Biostatistics

Mithat Gonen

Brenden Bready

Today’s Lecture

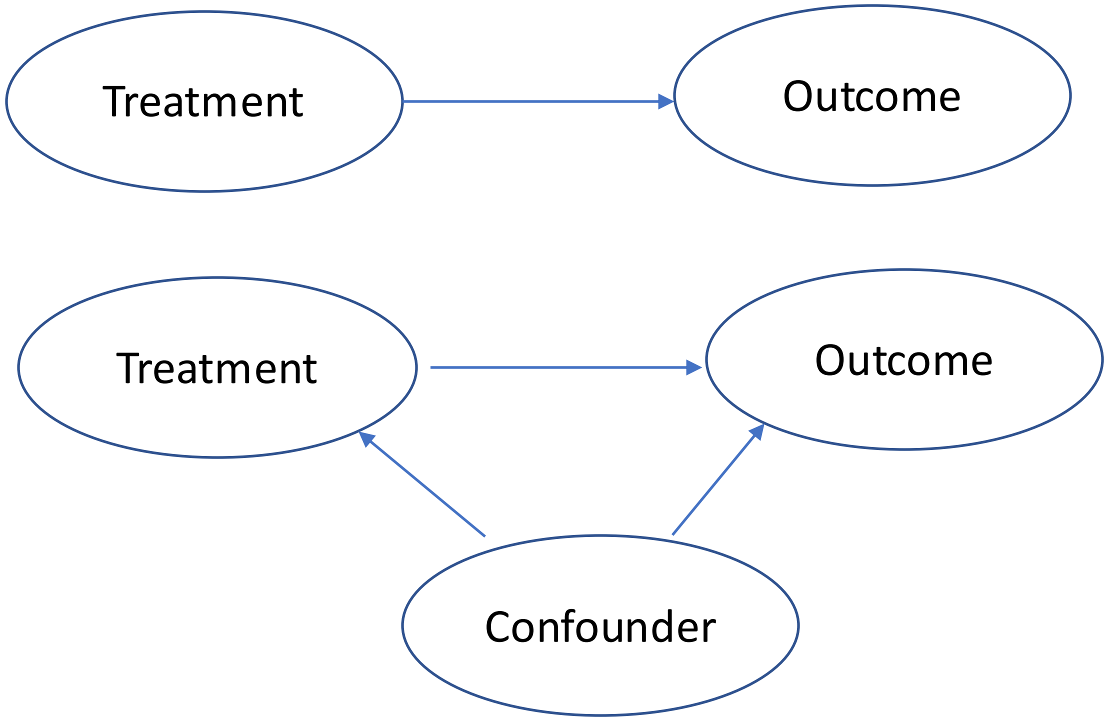
- Review:
  - Confounding
  - Matching
- New Material:
  - Stratification
  - Regression

Retrospective Study Design

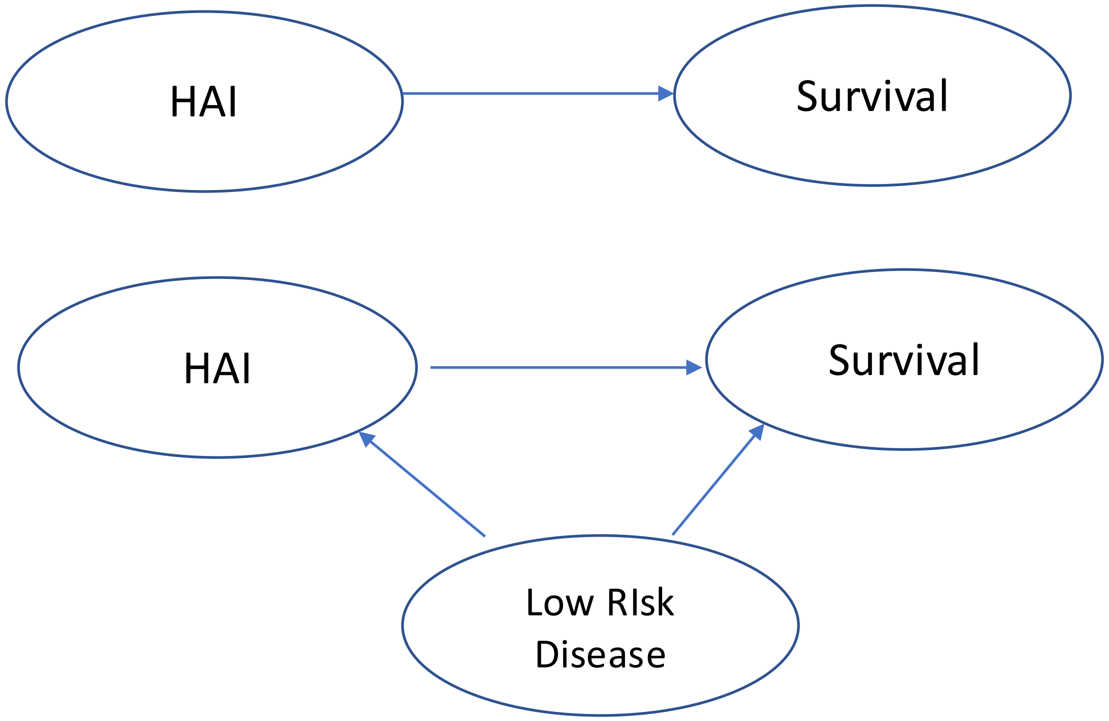
- Sounds like an oxymoron
- But hugely important
- Act as if this is a clinical trial
  - Primary objective/endpoint
  - Secondary objectives/endpoints
- Inclusion/Exclusion Criteria
- Define treatment arms
- …

What is a confounder?

- Something that is associated with both the treatment (exposure) and the outcome

