Biostatistics: What **Might** *Lowell Reed* Have Thought About Where it is and Where it is Headed?

2007 Lowell Reed Memorial Lecture
APHA Annual Meeting
Washington, DC
November 6, 2007

Scott L. Zeger

Frank Hurley - Catharine Dorrier Chair of Biostatistics
The Johns Hopkins University
Bloomberg School of Public Health

Lowell J. Reed 1886-1966

BS - U of Maine - 1907

PhD - Penn (math) 1915

Faculty - Johns Hopkins "Biometry and Vital Statistics" - 1918

Professor and (2nd) Chair - 1925

Dean SPH - 1937- 46

Head of Hopkins Hospital and Medicine, 1946-53

President of University, 1953-56

Contributions to Biostatistics Methods

Logistic model for growth - predicting asymptotic population size (with Raymond Pearl, Margaret Merrell)

ED-50 in toxicology (with H. Muench)

Abridged life table (with Margaret Merrell)

Reed-Frost epidemic model (with Wade Hampton Frost)

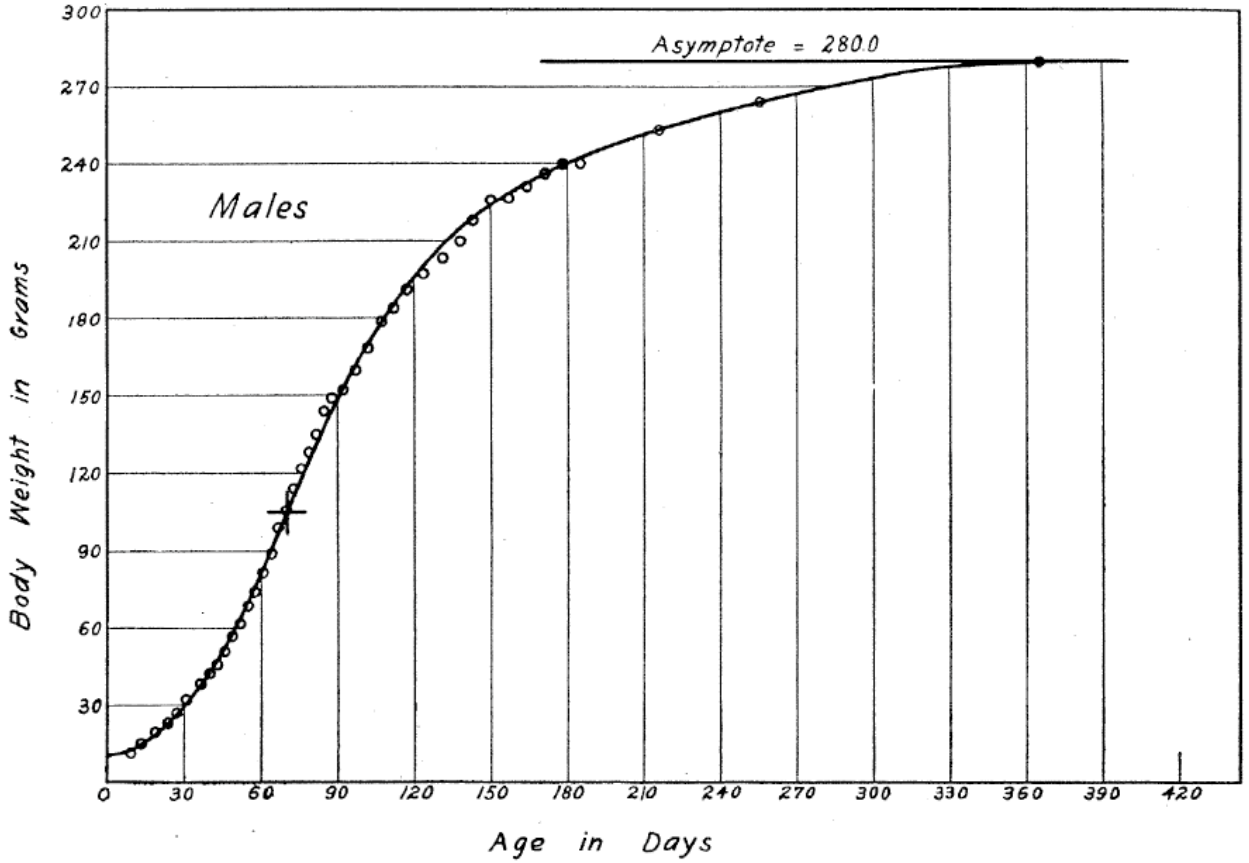


FIGURE 1

Growth of male albino rats (Donaldson's data). The circles give the observations in this and the following diagrams. The smooth curve is the graph of our equation I.

I. *Male Rats.* $$y = 7 + \frac{273}{1 + e^{4.3204 - 7.2196x + 30.0878x^2 - 0.5291x^3}},$$

where y = weight in grams,
and x = age in hundred day units.

Contributions to Education

Introduction to Biostatistics (with Merrell) for all public health students

Doctorate in Biostatistics

- Joe Berkson (Berkson versus Classical measurement error)
- Margaret Merrell

Continuing Education

Reed on W. Thurber Fales, "Vital Statistician"

"He saw the place of vital statistics in developing and extending our knowledge of disease, both from the clinical and epidemiologic point of view. He appreciated the administrative use of vital statistics and the responsibility of the statistician for supplying the health officer with current statistical information bearing on the conduct of the health department.

- Reed lecture presented to the Statistics Section of 1954 APHA Annual Meeting

Reed on Bradford Hill's "Medical Statistics"

"The task which Dr. Hill undertook is not an easy one, for he attempts not only to set forth certain procedures with sufficient clarity so that the nonmathematical reader will be equipped to apply them but also to show why they are needed and the philosophy underlying their development. It is gratifying to report that he succeeds admirably in this attempt. His success is largely due to the fact that he employs a wealth of medical illustrations and gives his explanations in terms of these examples rather than in mathematical language. The real strength of the book comes, however, from the interpretative discussion of results and emphasis on the logical principles basic in the reasoning." Reed, *JASA*, 1937.

Reed on Fisher's, "Design of Experiments"

"The mathematical concepts and methods used by the author…have all of the beauty that one so often finds in … pure mathematics. Considered, however, as an expression of applied mathematics, they seem to the reviewer to place too much stress on refinements that lead to the greatest efficiency in the analysis when the conclusions that are to be drawn…are very strongly influenced by assumptions and judgments on which the analysis is based…

One may wish that the author had devoted more attention to the methods by which the scientist may check the effects of some of the necessary assumptions" - Reed, *JASA*, 1944.

Reed on Specialization

"specialized statistical techniques for handling the data have been developed and this has led …to real specialization of statisticians themselves. Staying within the medical field…, we now have specialists in hospital statistics, in quality control of laboratory processes, in bioassay, in the mathematics of biology, and so on. The degree of specialization within medical statistics is in fact somewhat similar to the degree of specialization of medicine itself.

The extent of this is illustrated in Professor Cochran's experience when his daughter broke her arm. A call to a general practitioner met with the response that he did not handle children but suggested a pediatrician. The pediatrician when called said that he treated children, but did not set bones and suggested an orthopedist. The orthopedist said he did set bones and asked which arm it was, to which Professor Cochran, taking no chances asked, "Which arm do you set?" Reed, *JASA*, 1952.

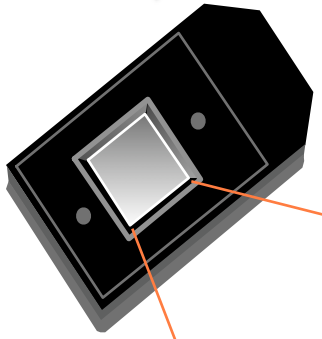
What **Might** Have Reed Said About Biostatistics Today and In the Future

Three Modern Day Examples

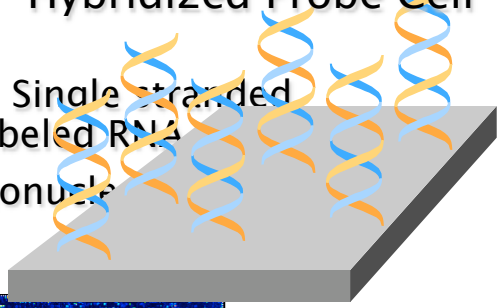
- Get your hands dirty - focus on ***measurement***
  - genomics
- Ask the ***right questions***; challenge the assumptions
  - Iraq mortality
- Promote ***transparency*** of ideas and methods
  - Air pollution and premature mortality

Get your hands dirty; focus on measurement

GeneChip Probe Array

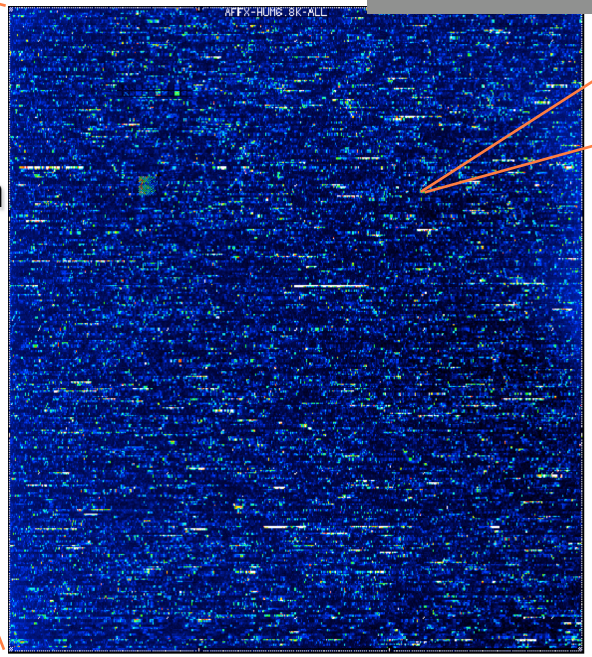


Hybridized Probe Cell



24μm

1.28cm



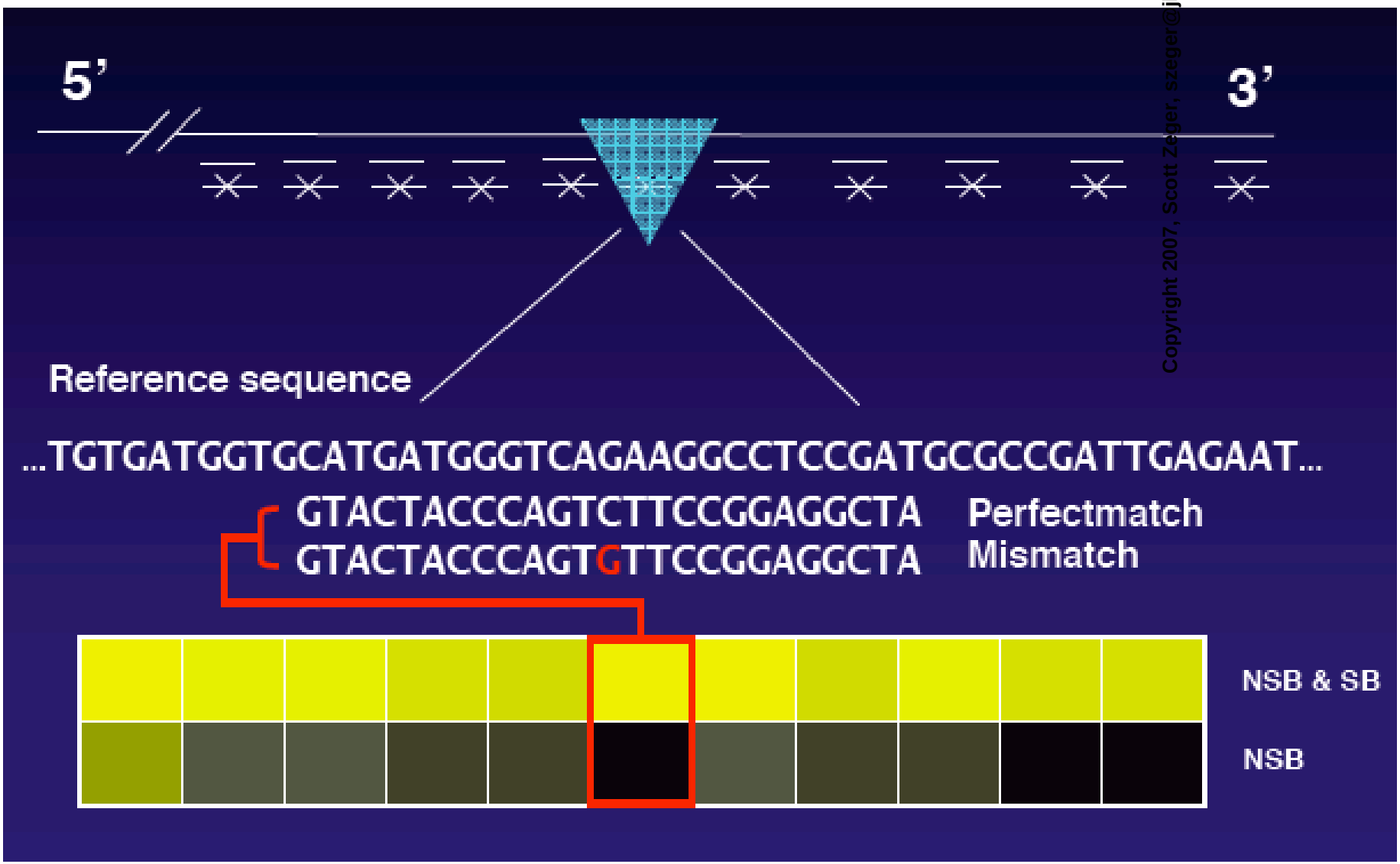
Millions of copies of a specific oligonucleotide probe

>200,000 different complementary probes

Image of Hybridized Probe Array

Compliments of D.

