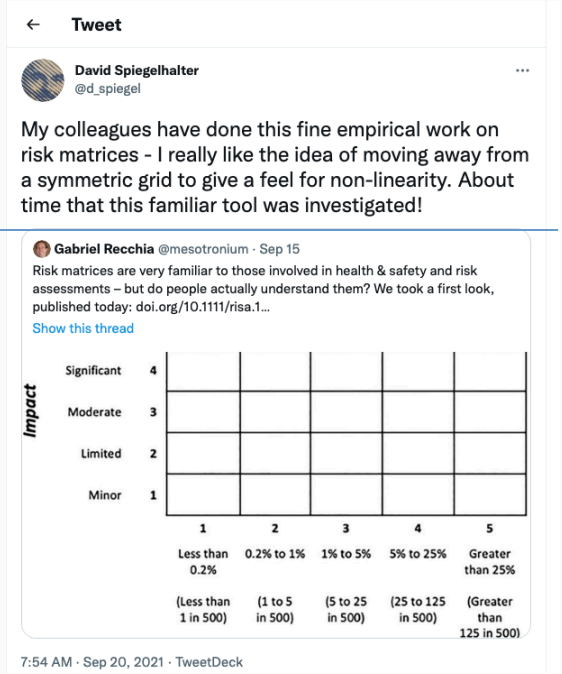
Methods of Applied Statistics I

STA2101H F LEC9101

Week 2

September 22 2021

29th → Wilson Hall (New College)



Today

Start Recording

1. Office hours, Upcoming events, HW 2
   OH: Monday 7pm-8.30pm, Wednesday 4pm-5.30pm, Zoom until further notice
2. Steps in analysis; types of studies
3. Linear Regression Part 2: recap, testing groups of variables, checking model assumptions, collinearity, $p > n$
4. In the News

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4. In the News

- SM – Statistical Models by Davison
- LM-1,2 – Linear Models with R by Faraway (1st and 2nd editions)
- ELM-1,2 – Extending the Linear Model with R by Faraway (1st and 2nd editions)
- CD – Principles of Applied Statistics by Cox & Donnelly

LM (both)

Upcoming

- Learning Individualized Treatment Rule for a Target Population
- Thursday 3.30 Link

About Guanhua Chen

I am an Assistant Professor of Biostatistics and Medical Informatics at the University of Wisconsin-Madison. I got my Ph.D. from the University of North Carolina at Chapel Hill in 2014 under the direction of Dr. Michael Kosorok. Before joining UW, I was an Assistant Professor of Biostatistics at Vanderbilt University.

Research Interest

Develop statistical learning methods for clinical and biomedical research. In particular, I am interested in analyzing heterogeneous, high-dimensional-omics data (genome, microbiome) and electronic health record data to advance precision medicine. My current research is supported by PCORI and NSF grants.

- Fridays at noon Toronto Data Workshop link

This term is a special series of talks featuring University of Toronto speakers on the relationship between data science and their other field of expertise.

Date	Speaker	Recording
Fri 24 September 2021, noon - 1pm	Karen Chapple, Geography, planning, cities	
Fri 1 October 2021, noon - 1pm	Special on 2021 Canadian Election	
Fri 8 October 2021, noon - 1pm	Fedor Dokshin, Sociology	

HW Question Week 2

STA2101F 2021

Due September 29 2021 11.59 pm

Homework to be submitted through Quercus

This question concerns the article "How people understand risk matrices..." by Sutherland et al., available on the course web site.

(a) What is a risk matrix? Find an example of a risk matrix for the assessment of risk related to either COVID-19 or wildfire. Provide the reference (link) to the example and a snapshot of one or two of the published risk matrices.
(b) The authors describe two randomized controlled experiments, in Sections 2 and 3, respectively. What are the units of analysis in these two experiments?
(c) In the first experiment, the authors describe derived variables: a "basic knowledge score", a "risk comparison score", a "prioritization score", the results of a "matrix preference test", and a "total numeracy score". Which of these are treated as response variables and which are treated as explanatory variables?
(d) What 'treatments' were randomly assigned to units in Experiment 1?

Steps in Analysis

- understand the physical background
- understand the objective
- make sure you know what the client wants
- put the problem into statistical terms

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← slow
takes time

- How were the data collected:
  - are the data observational or experimental? etc.
  - is there nonresponse
  - are there missing values
  - how are the data coded
  - what are the units of measurement
  - beware of data entry errors

data 'cleaning'
'carpentry'

LM ← plots, summary stat.