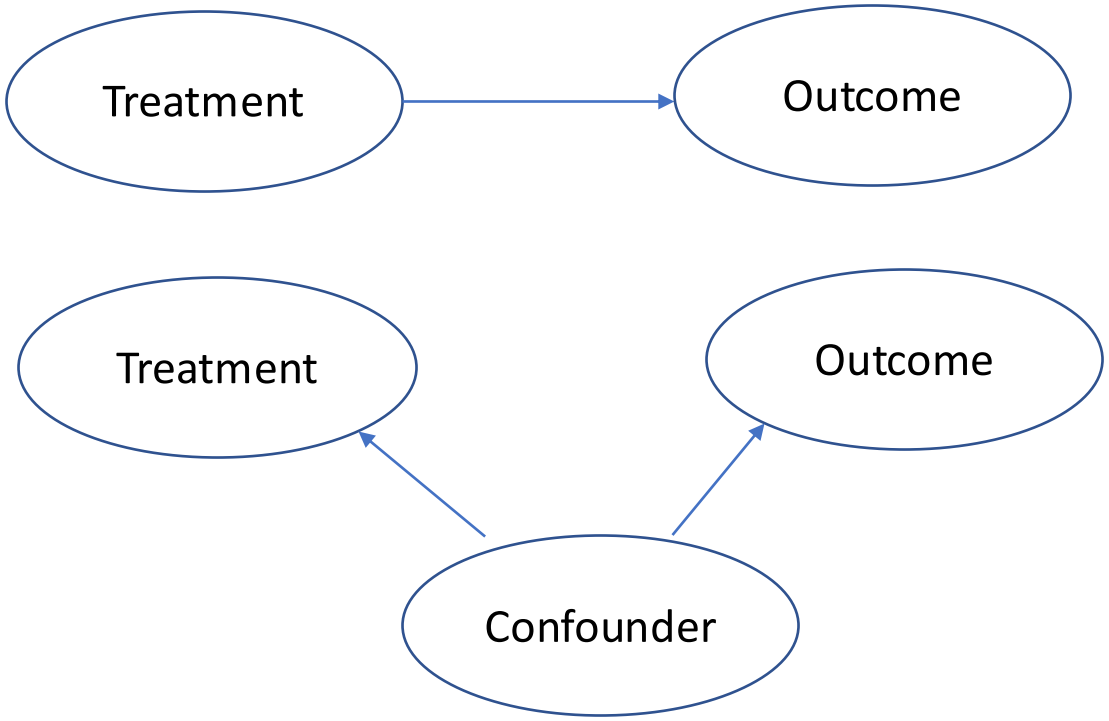


HAI example



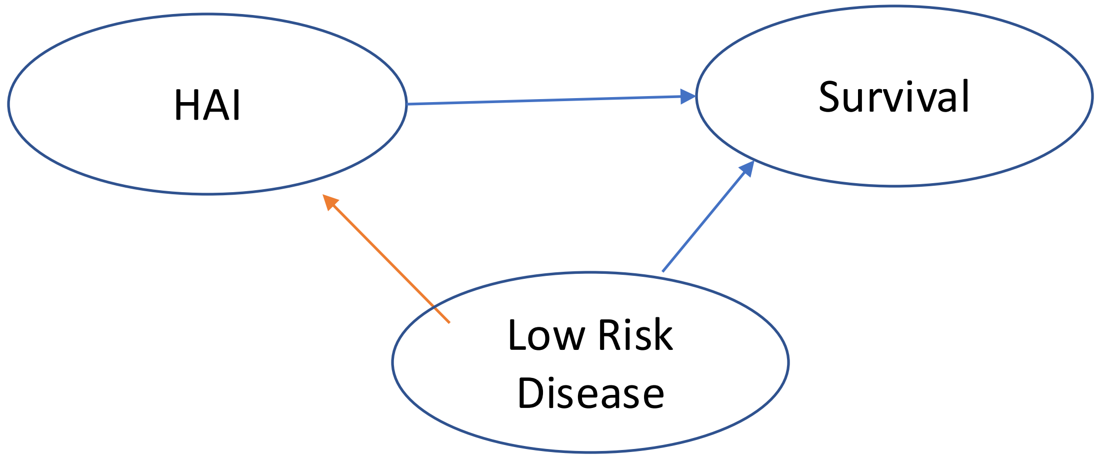
Why is this a problem?

- Even if there is no direct link between treatment and outcome, there is a still a link through confounding. Any analysis that do not account for the confounder will attribute that link to the treatment



How do we deal with confounding

- We need to find ways to remove the link between Treatment and Confounder through data analytic methods
- Remember: That’s what an RCT does (removes the link) by design. In an observational study we cannot use random assignment, hence we will need to achieve a similar effect by data analysis.



Matching

- If we compare all treated with all control, confounder raises its head
- What is we find a twin (a match) for each treated patient from the untreated (control) group.
  - Twin = Has the same value for the confounder
  - Suppose low risk is defined as number of liver tumors, time between primary and mets dx and CEA
  - For each patient who received HAI, I find someone who had exactly the same number of tumors, disease free interval and CEA but did not receive HAI
  - Now I have a data set where there is no link between Low Risk Disease and Treatment (I made it so, by “design”).
  - If there is still an association between treatment and outcome then it must be that the treatment causes the outcome

A hidden assumption

- “If there is still an association between treatment and outcome, then it must be that the treatment causes the outcome”
- I am making a very critical assumption here that I have not stated
- No other confounders !!!
- Hugely important.
- We are not making this assumption in a randomized study. Random assignment balances all confounders, observed and unobserved.
- Data analysis can at best balance observed and recognized confounders.

More on Matching

- Find a twin (a match) for each treated patient from the untreated (control) group.
- Easier said than done
- CEA: do I need an exact match? If a treated patient has a CEA of 87 and there is no control patient with a CEA of 87, but there is one with 86 is it OK to match them? Are they still twins?
- The difference we allow in matching is called a caliper. If we have a caliper of 10 for CEA, then 77 to 97 match a CE of 87.
- How to choose a caliper? Usually not obvious but can be consequential

Categorized Risk Factors Are a Problem in Matching

- CEA >= 200 is used in this disease as a risk factor. Can we match on that?
- Sure, but it is actually worse than a caliper
  - 1 matches 199
  - But 199 does not match 200

Isn’t it possible to fix this?

- Use as many confounders as you can think of to match
- Use a very small caliper (such as CEA) or insist on exact matching (number of tumors)
- Most of the time you cannot find a match for every treated patients if you insist on strict matching standards
- Exclude unmatched?

What happens if there are unmatched patients?

- Suppose we had 100 HAI patients to begin with
- We insisted on strict matching and we were able to match 60 of them
- And go ahead analyze this 60-60 matched cohort
- To what population does this generalize to?
- Only the population where the 60 matched HAI patients came from
- Can you define that population? The original 100 is (presumably) well-defined because you had inclusion/exclusion in your design (see the importance of design)

Leave no patients unmatched

- This means relax the matching criteria
  - Fewer confounders
  - Wider calipers
- But this means less twins more siblings → weaker control of confounding
- The entire field of dealing with confounders can be summarized with this struggle:
  - Bias/Validity tradeoff

Bias/Validity Tradeoff

- Bias is the outcome difference between treated and untreated patients that is due to confounders
- We match to make the treatment and control groups comparable
- If we there are unmatched patients we lose on validity
- If we relax matching rules to improve validity then the groups are less comparable and bias creeps in
- No good solution to this, kind of a Heisenberg principle for empirical research

A note on “Group” Matching

- Some people would call what I described as 1:1 matching
- And they would call also matching if treated and untreated groups are matched on average (i.e. mean CEA is the same in both). “Groups are well-matched, groups are matched on means etc”
- This really is not matching. It is something clinical literature made up. Do not use it.