Affymetrix Technology



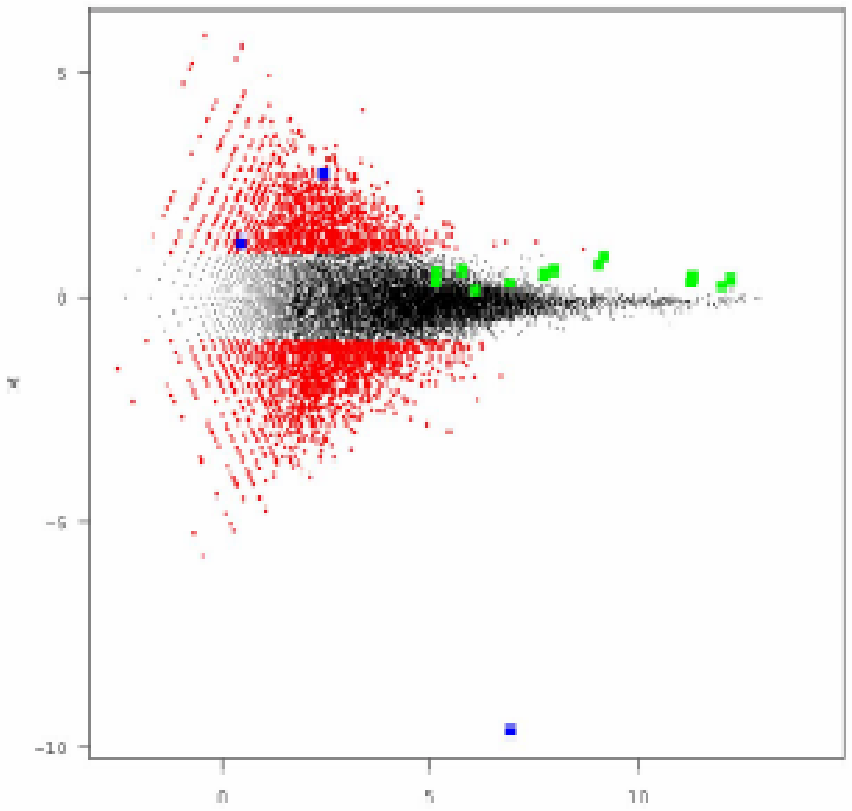
Competing Measures of Expression

GeneChip® MAS 5.0 software used

$$\text{Avg.diff} = \text{TukeyBiweight}\{PM_j - MM_j\}$$

Measuring Expression in a Spike-in Experiment

Original Affy Measure



Ranks
1
270
2074
3063
3935
4639
4652
5149
5372
5947
6448
6870
7037
7549
8429
9721

Competing Measures of Expression

Irizarry, et al. *Nucleic Acid Research; Biostatistics. 2003.* (2004 ASA Best Application)

Assume PM = Signal (S) + Background

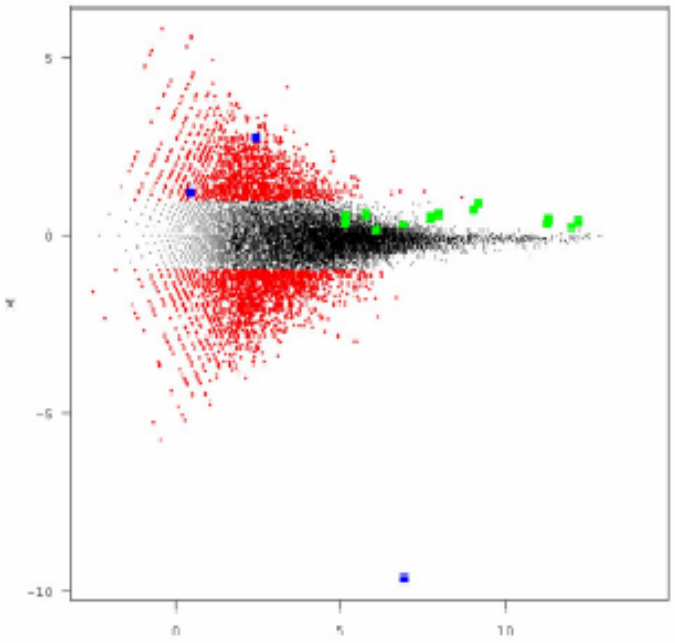
Minimize the MSE:

$$E\left[\left\{\log\left(\frac{\tilde{s}}{s}\right)\right\}^2 \middle| S>0, PM, MM\right]$$

Predict background B using many genes and/or G-C content of oligonucleotides

Irizarry, et al – Measuring Expression

MAS 5.0



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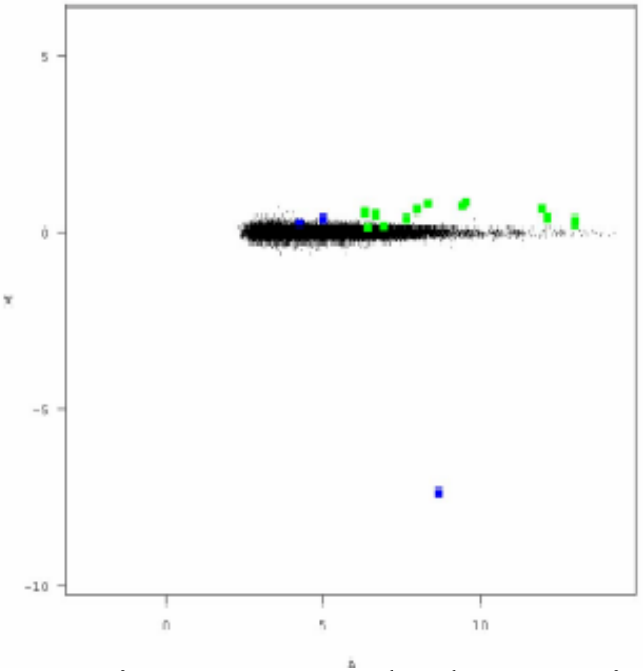
Standard Affy Measure

RMA



Ranks
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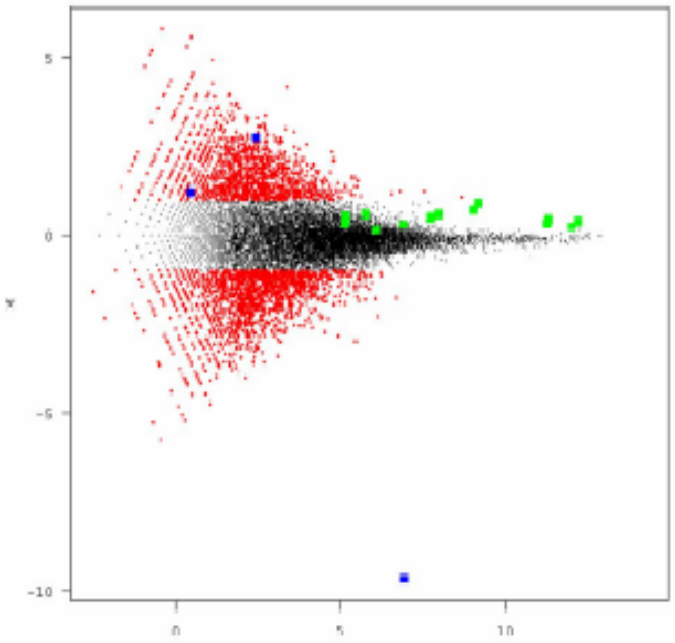
Irizarry, et al alternative

Irizarry, et al – Measuring Expression

MAS 5.0



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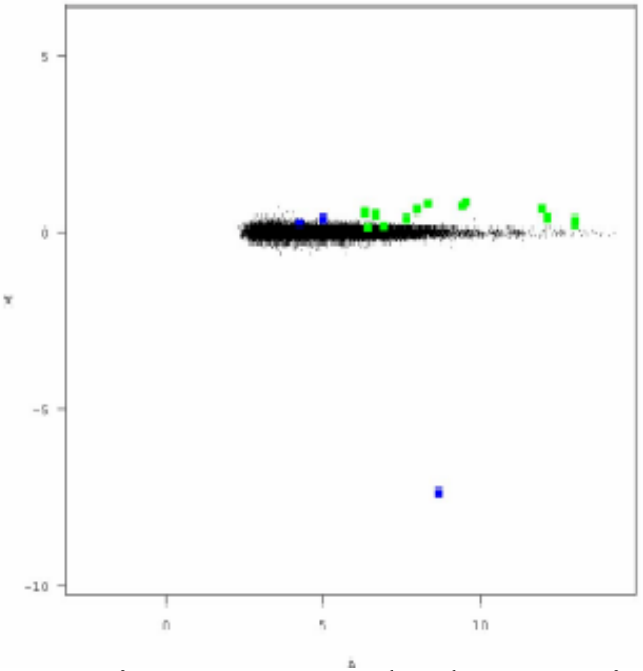

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2006 Iraq Mortality Survey - *Lancet*

Mortality after the 2003 invasion of Iraq: a cross-sectional cluster sample survey

Gilbert Burnham, Riyadh Lafta, Shannon Doocy, Les Roberts

Summary

Background An excess mortality of nearly 100 000 deaths was reported in Iraq for the period March, 2003–September, 2004, attributed to the invasion of Iraq. Our aim was to update this estimate.

Methods Between May and July, 2006, we did a national cross-sectional cluster sample survey of mortality in Iraq. 50 clusters were randomly selected from 16 Governorates, with every cluster consisting of 40 households. Information on deaths from these households was gathered.

Findings Three misattributed clusters were excluded from the final analysis; data from 1849 households that contained 12 801 individuals in 47 clusters was gathered. 1474 births and 629 deaths were reported during the observation period. Pre-invasion mortality rates were 5·5 per 1000 people per year (95% CI 4·3–7·1), compared with 13·3 per 1000 people per year (10·9–16·1) in the 40 months post-invasion. We estimate that as of July, 2006, there have been 654 965 (392 979–942 636) excess Iraqi deaths as a consequence of the war, which corresponds to 2·5% of the population in the study area. Of post-invasion deaths, 601 027 (426 369–793 663) were due to violence, the most common cause being gunfire.

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Bush dismisses Iraq death toll study

AP Associated Press

AP Photo: President Bush speaks during a news conference in the Rose Garden of the White House...

By MALCOLM RITTER, AP Science Writer

Thu Oct 12, 5:16 AM ET

NEW YORK - **President Bush** says he doesn't believe it. Some experts have a problem with it. But several others say it seems sound. Such was the varied reception for a controversial new study that estimated the **Iraq** war has led to the deaths of nearly 655,000 Iraqis as of July.

ADVERTISEMENT

Researchers from Johns Hopkins University in Baltimore and the Al Mustansiriya University in Baghdad derived that estimate from a door-to-door survey, conducted by doctors, of 1,849 households in Iraq. Taking the number of deaths reported by household residents, they extrapolated to a

"President Bush says he doesn't believe it."

Who's Counting?

BALONEY!

IT'S ONLY
65 THOUSAND.