Components of investigation

CD §1.2

- start with a scientific question
- assess how data could shed light on this
- plan data collection
- consider of sources of variation and how careful planning can minimize their impact

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- communicate the results: accurately

but not pessimistically

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- communicate the results: accurately
- visualization strategies, conveyance of uncertainties

but not pessimistically

Design and Analysis

- choice of material/individuals to study – “units of analysis”

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- "For studies of a new phenomenon it will usually be best to examine situations in which the phenomenon is likely to appear in the most striking form, even if this is in some sense artificial"

people
cities
families
plots of land
pots
plants

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- need to be clear at the design stage about broad features of the statistical analysis – more publicly convincing **and** “reduces the possibility that the data cannot be satisfactorily analysed”
- “it is unrealistic and indeed potentially dangerous to follow an initial plan unswervingly ... it may be a crucial part of the analysis to clarify the research objectives”

Experimental and observational studies

- experiment is a study in which all key elements are under the control of the investigator

"treatments"

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Experimental and observational studies

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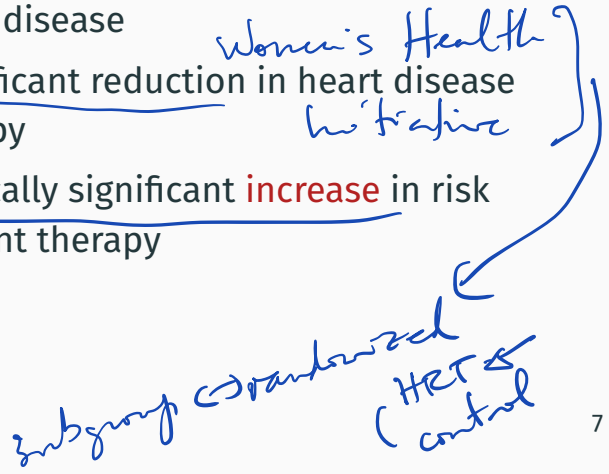
- Example: hormone replacement therapy and heart disease
- observational study – strong and statistically significant reduction in heart disease among women taking hormone replacement therapy
- women's health study (JAMA, 2002, p.321) – statistically significant increase in risk among women randomized to hormone replacement therapy



Hydroxychloroquine

ORIGINAL ARTICLE

Observational Study of Hydroxychloroquine in Hospitalized Patients with Covid-19

Joshua Geleris, M.D., Yifei Sun, Ph.D., Jonathan Platt, Ph.D., Jason Zucker, M.D., Matthew Baldwin, M.D., George Hripcsak, M.D., Angelena Labella, M.D., Daniel K. Manson, M.D., Christine Kubin, Pharm.D., R. Graham Barr, M.D., Dr.P.H., Magdalena E. Sobieszczyk, M.D., M.P.H., and Neil W. Schluger, M.D.

Article Figures/Media Metrics

14 References 300 Citing Articles

Abstract

June 18, 2020
N Engl J Med 2020; 382:2411-2418
DOI: 10.1056/NEJMoa2012410
Chinese Translation 中文翻译

June 2020

ORIGINAL ARTICLE

A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19

David R. Boulware, M.D., M.P.H., Matthew F. Pullen, M.D., Ananta S. Bangdiwala, M.S., Katelyn A. Pastick, B.Sc., Sarah M. Lofgren, M.D., Elizabeth C. Okafor, B.Sc., Caleb P. Skipper, M.D., Alanna A. Nascene, B.A., Melanie R. Nicol, Pharm.D., Ph.D., Mahsa Abassi, D.O., M.P.H., Nicole W. Engen, M.S., Matthew P. Cheng, M.D., et al.

