch
75	85	10	13.3%
100	110	10	10.0%
130	140	10	7.7%

How should we express the effect of an intervention?

- mean change?
- % change?
- mean change in log measurements?

pre	post	dif	% ch
75	85	10	13.3%
100	110	10	10.0%
130	140	10	7.7%

Ans. Correct interpretation should be driven by clinical relevance.

pre and post- bedrest data

sub	pre	post	dif
1	88.7	88.2	-0.5
2	85.1	102.1	16.9
3	106.3	98.6	-7.6
4	115.6	96.2	-19.4
5	62.6	77.3	14.8
6	85.4	82.5	-2.9
7	93.1	97.8	4.7
8	87.1	36	-51.1
9	80.7	64.6	-16.1
10	138.6	111.5	-27.1

Typical approaches to inference on the effect of bedrest:

subject	pre	post	diff
1	36.4	31.5	-4.9
2	48.8	40.1	-8.7
3	25.9	25.6	-0.3
etc

RPM ANOVA with phase (pre/post) as a factor

t-test of H_0 : mean diff = 0

t-test of H_0 : pct change of means = 0

t-test of H_0 : mean pct change = 0

Typical approaches to inference on the effect of bedrest:

subject	pre	post	diff
1	36.4	31.5	-4.9
2	48.8	40.1	-8.7
3	25.9	25.6	-0.3
etc

RPM ANOVA with phase (pre/post) as a factor ($\mu_{post} = \mu_{pre}$)

t-test of H_0 : mean diff = 0 ($\mu_{post} = \mu_{pre}$)

t-test of H_0 : pct change of means = 0 ($\mu_{post} = \mu_{pre}$)

t-test of H_0 : mean log pre = mean log post ($\zeta_{post} = \zeta_{pre}$)

t-test of H_0 : mean observed pct change = 0 (???)

ANOVA

Number of obs = 20 R-squared = 0.7828
 Root MSE = 14.526 Adj R-squared = 0.5414

Source	Partial SS	df	MS	F	Prob > F
Model	6843.84439	10	684.384439	3.24	0.0455
isub	6453.49865	9	717.055406	3.40	0.0414
post	390.345734	1	390.345734	1.85	0.2069
Residual	1899.05337	9	211.005931		
Total	8742.89776	19	460.152514		

t-test on differences

Variable	Obs	Mean	Std. Err.	Std. Dev.	[95% Conf. Interval]
dif	10	-8.835675	6.496244	20.54293	-23.5312 5.85985

mean = mean(dd)

t = -1.3601

Ho: mean = 0

degrees of freedom = 9

Ha: mean < 0

Ha: mean != 0

Ha: mean > 0

Pr(T < t) = 0.1034

Pr(|T| > |t|) = 0.2069

Pr(T > t) = 0.8966

Percent change in means

Variable	Obs	Mean	Std. Err.	Std. Dev.	[95% Conf. Interval]	
post	10	85.4812	6.958522	22.00478	69.73992	101.2225
pre	10	94.31687	6.662214	21.06777	79.24589	109.3878
diff	10	-8.835675	6.496244	20.54293	-5.85985	23.5312

$$\hat{r}_{\mu} = 100 \frac{\bar{y}_{post} - \bar{y}_{pre}}{\bar{y}_{pre}}$$

Testing $r_{\mu} = 0$ is the same as testing $\mu_{post} = \mu_{pre}$. ✓

t-test on differences of logs

One-sample t test

```
-----  
Variable |      Obs      Mean   Std. Err.   Std. Dev.   [95% Conf. Interval]  
-----+-----  
  log AES |         10  -.1180426   .097688    .3089166   -.3390283    .102943  
-----
```

```
      mean = mean(z)                                t = -1.2084  
Ho: mean = 0                                       degrees of freedom = 9
```

```
Ha: mean < 0  
Pr(T < t) = 0.1288
```

```
Ha: mean != 0  
Pr(|T| > |t|) = 0.2577
```

```
Ha: mean > 0  
Pr(T > t) = 0.8712
```

t-test on observed percent changes

One-sample t test

```
-----  
Variable |      Obs      Mean   Std. Err.   Std. Dev.   [95% Conf. Interval]  
-----+-----  
%ch AES  |         10  -.0775129   .0741236   .2343994   -.2451921   .0901664  
-----  
      mean = mean(pch)                                t = -1.0457  
Ho: mean = 0                                         degrees of freedom = 9  
  
      Ha: mean < 0  
Pr(T < t) = 0.1615  
  
      Ha: mean != 0  
Pr(|T| > |t|) = 0.3230  
  
      Ha: mean > 0  
Pr(T > t) = 0.8385
```

t-test on observed percent changes

One-sample t test

```
-----  
Variable |      Obs      Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]  
-----+-----  
%ch AES  |         10  -.0775129   .0741236   .2343994   -.2451921    .0901664  
-----  
      mean = mean(pch)                                t = -1.0457  
Ho: mean = 0                                         degrees of freedom = 9  
  
      Ha: mean < 0                                     Ha: mean != 0                                     Ha: mean > 0  
Pr(T < t) = 0.1615                                Pr(|T| > |t|) = 0.3230                                Pr(T > t) = 0.8385
```

What are we testing when we do this?

Objective: compare pre/post means

subject	pre	post	diff
1	36.4	31.5	-4.9
2	48.8	40.1	-8.7
3	25.9	25.6	-0.3
etc

- ✓ RPM ANOVA with phase (pre/post) as a factor
- ✓ t-test of H_0 : mean diff = 0
- ✓ t-test of H_0 : pct change of means = 0
- ✓ t-test of H_0 : mean log pre = mean log post
- ? t-test of H_0 : mean observed pct change = 0

“Bone density is decreased by 6% after ISS missions.”

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% change in means = -6% ?

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% change in means = -6% ?

mean % change = -6% ?

“Bone density is decreased by 6% after ISS missions.”

% change in means = -6% ?

mean % change = -6% ?



What's the difference?

pct change in means

$$100 \times \frac{\mu_{post} - \mu_{pre}}{\mu_{pre}}$$

estimated by

$$100 \times \frac{\bar{y}_{post} - \bar{y}_{pre}}{\bar{y}_{pre}} \quad ?$$

pct change in means $100 \times \frac{\mu_{post} - \mu_{pre}}{\mu_{pre}}$

estimated by $100 \times \frac{\bar{y}_{post} - \bar{y}_{pre}}{\bar{y}_{pre}}$?

mean pct change $\mu_{PC} = E \left(100 \times \frac{\mu_{i,post} - \mu_{i,pre}}{\mu_{i,pre}} \right)$

estimated by $\frac{1}{n} \sum_i \left\{ 100 \times \frac{(y_{i,post} - y_{i,pre})}{y_{i,pre}} \right\}$??

(average observed pct change)

An Example

subject	pre	post	diff	% ch
1	30	25	-5	-16.7
2	40	36	-4	-10.0
3	25	19	-6	-24.0
4	53	49	-4	-7.5
ave	37	32.25	-4.75	-14.6

estimated % change in means = $100 \times (-4.75/37) = -12.8$

estimated mean observed % change = -14.6

Interpretation of mean obs pct change

$$\text{mean } \underline{\text{obs}} \text{ pct change } \Psi = E \left(100 \times \frac{y_{i,\text{post}} - y_{i,\text{pre}}}{y_{i,\text{pre}}} \right)$$

$$\approx \frac{1}{n} \sum_i \left\{ 100 \times \frac{(y_{i,\text{post}} - y_{i,\text{pre}})}{y_{i,\text{pre}}} \right\} \quad \text{for "large" } n$$

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If it exists, Ψ is a population characteristic, but what does it mean?

