

A Picture is Worth a Thousand Words

Graphical Display of Data and Statistical Analysis for Clinical Research

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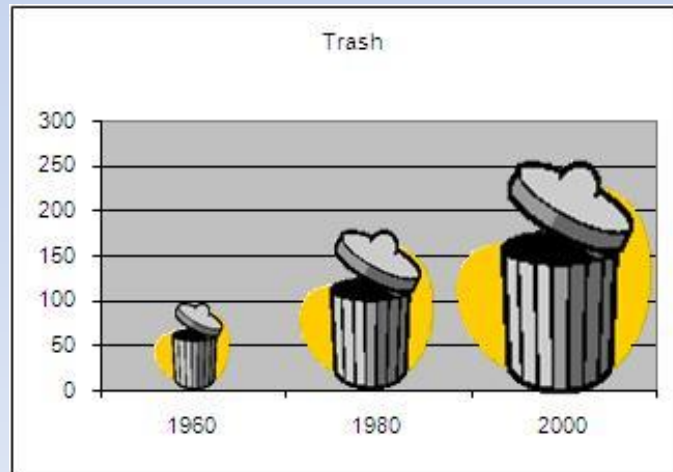
Graphical Display of Data and Statistical Analysis for Clinical Research

1. A picture is worth a thousand words
2. Know your target audience?
3. A look at raw data
4. Pesky Outliers
5. Graphics first
 1. Experimental Design and Inference
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 3. A note on error bars
 4. Consistency in key
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7. Interpretation
8. KISS

A Picture is Worth a Thousand Words

Make sure that the figures that you are presenting...

1. Accurately represent the data response: Precision
2. Stand alone from the manuscript text: Completeness
3. Convey the message that you are trying to present: Clarity
4. Are not misleading to the uninformed reader: Avoid Distortion



Know Your Target Audience?

You've formulated your hypothesis, designed and powered your study, followed your participants and collected your data.

Now what?

Who is your target audience?

- Regulatory Report (NIH, FDA, Industry)

- Interim Analysis/DSMB (Internal, External)

- Conference Presentation (Experts, Laypersons)

- Peer Reviewed Manuscript (Journal Audience)

Know Your Target Audience?

**The audience is only privy to the data that you reveal,
so...**

Regulatory and safety graphics may need to be drilled down to patient level data.

Between group hypothesis may only need to be represented by group or population level data.

Graphics for a web link may have less limits.

A Look at Raw Data

Prior to formulation of final figures and statistical analysis, Look at the raw data.

The raw data can provide information on...

- 1. The distribution of the data (bimodal, truncated etc...)*
- 2. Detection of possible Influential points or outliers*
- 3. Preliminary relationships between independent and dependent variables (linear, quadratic, stepwise).*

A Look at Raw Data

Some Examples

A Look at Raw Data

Hypothesis: based on pilot project data, X is positively and linearly related to Y.

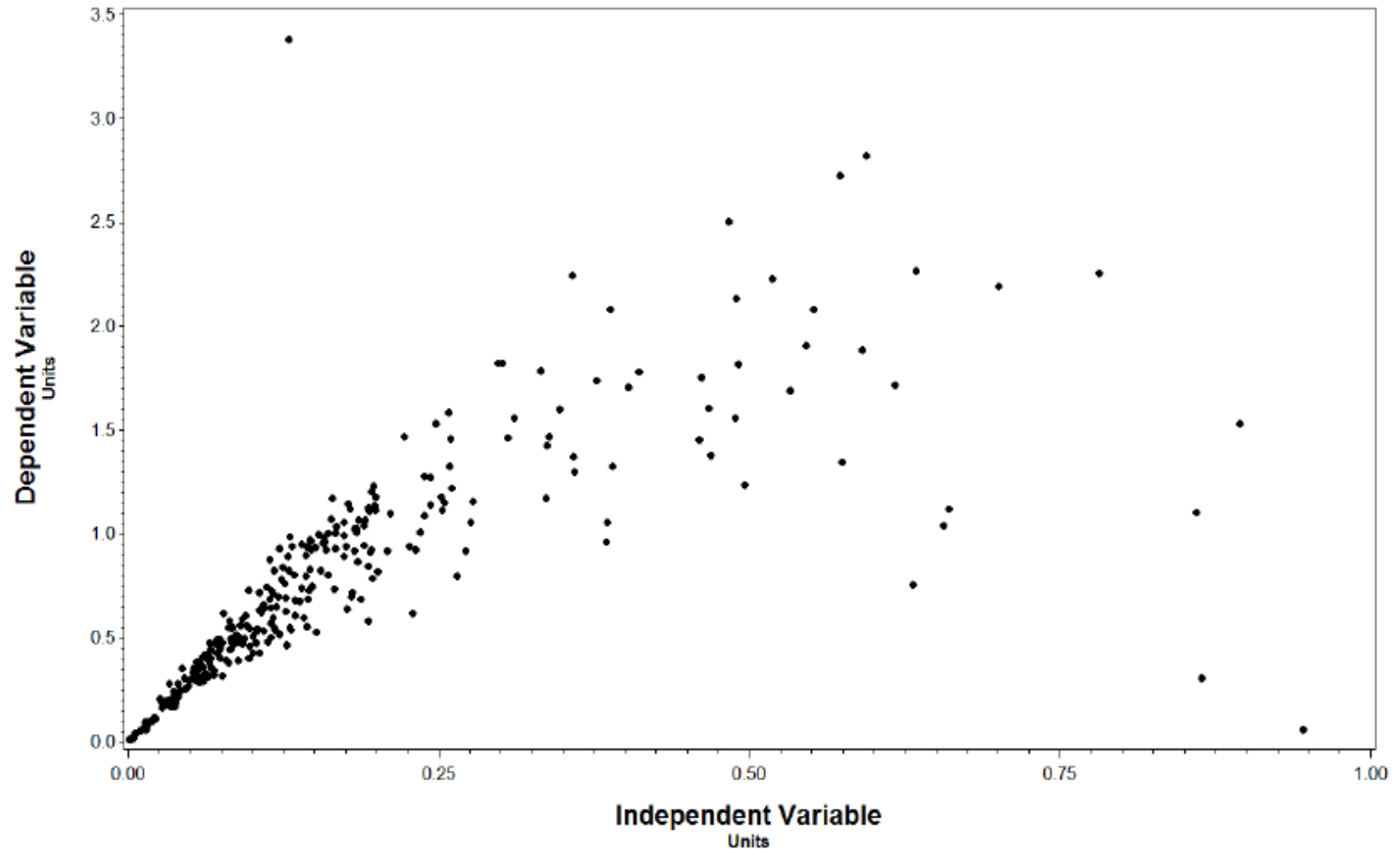
You receive data on 307 subjects with measured X and Y values. Run simple linear regression (SLR) to test the hypothesis.

Results: The relationship between X and Y is highly significant

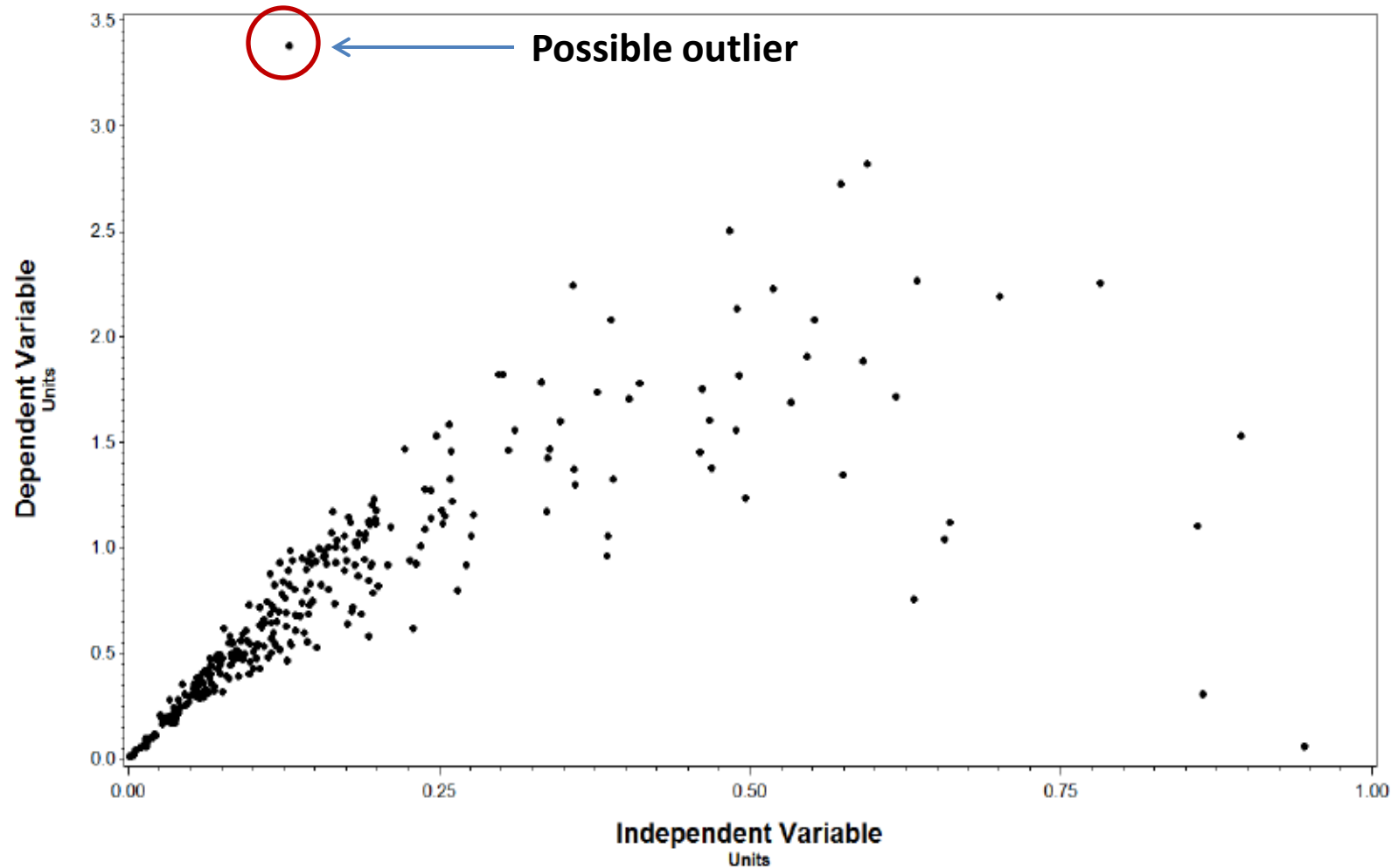
$$\beta=2.13 (SE_{\beta}=0.14); t_{305}=15.5; p<0.0001.$$