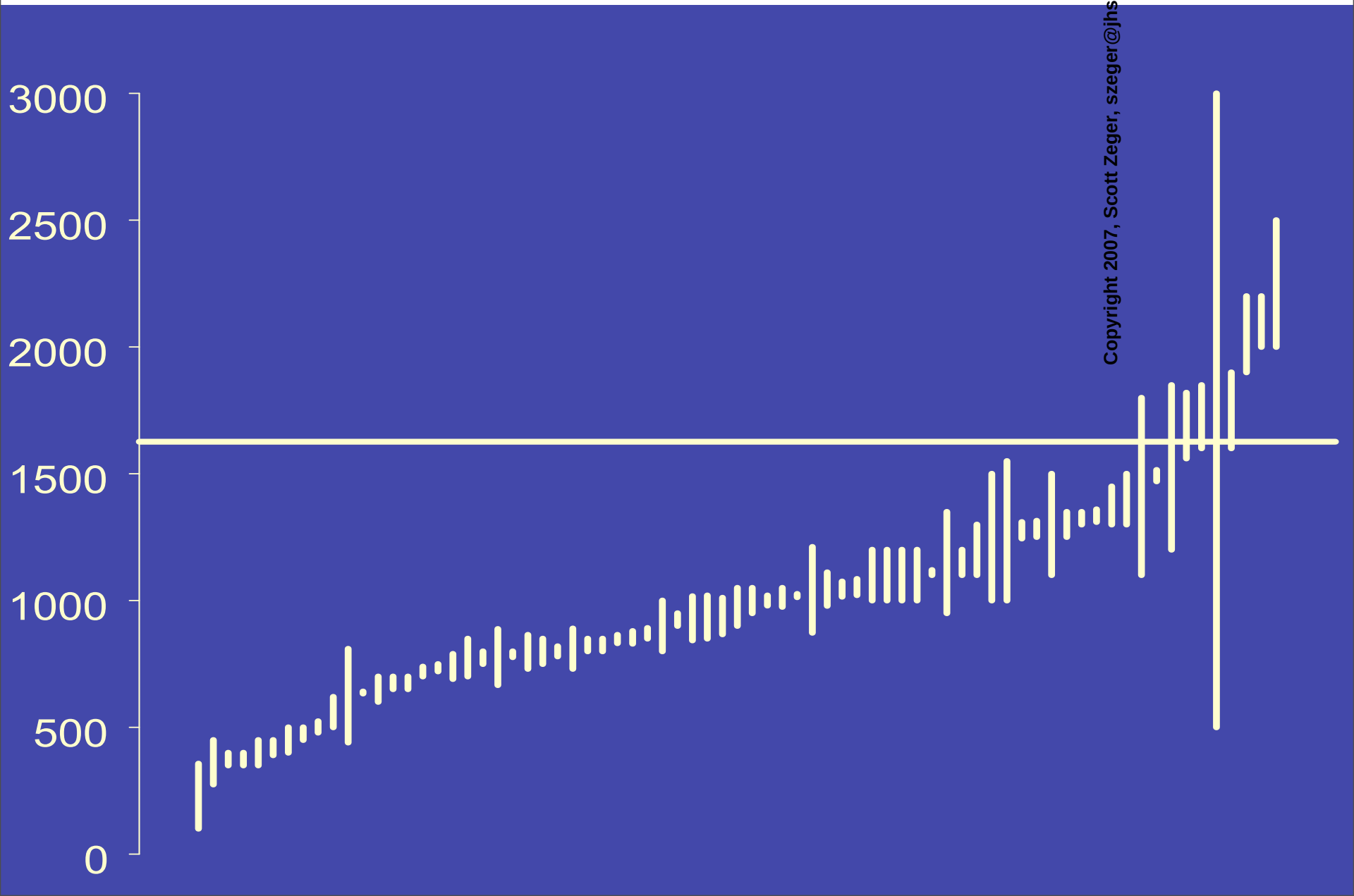
A MERE
COMMA.

DANZIGER

NYTS/CWS Oct 15 2006 (2944)

How Many Kisses in the Barrel? Ask the Experts

Results: Median opinion – 975; Coverage – 6/73



Civilians reported killed by military intervention in Iraq	
Min	Max
48829	54191
View Database...	

What do We Want to Know?

What do We Want to Know?

Nothing

What do We Want to Know

Nothing

What do We Want to Know

Nothing

Number of civilian deaths; number by violent causes

What do We Want to Know

Nothing

Number of civilian deaths; number by violent causes

Number of civilian deaths by violence in excess of *what would have occurred absent the U.S. invasion*

Targets of Inference

- Targets for inference - ascending order of uncertainty
  - Numbers of total deaths in Iraq per year
  - Numbers of violent deaths
  - Numbers of deaths "caused by" the U.S. invasion

Difficulty

- Total deaths in 2006
  - CIA 2006 Factbook: 5.38 deaths per 1,000 people per year on a population of 26.78 million = **144,000** deaths per year (https://www.cia.gov/cia/publications/factbook/geos/iz.html)

  - The United Nations Population Fund - 2006: 8.8 per 1,000 per year on population of 25.8 million = **227,000** (http://www.unfpa.org/profile/compare.cfm)

  - U.S. State Department Population Reference Bureau's 2006 World Data Sheet: 10 per 1,000 per year on a population of 29.6 million = **296,000** (http://www.prb.org/pdf06/06WorldDataSheet.pdf)

Lancet Surveys by faculty from Al Mustansiriya School of

Stage 1: Assign clusters to governorates proportionally to population size

	Mid-year 2004 population	Number of clusters
Baghdad	6554126	12
Ninewa	2554270	5
Basrah	1797758	3
Sulamaniyah	1715585	3
Thi-Qar	1493781	3
Babylon	1472405	3
Erbil	1418455	3
Diyala	1392093	3
Anbar	1328776	3
Salah al-Din	1119369	2
Najaf	978400	2
Wassit	971280	1
Qadissiya	911640	1
Tameem	854470	1
Missan	787072	1
Kerbala	762872	1
Muthanna	554994	0
Dahuk	472238	0
Total	27139584	47

Stage 2: Assign clusters within governorates proportionally to population size of sub-units (district / sub-district / township)

Stage 3: Identify the start house within the administrative unit

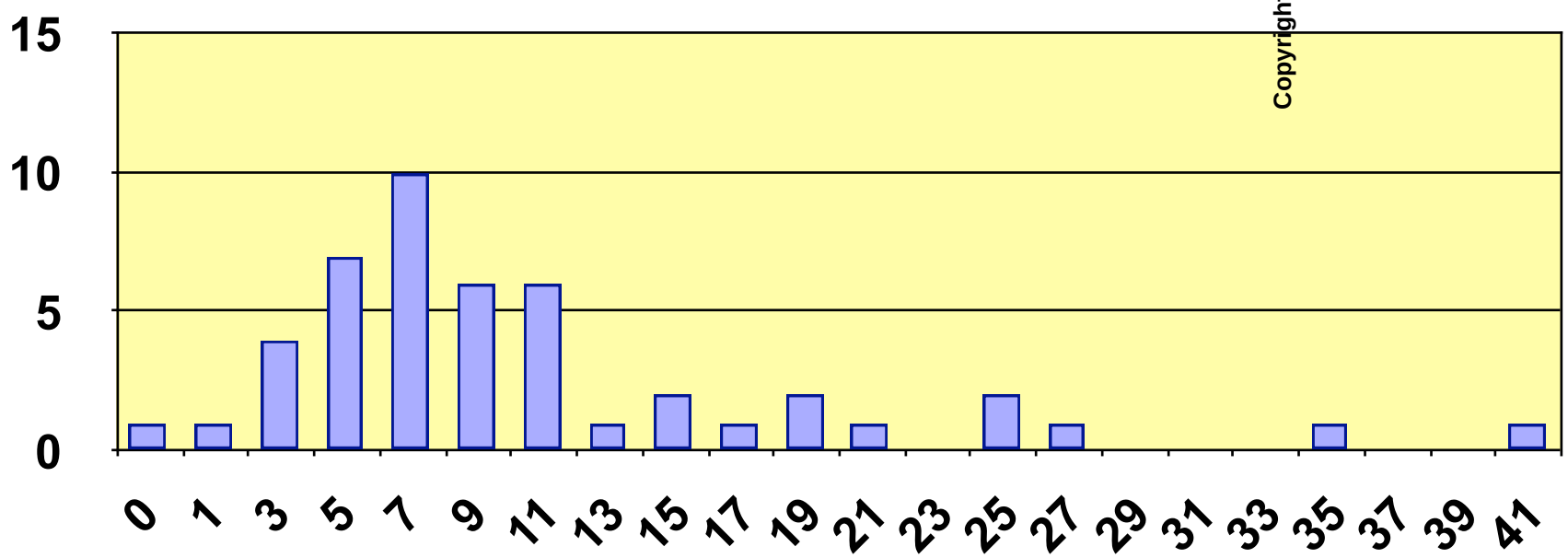
Many options for randomly selecting a start point:

- GPS, segmentation, central location w/ random direction and start distance, etc.

- For the Iraq study: random selection of a residential street and house number

Data Collection

- Two teams of interviewers - male and female medical doctor on each team
- Recall period between January 1, 2002 and date of interview
- Household size and sex of current household members
- All births and deaths between Jan 1, 2002 and the interview
  - Date of death
  - Cause of death
  - Details of violent deaths
- Inclusion and verification of deaths
  - To be included the deceased had to reside in the household for 3 months before death
  - Death certificates requested at conclusion of interview
    - Requested for 87% of deaths
    - Present in 92% of requests



Overview of 2006 Findings

Pre-invasion

(Jan 02-Mar 03, 13 mos)

82 deaths

- 2 violent (2%)

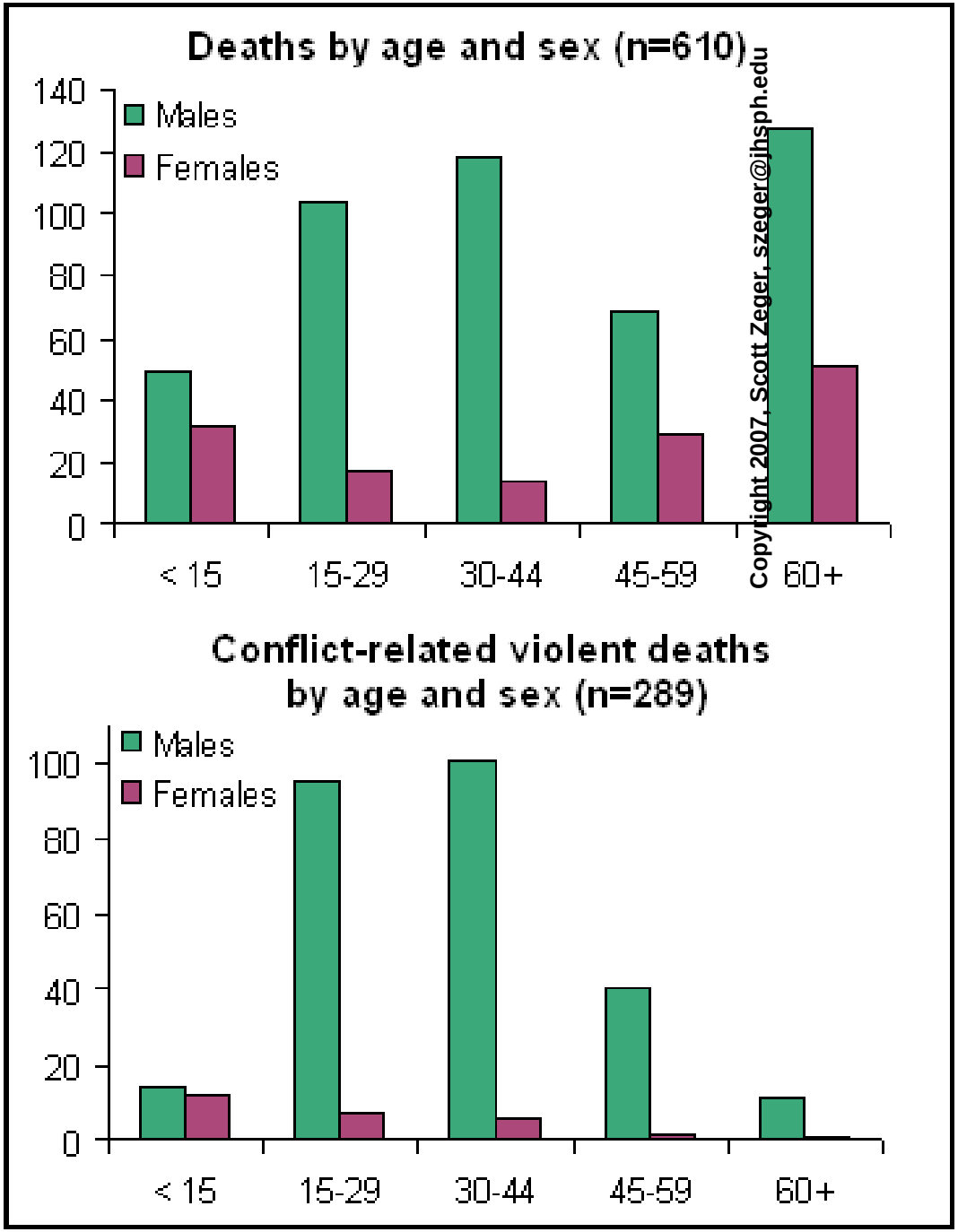
- CMR = 5.5/1000/yr
- Leading cause of death: cardiovascular disease (24%)
- VMR = 0.1/1000/yr