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If it exists, Ψ is a population characteristic,
but what does it mean?

$$\text{Is } \Psi \text{ the actual mean pct change } \mu_{PC} = E\left(100 \times \frac{\mu_{i,\text{post}} - \mu_{i,\text{pre}}}{\mu_{i,\text{pre}}}\right) ?$$

Interpretation of mean obs pct change

$$\text{mean obs pct change } \Psi = E \left(100 \times \frac{y_{i,\text{post}} - y_{i,\text{pre}}}{y_{i,\text{pre}}} \right)$$

$$\approx \frac{1}{n} \sum_i \left\{ 100 \times \frac{(y_{i,\text{post}} - y_{i,\text{pre}})}{y_{i,\text{pre}}} \right\} \quad \text{for "large" } n$$

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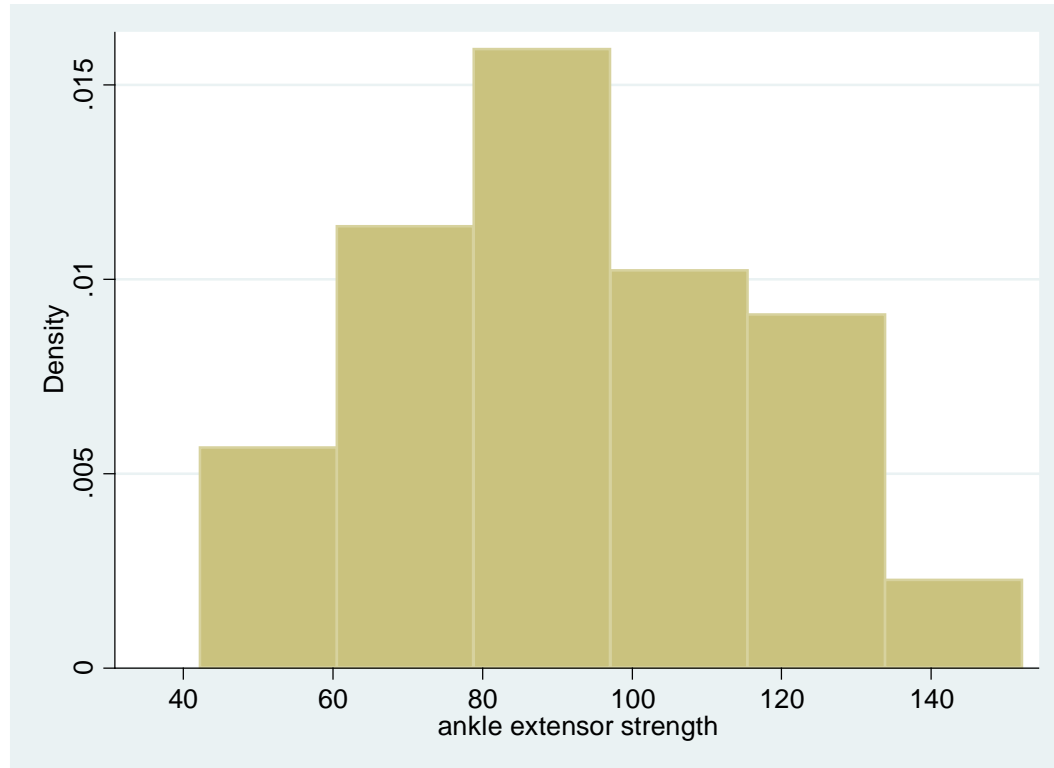
If not, how well does Ψ describe the effect of
spaceflight/bedrest over a population of subjects?



Simulation 1

- 10,000 “experiments”
- $N = 20$ simulated paired pre-post measurements of ankle extensor strength (AES) per experiment
- mean effect of “bedrest” : $\Delta = \mu_{post} - \mu_{pre}$
- t-test #1 – test $H_0: \Delta = 0$.
- t-test #2 – test $H'_0: \Psi = 0$.

actual AES data (N = 24, pre/post)



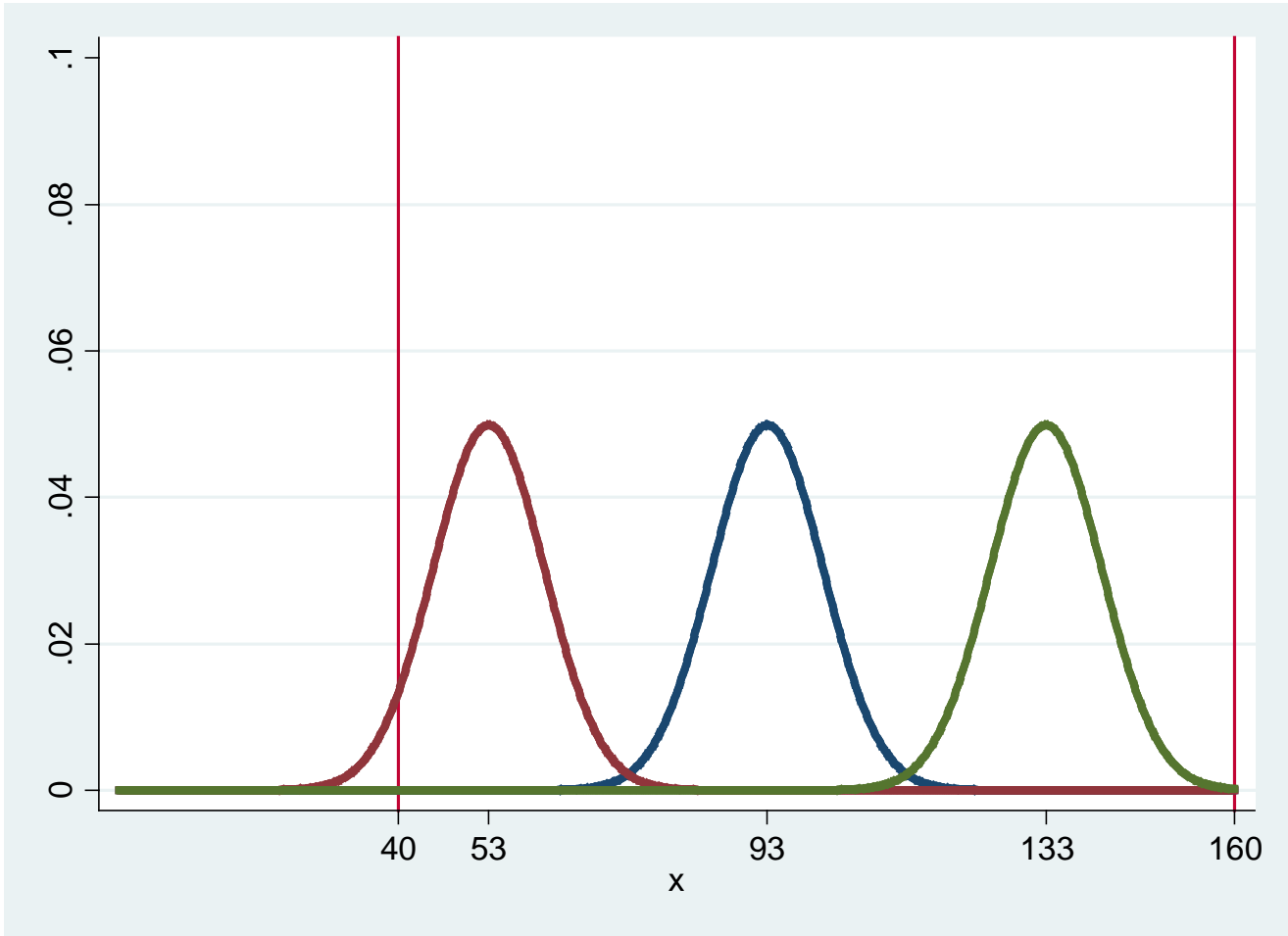
Variable	Obs	Mean	Std. Dev.	Min	Max
AES (pre)	24	103.0	23.0	67.8	152.1
AES (post)	24	82.8	22.9	42.2	128.1

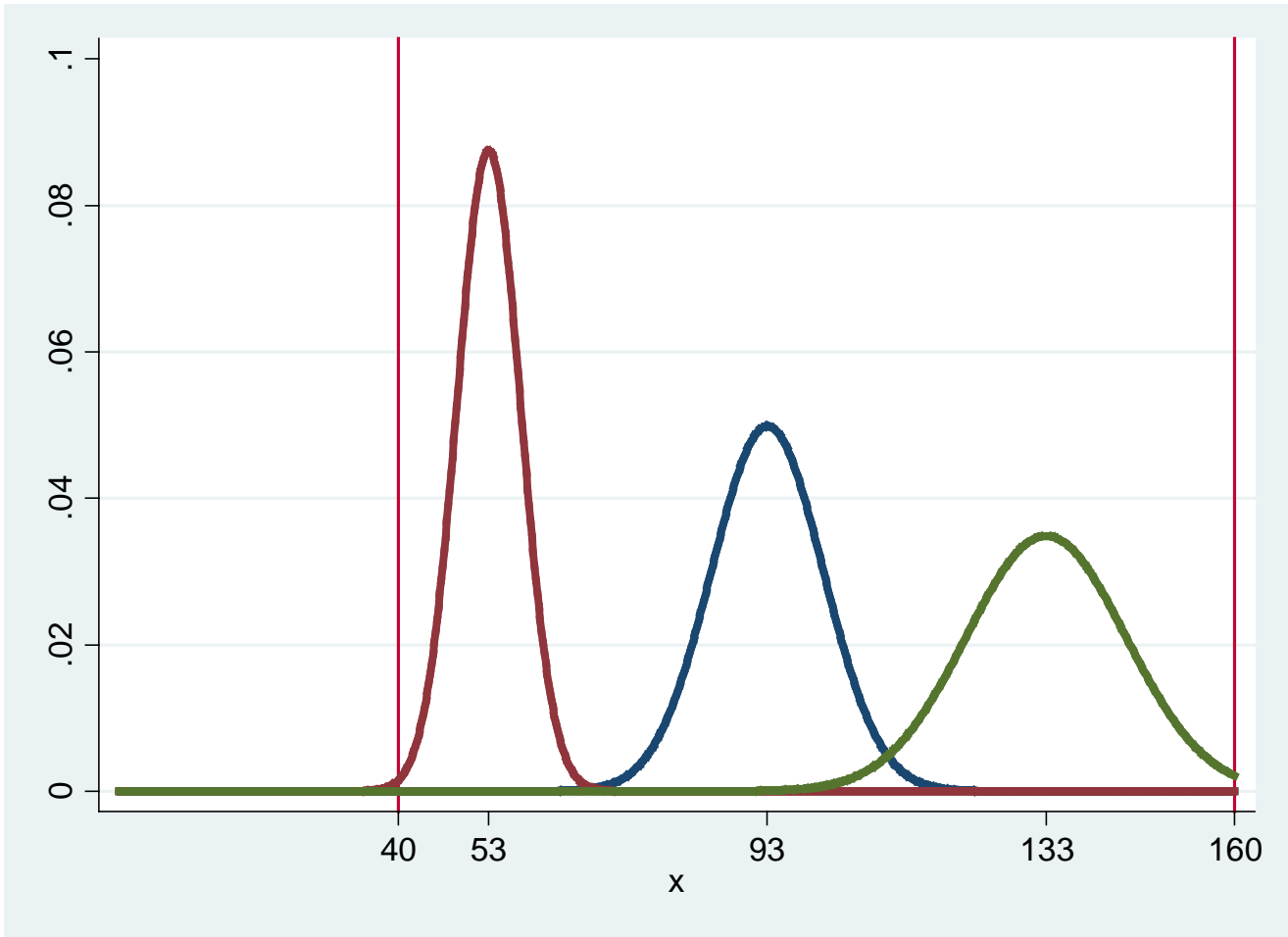
Simulation 1 (cont.)