And then you begin to plot the data for your accepted oral presentation at *The 35th Annual Large Meeting of Your Peers, Chicago, IL...*

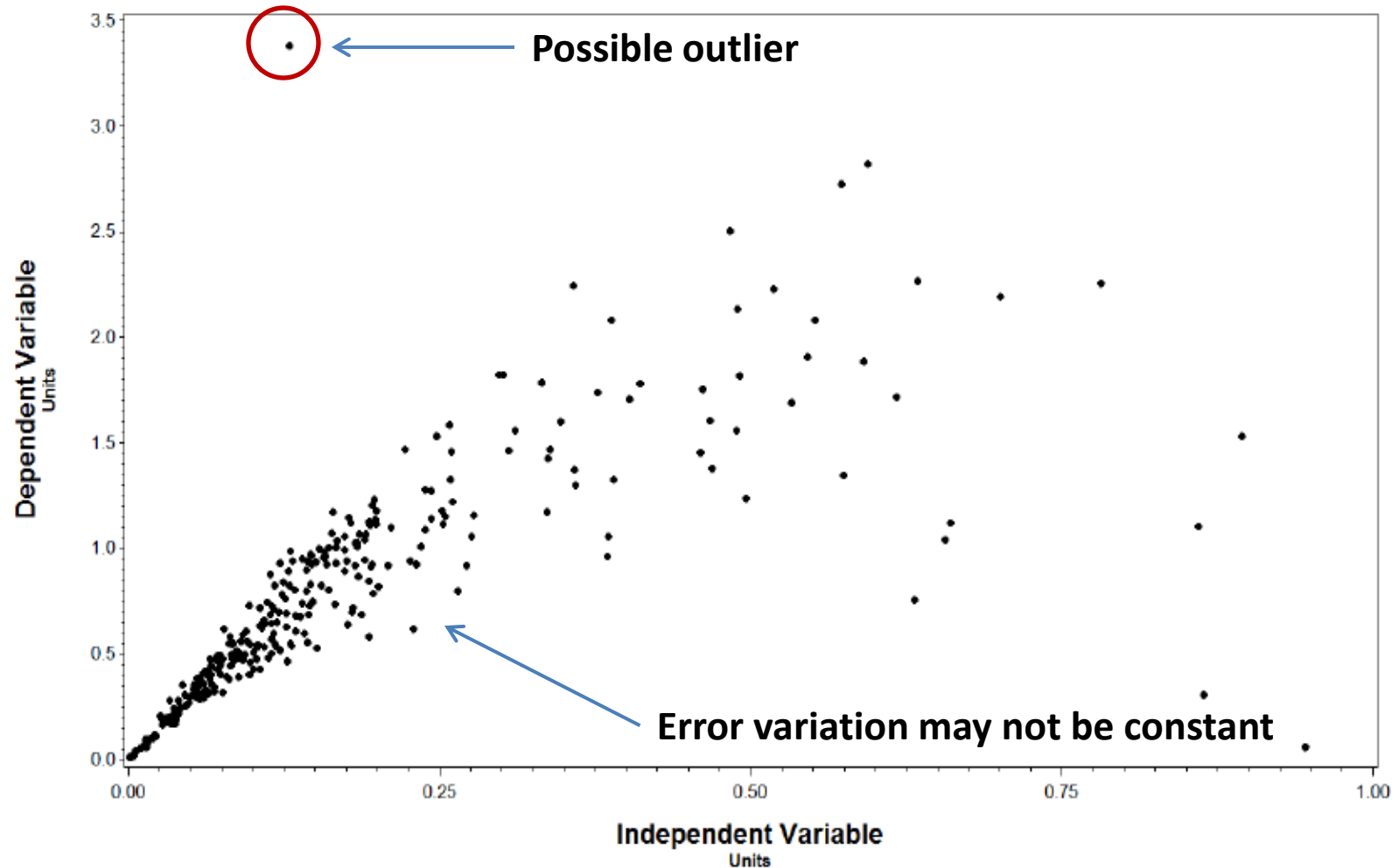
A Look at Raw Data



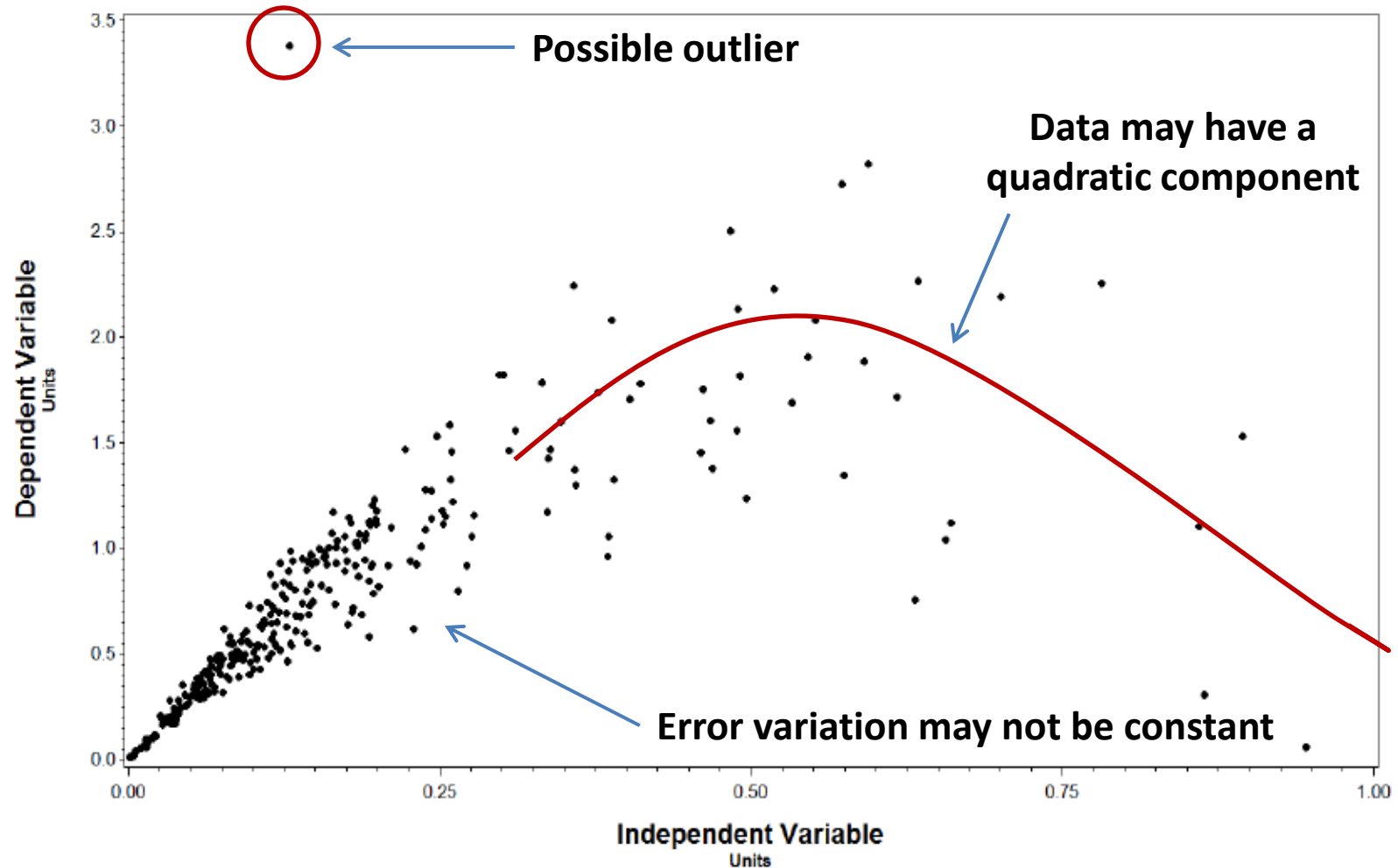
A Look at Raw Data



A Look at Raw Data



A Look at Raw Data



Simple Linear Regression may not be valid and thus, the inference may not be valid.

A Look at Raw Data

Hypothesis: In an observational study, participants were either exposed to substance A or B, it is hypothesized that the group exposed to A will have a more robust increase in Y as compared to those exposed to B.

A representative cohort of 200 participants were recruited where half were exposed to A and half to B.

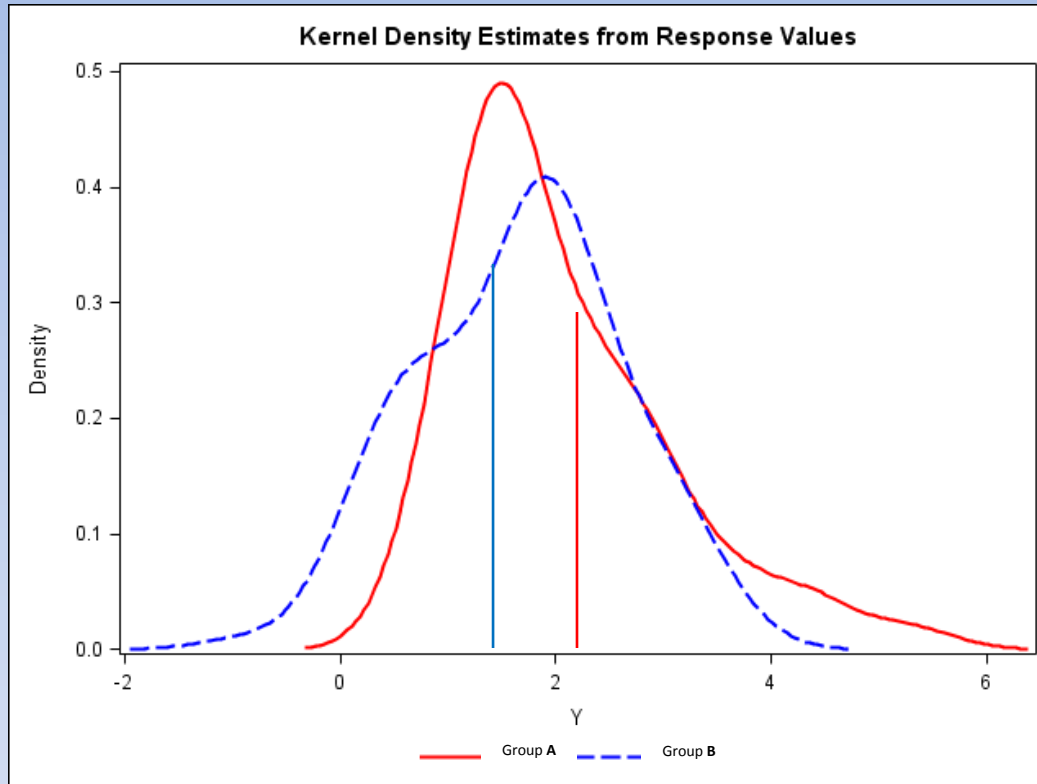
Outcome data are collected and a t-test is run between the two groups.