A note on 1:k matching

- Sometimes useful to capture the variability of the outcome in the control group
- Requires a large control group and most of the time impractical
- 1:2 match on 100 treated patients → 300 patient study
- Less powerful than 1:1 matched on 150 patients
- The rate limiting step is the number of treated patients.
- Do not 1:k match because it you think will increase your power, do it only to capture the variability in outcome

Statistical analysis of matched studies

- You cannot use typical two-sample (two group) tests
  - No two-sample t-test
  - No chi-square test
  - No log-rank test
- Instead
  - Paired t-test
  - McNemar test
  - Paired log-rank test

Summary of Matching

- Most matches are not twins. They are at best siblings with many differences between them
- Unmatched patients are a threat to the validity of conclusions
- Most of the time matching is not a great way to deal with confounding for these reasons
- But it has great face value: a lot of clinicians think “a matched cohort” is great even if they do not understand where we traded off between bias and validity

Stratification

- Can we match on a single categorical variables?
- Consider a different example: adjuvant treatment in localized colon cancer. All stage III’s get it and so do some stage II’s.
- If we are doing an observational treatment comparison can we simply match on stage II vs III?

Technically yes

- For each treated stage II patient, randomly choose an untreated stage II patient
- Can we call this a match?
- In the eye of the beholder
- If the matching group definitions are very broad and if there are only a few categories to match, then it may be better to use stratification instead of matching

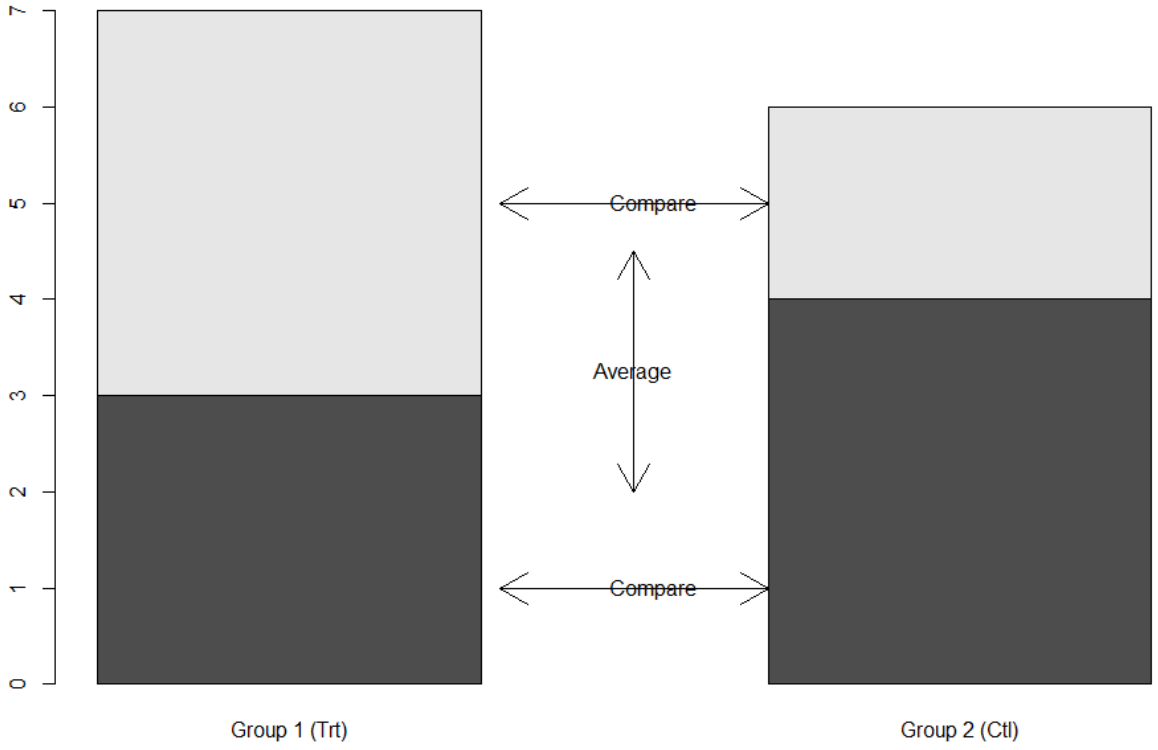
What is stratification?

- Form (a few) strata from the confounding variables
- Compare treatment and control within each strata (using everyone in that strata)
- Average these comparisons across strata
- No patients excluded, so validity is intact
- What about bias?

Bias in stratification

- Stratification also compares like to like, except that it defines “like” based on a very loosely defined criteria (like Stage II vs III)
- In that sense it is a little like matching on a few variables with large caliper
- → Bias is a concern
- Strengths
  - Transparent: no excluded patients, no arbitrary calipers

Stratification



Regression

- Start simple, outcome Y and one input variable (predictor, covariate) X, both continuous.
- I will write Y = f(X), where f(.) generically denotes a function. Our general aim is to figure this f(.) thing out
- If you have one X you can try many types of f's or even leave it unspecified. But for multivariable regression (many X's) we will limit ourselves in this class to a linear form.
- $E(Y) = \alpha + \beta X$, where E(.) means "expected value" or "mean of"
- α and β are parameters (remember populations vs sample; parameter vs estimate)

Linear Regression

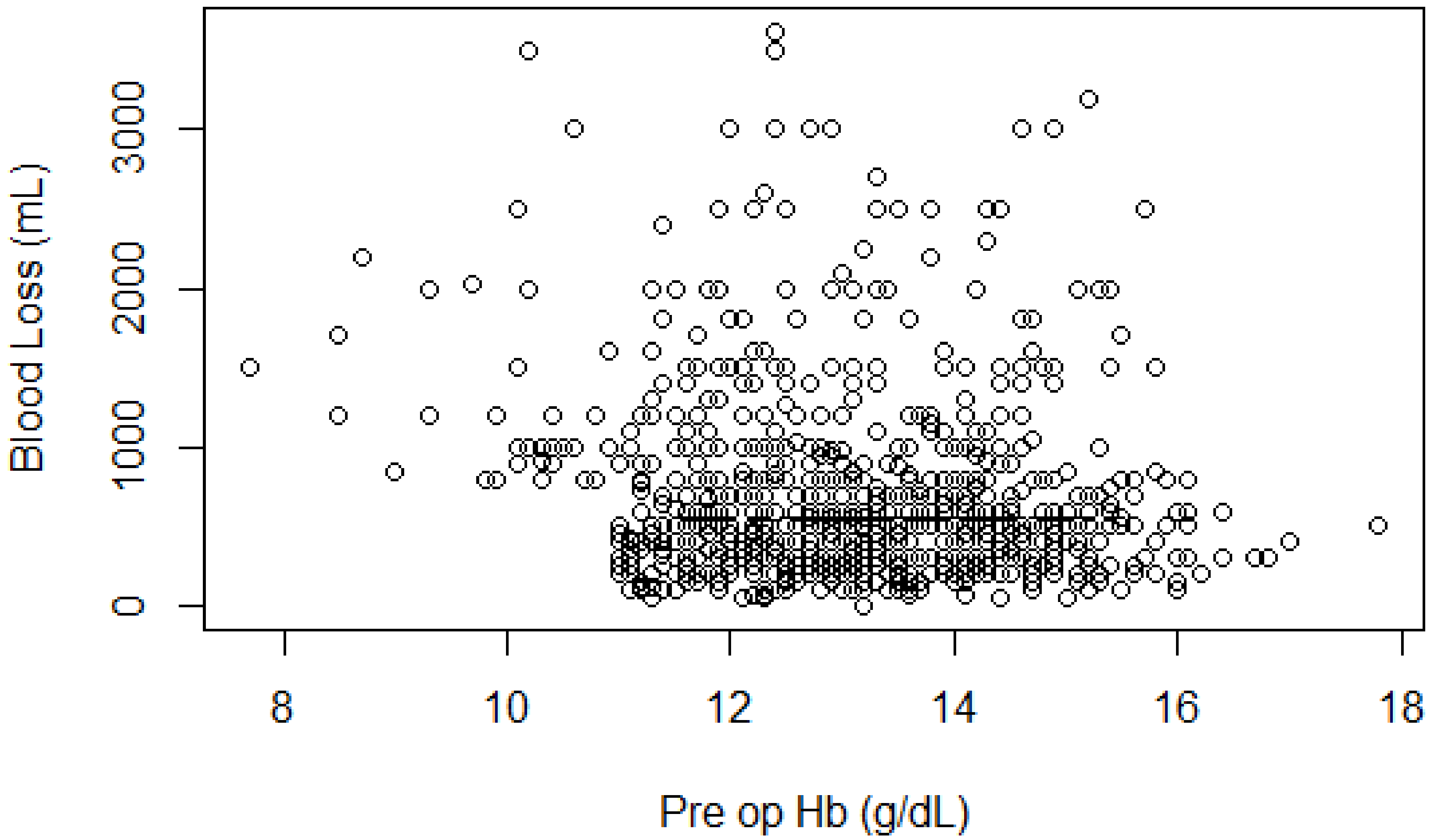
- $E(Y) = \alpha + \beta X$, where E(.) means “expected value” or “mean of”
- α and β are parameters (remember populations vs sample; parameter vs estimate)
- When have estimates instead of parameters the equation will look like
- $Pred(Y) = a + bX$
- a and b are estimates
- Pred(Y) means predicted value of Y