- distribution of pre-means (between subjects)
- distribution of post-means (between subjects)
- distribution around subject-specific means (within subjects)

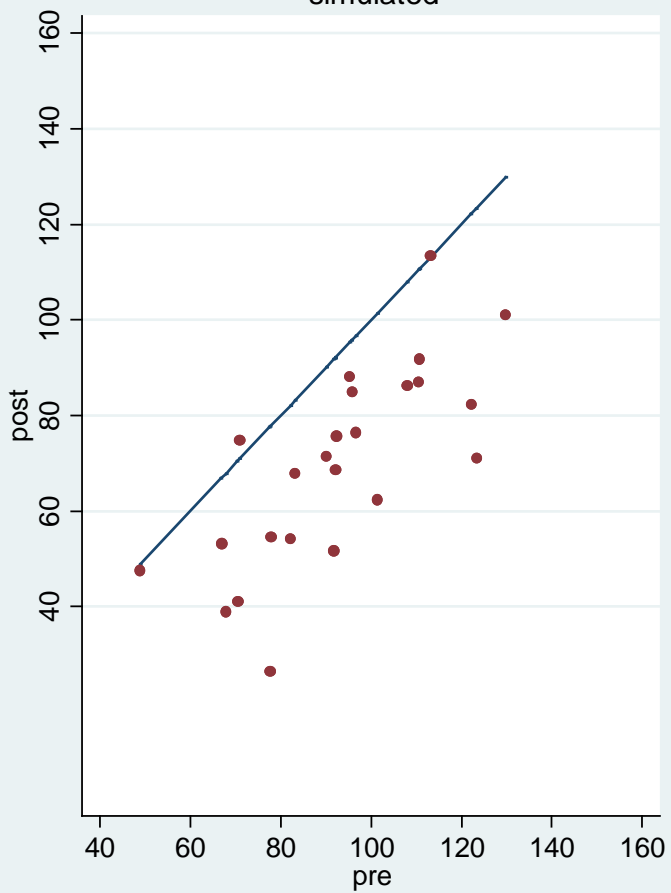
Simulation 1 (cont.)

- distribution of pre-means (between subjects)
- distribution of post-means (between subjects)
- distribution around subject-specific means (within subjects)
 - constant SD
 - constant CV (SD/mean)
 - other ?