Results: The group exposed to A has a significantly greater response than the those exposed to B

(Mean $\pm$ SEM: 2.06 ± 0.10 vs. 1.67 ± 0.09 ; $p=0.005$)

A Look at Raw Data

A Look at the distribution of the data in each treatment group



The B group (Blue Line) appears to have an approximately normal distribution while the A group (Red Line) appears to have a lognormal distribution. When running the non-parametric analog to the t-test (Wilcoxon Rank Sums test), the strength of the difference becomes attenuated ($p=0.077$ vs. $p=0.005$). In fact, the median Y value is actually lower in the Group A as compared to the Group B.

Pesky Outliers

There are data points that simply don't make sense...

What to do with those data points?

You cannot simply delete data because it is far from the expected distribution of the data.

Using a “standard deviation approach” or other rules may make distributional assumptions about the data, which may not be the case.

Make sure the data in question are not errors.

Attempt transformations of the data

Your model process may not be normal and you'll need to use an appropriate non-normal distribution.

Graphics First

The design of the experiment should guide tables and figures to best explain the results of the hypothesis.

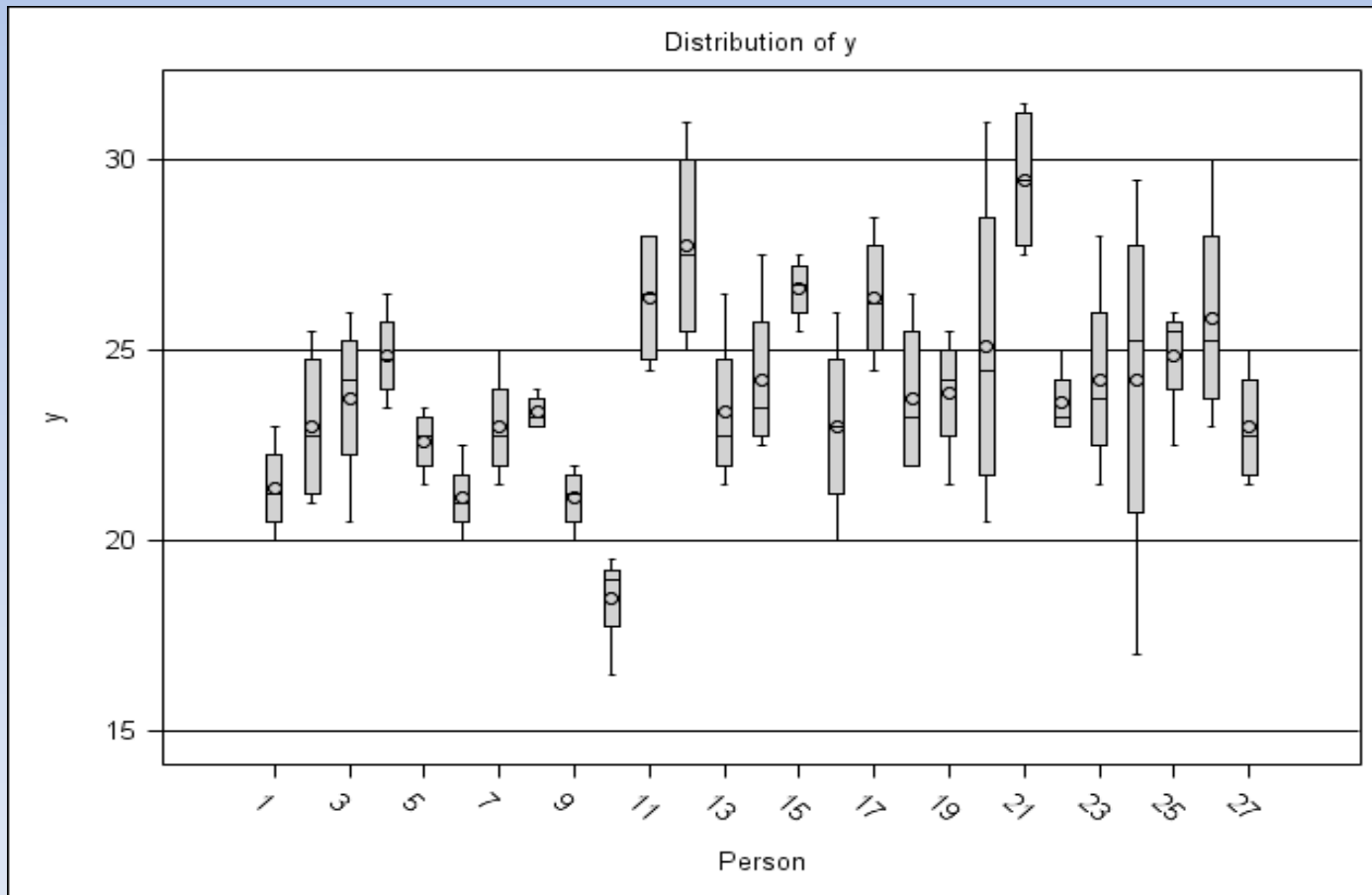
After looking at the raw data and determining that the data meet the general assumptions of the models you intend to use in your analysis, We can begin the production of tables and figures.

Tables and figures should be produced in such a way that they complement the analysis that will be performed.

Graphics First

If your Aim is to test a between subject or a between group difference

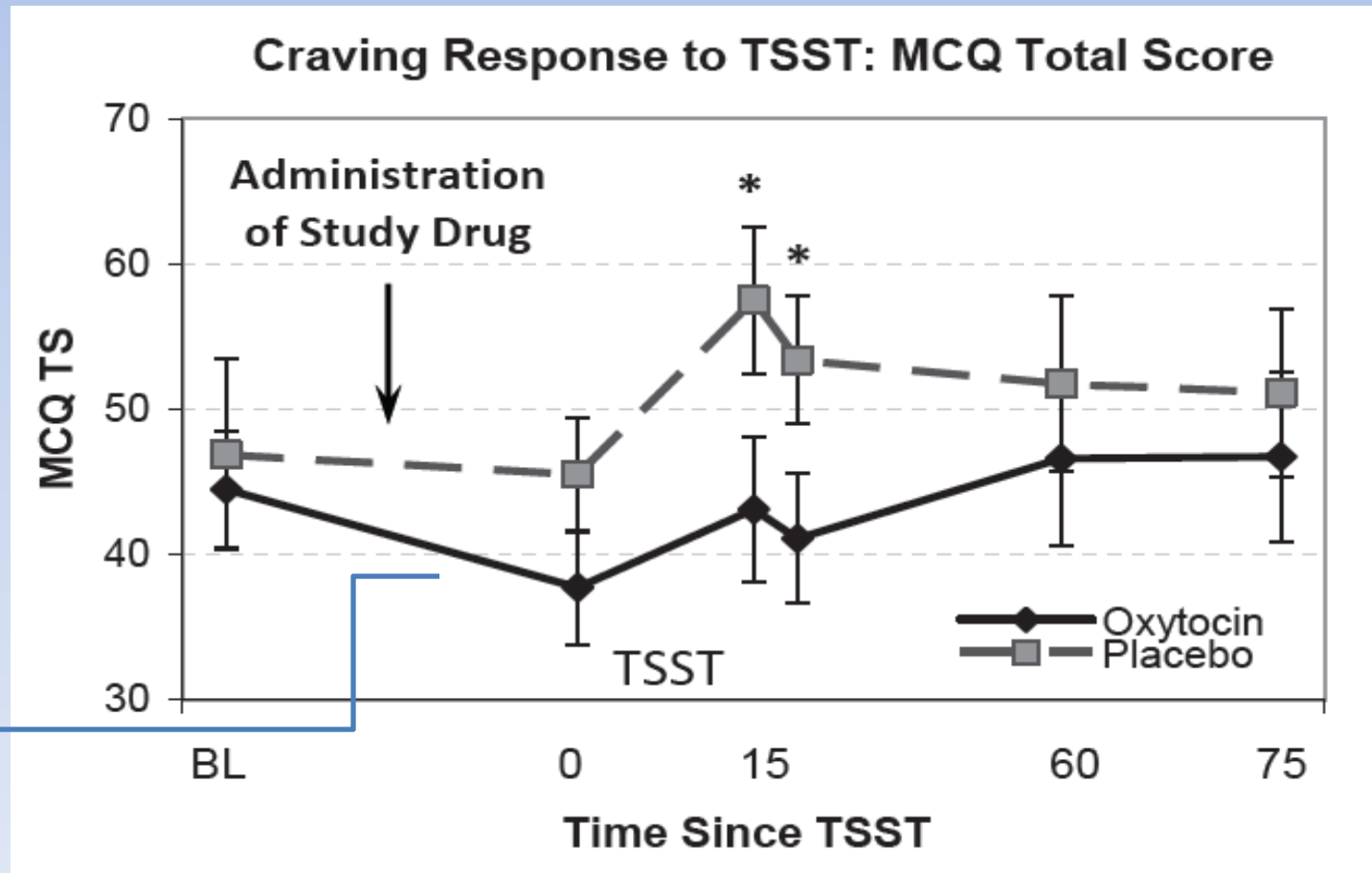
box and whisker plots or dot plots with error bars



Graphics First

If your Aim is to test a between group difference over time

Connected Dot plots with error bars are great here!