Estimation vs Prediction

- Finding the best-fit value of a parameter → Estimation
  - a and b are parameters
- Finding the best-fit value of an observation → Prediction
  - Pred(Y) is a prediction
- In regression and almost all other models
  - We first estimate the parameters (increasingly called training the model)
  - We then generate predictions of the outcome

When Y is continuous

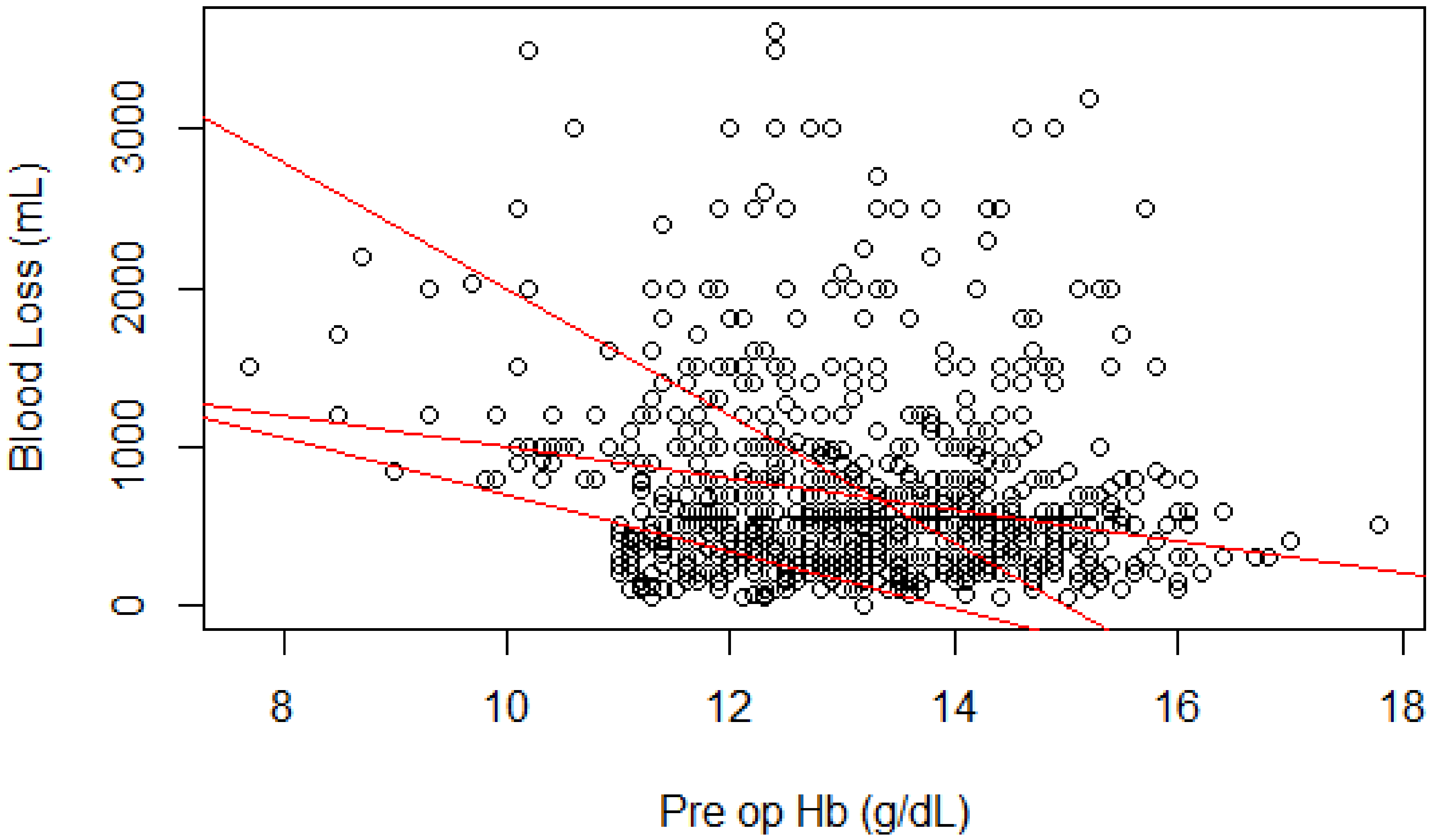
- No good examples in oncology
- Our interesting outcomes are either binary or censored
- But regression is best taught with a continuous outcome
- So we will spend this lecture on using a somewhat artificial example
- Pre-operative hemoglobin vs surgical blood loss
  - I doctored the data a little to make my points so do not conclude anything medical from this analysis



Blood Loss (mL)
0
1000
2000
3000
8
10
12
14
16
18
Pre op Hb (g/dL)