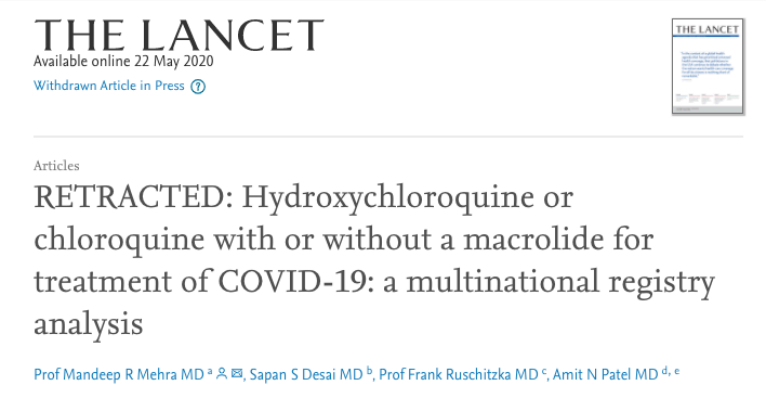
Article Figures/Media Metrics

18 References 128 Citing Articles Letters 11 Comments

August 6, 2020
N Engl J Med 2020; 383:517-525
DOI: 10.1056/NEJMoa2016638

August 2020

Hydroxychloroquine



THE LANCET

Available online 22 May 2020

Withdrawn Article in Press

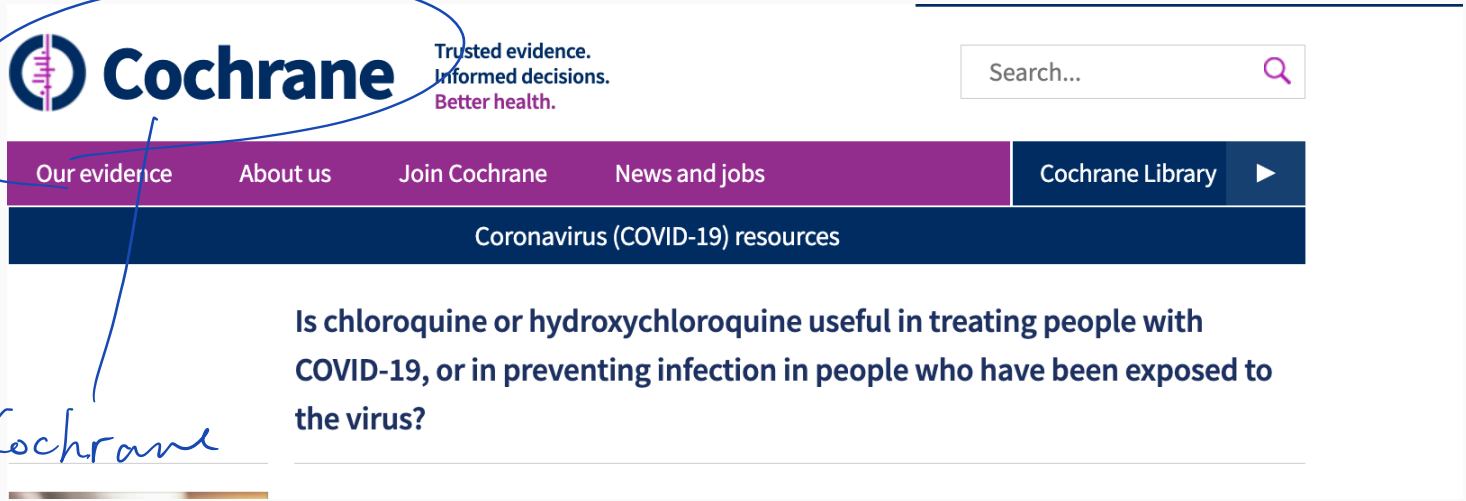
Articles

RETRACTED: Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis

Prof Mandeep R Mehra MD [a], Sapan S Desai MD [b], Prof Frank Ruschitzka MD [c], Amit N Patel MD [d, e]

retracted

… hydroxychloroquine



"Cochrane Reviews"

Cochrane Reviews

meta-analysis "Study of studies"

… hydroxychloroquine

Cochrane Reviews ▾ Trials ▾ Clinical Answers ▾ About ▾ Help ▾

Cochrane Database of Systematic Reviews | Review - Intervention

Chloroquine or hydroxychloroquine for prevention and treatment of COVID-19

Bhagteshwar Singh, Hannah Ryan, Tamara Kredo, Marty Chaplin, Tom Fletcher Authors' declarations of interest