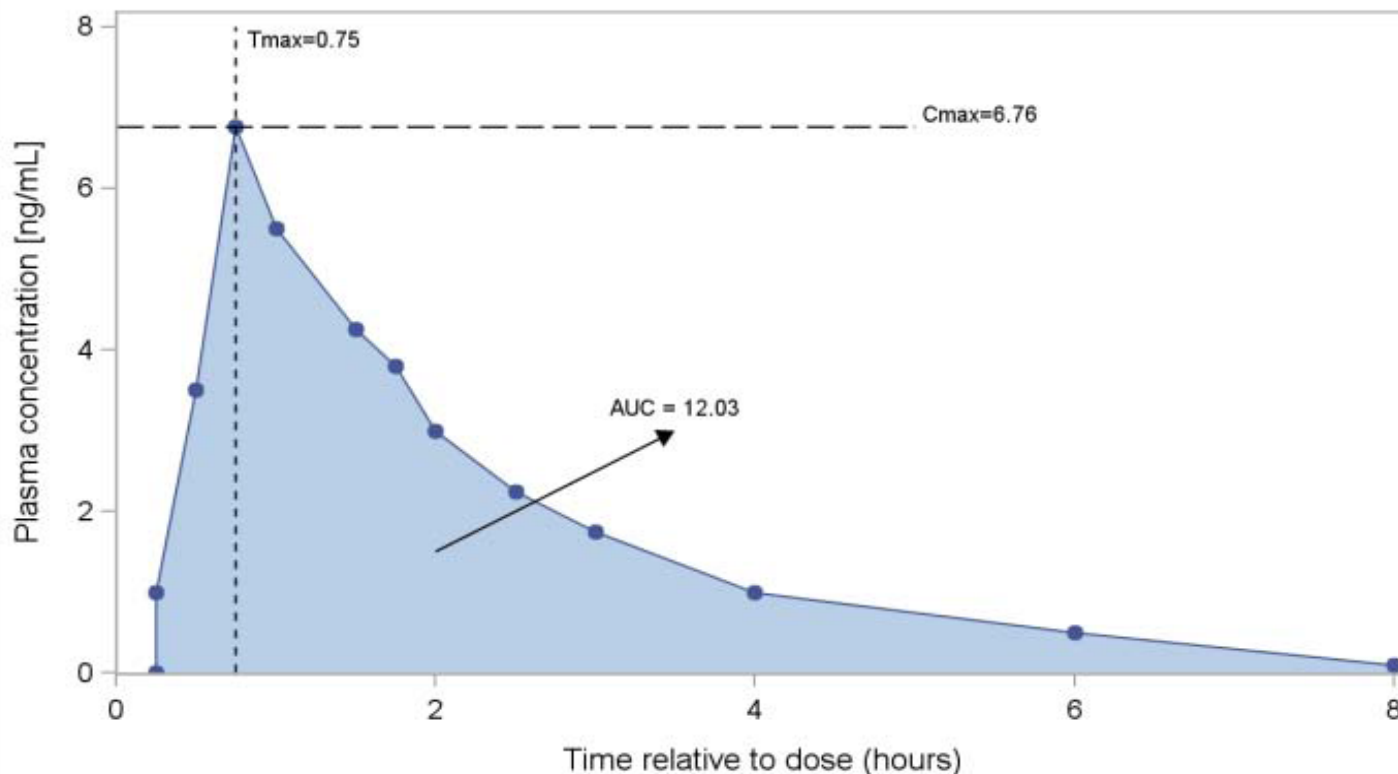


Graphics First

If your Aim is to look into a dose-response

Connected Dot plots with the AUC highlighted can be helpful

Pharmacokinetic Study: Plasma Concentration Profile



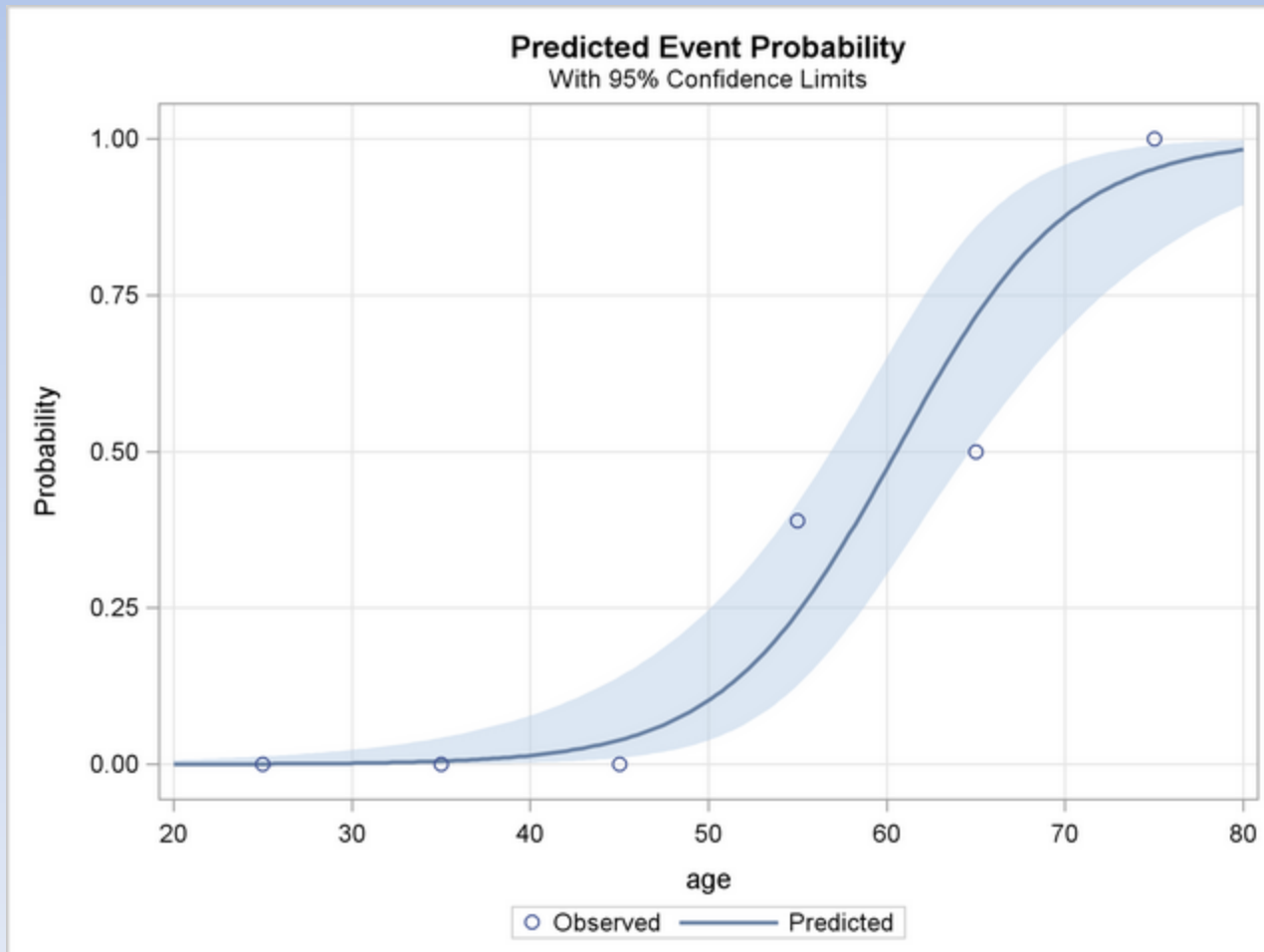
AUC = area under the concentration curve

C_{max} = peak concentration of the drug in the body; T_{max} = time to reach the peak concentration of the drug from dosing

Graphics First

If your Aim is to analyze the binary outcomes

Probability/Logit plots can accurately show the relationship between exposure/treatment and the probability of event occurrence.

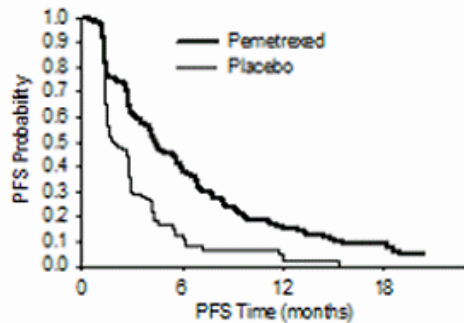


Graphics First

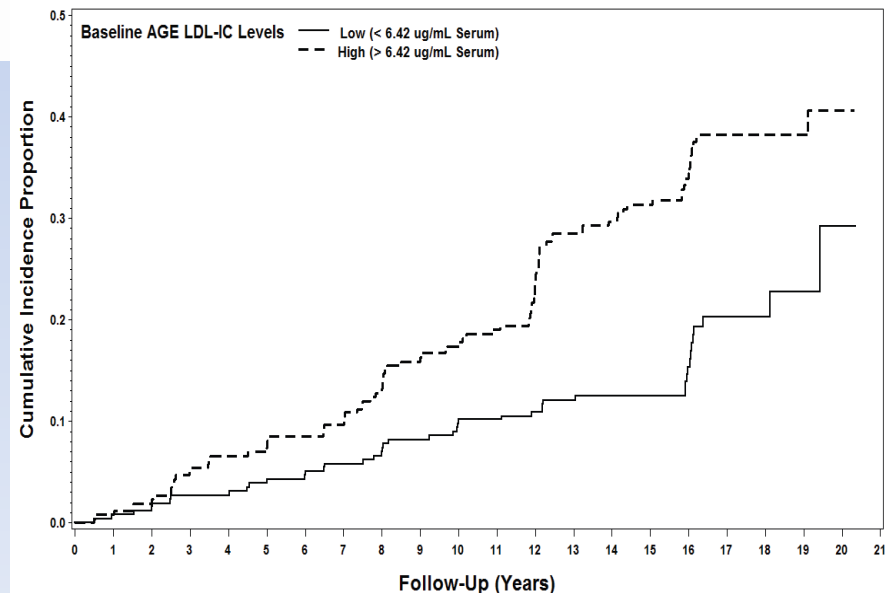
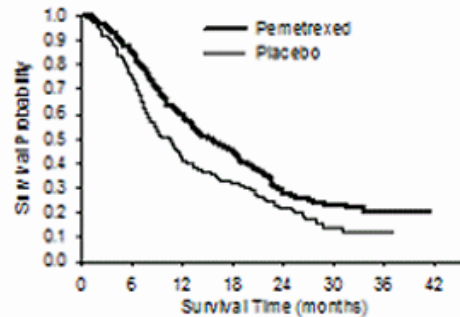
If your Aim is to analyze the time to an event

Kaplan-Meier, Survival Curves, or Cumulative Incidence Plots

Progression-Free Survival



Overall Survival



Graphics First

The error bars in a particular figure could note...