How to find the best fitting line

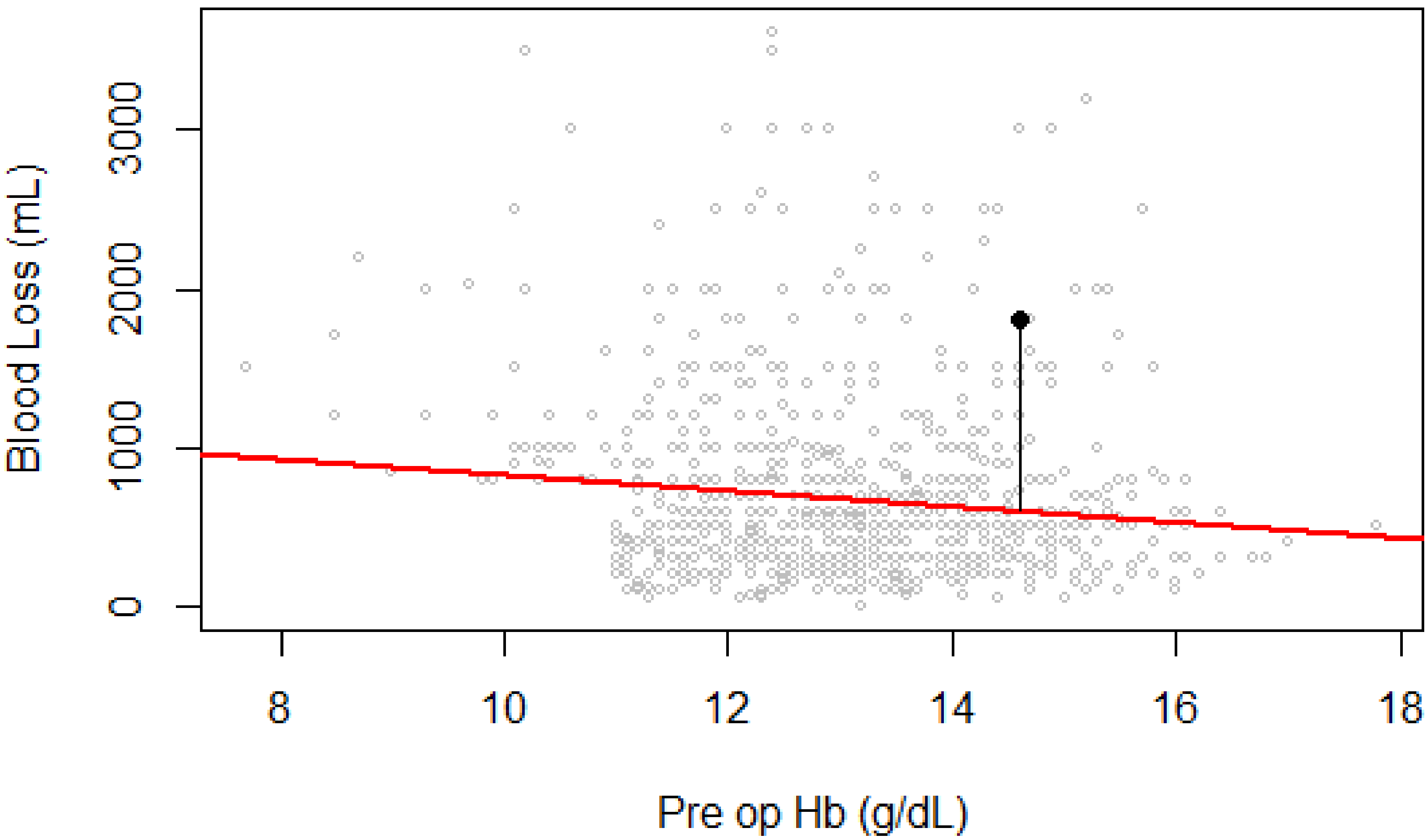
- Never mind (for the purposes of this class) that the general trend in this scatterplot does not look like a line or much of anything
- Imagine yourself (next set of slides) trying many different lines
- Which one fits best?
- What does “best fit” mean?



Blood Loss (mL)
0
1000
2000
3000
8
10
12
14
16
18
Pre op Hb (g/dL)

Best fit

- In this context of continuous Y, the most commonly used best fit criterion is “minimize the deviations from the fitted line”
- Deviations: the distance between a point and the fitted line
- Imagine going through this
  - For every possible line going through this data set
  - Calculate the deviation for each point
  - Add them up
  - Choose the line with the smallest sum of deviations
- Known as the least squares method



Blood Loss (mL)
0
1000
2000
3000
8
10
12
14
16
18
Pre op Hb (g/dL)

Least Squares

- We do not really try all the lines, there is a formula that gives a and b for a given set of points
- Least Squares is the oldest method for estimating regression coefficients
- Widely used
- DOES NOT generalize to other outcomes (binary, censored)
- We will not spend any appreciable time on it

Residuals

- Y – pred(Y) are called residuals
- Can you see on the previous graph that residual is the same as deviation?
- Residuals are very important in least squares regression
- Just like least squares does not generalize well to other outcomes
- But the idea of a deviation generalizes and we will continue to use that concept

Goodness of fit

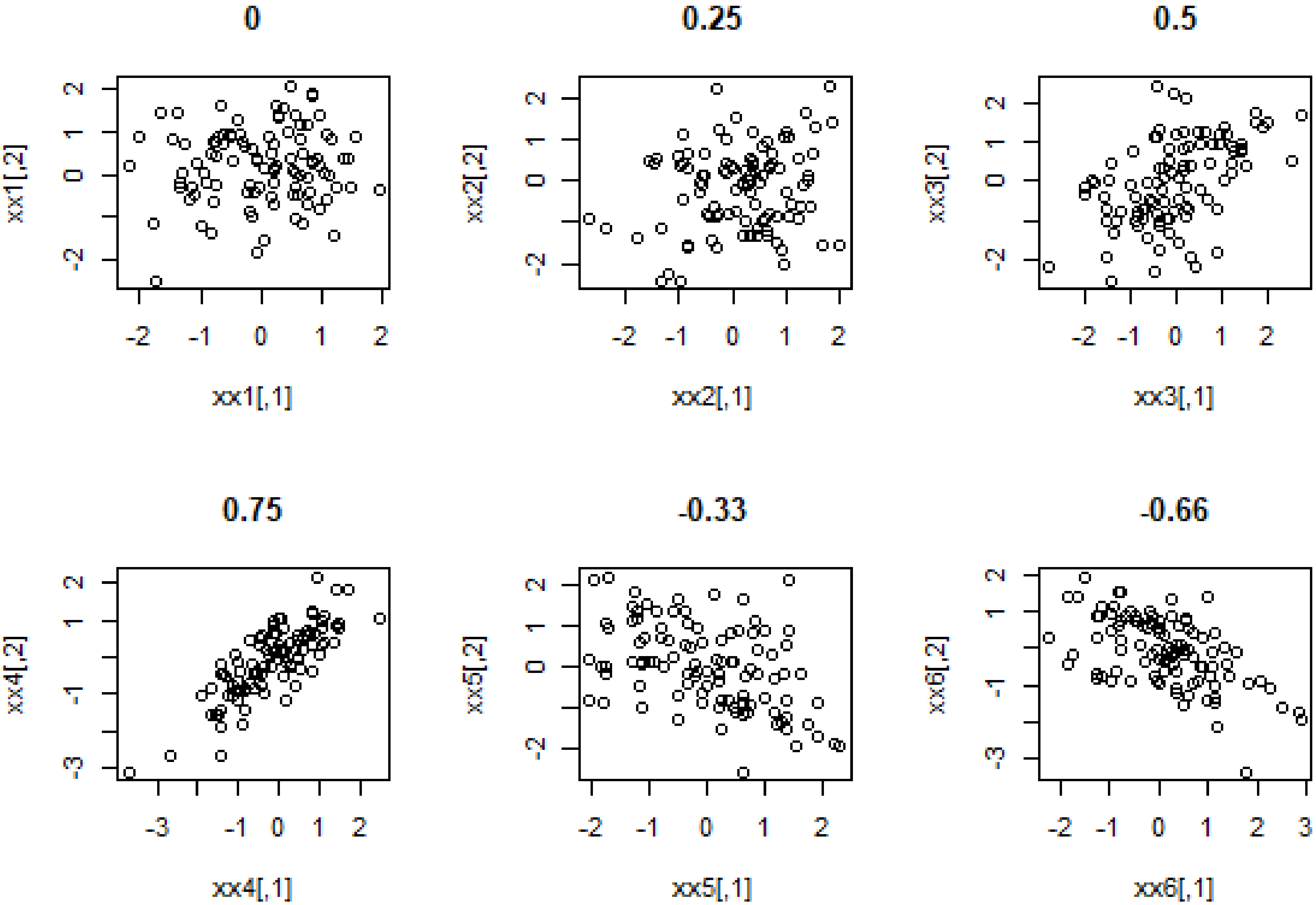
- Best fit does not mean good fit
- Can we quantify how well the best fit line fits the data?
- When Y is continuous we use R^2
- R^2 does not generalize well either but commonly reported used when someone uses least squares
- Between 0 and 1: higher values indicating better fit