Version published: 12 February 2021 Version history

https://doi.org/10.1002/14651858.CD013587.pub2

Collapse all Expand all

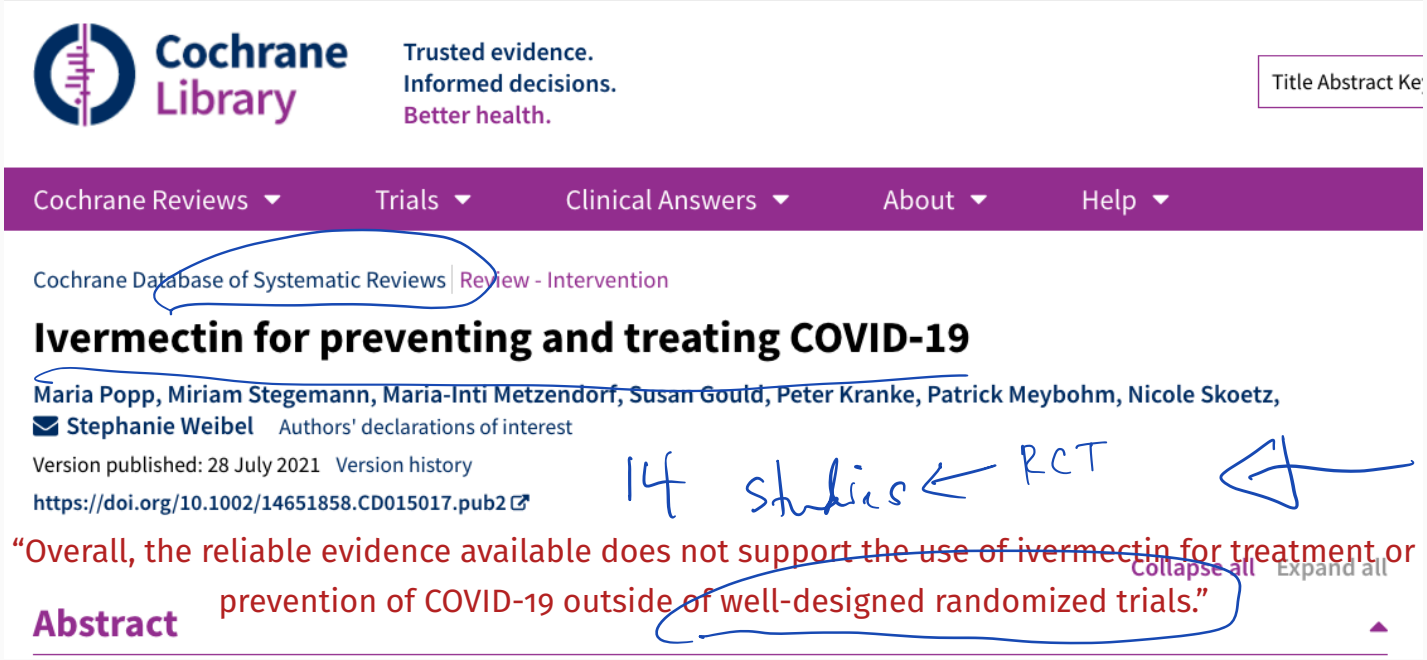
Abstract

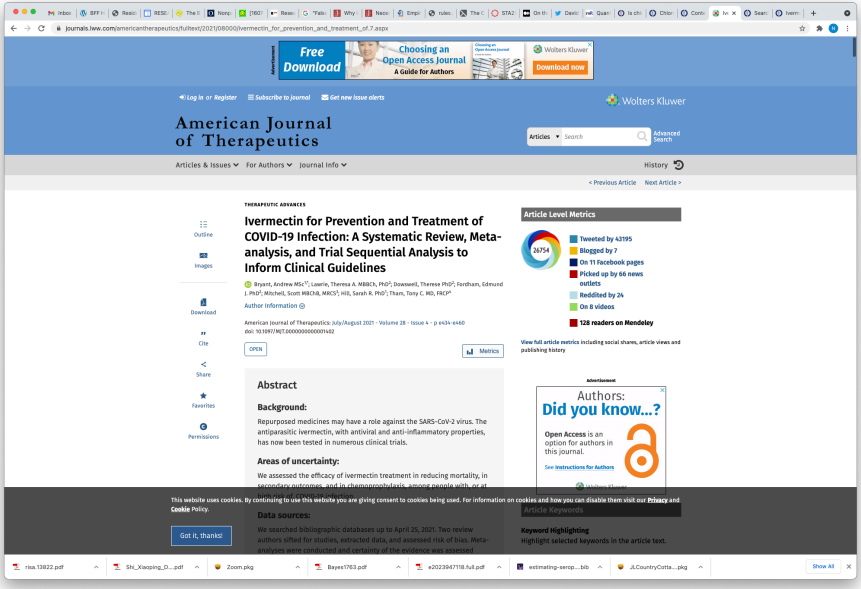
Hydroxychloroquine does not reduce deaths from COVID-19, and probably does not reduce the number of people needing mechanical ventilation.

Hydroxychloroquine caused more unwanted effects than a placebo treatment, though it did not appear to increase the number of serious unwanted effects.

We do not think new studies of hydroxychloroquine should be started for treatment of COVID

… hydroxychloroquine


Cochrane Library
Trusted evidence.
Informed decisions.
Better health.
Title Abstract Ke
Cochrane Reviews
Trials
Clinical Answers
About
Help
Cochrane Database of Systematic Reviews | Review - Intervention
Ivermectin for preventing and treating COVID-19
Maria Popp, Miriam Stegemann, Maria-Inti Metzendorf, Susan Gould, Peter Kranke, Patrick Meybohm, Nicole Skoetz,
Stephanie Weibel Authors' declarations of interest
Version published: 28 July 2021 Version history
https://doi.org/10.1002/14651858.CD015017.pub2
14 studies ← RCT
"Overall, the reliable evidence available does not support the use of ivermectin for treatment or prevention of COVID-19 outside of well-designed randomized trials."
Collapse all Expand all
Abstract



"Moderate-certainty evidence finds that large reductions in COVID-19 deaths are possible using ivermectin. ... The apparent safety and low cost suggest that ivermectin is likely to have a significant impact on the SARS-CoV-2 pandemic globally."