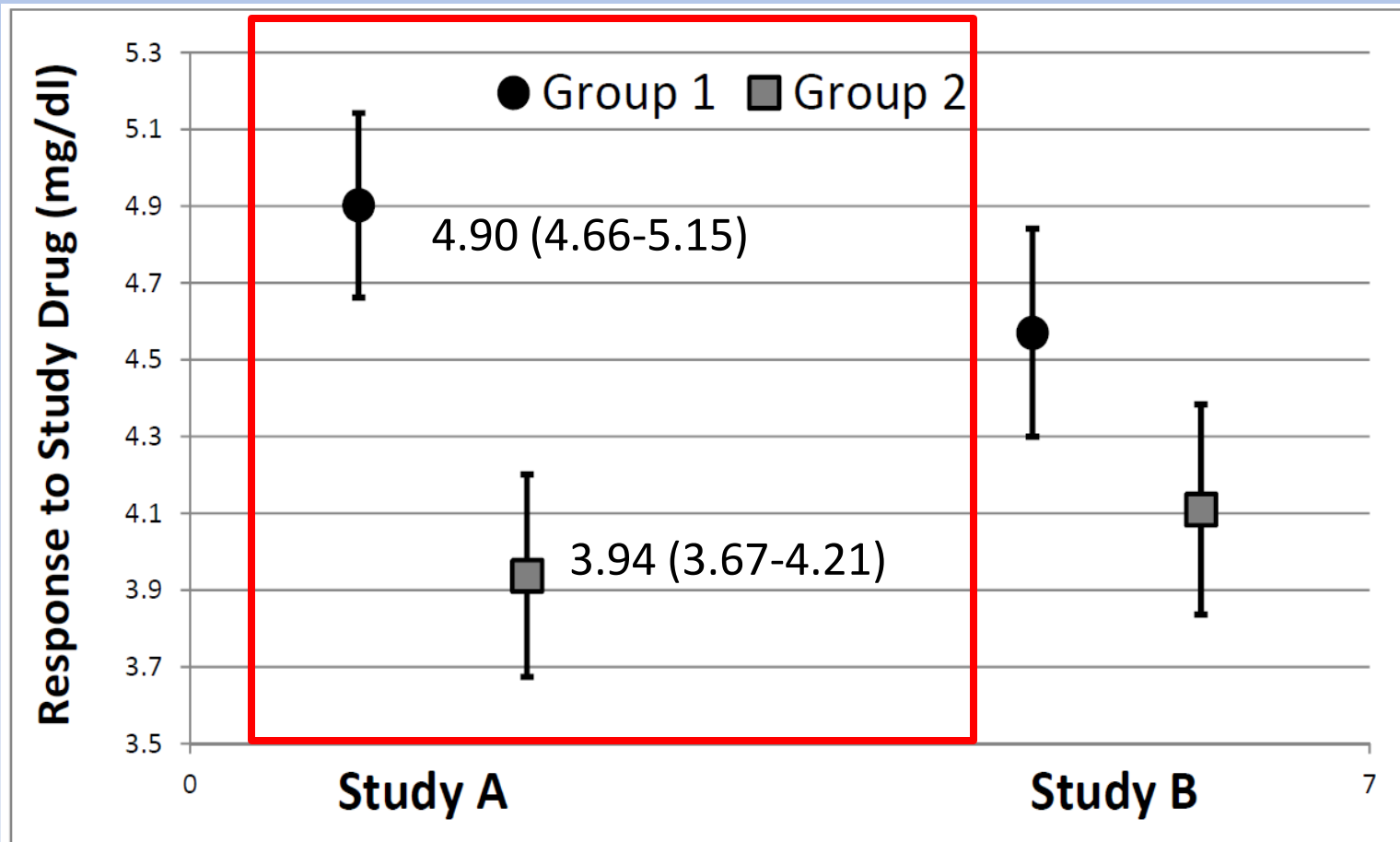
1. Standard Error (precision)
2. Standard Deviation (population variance)
3. 95% Confidence Interval
4. Full Data Range (box plot)
5. Inner quartile range (with median)

What you choose to use will impact the interpretation of the figure, so be deliberate and make sure to stay consistent across figures. The figure legend should clearly state what the error bars represent.

Graphics First

The Figure below show independent group means and associated 95% confidence intervals for two studies...

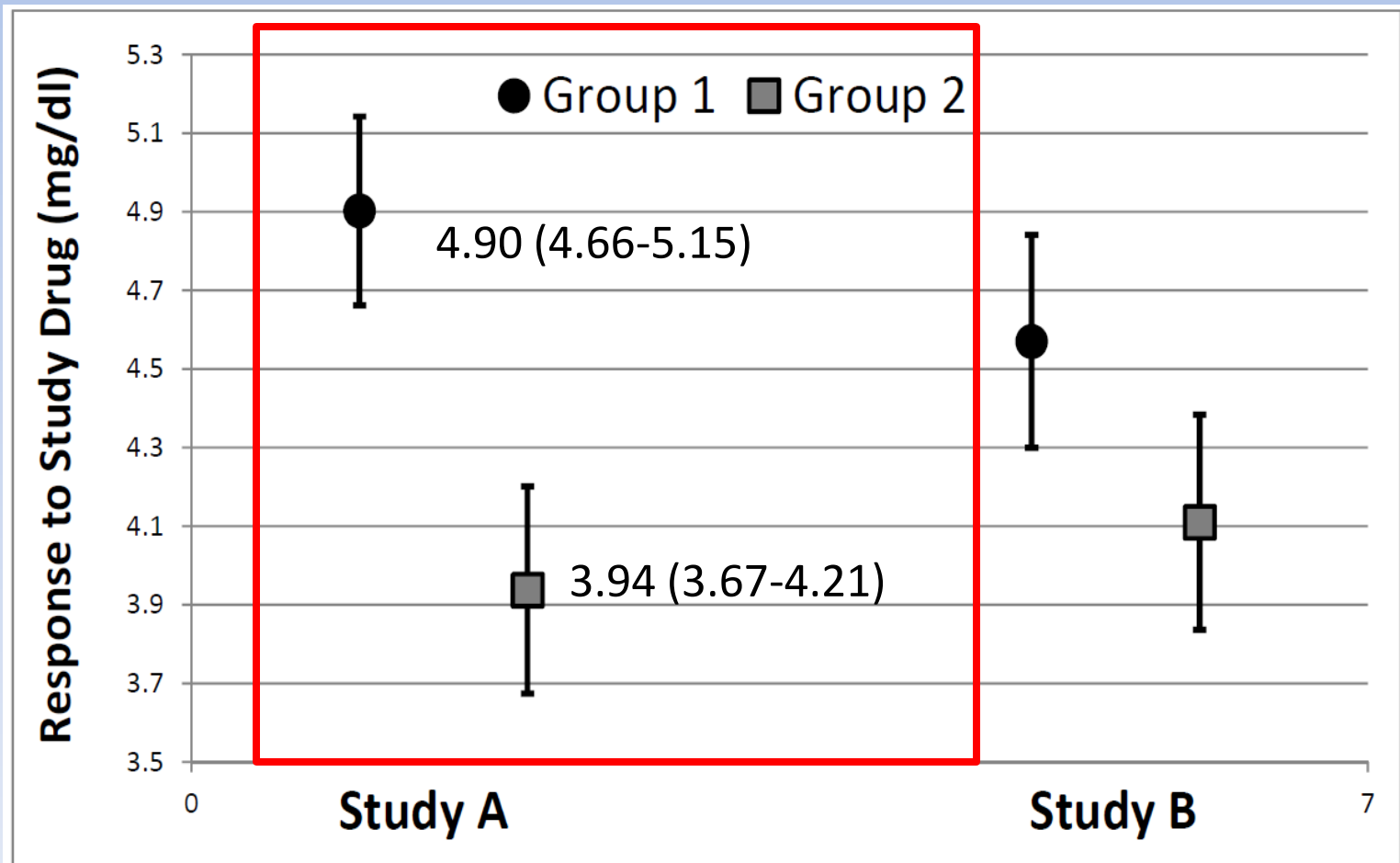
Are these two groups in Study A statistically Different?



Graphics First

Yes, Non-overlapping 95% confidence intervals between independent groups indicates statistical significantly different groups.