Post-invasion

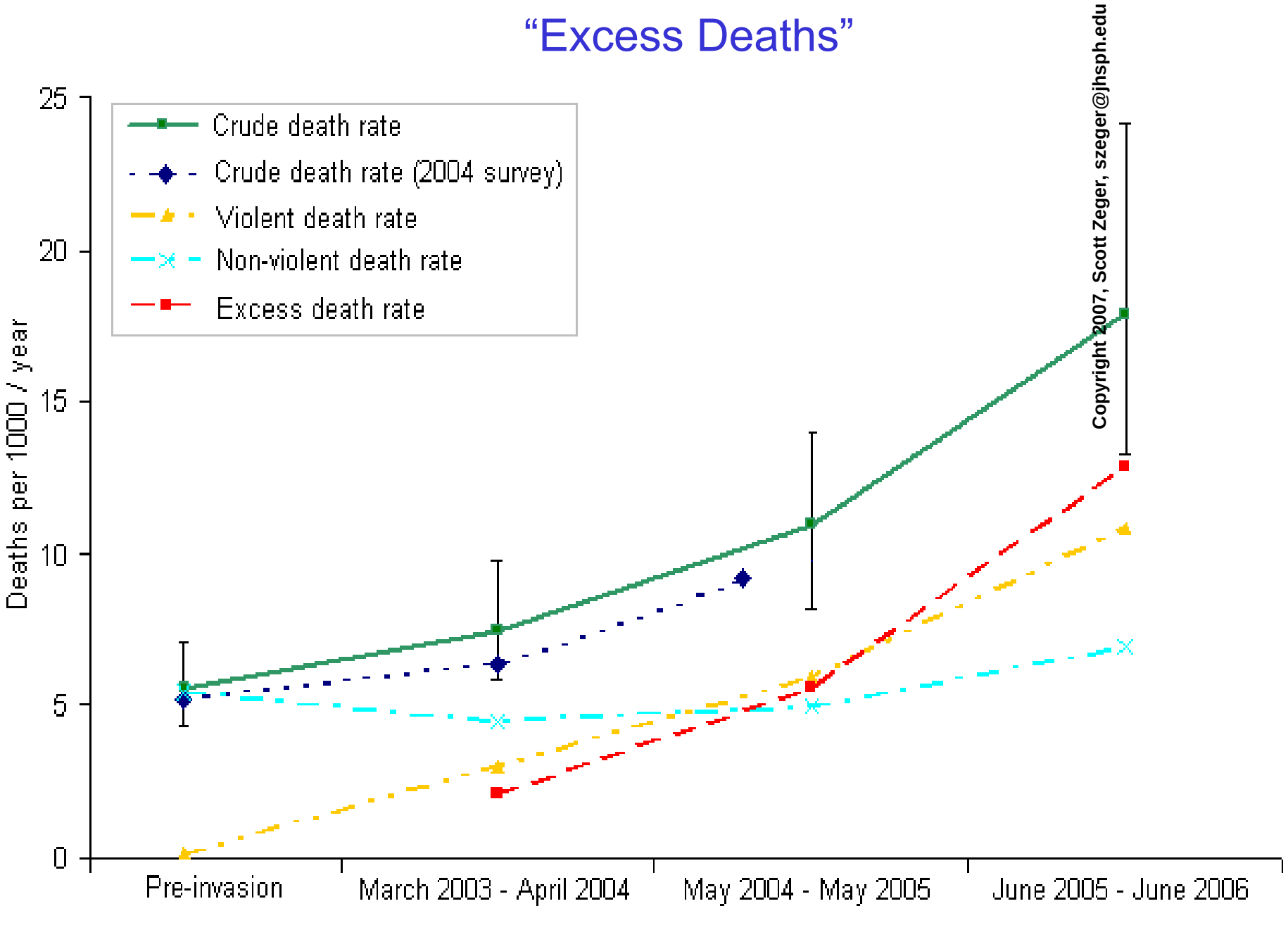
(Mar 03-Jun 06, 39 mos)

- 547 deaths
  - 302 violent (46%)
- CMR = 13.2/1000/yr
- Leading cause of death: gunshots (31%)
- VMR = 7.2/1000/yr
  - 91% of violent deaths are among males

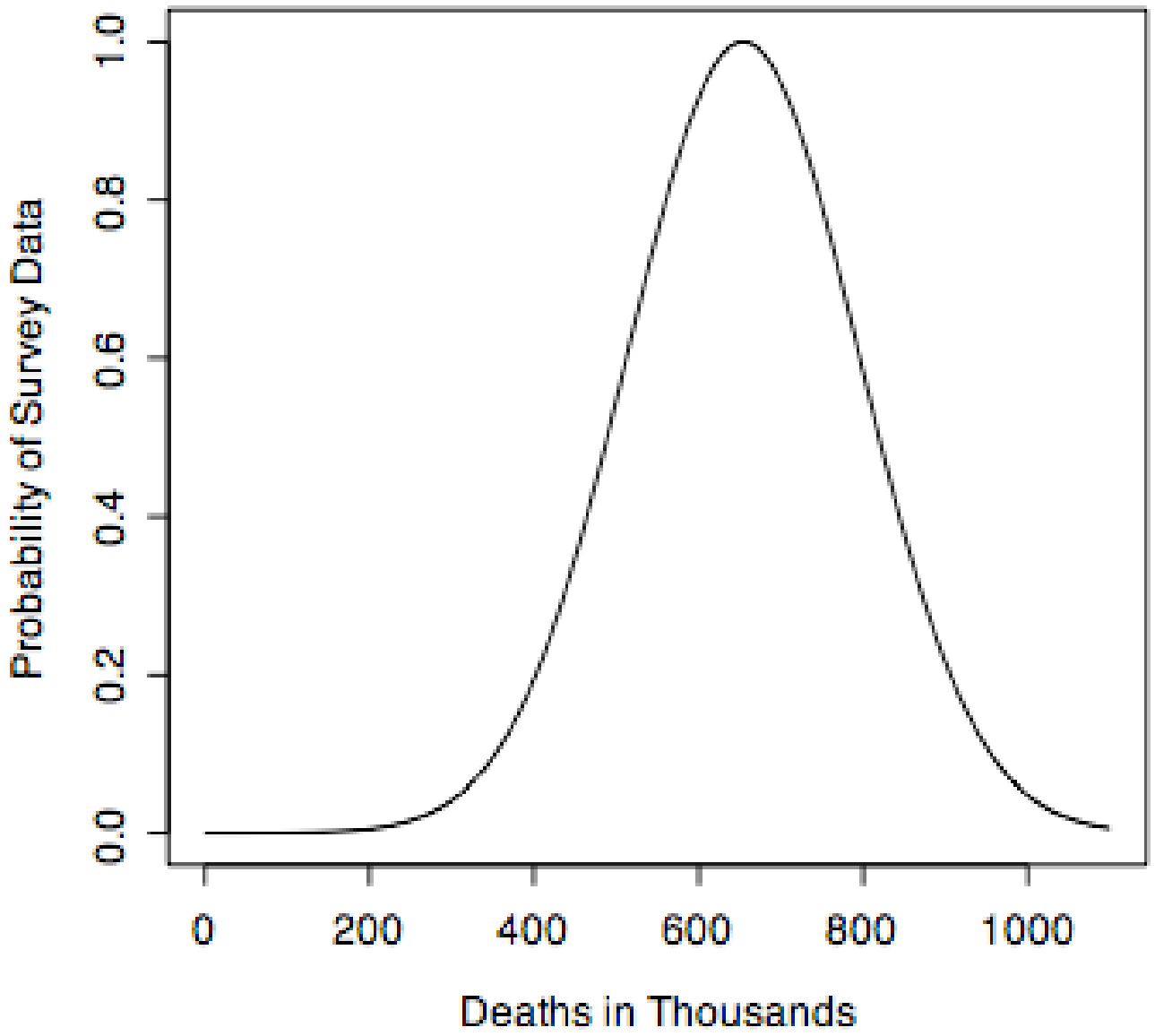
Deaths by age during the study period



“Excess Deaths”



Likelihood Function for Excess Deaths



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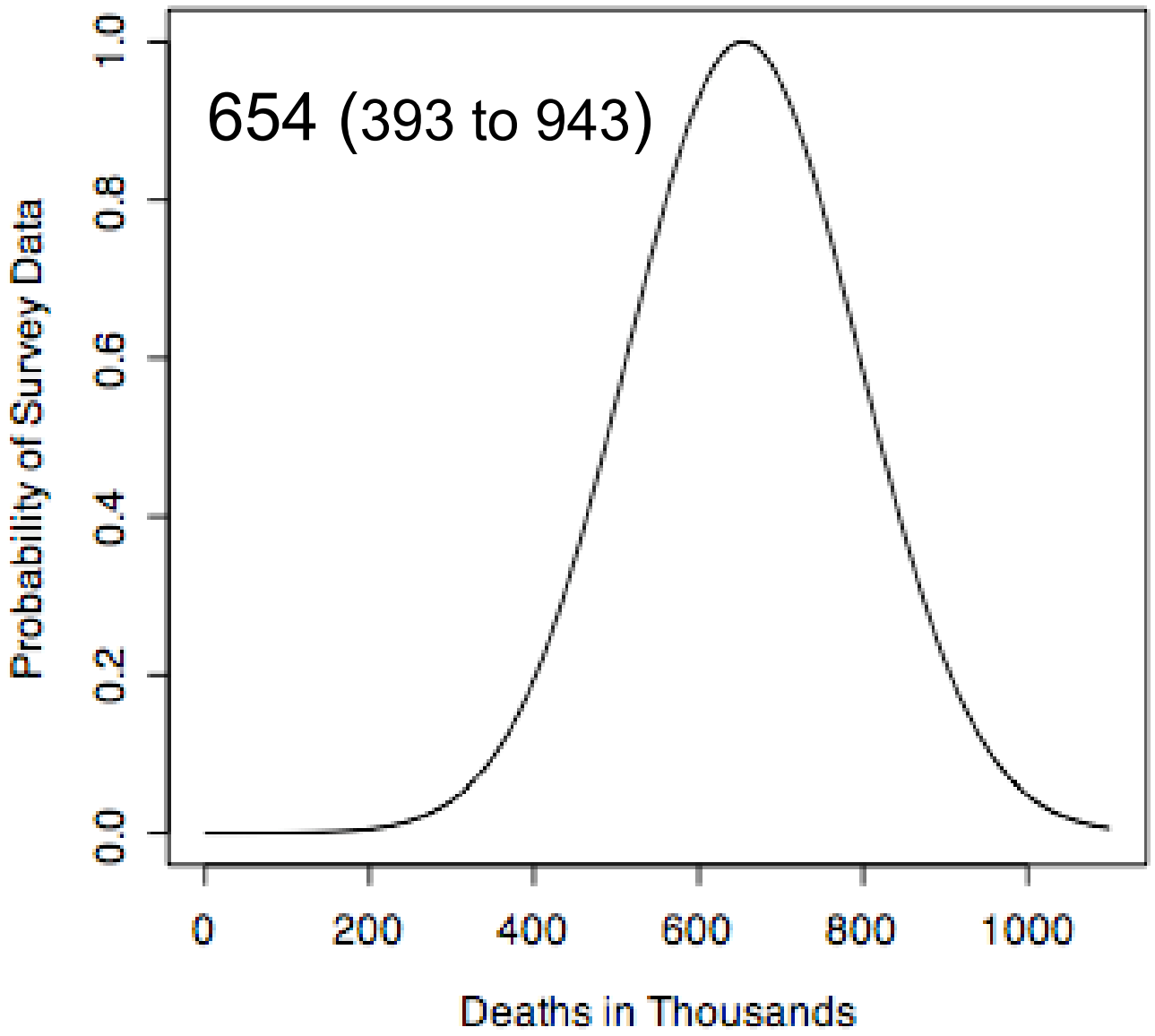
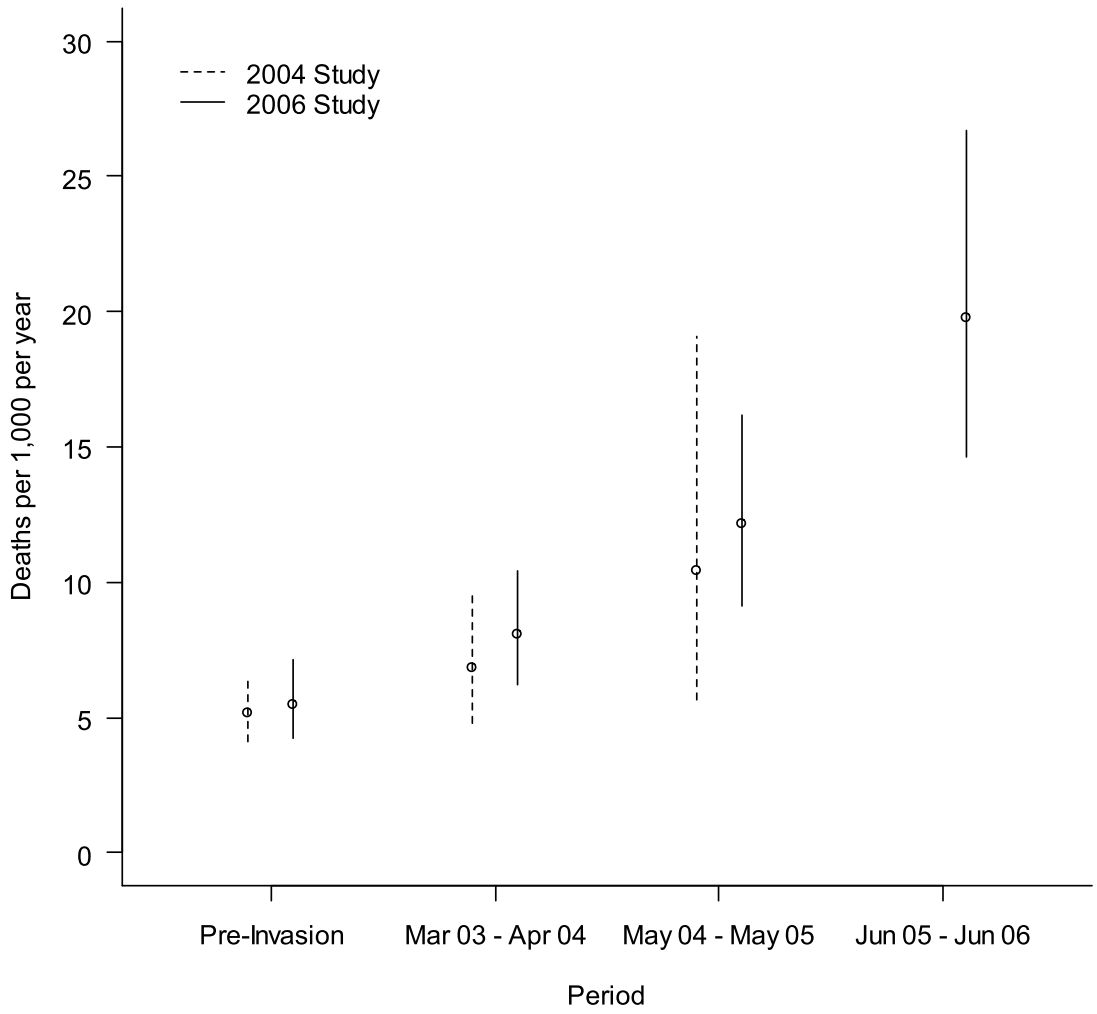
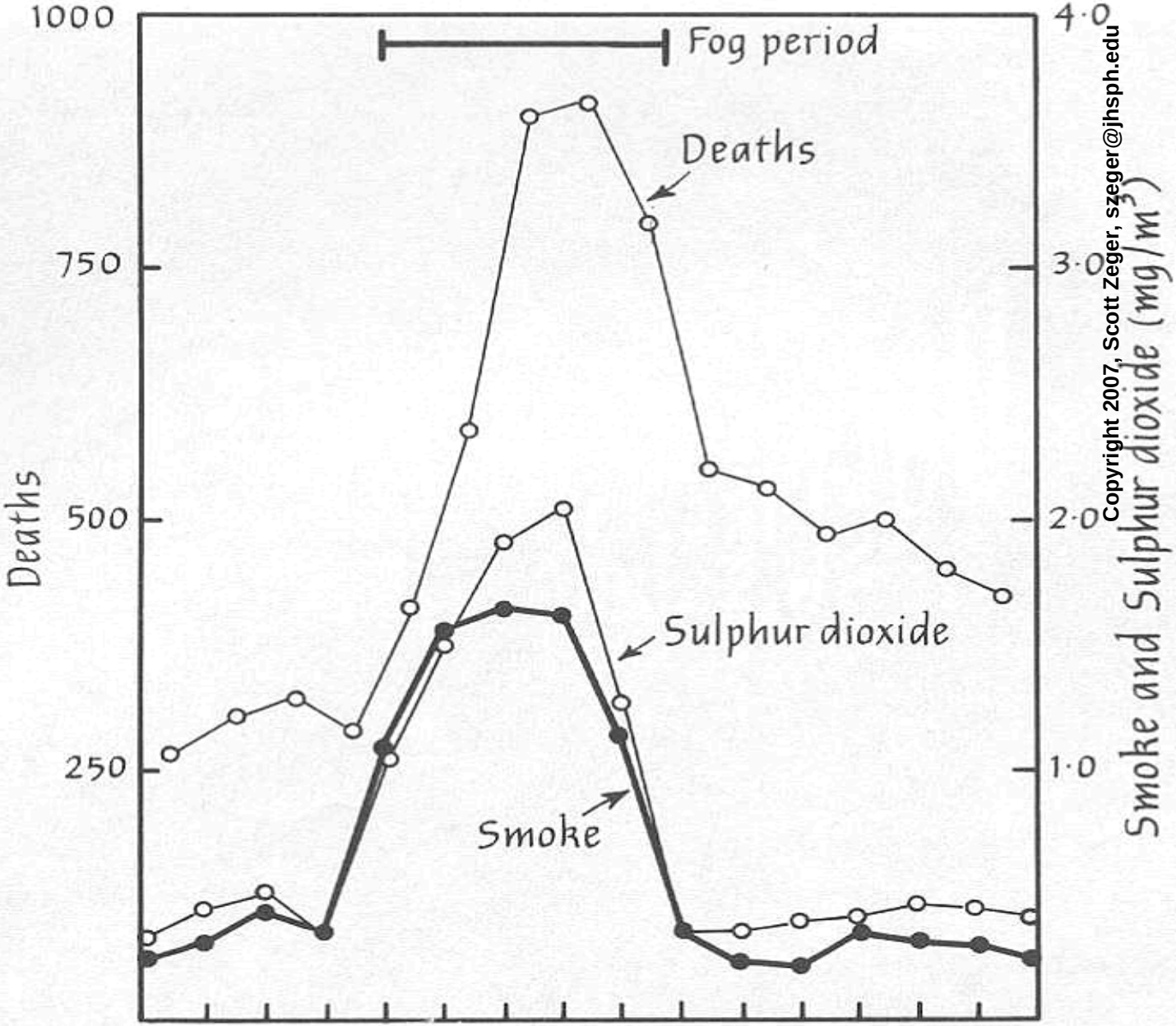