Linear regression recap

- generic form of linear regression, in matrix notation $y = X\beta + \epsilon$
- least squares estimate of β is $\hat{\beta}_{ls} = (X^T X)^{-1} X^T y$
- $\hat{\beta}$ has expected value β and variance-covariance matrix $\sigma^2 (X^T X)^{-1}$

$\hat{\beta}_j \not\perp \hat{\beta}_{j'}$

$y_{n\times 1}$ $X_{n\times p}$

under the model

$E(Y|X) = X\beta$

$Var(Y|X) = \sigma^2 I$

constant and indep

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- this is the maximum likelihood estimate if $\epsilon \sim N(0, \sigma^2 I)$
- $\hat{\beta} \sim N(\beta, \sigma^2(X^{\mathrm{T}}X)^{-1})$
- $\tilde{\sigma}^2 = (y - X\hat{\beta})^{\mathrm{T}}(y - X\hat{\beta})/(n - p)$
- leads to t-tests for individual components β_j

called s^2 in SM

and confidence intervals

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- X is an $n \times p$ matrix of explanatory variables, which may be
  - measured in the sample (SM Ex 8.3),
  - fixed by design (SM Ex 8.4),
  - introduced to make the model more flexible (SM Ex 8.2)
  - X often called the design matrix

highly "nonlinear" in underlying measures

SM – Davison

in R, `model.matrix`

(ITALM)

$[1, x, x^2, x^3, x^4]$

Aside: Lazy Notation

- $y_i = x_i^{\mathrm{T}}\beta + \epsilon_i, \quad i = 1, \ldots, n$
- $\boldsymbol{y} = X\boldsymbol{\beta} + \boldsymbol{\epsilon}, \quad \boldsymbol{y}, \boldsymbol{\epsilon}$ vectors of length n
- $y = X\beta + \epsilon,$ also vectors of length n — the lazy way

- a generic observation $y \in \mathbb{R}$ for a generic vector of covariates $x \in \mathbb{R}^{\mathrm{I}}$ often written

$$y = x^{\mathrm{T}}\beta + \epsilon$$

or even $x\beta + \epsilon$

- "where we hope there is no confusion"

Aside: ancillarity

SM Ex.12.4; Cox 2006 §4.3.1

- in a statistical model (i.e. likelihood function) that factorizes, in a way that separates the parameters, there are strong theoretical (and often practical) reasons for using only the relevant factor for inference
- in our example, even if (y, X) have a $(p+1)$-dimensional distribution (maybe even jointly multivariate normal), it would typically be the case that β, which by definition is $\mathbb{E}(y \mid X)$, is not a parameter of the distribution of X.

$E(y|X;\beta)$ $\mathrm{var}(y|X;\sigma^2)$

$f_X(x;\cancel{\theta})$ ← no β or σ^2 here

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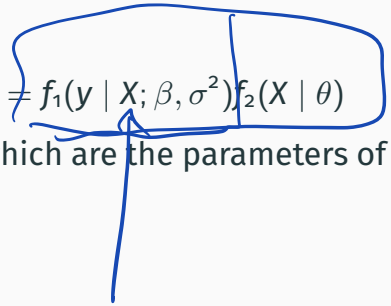
- So we would have something like

$$f(y, X; \beta, \sigma^2, \theta) = f_1(y \mid X; \beta, \sigma^2) f_2(X \mid \theta)$$

- and we base our inference for β and σ^2 (which are the parameters of interest, by assumption) on $f_1(y \mid X; \beta, \sigma^2)$



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- in technical terms X is ancillary for (β, σ^2)
- If we did decide to include the variability in X as part of our analysis, our inference about β would be much less precise, and needlessly so, because we are worrying about explanatory variable values that were not seen in our data set

Comparing Models

- residual sum of squares

smallest

$$SS(\hat\beta) = (y - X\hat\beta)^T(y - X\hat\beta) = (y-\hat y)^T(y-\hat y)$$
$$= RSS_\Omega = RSS$$

- Decomposition of variance

$\sum_{i=1}^n y_i^2$

$$y^Ty = (y - \hat y + \hat y)^T(y - \hat y + \hat y)$$
$$= (y-\hat y)^T(y-\hat y) + 2(0) + \hat y^T\hat y$$

- Typically first column of X is $(1, \ldots, 1)^T$, so $y = \beta_0 + X_2\beta_{(2)} + \epsilon$, say; then decomposition becomes

$\hat y = X\hat\beta$

$= X(X^TX)^{-1}X^Ty$

Total SS (corrected for β_0)

$$\sum (y_i - \bar y)^2 = \sum (y_i - x_{2i}^T\hat\beta_{(2)})^2 + \hat\beta_{(2)}X_2^TX_2\hat\beta_{(2)}$$

$$(y - \bar y\underset{\sim}{1})^T(y - \bar y 1)$$

$$(y - X_2\hat\beta_{(2)})^T(y - X_2\hat\beta_{(2)})$$

... comparing models

$$\sum_{i=1}^{n}(y_i - \bar{y})^2 = (y - X\hat{\beta})^{\mathrm{T}}(y - X\hat{\beta}) + \hat{\beta}^{\mathrm{T}}(X^{\mathrm{T}}X)\hat{\beta}$$

Total SS = Residual SS + Regression SS

- LHS is
- comparison of LHS to $SS(\hat{\beta})$ reflects
-

$$F = \frac{(TSS - RSS)/(p-1)}{RSS/(n-p)} \sim F_{p-1,\,n-p}$$

- here $\beta = (\beta_1, \beta_2, \ldots, \beta_p)$, but we don't care about β_1