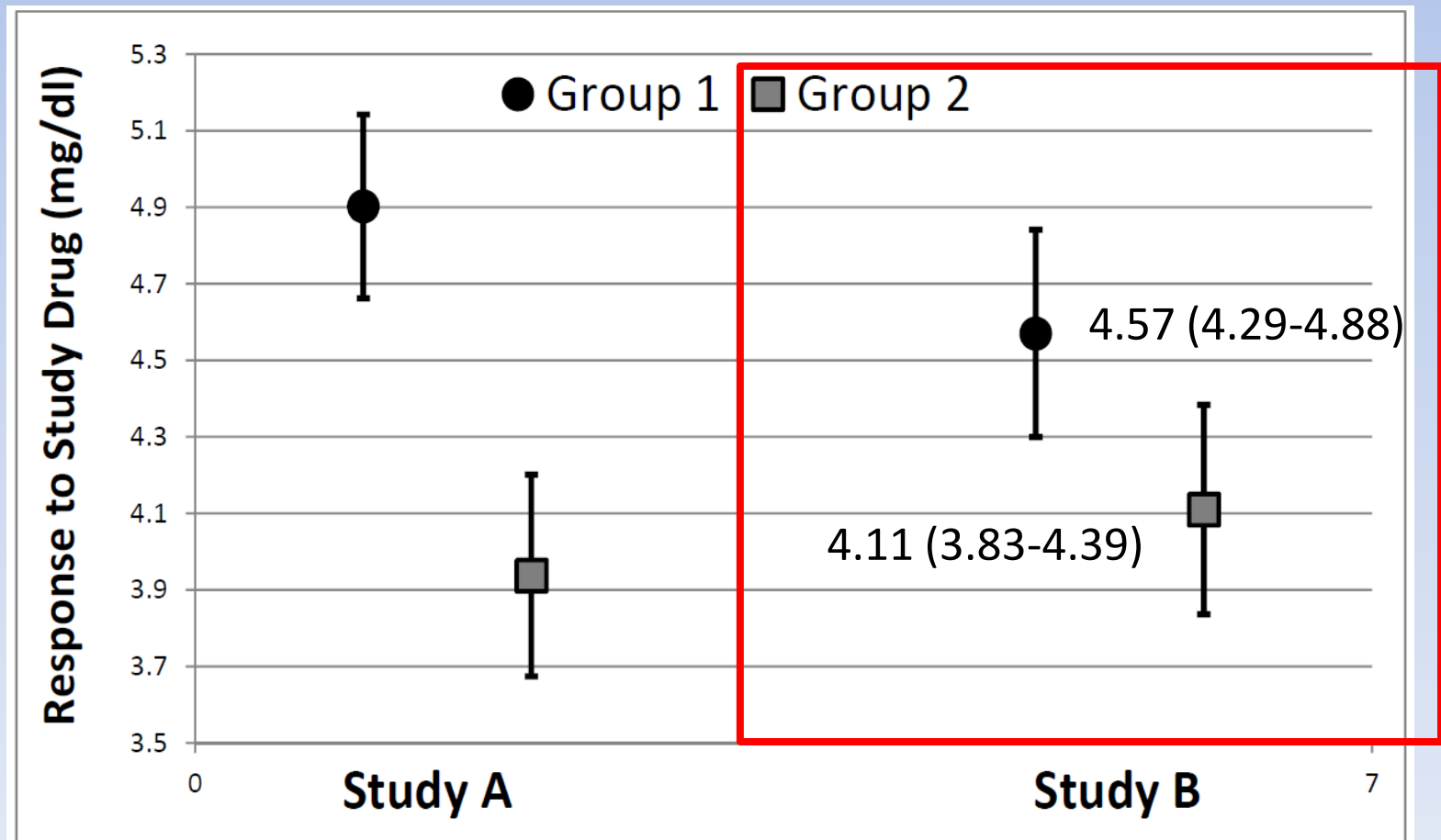
Diff(95% CI)=0.96(0.60-1.33); $P<0.001$



Graphics First

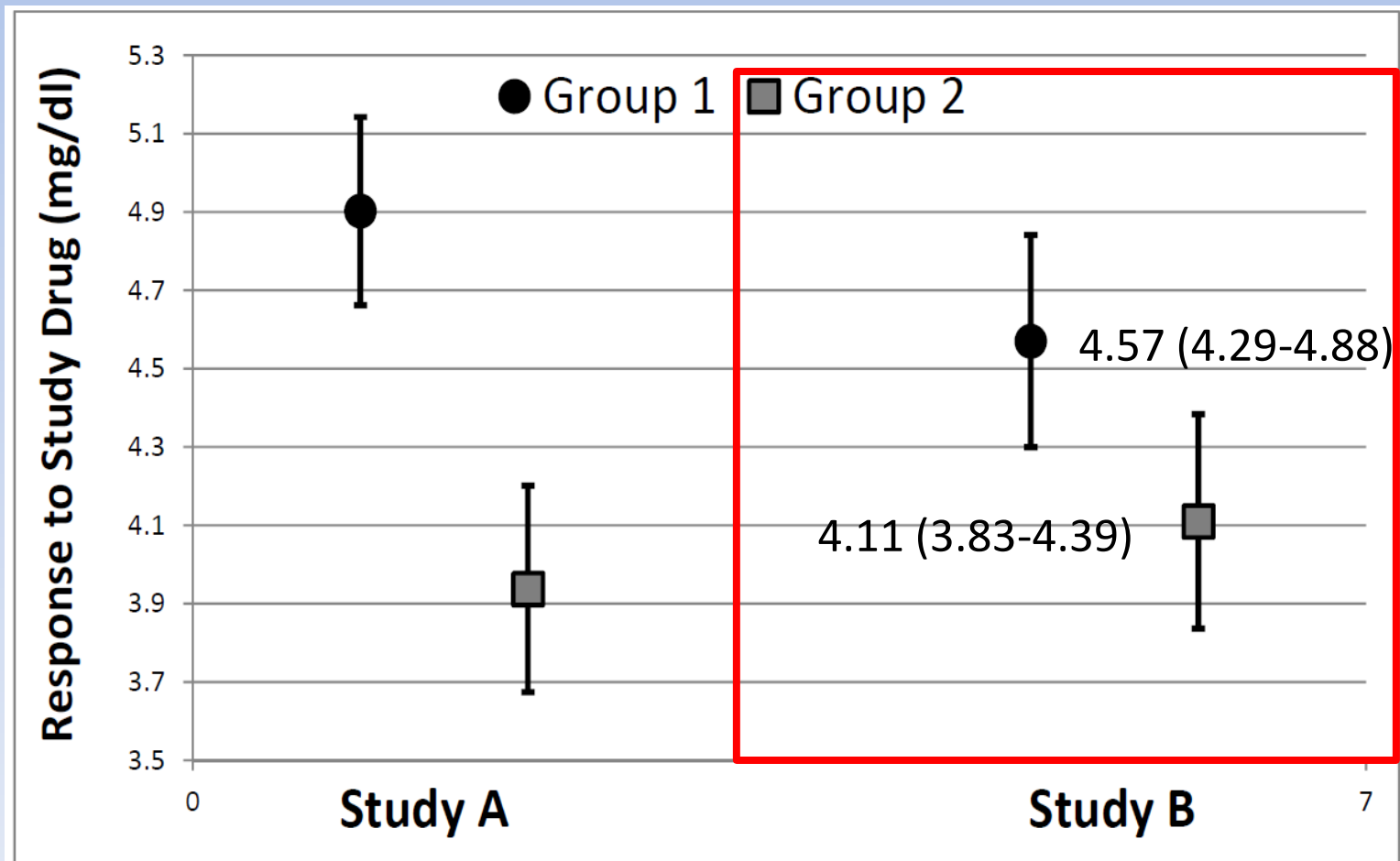
The Figure below show independent group means and associated 95% confidence intervals for two studies...

Are these two groups in Study B statistically Different?



Graphics First

Not enough information is provided to determine if the two groups are different.



Graphics First

However, the two groups shown in **Study B** are statistically different!

Diff(95% CI)=0.46(0.07-0.85); P=0.022

In the simplest of cases, the confidence intervals around each group mean is calculated using the standard error that particular mean (say, SE_1 and SE_2), the confidence interval for the difference between the means is calculated using the root of the sums of the squares of the individual standard errors [$\sqrt{SE_1^2 + SE_2^2}$]. Since it is always mathematically the case that $\sqrt{SE_1^2 + SE_2^2} \leq (SE_1 + SE_2)$, as the difference between the groups grows farther from zero ($\Delta \rightarrow \infty$), the confidence interval around difference becomes significant before the confidence intervals of the individual means fail to overlap.

Graphics First

However, the two groups shown in **Study B** are statistically different!

Diff(95% CI)=0.46(0.07-0.85); P=0.022

When comparing two estimates, it will always be the case that if the confidence intervals do not overlap, then the two group estimates **will be** statistically significantly different.

However, the opposite case is not true. You cannot to determine the statistical significance of the difference between two estimates based on overlapping confidence intervals of the individual estimates.

Graphics First

Consistency from figure to figure is key for the reader to follow your story...

Use the same axis magnitudes when possible

Stay consistent with grouping labels and line colors

Figures should use the same standard text font and size

Units of measurement should be labeled in the same manner across all figures

Many journals don't accept panels of figures that are not consistent or related in an attempt to skirt figure limits.

Legends, Labels and Captions

Figure Legends are the readers guide to understanding the data

Figure legends should always included...

A description of what is presented: *“comparison of the CRP to experimental stimuli A and B on a population of type 1 diabetics”*

A description of how it is presented: *“Data are shown as means and associated standard errors/95% Conf. Intervals/SDs”*

The sample size for the experiment, overall or by group: *“Group A, n=159; Group B, n=162”*

Definitions of all abbreviations used in the figure: *“CRP=C-Reactive Protein”*

Other Test results and information as they apply to the Study.

Although many basic science figures contain specific statistical methods, this practice is not necessary in clinical papers and methods should be addressed in the manuscript.

Legends, Labels and Captions

Figure labels are an important factor in understanding the data

The Axis label should accurately note the variable and the appropriate units of measure.

The Axis should have clear values shown that related to the experimental design. *i.e. X-axis label for a pre post design should not read 0 and 1.*

The Axis range should be appropriate to show clinical relevance and not skew the readers perception of responses or group differences.