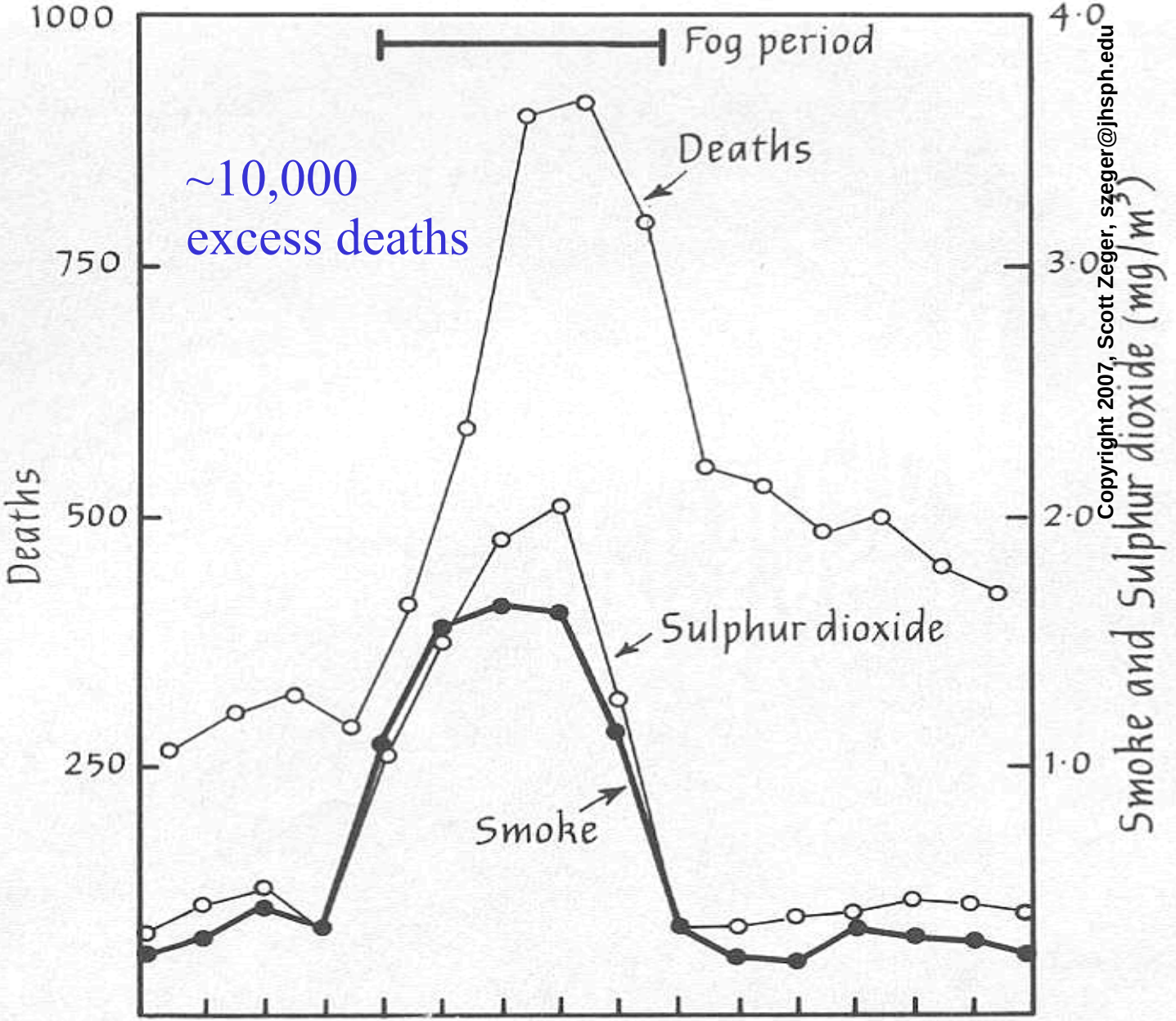


Ask the right questions; challenge assumptions

Promote ***transparency*** of ideas and methods

London, 12 noon, December, 1952; Particulate levels – 3,000 μg/m^3





Key Epidemiologic Evidence for Continued Health Risk of Air Pollution

- Chronic exposures: cohort studies
  - Six Cities Study (e.g. Dockery, et al , 1993)
  - American Cancer Study (e.g. Pope, et al, 2002)

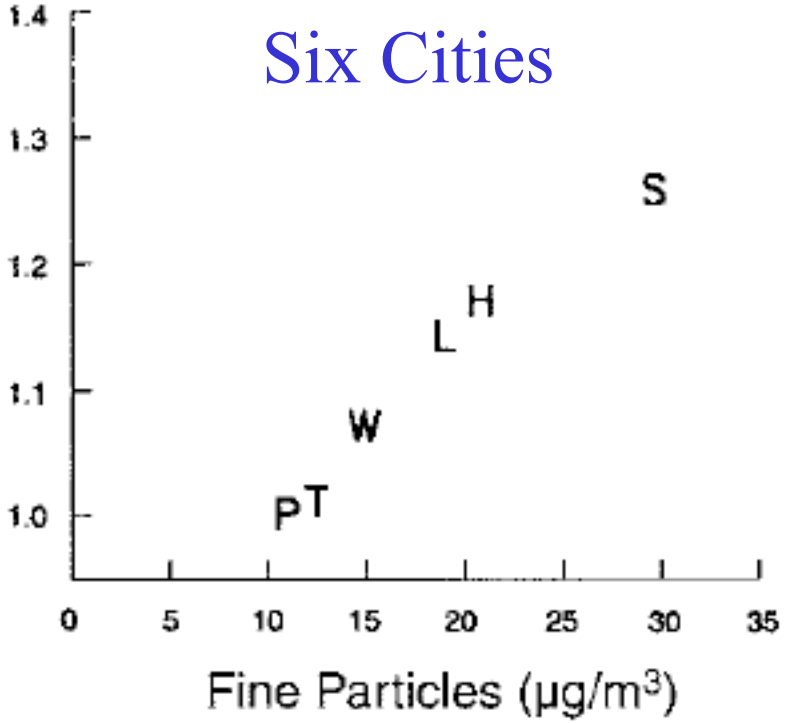
- Acute exposures: multi-city time series studies
  - NMMAPS (90 U.S.cities; e.g. Samet, et al, 2000)
  - APHEA (29 Eur cities; e.g.Katsouyanni, et al, 2003)
  - CANADIAN (8 Cities; e.g. Burnett, Goldberg, 2003)