Correlation

- An everyday word with a precise meaning in statistics
- Correlation is the (signed) square root of R2
- Sign comes from the sign of b (slope)
- Sleight of hand: parameter or estimate?

More on correlation

- Actually a parameter but its definition requires more math than we want here
- As most parameters it can be estimated
- Square root of R2 is one way to estimate: Pearson correlation
- Many other ways: Spearman (rank), Kendall's tau, ….
- Does not generalize well either, but comes in handy as a concept and also in variable selection

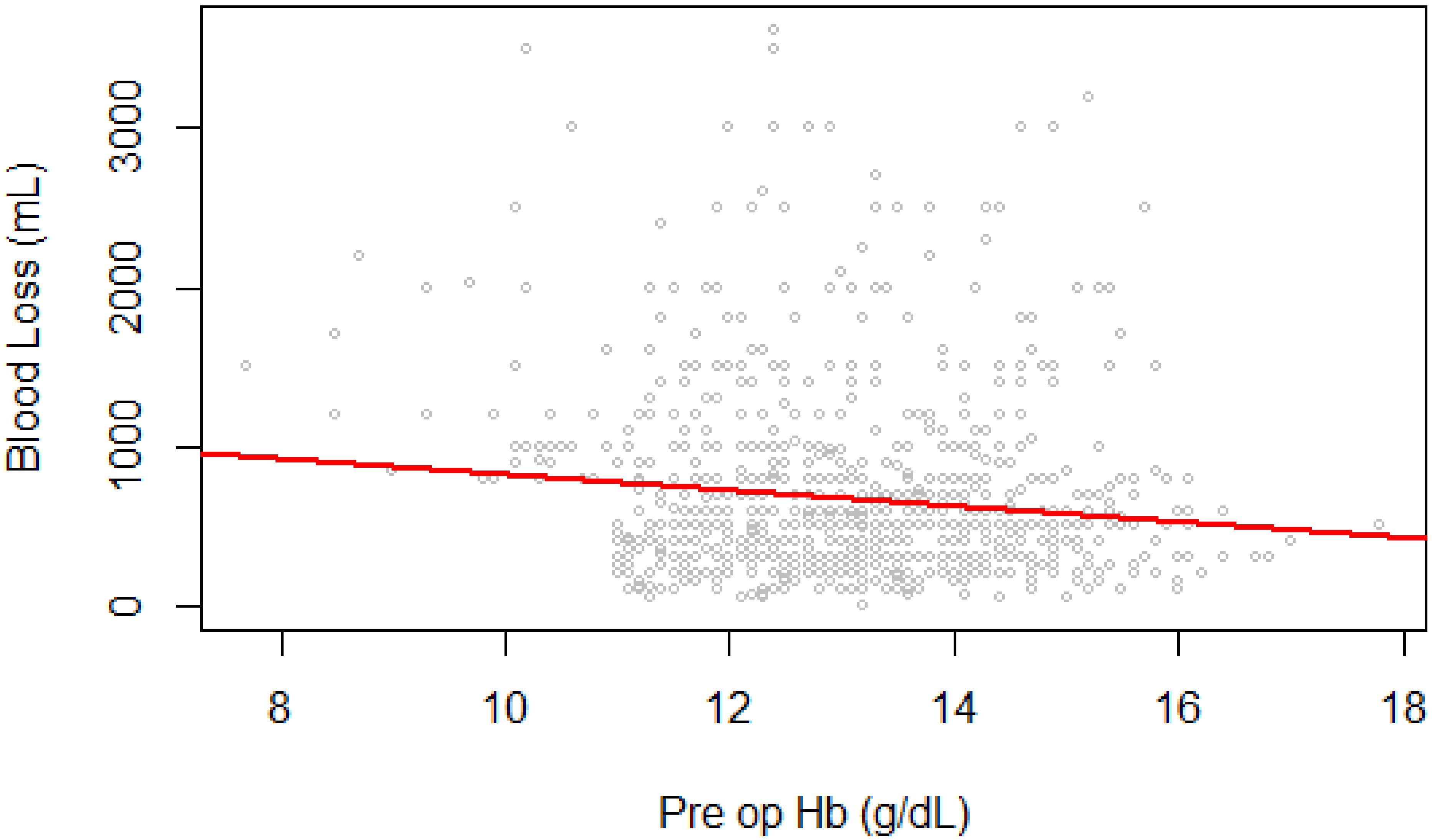


0
0.25
0.5
0.75
-0.33
-0.66
xx1[,1]
xx1[,2]
xx2[,1]
xx2[,2]
xx3[,1]
xx3[,2]
xx4[,1]
xx4[,2]
xx5[,1]
xx5[,2]
xx6[,1]
xx6[,2]