Legends, Labels and Captions

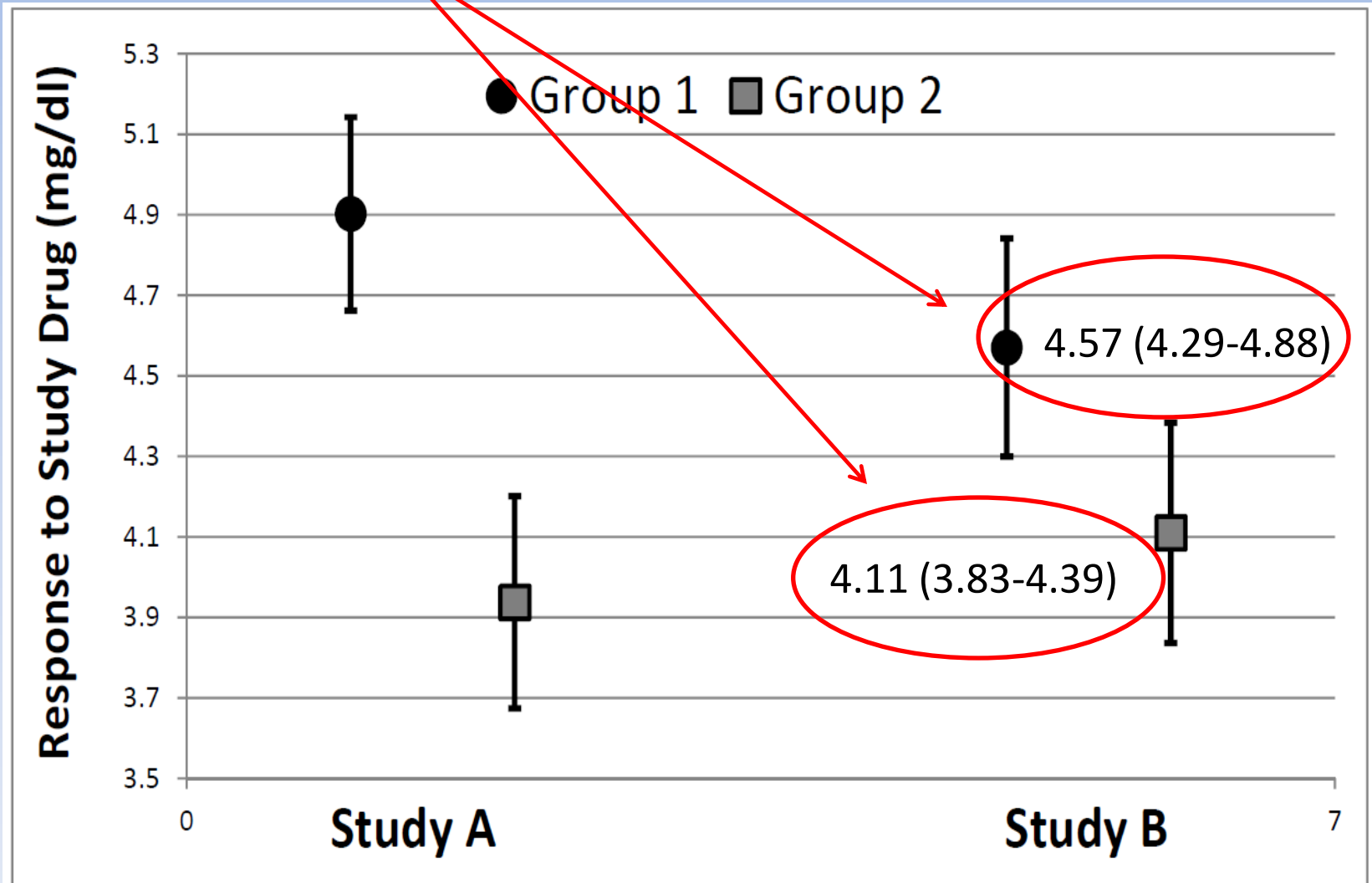
Within figure captions should be used sparingly.

Generally, the data key is included whenever different subjects, groups, or experimental units are shown on a figure. This is used to easily identify group differences or difference in experimental units.

Other captions containing statistical results (P values, R-Square values, sample sizes or equations) should be included in the figure legend when possible, although there are exceptions.

Legends, Labels and Captions

Within figure captions should be used sparingly.



Interpretation

Your figure will be interpreted based on the presentation of the data.

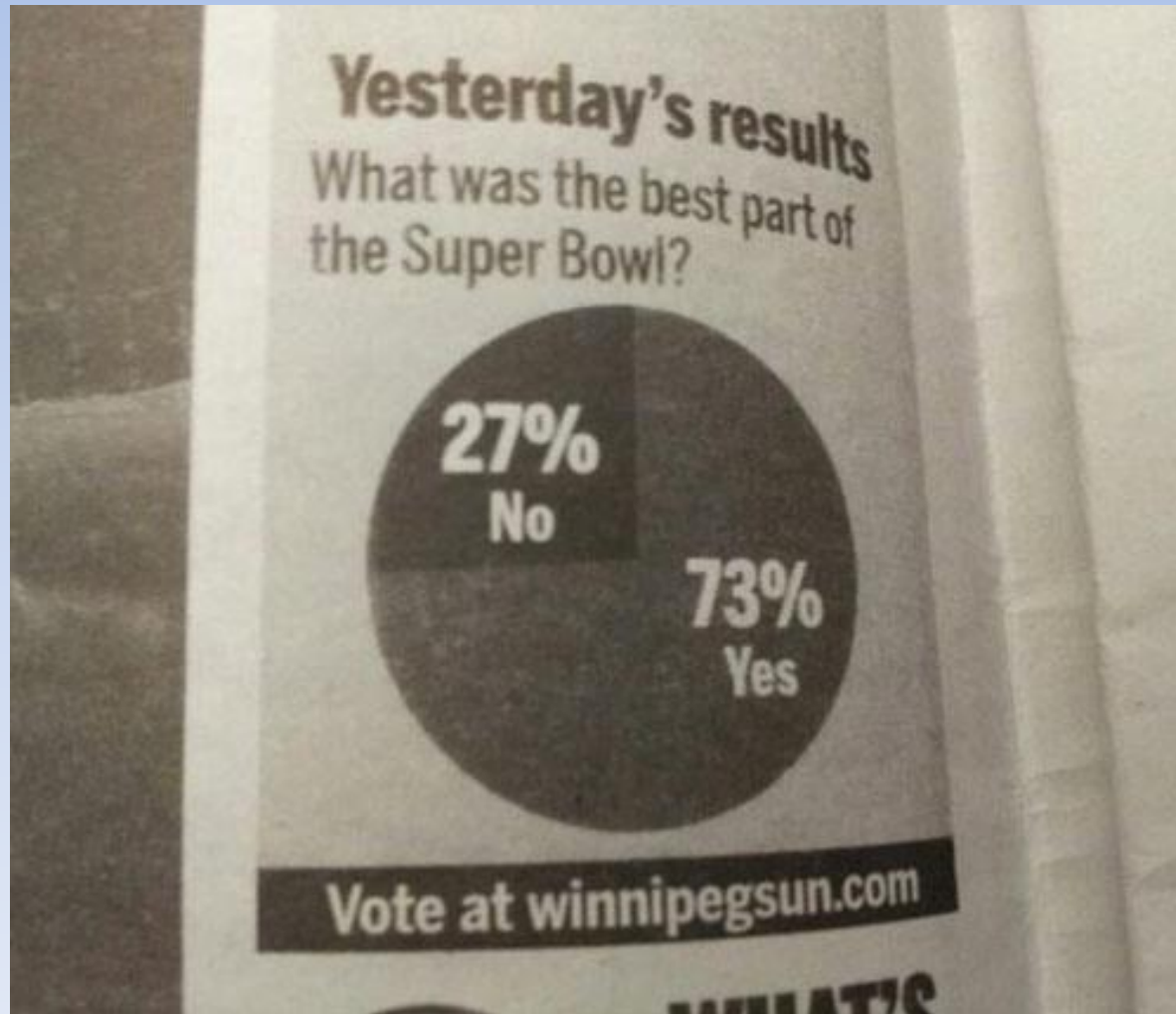
Figures should be able to be interpreted in the framework of the hypothesis that is being tested and presented.

Figures should not be used to skew the interpretation of the results.

If your data analysis is performed using a covariate adjusted model, you should attempt to create your figures using adjusted means rather than raw data values.

Interpretation

Make sure that the figure you are presenting clearly represents the question you want to answer



Interpretation

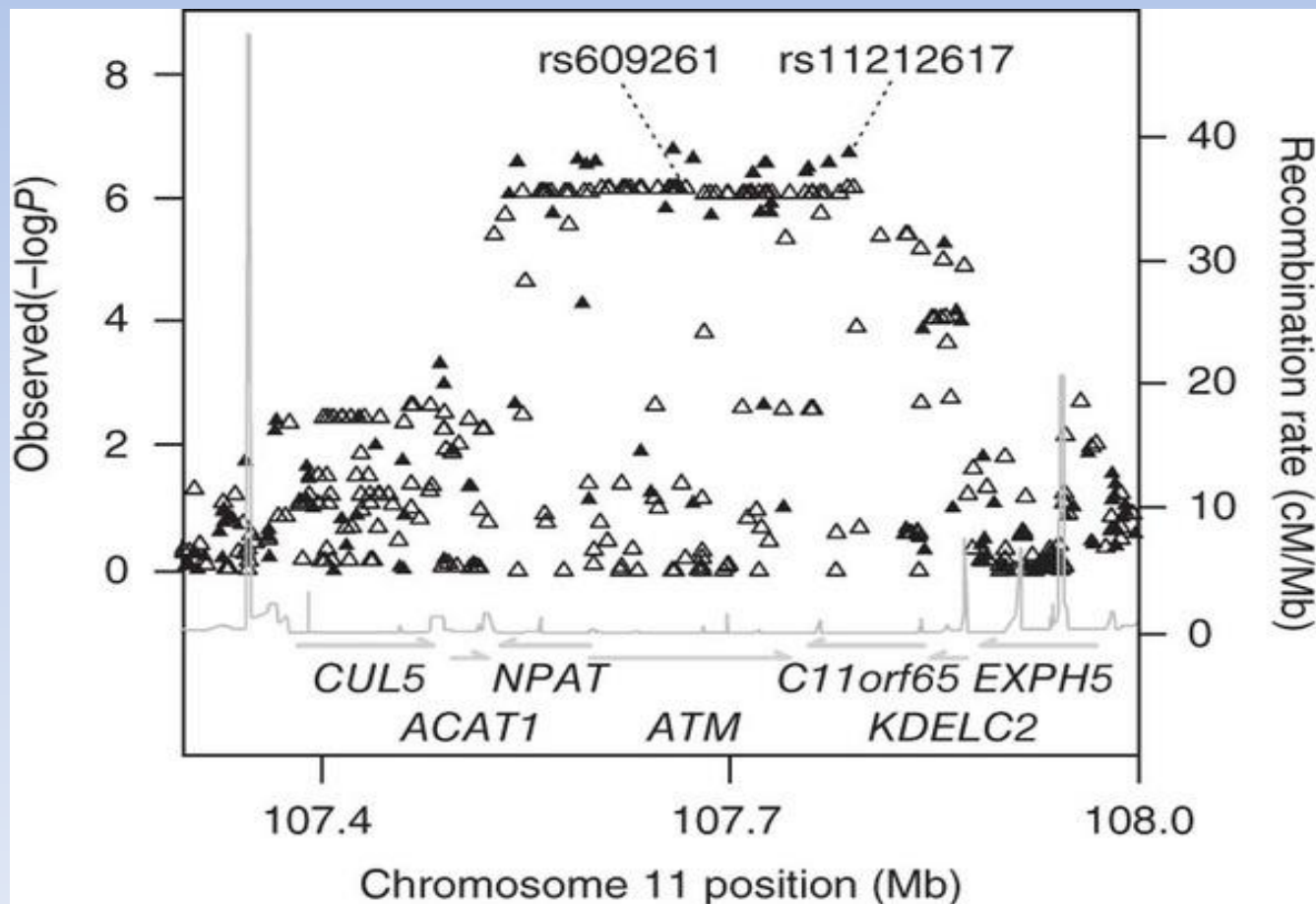
Interpretation of the figure can be influenced by color choices, choose wisely.