RSS, $SS(\hat{\beta})$

"analysis of variance"

under model

$(\beta_0, \beta_1, \ldots, \beta_{p-1})$

... comparing models

- same argument can be derived for comparing submodels

$q \times 1$

$$y = X_1\beta_1 + X_2\beta_2 + \varepsilon \qquad ?\ \beta_2 = 0\ ?$$

fit full model $\quad RSS_{full} \quad RSS_\Omega \quad \leftarrow p$ par's

fit reduced $\quad RSS_{red} \quad RSS_\omega \quad \leftarrow p-q$

$RSS_{red} \geq RSS_{full}$

$y = X_1\beta_1 + \varepsilon$

$$F = \frac{(RSS_{red} - RSS_{full})/(p-q)}{RSS_{full}/(n-p)} \sim F_{p-q,\,n-p}$$

... comparing models

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... comparing models

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- see LM 3.1, SM §8.2 (p.367) for connection to likelihood ratio test

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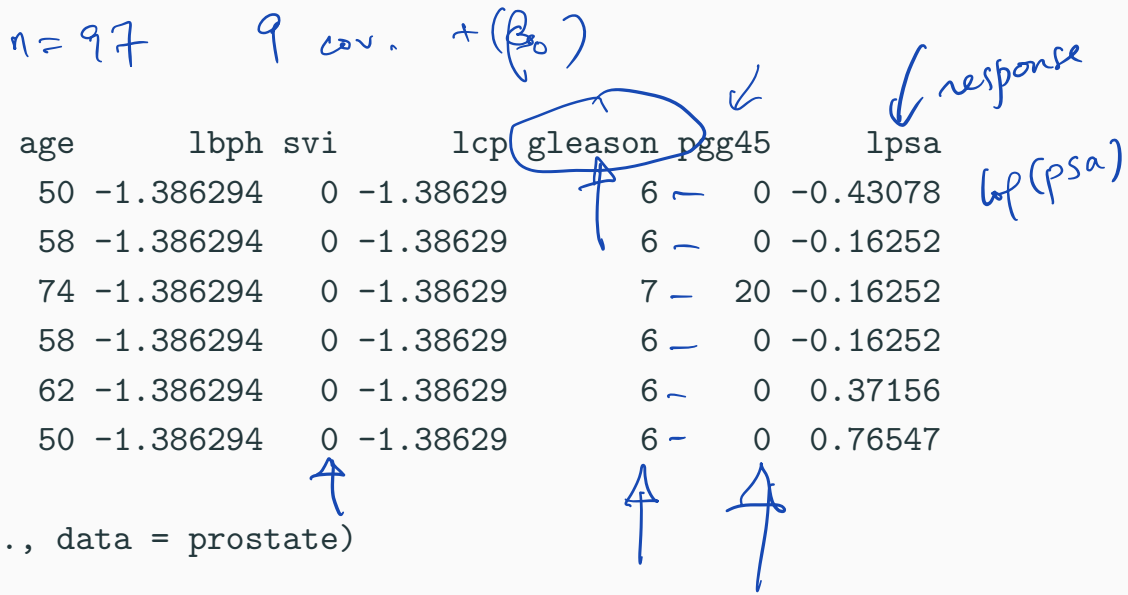
- when would we want to do this?

... comparing models

```
head(prostate)
#     lcavol lweight age      lbph svi      lcp gleason pgg45      lpsa
1 -0.5798185  2.7695  50 -1.386294   0 -1.38629       6     0 -0.43078
2 -0.9942523  3.3196  58 -1.386294   0 -1.38629       6     0 -0.16252
3 -0.5108256  2.6912  74 -1.386294   0 -1.38629       7    20 -0.16252
4 -1.2039728  3.2828  58 -1.386294   0 -1.38629       6     0 -0.16252
5  0.7514161  3.4324  62 -1.386294   0 -1.38629       6     0  0.37156
6 -1.0498221  3.2288  50 -1.386294   0 -1.38629       6     0  0.76547

model1 <- lm(lpsa ~ ., data = prostate)
```