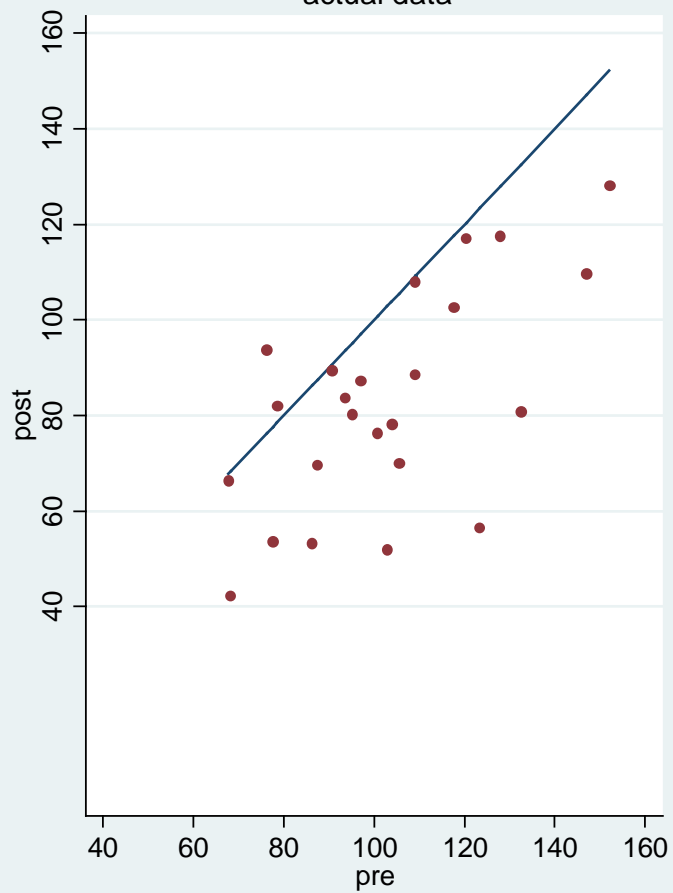




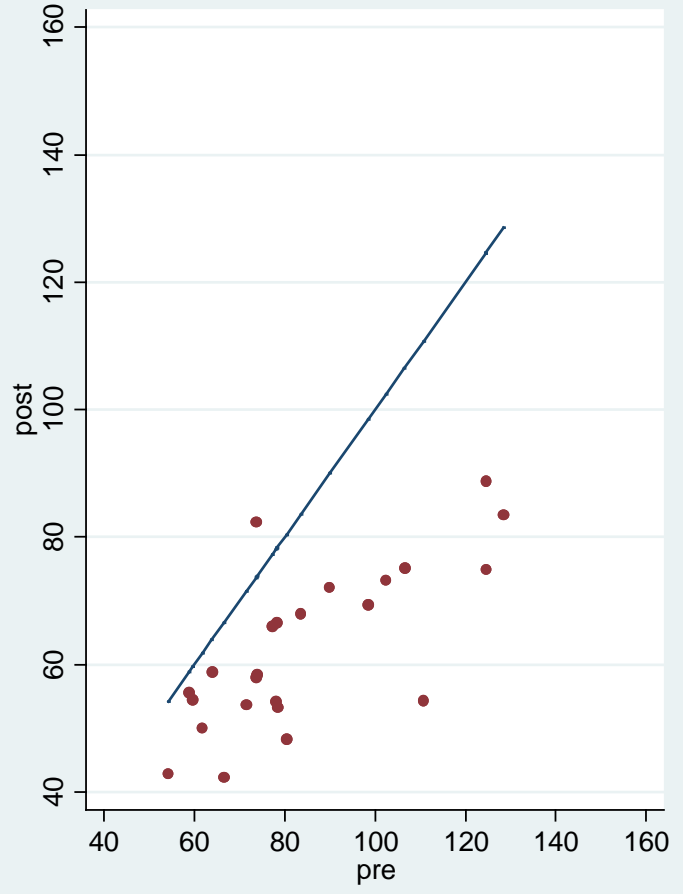
AES strength
simulated



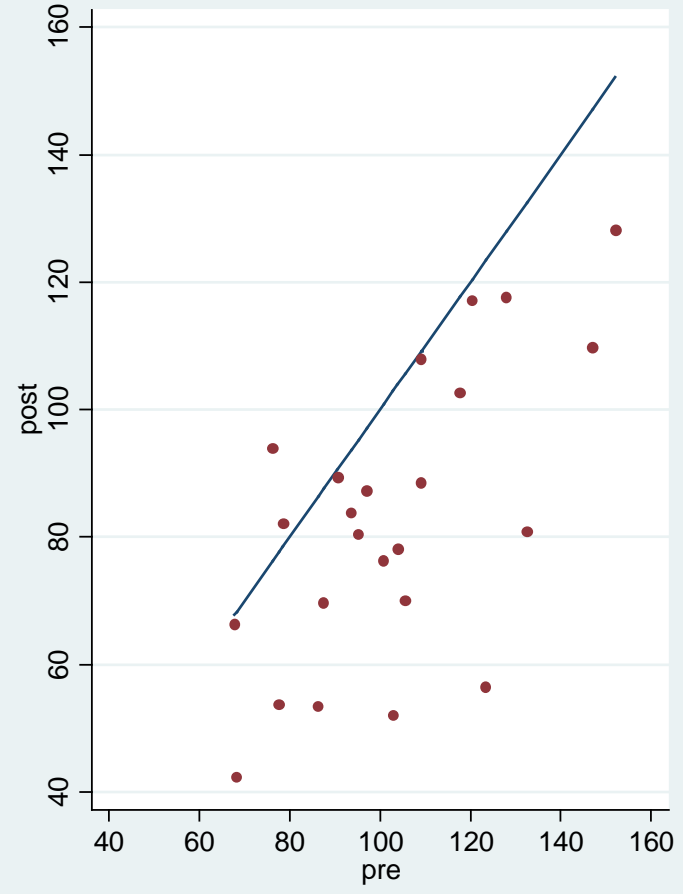
AES strength
actual data



AES strength
simulated



AES strength
actual data



Simulation 1 (cont.)

- 10,000 “experiments”
- $N = 20$ simulated paired pre-post measurements of ankle extensor strength (AES) per experiment
- mean effect of “bedrest” : $\Delta = \mu_{post} - \mu_{pre} = 0$

- t-test #1 – test $H_0: \Delta = 0$. $\Delta = E(y_{i,post} - y_{i,pre})$

- t-test #2 – test $H'_0: \Psi = 0$. $\Psi = E\left(100 \times \frac{y_{i,post} - y_{i,pre}}{y_{i,pre}}\right)$

Simulation 1 (cont.)

- 10,000 “experiments”
- $N = 20$ simulated paired pre-post measurements of ankle extensor strength (AES) per experiment
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Output:

- 10,000 “t”-values and p-values for t-test #1
- 10,000 “t”-values and p-values for t-test #2

Expected Results

If H_0 ($\Delta = 0$) is true:

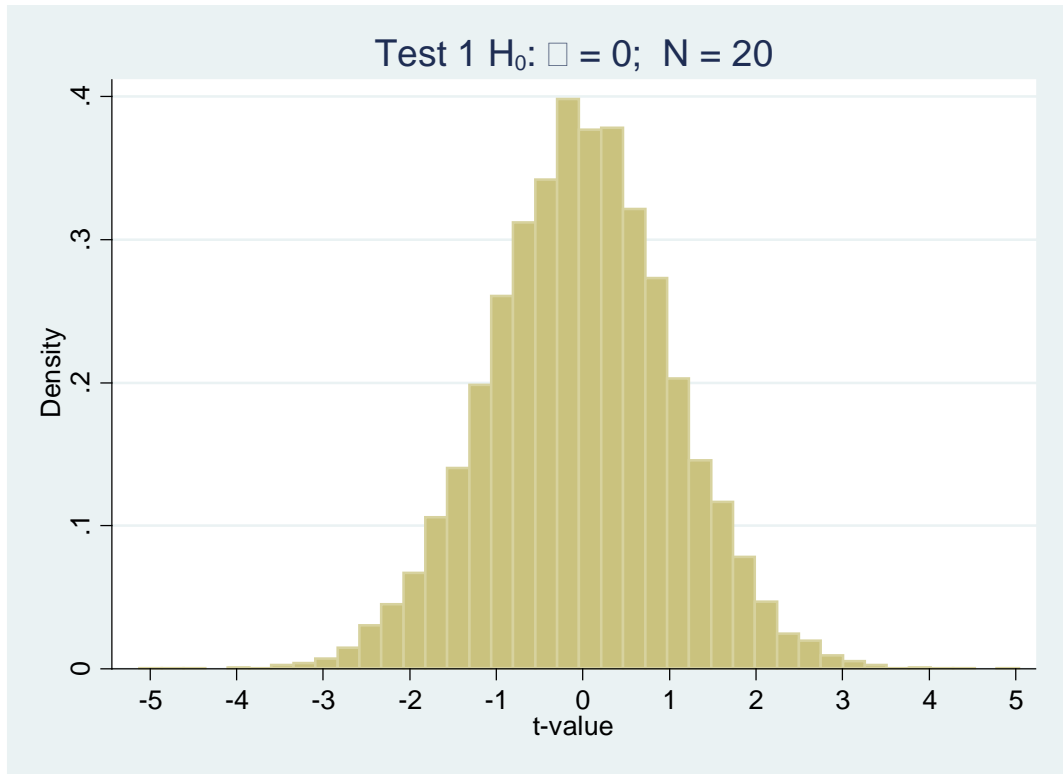
t-values for test 1 should be distributed as $t(19)$

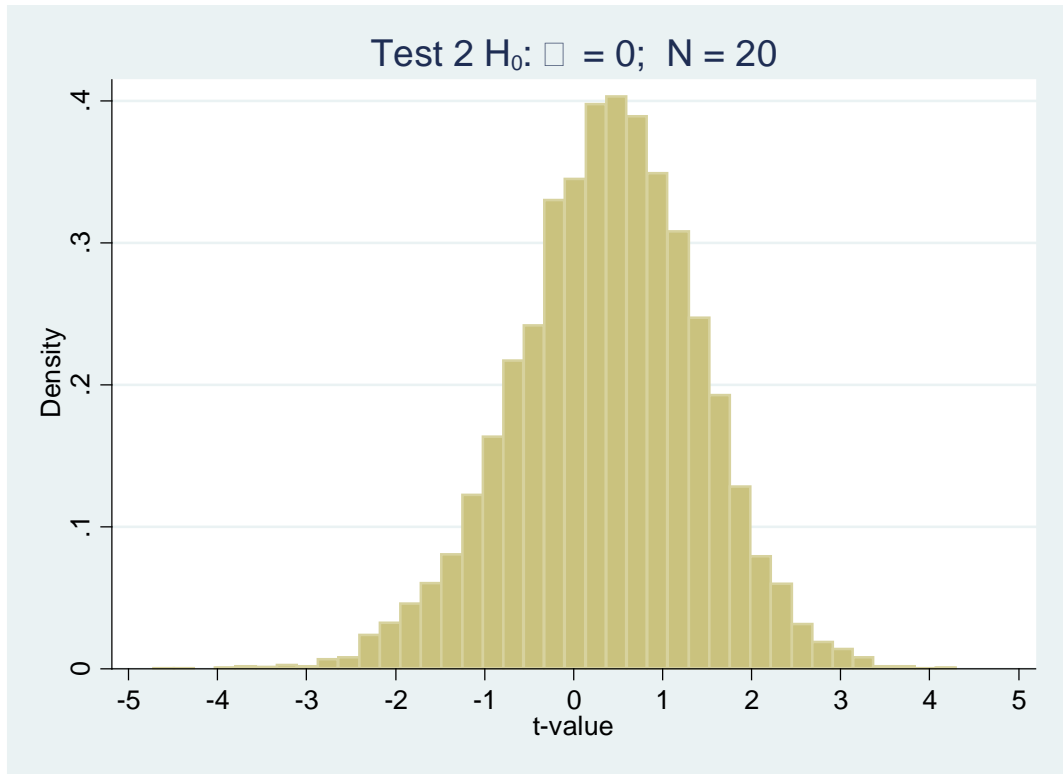
p-values for test 1 should be distributed as $U(0,1)$

If H'_0 : ($\Psi = 0$) is true:

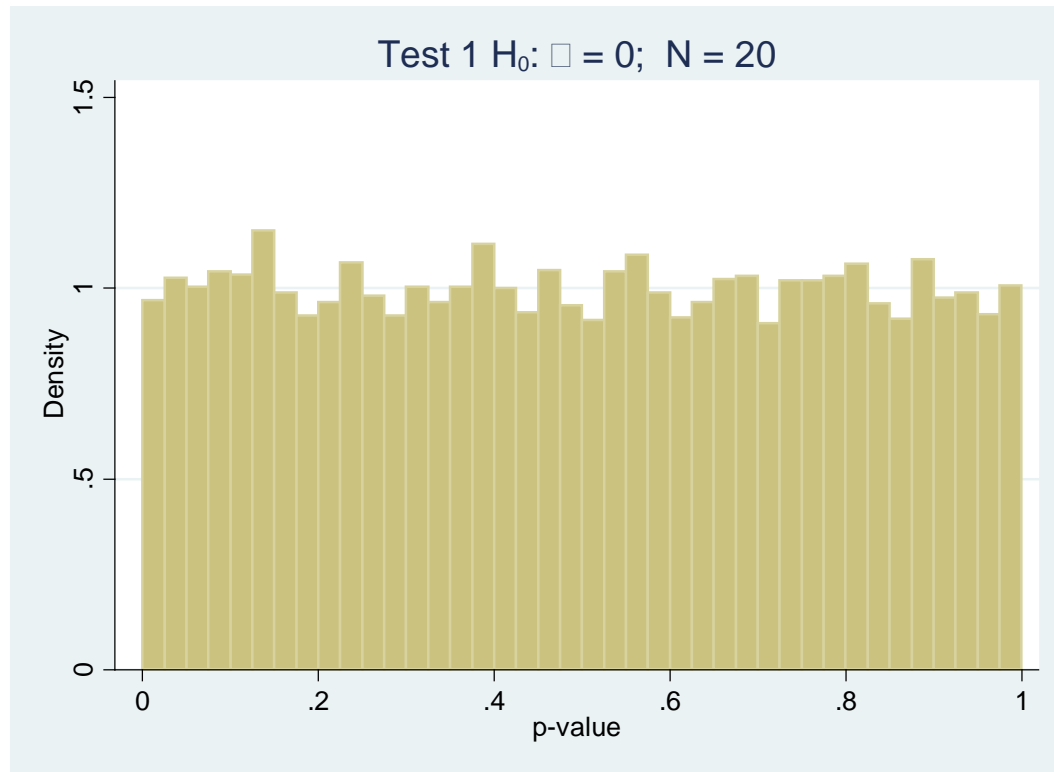
t-values for test 2 should be distributed as $t(19)$

p-values for test 2 should be distributed as $U(0,1)$

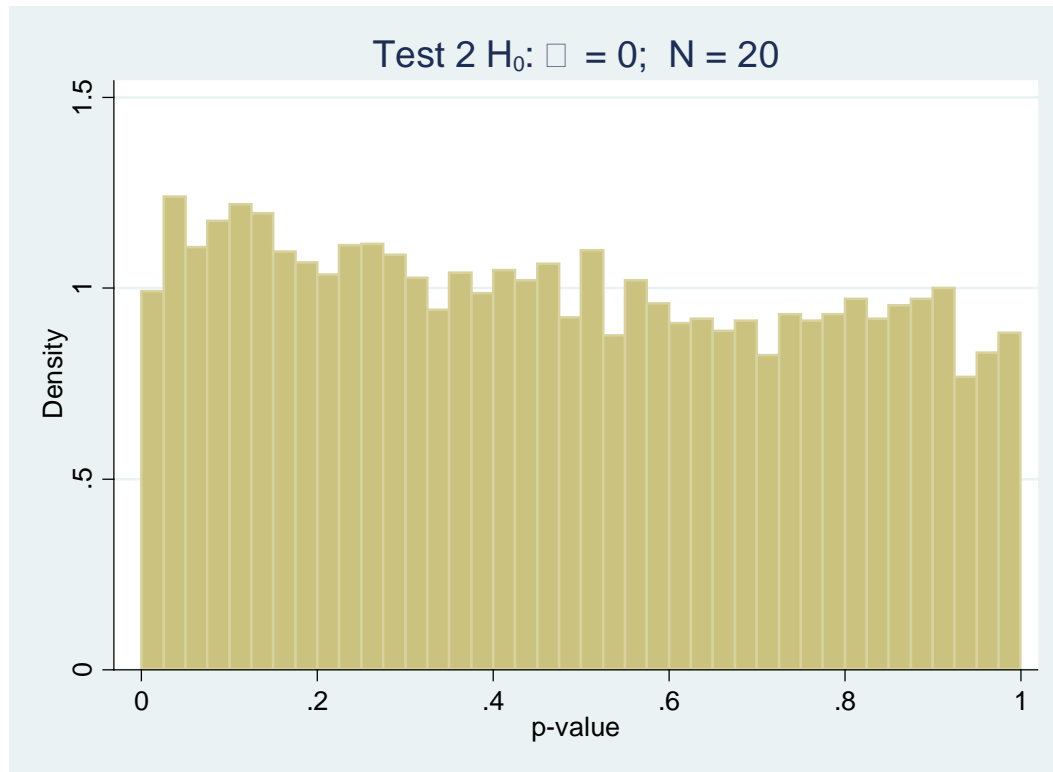




P < .05 = 499



$P < .05 = 558$



Simulation 2

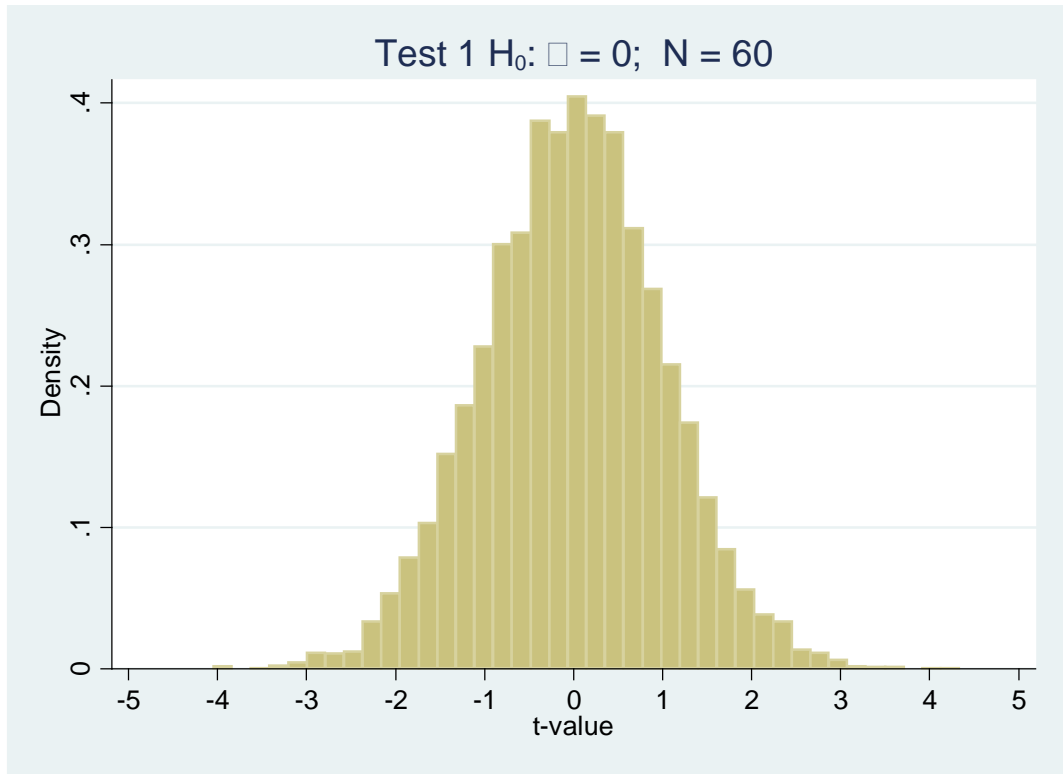
- 10,000 “experiments”
- $N = 60$ simulated paired pre-post measurements of ankle extensor strength (AES) per experiment
- mean effect of “bedrest” : $\Delta = \mu_{post} - \mu_{pre} = 0$

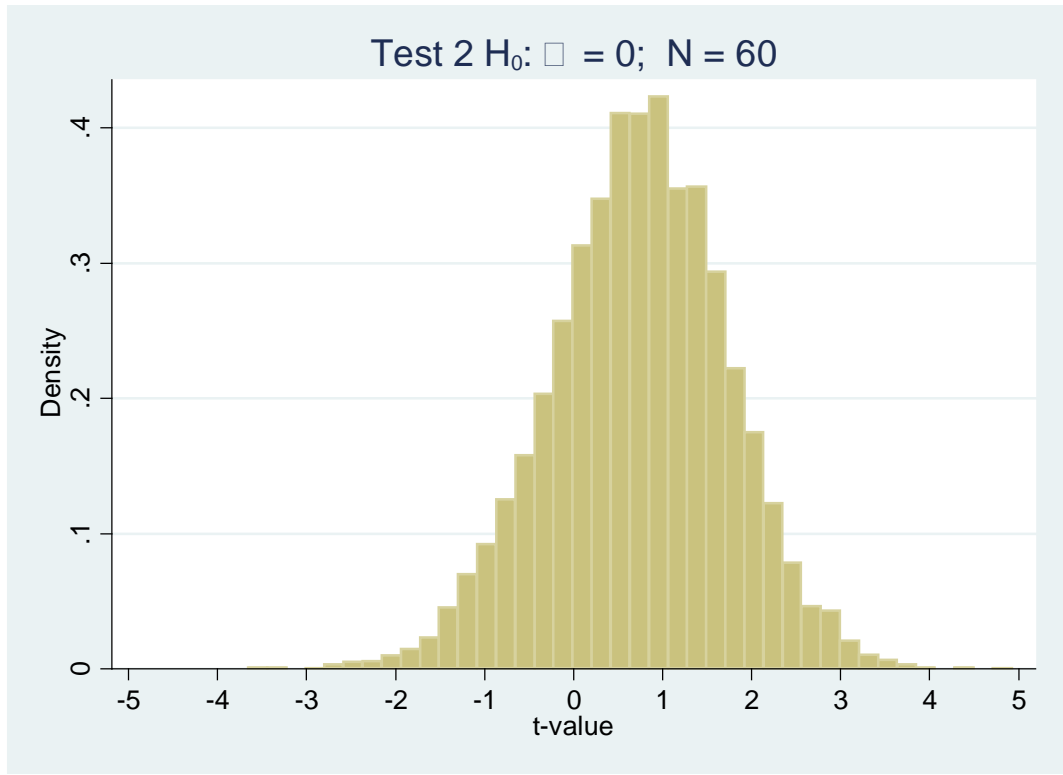
- t-test #1 – test $H_0: \Delta = 0$. $\Delta = E(y_{i,post} - y_{i,pre})$