Cohort Studies

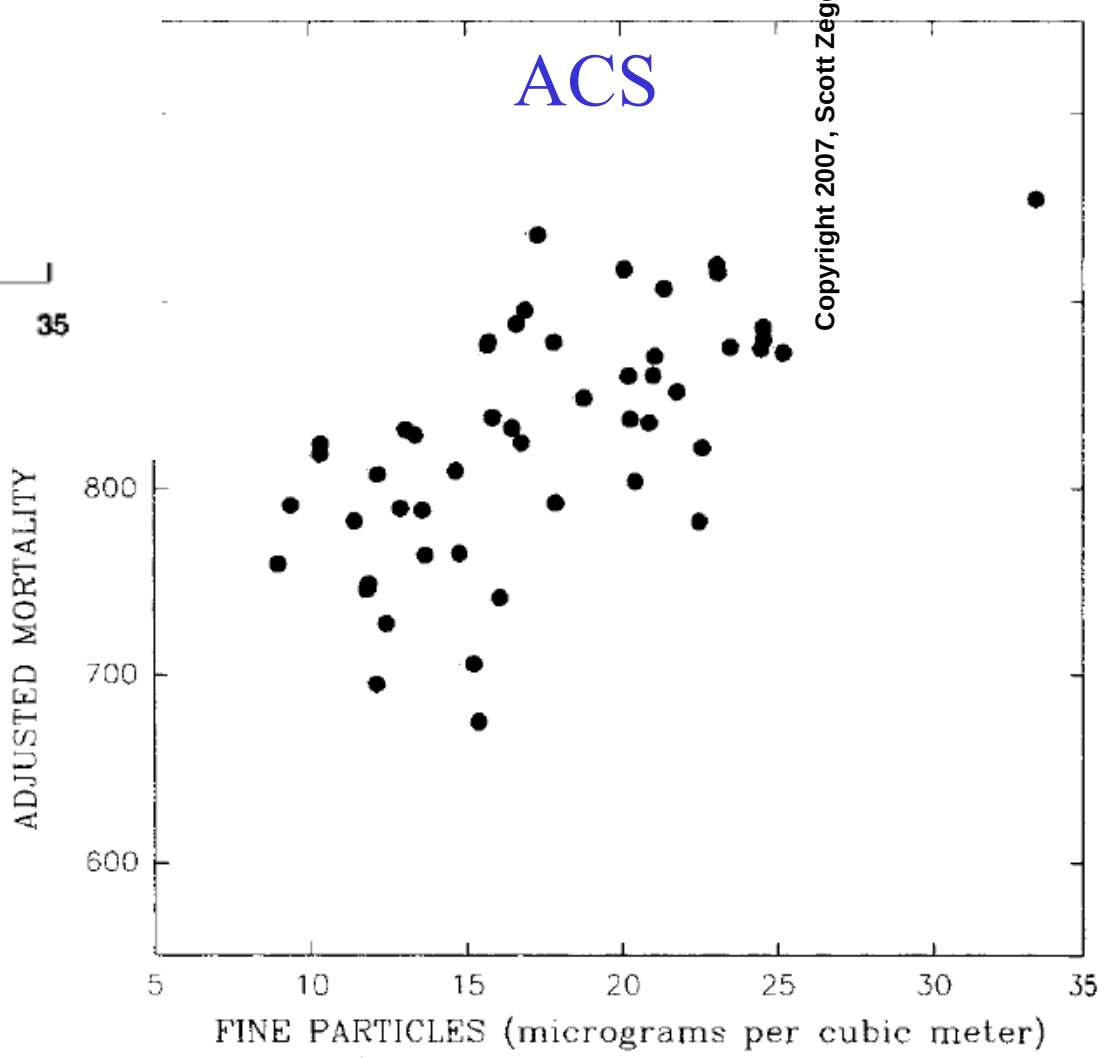
	Six Cities	ACS
People	8,111	500,000+
Person years	158,978	7.5M
Deaths	2,732	60,000+
Cities	6	50
Exposure	Yearly average	Yearly average
Covariates	Age,smoking, exercise,+	Age, smoking, exercise, +
Total mortality RR	**1.16***	**1.07***
Cardiovascular RR	**1.28***	**1.12***
Lung cancer RR	**1.27***	**1.02***

*** - per 10 μg / m3**

Six Cities



ACS



Public Health Significance

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In US, EPA estimates on order of 10,000 particle-attributable deaths per year if cohort relative risks represent a causal effect

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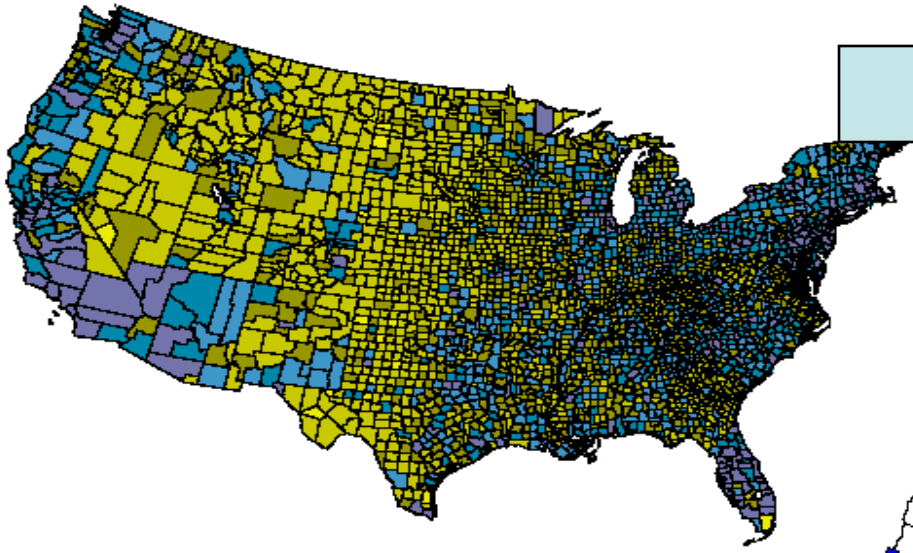
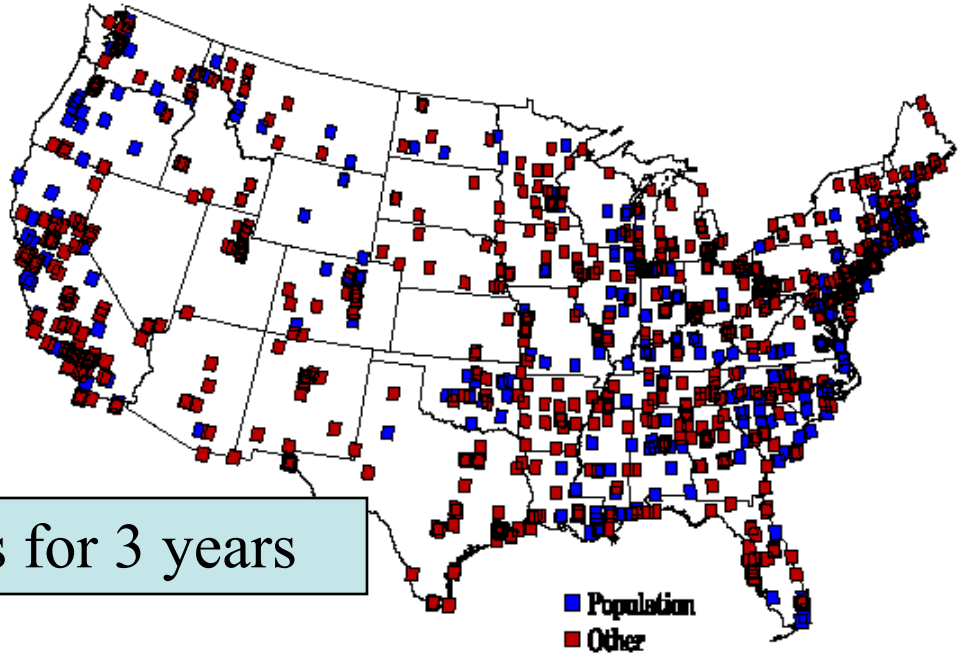
Smoking – 400,000 smoking attributable deaths per year

Medicare Air Pollution Study (MCAPS)
50 million Persons 65+

2 million deaths per year





PM2.5 at 327 locations for 3 years

All Cause Mortality Increase per 10 µg/m3 PM2.5
MCAPS Estimates for 250 Counties

	Ages			
Adjustment	All	65-74	75-84	85+
Age-Gender (AG)	4.4 7.6 10.8	10.2 15.4 20.6	4.8 8.0 11.3	-3.1 -0.50 2.1
AG + SES	6.0 8.5 11.0	10.2 14.3 18.5	6.5 9.1 11.6	0.20 2.4 4.6
AG+SES+COPD	5.4 7.6 9.7	8.4 11.9 15.4	6.3 8.5 10.7	0.60 2.6 4.7

Decomposing Relative Risk Estimates by Distance and Region

- If the association of PM with mortality is causal, it should be apparent, on average, in comparisons of all pairs of cities

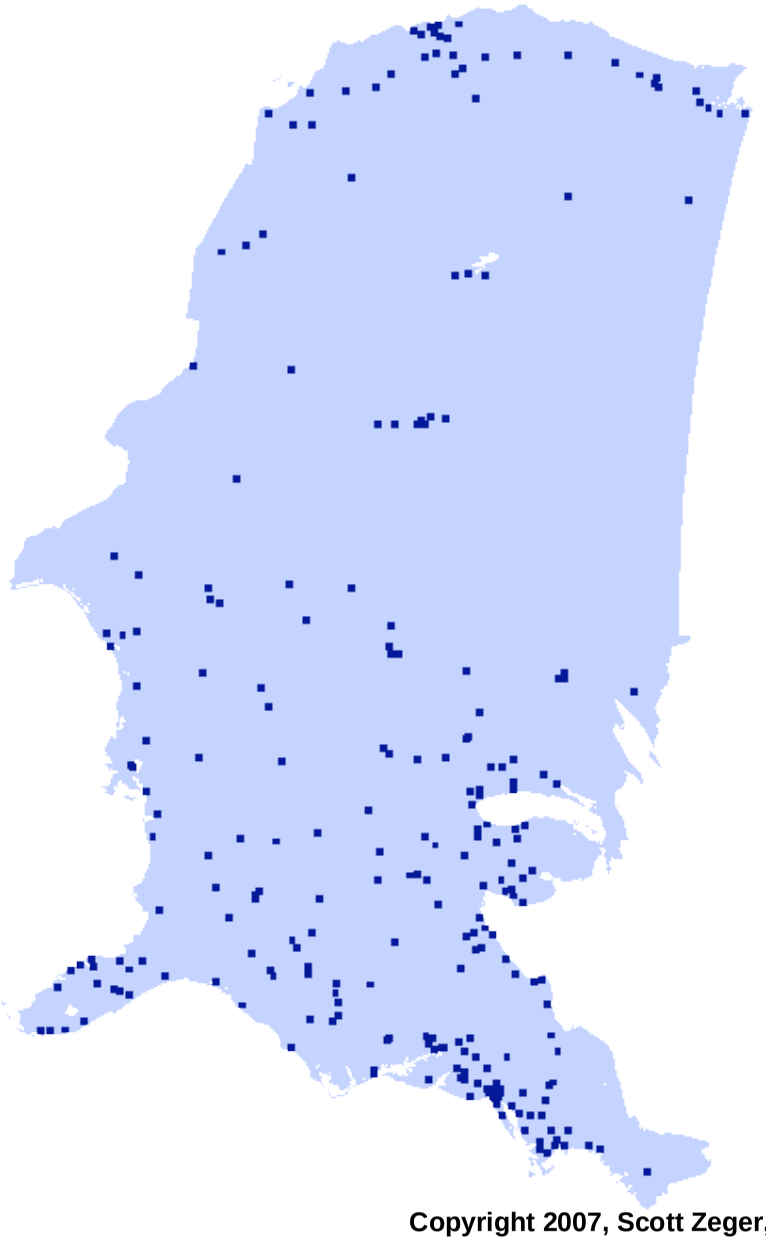
- Estimate separate PM effects by distance, region, …