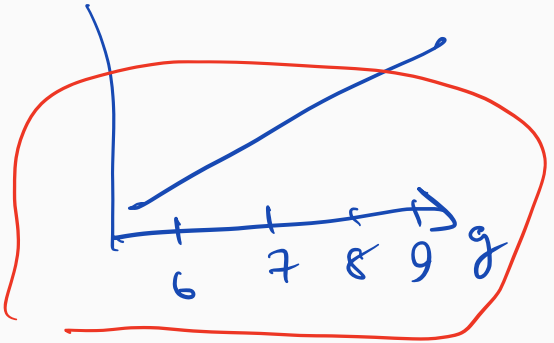


... comparing models

```
> summary(model1)

Coefficients:
             Estimate Std. Error t value Pr(>|t|)
(Intercept)  0.669337   1.296387   0.516  0.60693
lcavol       0.587022   0.087920   6.677 2.11e-09 ***
lweight      0.454467   0.170012   2.673  0.00896 **
age         -0.019637   0.011173  -1.758  0.08229 .
lbph         0.107054   0.058449   1.832  0.07040 .
svi          0.766157   0.244309   3.136  0.00233 **
lcp         -0.105474   0.091013  -1.159  0.24964
gleason      0.045142   0.157465   0.287  0.77503
pgg45        0.004525   0.004421   1.024  0.30886
---
Residual standard error: 0.7084 on 88 degrees of freedom

F-statistic: 20.86 on 8 and 88 DF,  p-value: < 2.2e-16
```



"n.s."

$\hat{\beta}_g = .045 \ (\pm .157)$

(skip gleason)

$H_0: \beta = 0$

$\beta_2 = \dots = \beta_4 = 0$

... comparing models

```
model3 <- lm(lpsa ~ lcavol + lweight  + age + lbph + svi, data = prostate)
anova(model3,model1)
Analysis of Variance Table

Model 1: lpsa ~ lcavol + lweight  + age + lbph + svi
Model 3: lpsa ~ lcavol + lweight + age + lbph + svi + lcp + gleason +
    pgg45
  Res.Df    RSS Df Sum of Sq     F Pr(>F)
1     91 45.526
2     88 44.163  3   1.3625 0.905 0.4421
```

$$F = \frac{(RSS_{red} - RSS_{full})/3}{RSS_{full}/88} = .905$$

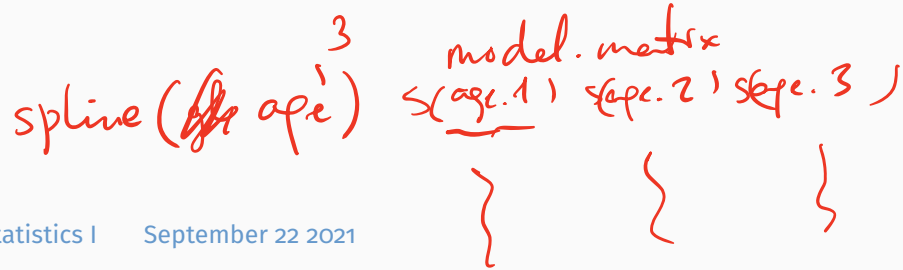
does this make sense?

$H_0: \beta_7 = \beta_8 = \beta_9 = 0$

Factor variables

- *F*-tests are used when the columns to be removed form a group
- if a covariate is a factor, i.e. categorical, then `lm` will construct a set of dummy variables as part of the model matrix
- these variables should either all be in, or all be out

in most cases



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- ```
  prostate$gleason_factor <- factor(prostate$gleason)
  levels(prostate$gleason_factor)
[1] "6" "7" "8" "9"
  model3 <- lm(lpsa ~ .-gleason, data=prostate)
```

$y = \beta_0 + \beta_1 \text{lcavol} + \beta_2 \ldots + \beta_8 gl_2 + \beta_9 gl_3 + \beta_{10} gl_4$
```

... factor variables

```
model4 <- lm(lpsa ~ .-gleason, data=prostate)
summary(model4)
> Coefficients:
                  Estimate Std. Error t value Pr(>|t|)
(Intercept)       0.913282   0.840838   1.086  0.28044
lcavol            0.569988   0.090100   6.326 1.09e-08 ***
lweight           0.468791   0.169610   2.764  0.00699 **
age              -0.021749   0.011361  -1.914  0.05890 .
lbph              0.099685   0.058984   1.690  0.09464 .
svi               0.745879   0.247398   3.015  0.00338 **
lcp              -0.125112   0.095591  -1.309  0.19408
pgg45             0.004990   0.004672   1.068  0.28848
gleason_factor7   0.267607   0.219419   1.220  0.22595
gleason_factor8   0.496820   0.769267   0.646  0.52011
gleason_factor9 -0.056215   0.500196  -0.112  0.91078
```

3 pt. est. all related gleason score.

... factor variables

```
> anova(model1,model4)
Analysis of Variance Table

Model 1: lpsa ~ (lcavol + lweight + age + lbph + svi + lcp + gleason +
    pgg45 + gleason_factor) - gleason
Model 2: lpsa ~ lcavol + lweight + age + lbph + svi + lcp + gleason +
    pgg45
  Res.Df    RSS Df Sum of Sq      F Pr(>F)
1     86 42.724
2     88 44.163 -2   -1.4392 1.4485 0.2406
```

89 44.204 -3 −1.4805 .9934 .3999

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- see, e.g. Example 8.4 in SM

also Ch 14 in LM-2; Ch 13 in LM-1

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- more generally we might have $X^{\mathrm{T}}X$ block diagonal, e.g.

interpretation: is importance? better

insight into "structure" of dep. of y on X

or "causal str." of X on y.