- t-test #2 – test $H'_0: \Psi = 0$. $\Psi = E\left(100 \times \frac{y_{i,post} - y_{i,pre}}{y_{i,pre}}\right)$

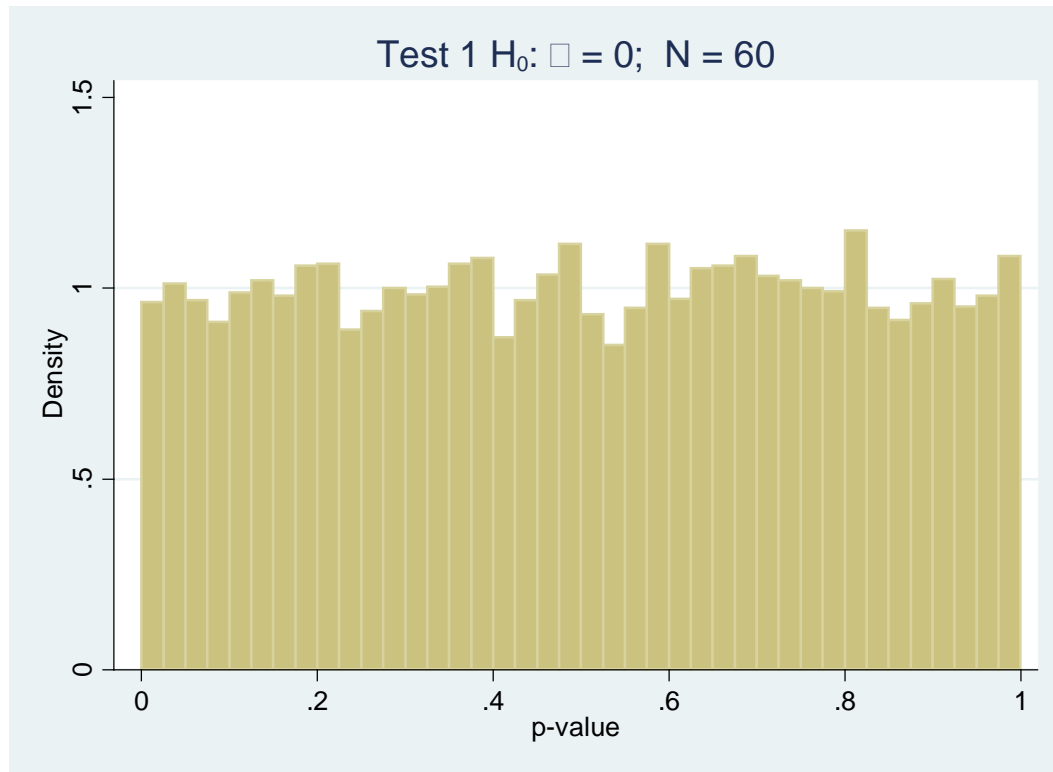
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- 10,000 “t”-values and p-values for t-test #2

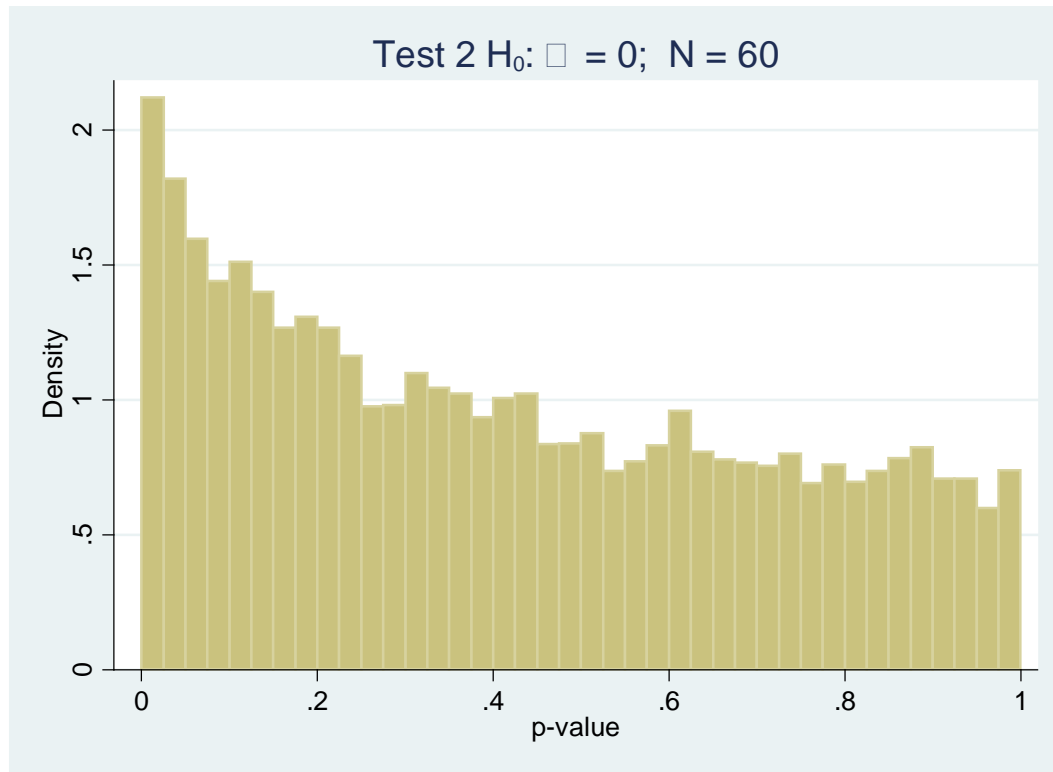




$P < .05 = 492$



$P < .05 = 985$



What's going on ??

What's going on ??

Ans: $\Psi \neq 0$

Estimating Ψ

Simulation of pre, post AES values with $\Delta = \mu_{post} - \mu_{pre} = 0$

$$\Psi = E \left(100 \times \frac{y_{i,post} - y_{i,pre}}{y_{i,pre}} \right)$$

$N = 10^3, 10^4, 10^5, \text{ and } 10^6$

Estimating Ψ

Simulation of pre, post AES values with $\Delta = \mu_{post} - \mu_{pre} = 0$

$$\Psi = E\left(100 \times \frac{y_{i,post} - y_{i,pre}}{y_{i,pre}}\right)$$

N	Mean	Std. Err.	Std. Dev.	[95% Conf. Interval]
1000	1.950	.639	20.2	0.696 3.204
10000	2.028	.207	20.7	1.623 2.435
100000	2.079	.066	20.9	1.949 2.209
1000000	2.048	.021	20.9	2.007 2.089

Estimating Ψ

Simulation of pre, post AES values with $\Delta = \mu_{post} - \mu_{pre} = 0$

$$\Psi = E\left(100 \times \frac{y_{i,post} - y_{i,pre}}{y_{i,pre}}\right)$$

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1000000	2.048	.021	20.9	2.007 2.089