Back to the Example

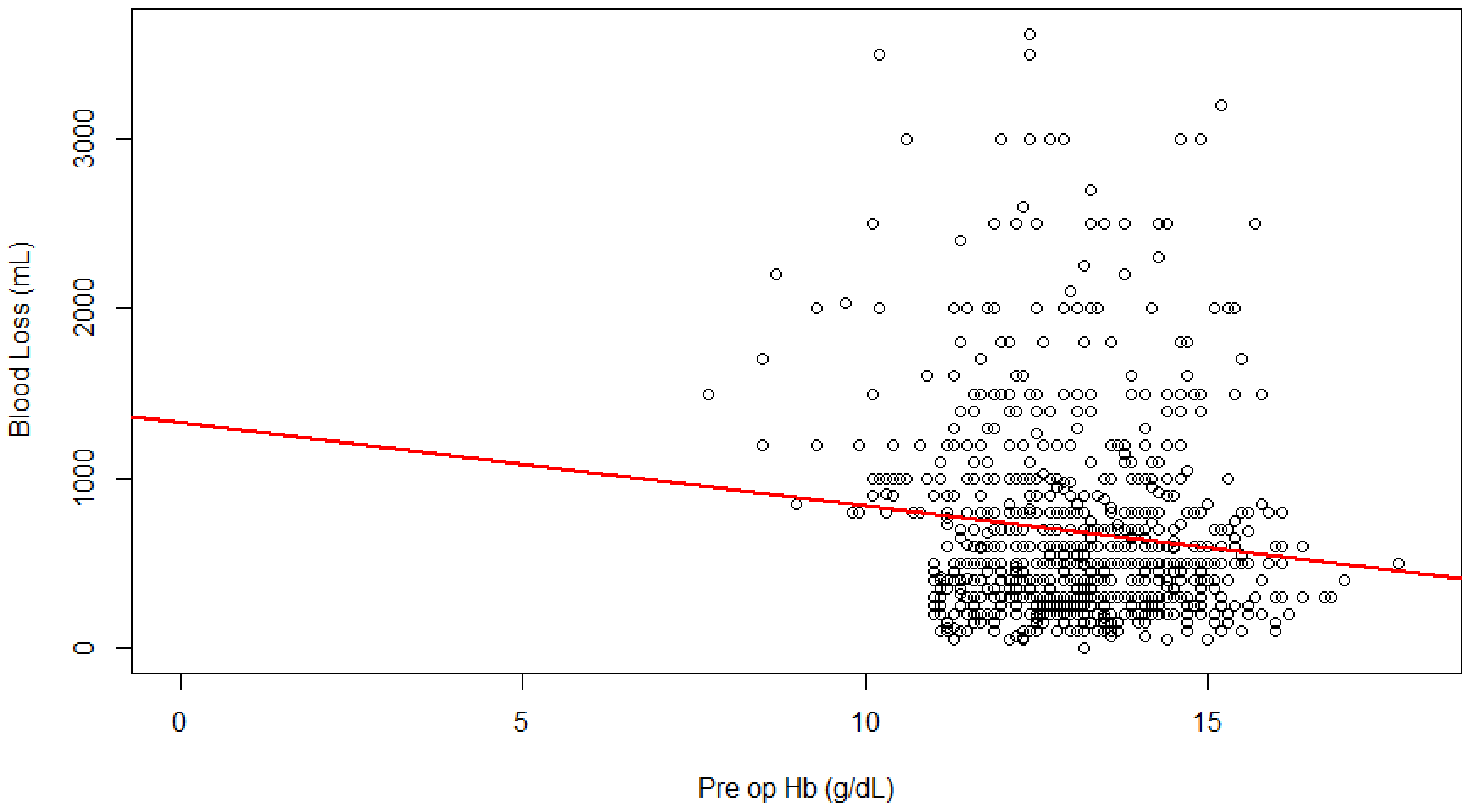
- How to report a regression analysis?
- Report point estimates of a and b, along with confidence intervals and p-values for testing if the underlying coefficient is 0
- Report R2

Parameter	Estimate	95% CI (Lower Bound)	95% CI (Upper Bound)	p
Intercept	1330.35	966.20	1694.51	<0.0001
Hb	-49.41	-77.10	-21.72	0.0005
R2	?			


Blood Loss (mL)
0
1000
2000
3000
8
10
12
14
16
18
Pre op Hb (g/dL)

Intercept and Slope

- Pred(Y) = a + b*X
  - When X = 0 → Pred(Y) = a + b*0 = a
  - Intercept (a) is the point where the line crosses the vertical axis (Y value for X = 0)
- Slope
  - For X: Pred(Y) = a + b*X
  - For X+1: Pred(Y) = a + b*(X+1)
  - The difference in Pred(Y) when X goes up by one unit is: a + b*(X+1) – (a + b*X) = a + b*X + b – a – b*x = b
  - Slope is the change in Y when X changes one unit



Blood Loss (mL)
0
1000
2000
3000
0
5
10
15
Pre op Hb (g/dL)

Parameter	Estimate	95% CI (Lower Bound)	95% CI (Upper Bound)	p
Intercept	1330.35	966.20	1694.51	<0.0001
Hb	-49.41	-77.10	-21.72	0.0005
R2	0.012 !!!!!!			

Multivariable (multivariate) regression

- We have more than one X
- And some of these X's can be continuous, some can be categorical
- I will first add a categorical variable to the mix
- It is very very very important to write the regression equation every time
- X1 is continuous, X2 is binary
- Pred(Y) = a + b1*X1 + b2*X2