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```
plot(model1)
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plot(model1)
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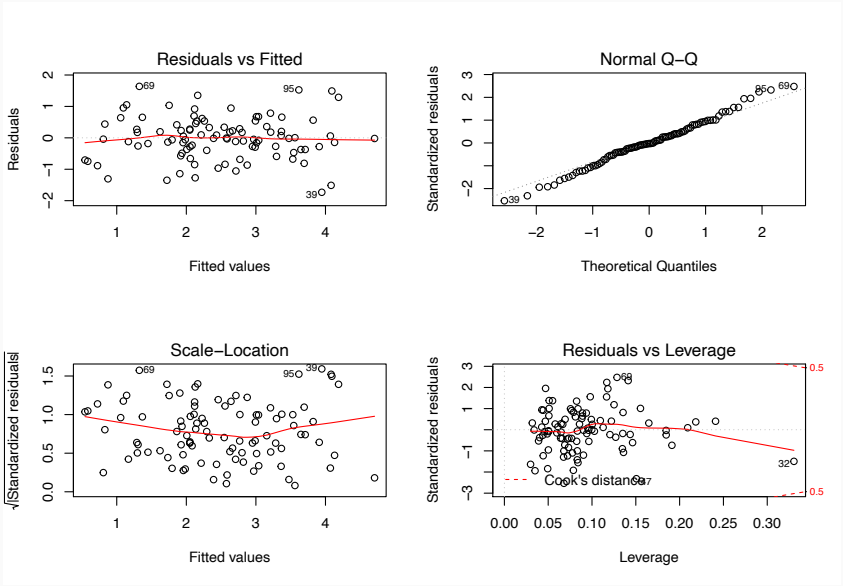

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https://data.library.virginia.edu/diagnostic-plots/

Collinearity

- simple model $y_i = \beta_0 + \beta_1 x_{1i} + \beta_2 x_{2i} + \epsilon_i, \quad i = 1, \dots n$
- if $x_1 \perp x_2$, then interpretation of β_1 and β_2 clear
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- measurable increase in mortality on high-pollution days
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- high temperatures and high levels of pollutants tend to co-occur +++
- mathematically, $X^{\mathrm{T}}X$ is nearly singular, or at least ill-conditioned, so calculation of its inverse is subject to numerical errors
- if $p > n$ then $X^{\mathrm{T}}X$ not invertible, no LS solution

ridge, Lasso

On the 'Breast cancer epidemic' poster

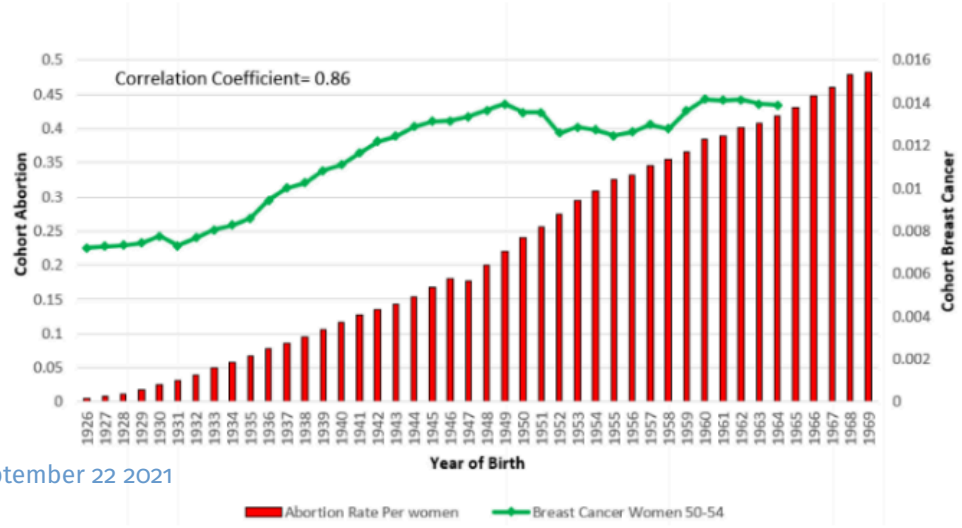
A poster and presentation at the RSS conference featured flawed analysis.

Anthony B. Masters 6 days ago · 4 min read ★

First: Correlation is not causation

Tyler Vigen

Figure 5. England & Wales. Cumulated Cohort Incidence for Birth cohorts of Women. Breast Cancer within ages 50-54 and cumulated cohort abortion rates. Correlation coefficient 0.86.



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Large prospective cohort studies do not imply heightened risks of breast cancer after abortion.

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There is an established increased risk of breast cancer using contraceptive pills. Breast cancer is rare among young women. Increased risk during this time means a low number of additional cases.

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Fourth, methods and sources are unclear

In the News

link