$\Delta = 0, \mu_{PC} = 0, \text{ but } \Psi = 2.05 \% !$

Estimating Ψ

Simulation of pre, post AES values with $\Delta = \mu_{post} - \mu_{pre} = 0$

$$\Psi = E\left(100 \times \frac{y_{i,post} - y_{i,pre}}{y_{i,pre}}\right)$$

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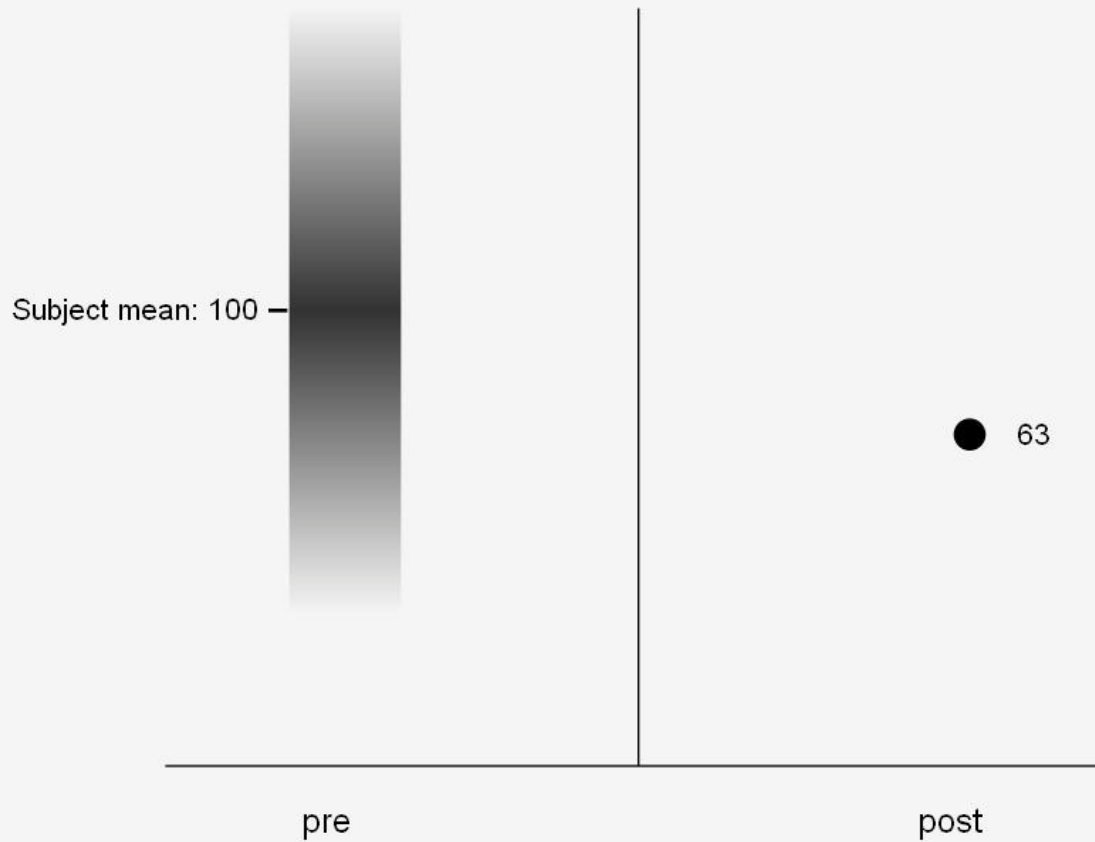
$\Delta = 0, \mu_{PC} = 0, \text{ but } \Psi = 2.05 \% !$

Does this mean that sham bedrest causes AES to increase by 2.05% ???

Ψ depends on the within-subject CV (sd/mean)

CV	Ψ (%)
0.01	0.01
0.05	0.23
0.10	1.04
0.12	1.55
0.14	2.05
0.16	2.70
0.18	3.53
0.20	4.53

A single pre value is not a stable baseline ...



next

What if $\Delta \neq 0$?
(mean post \neq mean pre)

pre mean = 91.75

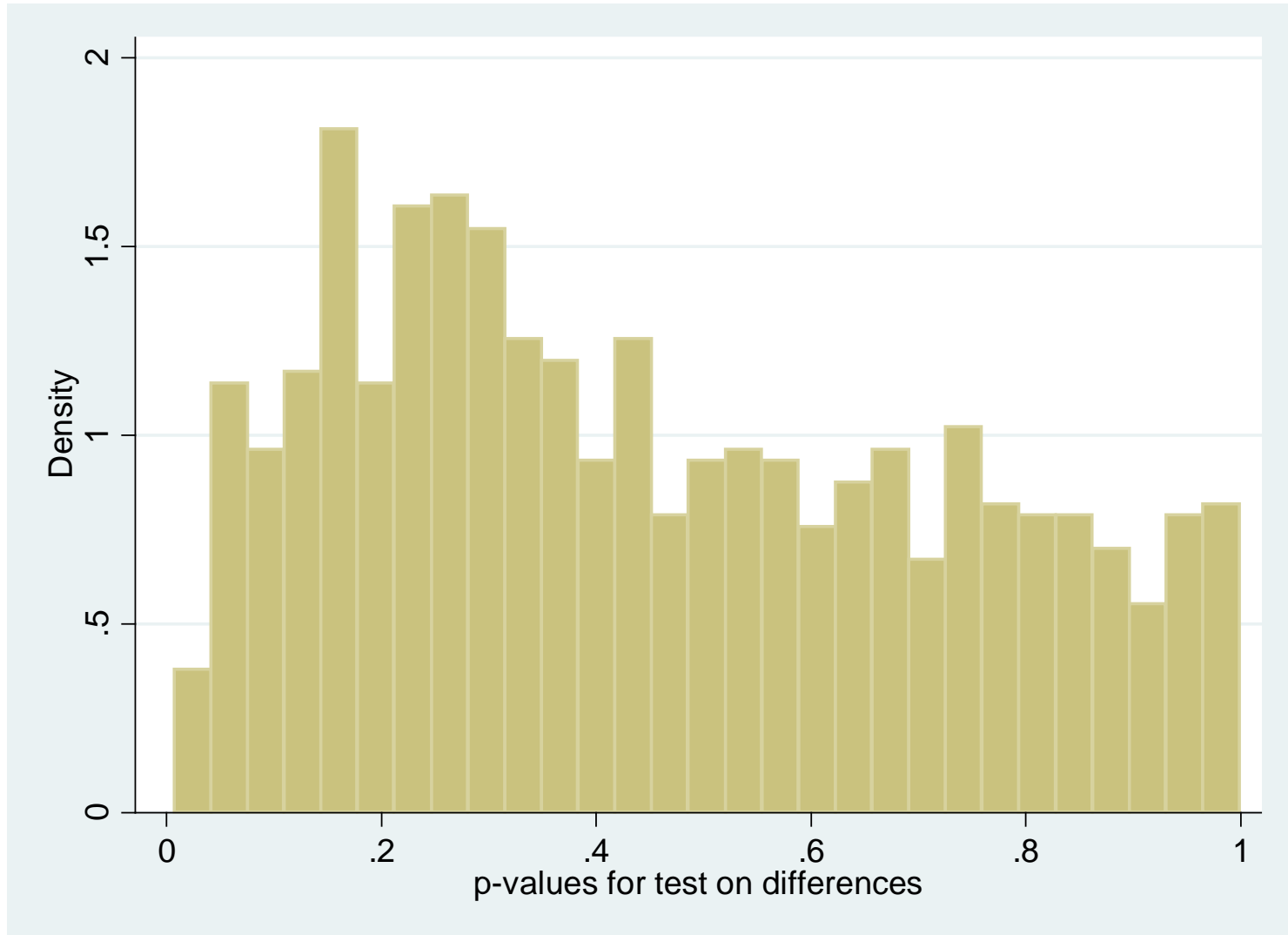
post mean = pre mean + Δ

n	Δ	pow(d)	pow(pct ch)	% ch mean	Ψ
20	-11.5	0.82	0.74	-24.5	-11.1
30	-9.2	0.80	0.65	-10.0	-8.3
40	-7.8	0.78	0.59	-8.5	-6.5
60	-6.4	0.79	0.56	-7.0	-5.5