Keep it Simple

Make sure your figure is simple and can stand alone

Figure 1. Regional association plots around the ATM locus for the logistic regression analysis. The solid and open triangles are from directly typed and imputed SNPs, respectively



K. Zhou, C. Bellenguez, *et al.* Common variants near ATM are associated with glycemic response to metformin in type 2 diabetes *Nat. Genet.*, 43 (2011), pp. 117–120

Keep it Simple

Make sure your figure is simple and can stand alone

Avoid 3 dimensional charts and figures when possible.

Use thick lines that will show well when the image is shrunk for printing.

If many line styles are chosen, pick patterns that are easily distinguished.

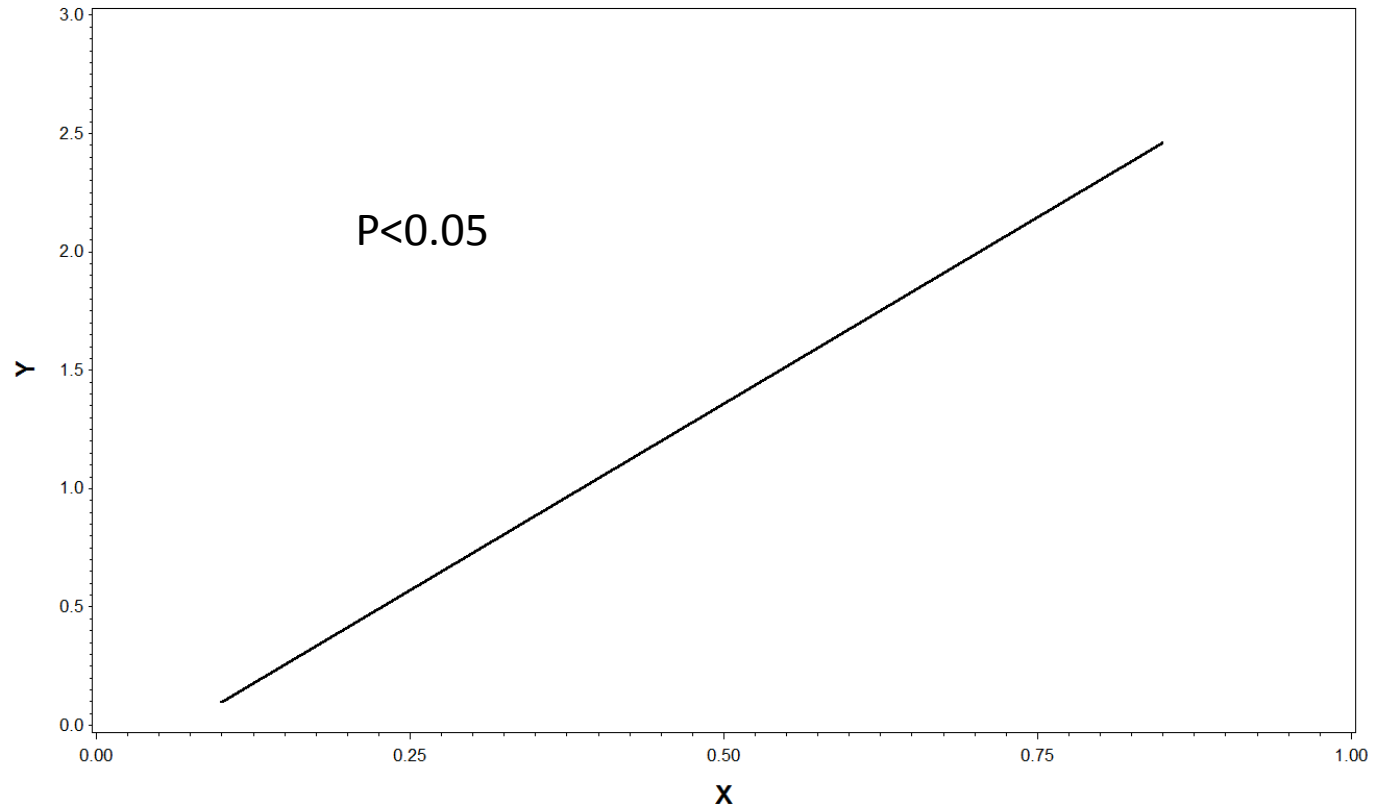
Try to use black and white images with no unnecessary shading.

Avoid background shading and it usually scans unevenly and can project unwanted patterns.

Keep it Simple

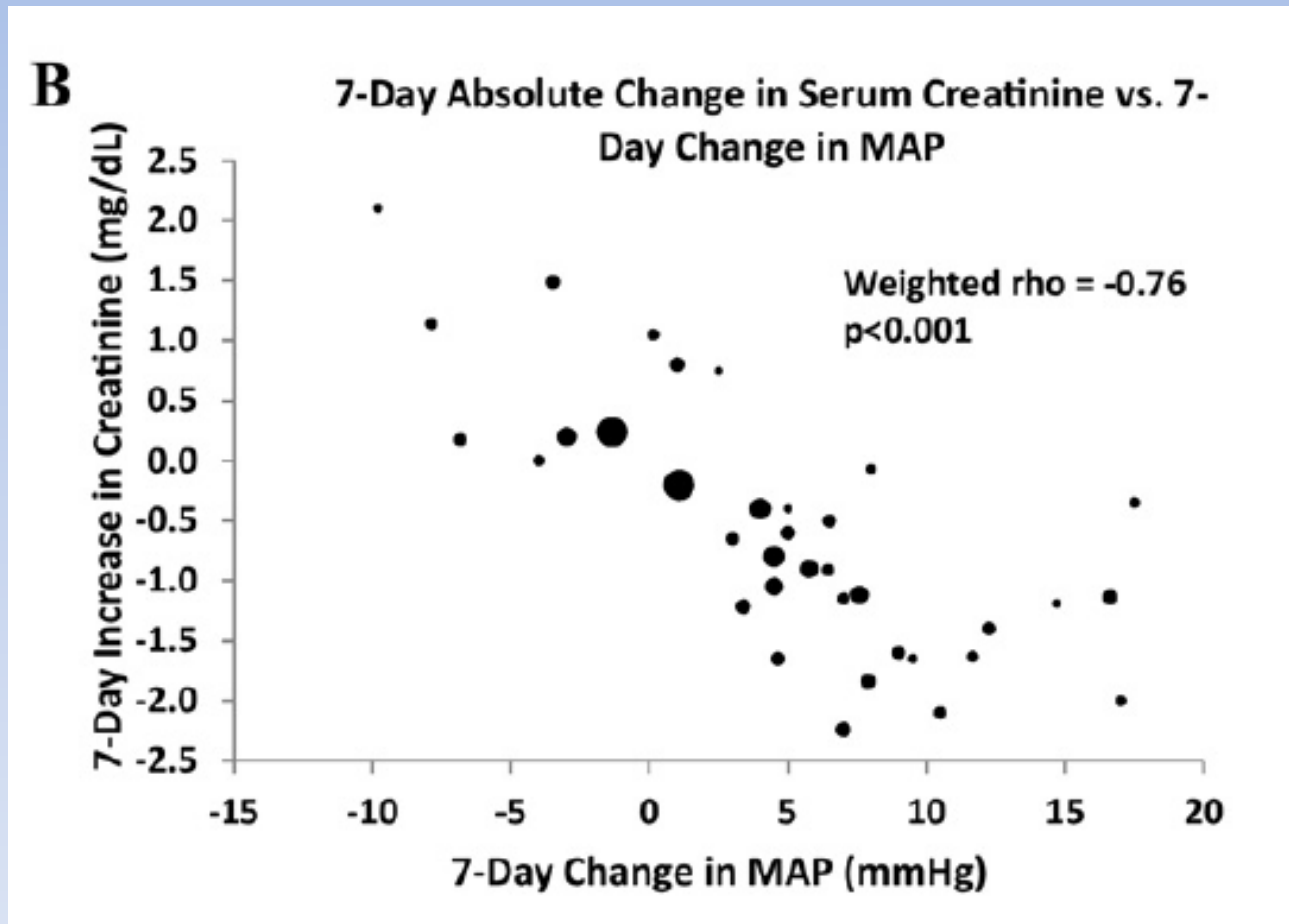
But not too simple!

Figure 1. Relationship between independent and dependent variables.



A Nice Example

Figure 2. Correlation between increase in mean arterial pressure (MAP) and change in kidney function. Diameter of each data point reflects relative sample size of cohort. Abbreviation: % Δ , percentage change.



J.C. Velez, P.J. Nietert. Therapeutic response to vasoconstrictors in hepatorenal syndrome parallels increase in mean arterial pressure: a pooled analysis of clinical trials. *Am J Kidney Dis*, 58 (6) (2011), pp. 928–938

Useful References

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- HR Pauli, DJ Garbutt. TS11 Clinical Trials Reporting with SAS ODS Graphics. PhUSE, 2009
<http://www.lexjansen.com/phuse/2009/ts/ts11.pdf>