Continuous and binary variables in regression

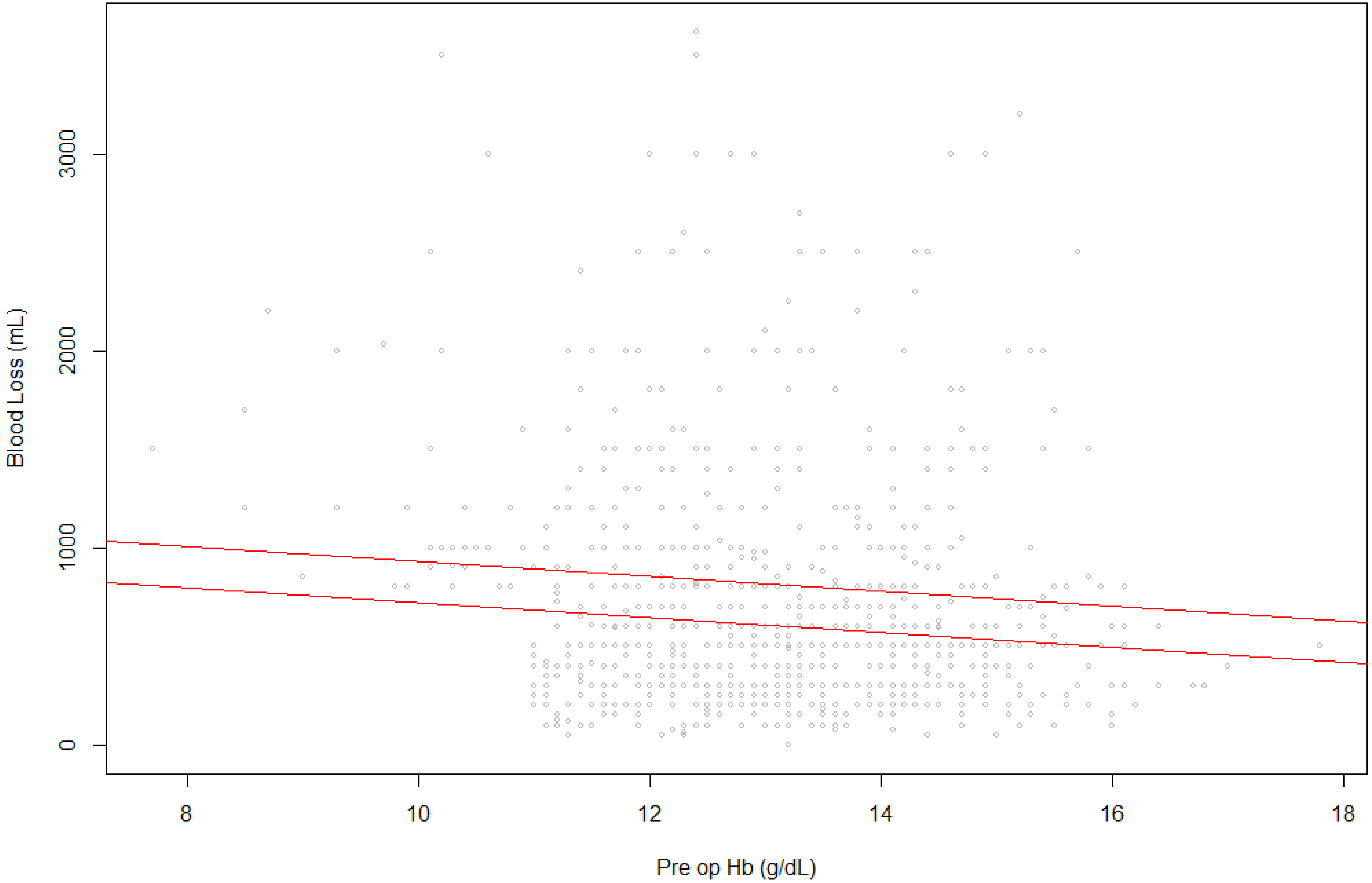
- $Pred(Y) = a + b1*X1 + b2*X2$
- Remember X2 is binary, so either 0 or 1
- When $X2 = 0$
  - $Pred(Y) = a + b1*X1$
- When $X2 = 1$
  - $Pred(Y) = a + b1*X1 + b2$
  - $Pred(Y) = (a + b2) + b1*X1$

Continuous and binary variables in regression

- Pred(Y) = a + b1*X1 + b2*X2
- Remember X2 is binary, so either 0 or 1
- When X2 = 0
  - Pred(Y) = a + b1*X1
- When X2 = 1
  - Pred(Y) = a + b1*X1 + b2
  - Pred(Y) = (a + b2) + b1*X1

Continuous and binary variables in regression

- Pred(Y) = a + b1*X1 + b2*X2
- X2 = 0 → Pred(Y) = a + b1*X1
- When X2 = 1 → Pred(Y) = (a + b2) + b1*X1
- Same slope, different intercept
- Parallel lines


Blood Loss (mL)
0
1000
2000
3000
Pre op Hb (g/dL)
8
10
12
14
16
18

Parameter	Estimate	95% CI (Lower Bound)	95% CI (Upper Bound)	p
Intercept	1103.69	734.50	1472.89	<0.0001
Hb	-37.93	-65.56	-10.29	0.0071
Binary Variable	206.26	127.55	284.98	<0.0001
R2	0.012 !!!!!!			

Parameter	Estimate	95% CI (Lower Bound)	95% CI (Upper Bound)	p
Intercept	1103.69	734.50	1472.89	<0.0001
Hb	-37.93	-65.56	-10.29	0.0071
Binary Variable	206.26	127.55	284.98	<0.0001
R2	0.041			

Pred(Y) for X2 = 0 → 1103.69 – 37.93*Hb

Pred(Y) for X2 = 1 → 1309.95 – 37.93*Hb

What if we want different slopes

- We need to use an interaction
- Pred(Y) = a + b1*X1 + b2*X2 + b12*X1*X2
- When X2 = 0
  - Pred(Y) = a + b1*X1
- When X2 = 1
  - Pred(Y) = (a + b2) + (b1 + b12)*X1
- Different intercepts and slopes

Parameter	Estimate	95% CI (Lower Bound)	95% CI (Upper Bound)	p
Intercept	864.78	501.49	1428.06	<0.0001
Hb	-27.44	-62.23	7.35	0..122
Binary Variable	574.90	-171.88	1321.68	0.131
Hb*Binary Variable	-28.44	-85.73	28.86	0.330

Pred(Y) for X2 = 0 → 864.78 – 27.44*Hb

Pred(Y) for X2 = 1 → 1449.68 – 55.88*Hb

Parameter	Estimate	95% CI (Lower Bound)	95% CI (Upper Bound)	p
Intercept	864.78	501.49	1428.06	<0.0001
Hb	-27.44	-62.23	7.35	0..122
Binary Variable	574.90	-171.88	1321.68	0.131
Hb*Binary Variable	-28.44	-85.73	28.86	0.330

Are the slopes statistically different?

$Pred(Y) = a + b1*X1 + b2*X2 + b12*X1*X2$

When does this model reduce to equal-slopes model

$Pred(Y) = a + b1*X1 + b2*X2$

Parameter	Estimate	95% CI (Lower Bound)	95% CI (Upper Bound)	p
Intercept	864.78	501.49	1428.06	<0.0001
Hb	-27.44	-62.23	7.35	0..122
Binary Variable	574.90	-171.88	1321.68	0.131
Hb*Binary Variable	-28.44	-85.73	28.86	0.330

Are the slopes statistically different?

Pred(Y) = a + b1*X1 + b2*X2 + b12*X1*X2

When does this model reduce to equal-slopes model

Pred(Y) = a + b1*X1 + b2*X2

When b12 = 0!

So test for b12 = 0

Adding more variables

- Once you have two continuous predictors (X's) in the model it becomes difficult to visualize, more than 2 impossible
- So we need to "imagine" points in higher dimensional spaces that only exist in our minds (and in mathematical representations)
- But the idea of a "slope", "residual" etc applies

Parameter	Estimate	95% Lower	95% Upper	P
Intercept	1303.07	501.49	1428.06	<0.001
Hb	-37.52	-62.23	7.35	0.008
Binary Variable	207.473	-171.88	1321.68	<0.001
Age	-3.48	-85.73	28.85	0.018
R2	0.046			

Interpretation of coefficients

- Change in Pred(Y) corresponding to one unit change in X keeping others constant
- Binary: one unit means going from 0 to 1
- Continuous: depends on units of measurement
- Age: Take two patients with same Hb and X2, Pred(Y) goes down by 3.48 when age goes up by one year
- X2: Take two patients with same Hb and Age. The one with X2 = 1 has Pred(Y) higher by 207.47

Take a look at all the different models we fit

- Estimates jumped around quite a bit
- Model results are usually sensitive to which variables are included and excluded
- Variable selection is the Achilles heel of multivariate regression
- More on this in next lectures