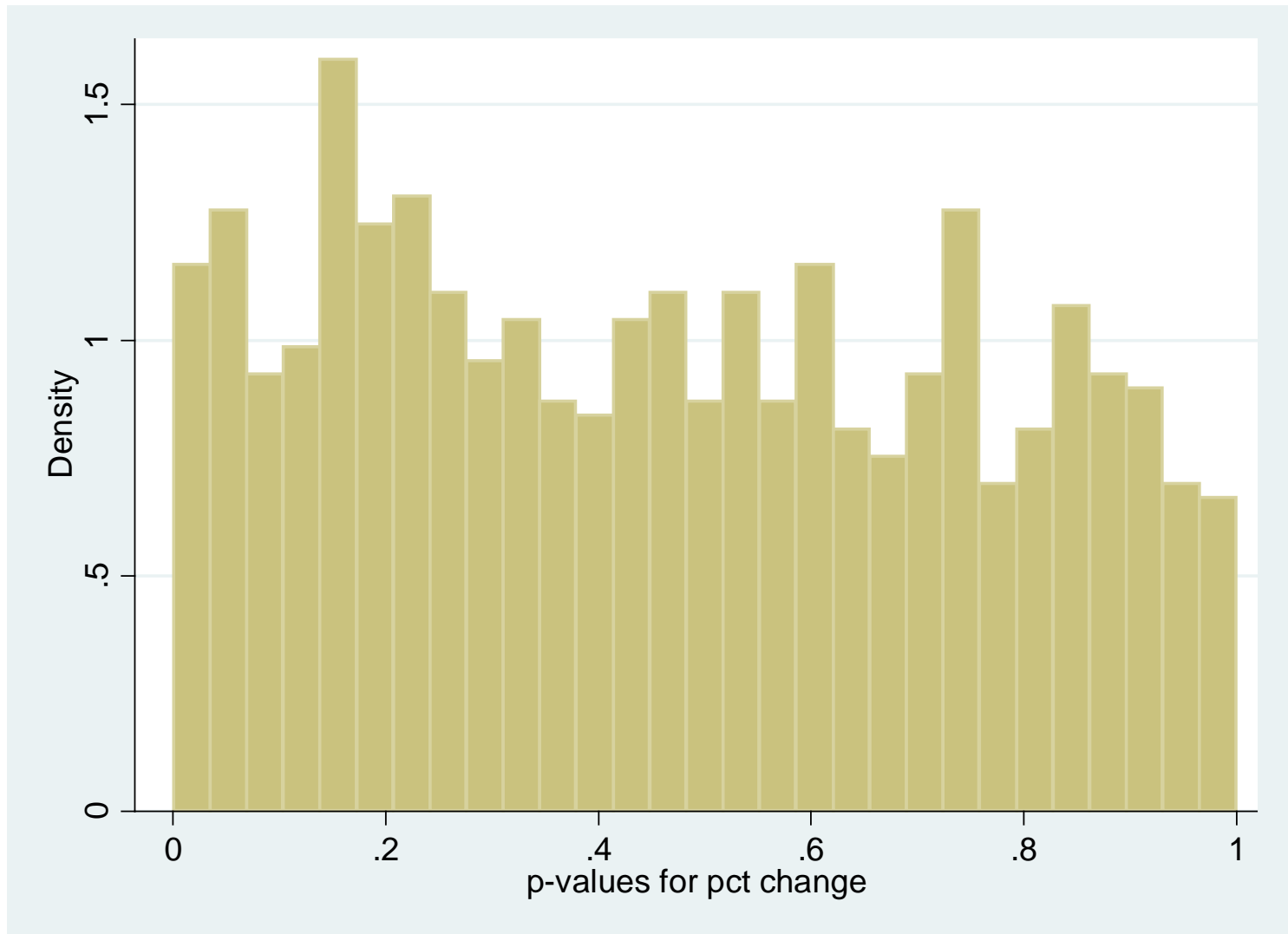
What about data varying over several orders of magnitude?

Should we analyze logs or percent changes?

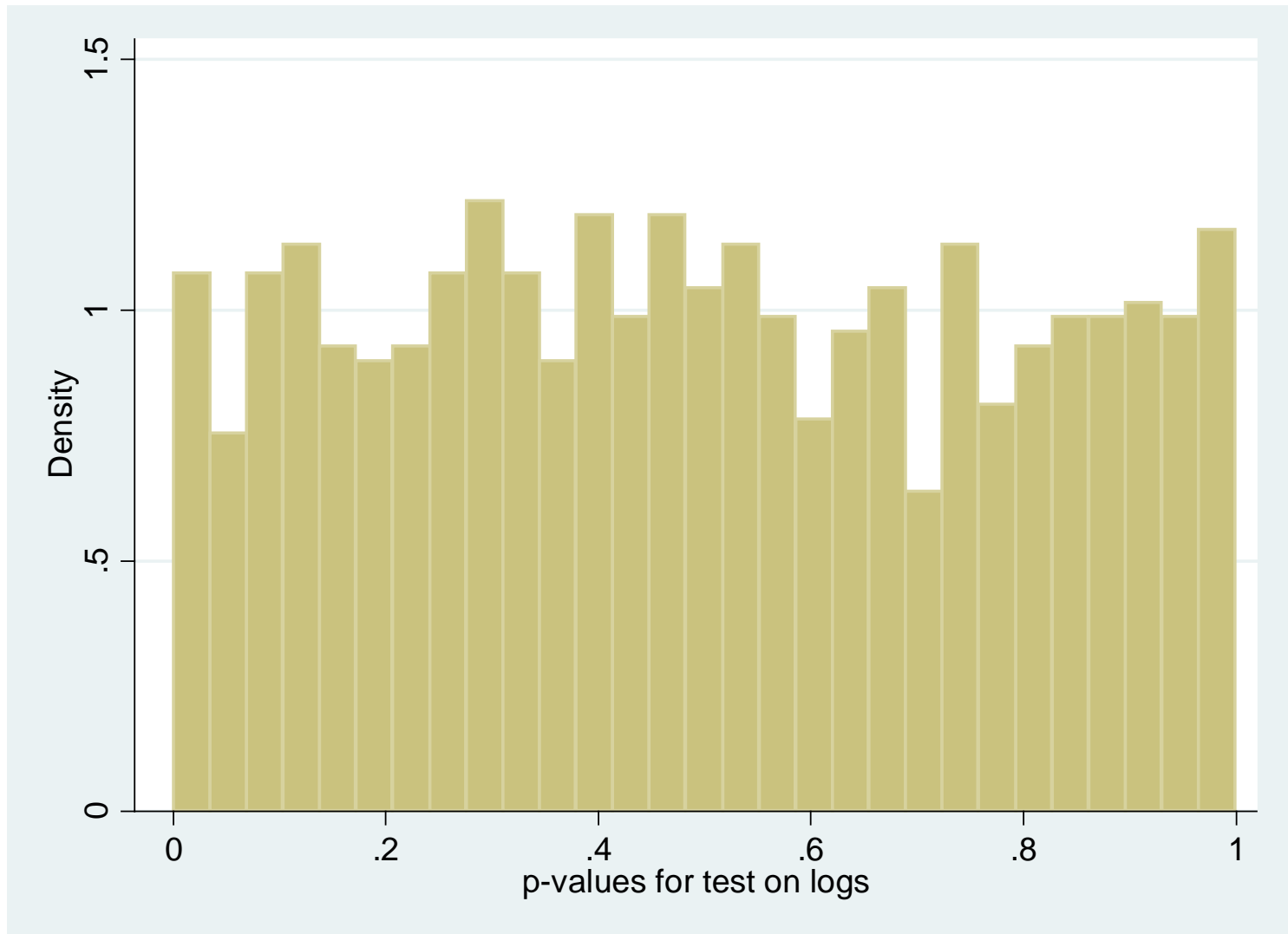
t-test on differences



t-test on pct change



t-test on differences of logs



Comparing experimental groups of subjects

sub	pre	post	diff	group
1	36.4	31.5	-4.9	C
2	48.8	40.1	-8.7	C
3	25.9	19.6	-6.3	C
...	C
10	40.5	38.2	-2.3	C
1	36.4	31.5	-4.9	E
2	48.8	46.1	-2.7	E
3	25.9	25.6	-0.3	E
...	E
15	37.7	37.0	-0.7	E

Ψ_1

Ψ_2

Comparing experimental groups of subjects

Equal CV's

Bias in average observed % change
approximately cancels so result of inference
using % change as data and comparing means
are about the same as t-test on differences.

Comparing experimental groups of subjects

Equal CV's

Bias in average observed % change approximately cancels so result of inference using % change as data and comparing means are about the same as t-test on differences.

But what does it mean to report average values of % change for each group?

Comparing experimental groups of subjects

Unequal CV's

Biases in averages of observed % change do not cancel and thus inference itself is biased (size of test not 0.05)

Conclusions

If outcome measure >0 and does not vary over several orders of magnitude, analyze original data.

You can estimate or make inference on the % change in the mean response from the above analysis.

Conclusions (cont.)

Within an experimental group, there is a positive bias when analyzing individual percent changes as data.

- Average observed percent change does not estimate either the population mean percent change nor the percent change in the population means.
- Type I error rate $> \alpha$ (e.g. 0.05) when no actual effect
- Reduced power when there really is an effect
- Effect of bias on inference becomes more evident as sample size increases.

Conclusions (cont.)

When comparing experimental groups, if CV's are similar, much of the bias cancels, thus the results of inference on mean % change is similar to results of inference on differences or ANOVA.

However difficult to characterize each group in terms of average observed % change because of the individual biases.

If CV's differ, inference on % change is biased (α -level not 0.05).

Conclusions (cont.)

If outcome measure >0 and *does* vary over several orders of magnitude, analyze *logs* of original data.

- stabilizes variance
- ANOVA, t-tests perform as advertised
- ANOVA, t-tests perform poorly on original data
- analysis of pct change is also biased as before

Next time:

- Improving estimation of mean percent change (μ_{PC})
- Using regression models that use pre-data to help explain post-data.
- Regression to the mean and how it can lead to misleading conclusions.
- Instrumental variables to correct bias in regression models with random errors in predictors.