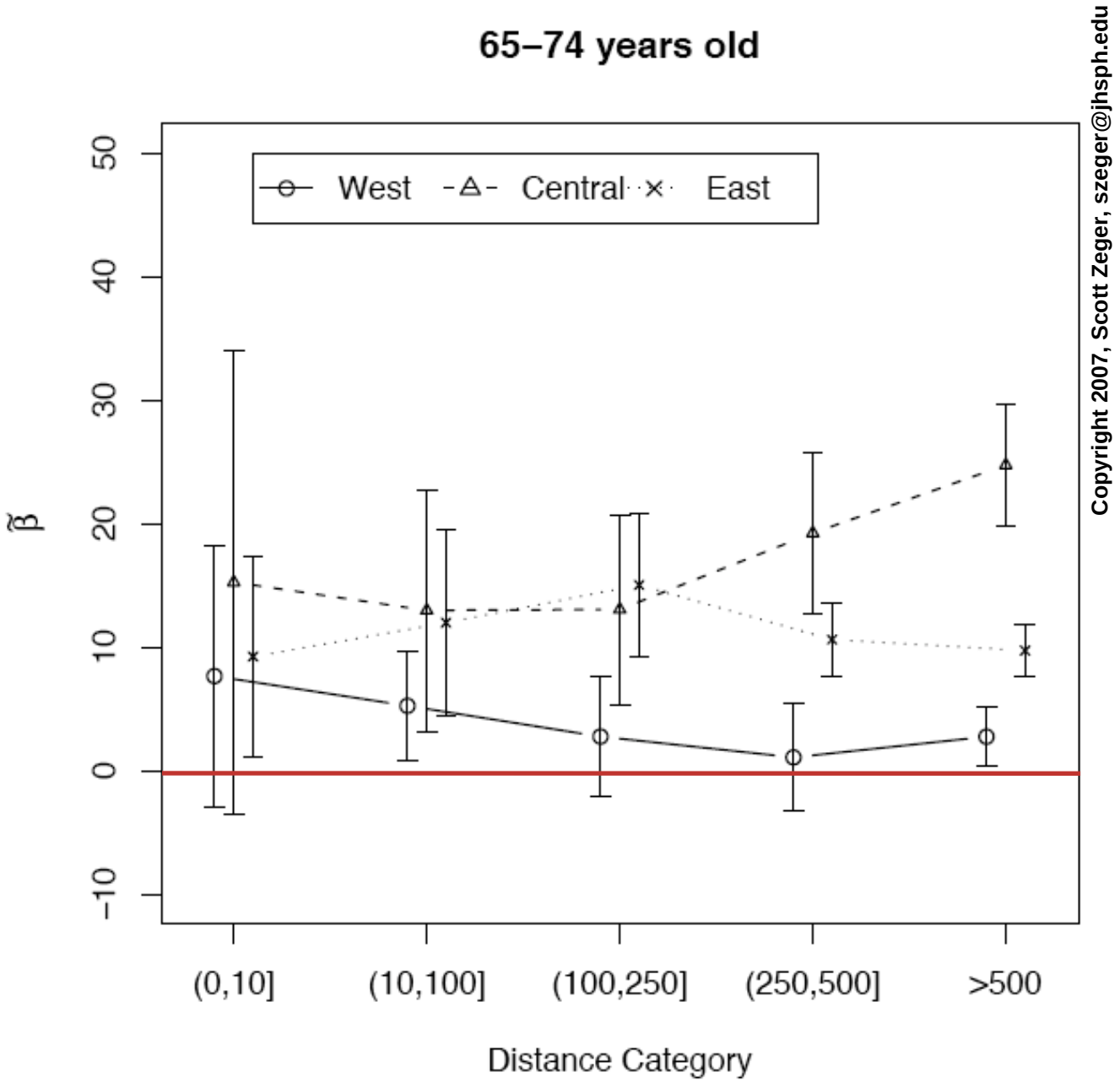
Pairwise Relative Risks

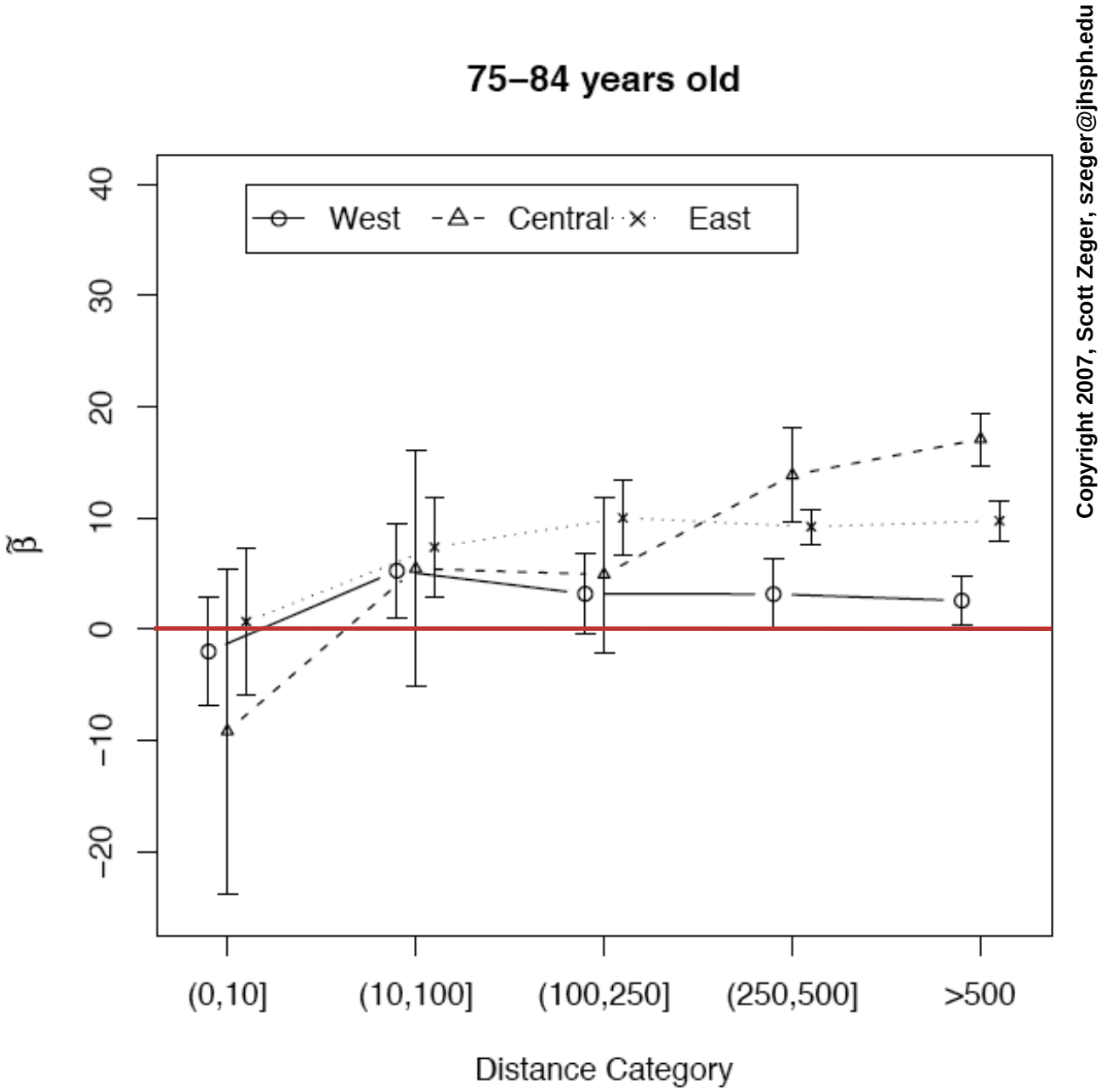
$$\log RR_{jk} = \log\{mort_j/mort_k\}/(x_j - x_k)$$

$$d_{jk} = |u_j - u_k|$$

Estimate average log RR for strata of d, within regions







Levels in Replication

Investigator

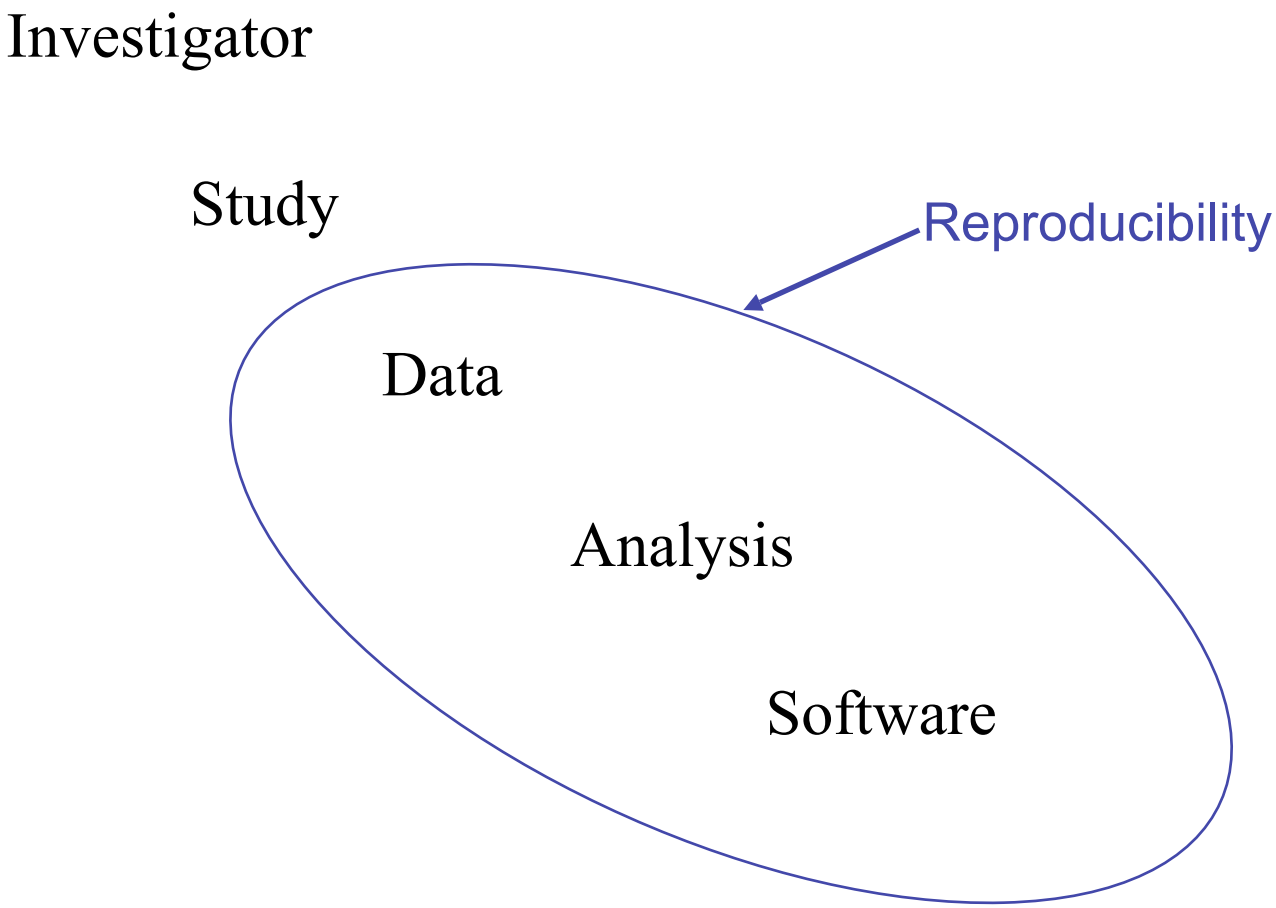
Study

Data

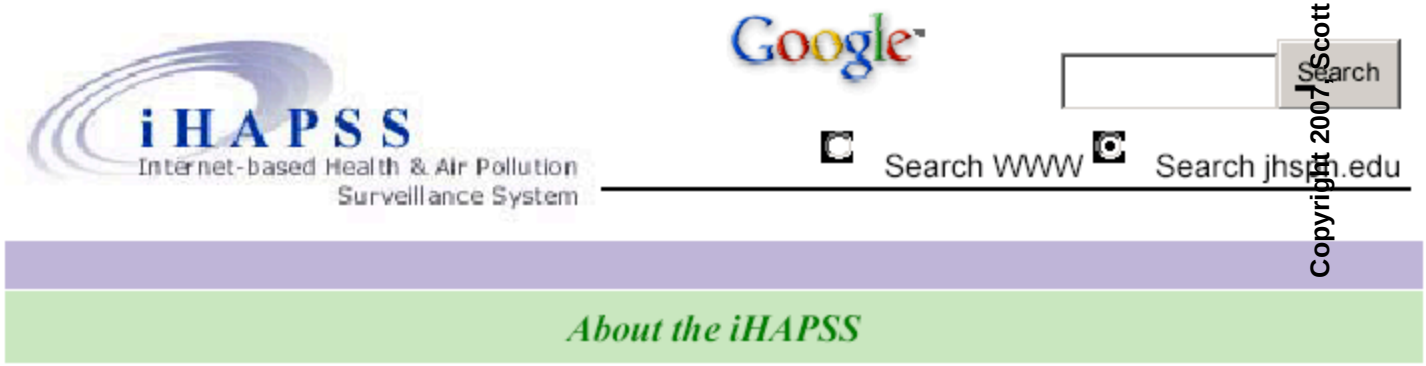
Analysis

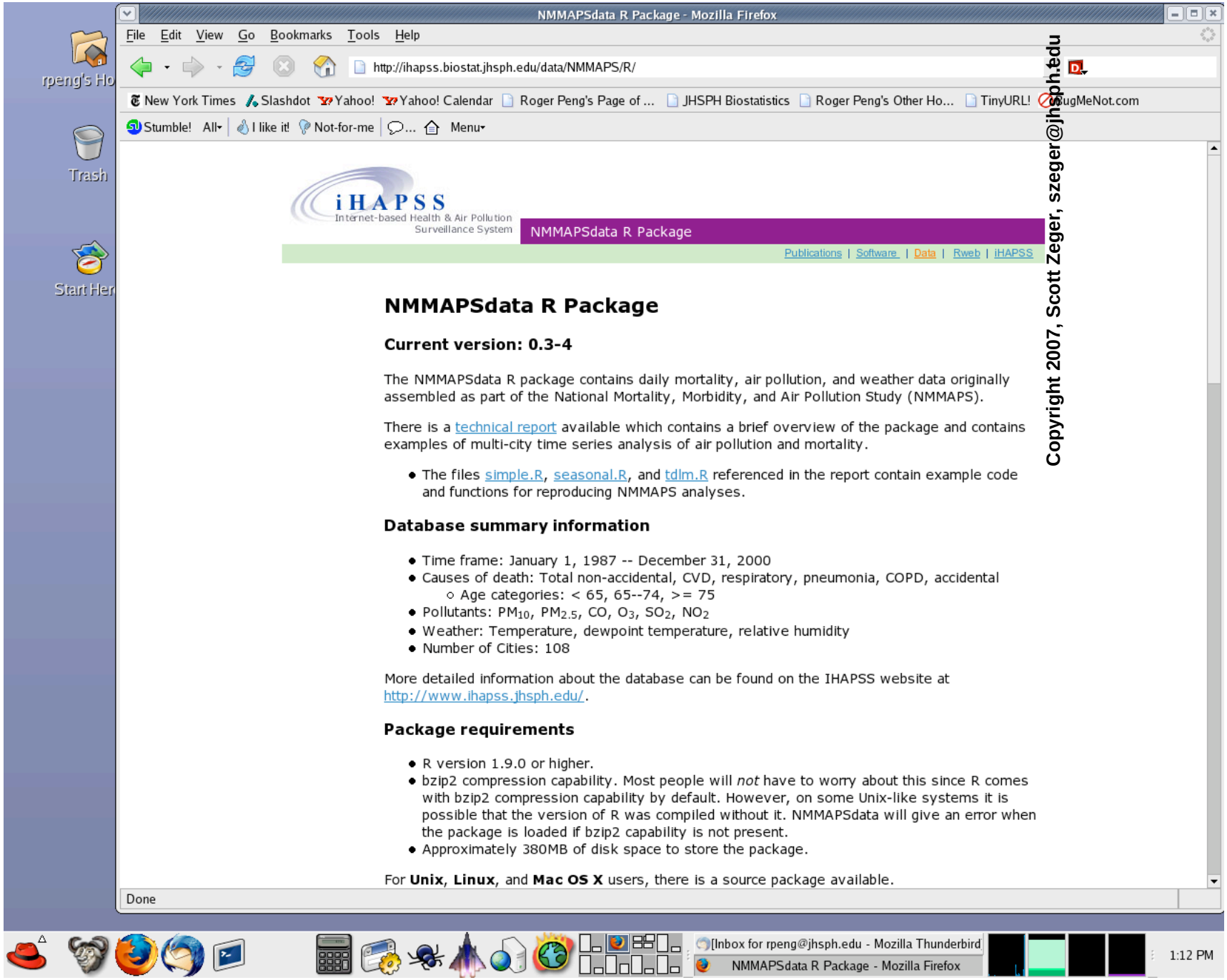
Software

Levels in Replication



internet Health and Air Pollution Surveillance System (iHAPSS) + R package




NMMAPSdata R Package - Mozilla Firefox
File Edit View Go Bookmarks Tools Help
http://ihapss.biostat.jhsph.edu/data/NMMAPS/R/
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Stumble! All I like it! Not-for-me Menu
iHAPSS
Internet-based Health & Air Pollution Surveillance System
NMMAPSdata R Package
Publications | Software | Data | Rweb | iHAPSS
NMMAPSdata R Package
Current version: 0.3-4
The NMMAPSdata R package contains daily mortality, air pollution, and weather data originally assembled as part of the National Mortality, Morbidity, and Air Pollution Study (NMMAPS).
There is a technical report available which contains a brief overview of the package and contains examples of multi-city time series analysis of air pollution and mortality.
The files simple.R, seasonal.R, and tdlm.R referenced in the report contain example code and functions for reproducing NMMAPS analyses.
Database summary information
Time frame: January 1, 1987 -- December 31, 2000
Causes of death: Total non-accidental, CVD, respiratory, pneumonia, COPD, accidental
Age categories: < 65, 65--74, >= 75
Pollutants: PM10, PM2.5, CO, O3, SO2, NO2
Weather: Temperature, dewpoint temperature, relative humidity
Number of Cities: 108
More detailed information about the database can be found on the IHAPSS website at http://www.ihapss.jhsph.edu/.
Package requirements
R version 1.9.0 or higher.
bzip2 compression capability. Most people will not have to worry about this since R comes with bzip2 compression capability by default. However, on some Unix-like systems it is possible that the version of R was compiled without it. NMMAPSdata will give an error when the package is loaded if bzip2 capability is not present.
Approximately 380MB of disk space to store the package.
For Unix, Linux, and Mac OS X users, there is a source package available.
Done
Copyright 2007, Scott Zeger, szeger@jhsph.edu
[Inbox for rpeng@jhsph.edu - Mozilla Thunderbird
NMMAPSdata R Package - Mozilla Firefox
1:12 PM

Transparency

- By looking at observational data from many perspectives

- By encouraging others to look too

Main Points, Once Again

- Lowell Reed was an early giant in American biostatistics: scientist; educator; administrator

- If he were here today, he *MIGHT* tell us to:
  - Get hands dirty; focus on ***measurement***
  - Ask the ***right questions***; challenge the assumptions
  - Promote ***transparency***

Key Contributors

Measurement	Iraq Invasion	Air Pollution
Rafael Irizarry	Les Roberts	Francesca Dominici
Jean Wu	Gil Burnham	Aidan McDermott
…	Elizabeth Johnson	Jon Samet
	Many Iraqi staff	Roger Peng
		Leah Welty
		Holly Janes
		Yun Lu

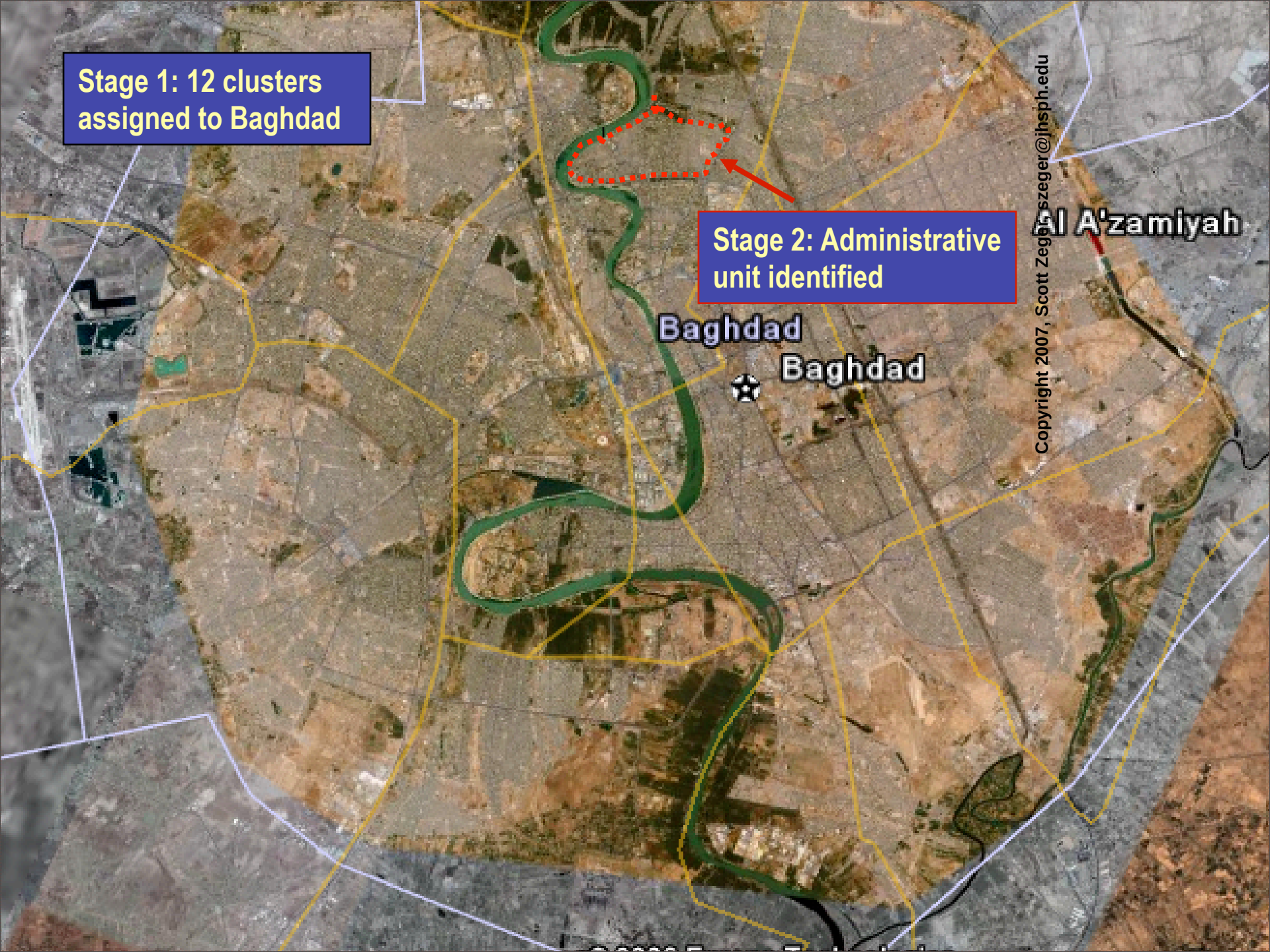
Thank you

Reed on Math Curricula for Scientists

"the increasing use of mathematical methods in such sciences as chemistry, biology, etc., has led to an effort to broaden the teaching of mathematics by introducing new applications. The result has been a new group of textbooks under such titles as 'Calculus for Chemical Students', 'Mathematics for Agricultural Students', etc.

…these texts seem to me to miss the point in that they imply that calculus for chemistry students is distinct from calculus for other groups. This I do not believe to be the case. …

he needs to be trained to take a problem in his particular field and translate it into mathematical language." - *Am Math Monthly*, 1920 .


Stage 1: 12 clusters assigned to Baghdad
Stage 2: Administrative unit identified
Baghdad
Baghdad
Al A'zamiyah
Copyright 2007, Scott Zeger, szeger@jhsph.edu

2nd stage—where in cluster no. 5?


Main streets listed
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© 2006 Europa Technologies
Image © 2006 DigitalGlobe
Google
Pointer 33°23'31.36" N 44°22'43.14" E elev 38 m
Streaming 100%
Eye alt 1.42 km


Main streets
Main street selected è
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© 2006 Europa Technologies
Image © 2006 DigitalGlobe
Google
Pointer 33°23'31.36" N 44°22'43.14" E elev 38 m
Streaming 100%
Eye alt 1.42 km


Main streets
Stage 3: Identification of the starting house
Main street selected è
Start house
Side streets that intersect with selected main street and others in the area
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Pointer 33°23'31.36" N 44°22'43.14" E elev 38 m
Streaming 100%
Eye alt 1.42 km

Selection of Households in the Cluster


Start house
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Google
Pointer 33°23'31.36" N 44°22'43.14" E elev 38 m
Streaming 100%
Eye alt 1.42 km

	Children (0–14 years)	Adults (15–59 years)		Elderly people (60+ years)	All deaths by cause†
		Men	Women		
Pre-invasion (n=82)					
Non-violent deaths	14 (100%)	19 (95%)	6 (100%)	40 (96%)	80 (98%)
Heart disease/stroke	0	6 (30%)	2 (33%)	12 (29%)	20 (24%)
Cancer	1 (7%)	5 (25%)	1 (17%)	8 (20%)	15 (18%)
Chronic illness	1 (7%)	5 (25%)	0	9 (22%)	15 (18%)
Infant	11 (79%)	NA	NA	NA	11 (13%)
Accident	0	3 (15%)	2 (33%)	2 (5%)	7 (9%)
Old age	NA	NA	NA	8 (20%)	8 (10%)
Infectious disease	0	0	0	1 (2%)	1 (1%)
Other (non-violent)	1 (7%)	0	1 (17%)	0	3 (4%)
Violent deaths	0	1 (5%)	0	1 (2%)	2 (2%)
Other explosion/ordnance	0	1 (5%)	0	0	1 (1%)
Air strike	0	0	0	1 (2%)	1 (1%)
Total deaths	14 (100%)	20 (100%)	6 (100%)	41 (100%)	82 (100%)
Post-invasion (n=547)					
Non-violent deaths	40 (60%)	37 (14%)	39 (72%)	126 (92%)	247 (46%)
Heart disease/stroke	1 (2%)	15 (6%)	11 (20%)	74 (54%)	102 (19%)
Cancer	1 (2%)	5 (2%)	14 (26%)	11 (8%)	33 (6%)
Chronic illness	0	5 (2%)	3 (6%)	18 (13%)	28 (5%)
Infant	29 (43%)	NA	NA	NA	29 (5%)
Accident	8 (12%)	5 (2%)	6 (11%)	4 (3%)	23 (4%)
Old age	NA	NA	NA	19 (14%)	19 (4%)
Infectious disease	1 (2%)	1 (0%)	1 (2%)	0	3 (1%)
Other (non-violent)	0	6 (2%)	4 (7%)	0	10 (2%)
Violent deaths	26 (39%)	235 (86%)	15 (28%)	11 (8%)	300 (55%)
Gunshot	3 (5%)	142 (49%)	6 (11%)	9 (7%)	169 (31%)
Other explosion/ordnance	4 (6%)	33 (12%)	2 (4%)	1 (1%)	42 (8%)
Air strike	13 (20%)	23 (9%)	2 (4%)	1 (1%)	39 (7%)
Car bomb	3 (5%)	28 (10%)	5 (9%)	0	38 (7%)
Unknown (violent)	1 (2%)	5 (2%)	0	0	6 (1%)
Accident	2 (3%)	4 (1%)	0	0	6 (1%)
Total deaths	66 (100%)	272 (100%)	54 (100%)	137 (100%)	547 (100%)

Data are number (% of deaths within age group). NA=not applicable. *Age was reported for 610 of 629 deaths that occurred; sex reporting was complete. †Includes deaths with unknown age. Causes of death were much the same between the sexes both pre-invasion and post-invasion for children (p=0·342 pre-invasion and p=0·189 post-invasion) and elderly individuals (p=0·215 pre-invasion and p=0·483 post-invasion). Causes of death were much the same by sex in adults pre-invasion (p=0·297), but significantly different post-invasion (p<0·0001).

Table 2: Pre-invasion and post-invasion deaths by age and cause (n=629)*

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Mortality Data