



thrive

Statistics with Registry Data

Learning Objectives



The participants will:

- Understand basic statistical methods and principles in order to assess the validity of studies in the literature
- Discuss various statistical techniques as they apply to our population based studies
- Understand the potential limitations and applications of statistical methods when conducting or reviewing clinical studies

A Jumping Off Point



Hazardous journeys

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, Jill P Pell

Abstract

Objectives To determine whether parachutes are effective in preventing major trauma related to gravitational challenge.

Design Systematic review of randomised controlled trials.

Data sources: Medline, Web of Science, Embase, and the Cochrane Library databases; appropriate internet sites and citation lists.

Study selection: Studies showing the effects of using a parachute during free fall.

Main outcome measure Death or major trauma, defined as an injury severity score > 15.

Results We were unable to identify any randomised controlled trial of parachute intervention.

Conclusions As with many interventions intended to prevent ill health, the effectiveness of parachutes has not been subjected to rigorous evaluation by using randomised controlled trials. Advocates of evidence based medicine have criticised the adoption of interventions evaluated by using only observational data. We think that everyone might benefit if the most radical protagonists of evidence based medicine organised and participated in a double blind, randomised, placebo controlled, crossover trial of the parachute.

Introduction

The parachute is used in recreational, voluntary sector, and military settings to reduce the risk of orthopaedic, head, and soft tissue injury after gravitational challenge, typically in the context of jumping from an aircraft. The perception that parachutes are a successful intervention is based largely on anecdotal evidence. Observational data have shown that their use is associated with morbidity and mortality, due to both failure of the intervention^{1,2} and iatrogenic complications.³ In addition, "natural history" studies of free fall indicate that failure to take or deploy a parachute does not inevitably result in an adverse outcome.⁴ We therefore undertook a systematic review of randomised controlled trials of parachutes.

Methods

Literature search

We conducted the review in accordance with the QUOROM (quality of reporting of meta-analyses) guidelines.⁵ We searched for randomised controlled trials of parachute use on Medline, Web of Science, Embase, the Cochrane Library, appropriate internet sites, and citation lists. Search words employed were "parachute" and "trial." We imposed no language restriction and included any studies that entailed jumping from a height greater than 100 metres. The

accepted intervention was a fabric device, secured by strings to a harness worn by the participant and released (either automatically or manually) during free fall with the purpose of limiting the rate of descent. We excluded studies that had no control group.

Definition of outcomes

The major outcomes studied were death or major trauma, defined as an injury severity score greater than 15.⁶

Meta-analysis

Our statistical approach was to assess outcomes in parachute and control groups by odds ratios and quantified the precision of estimates by 95% confidence intervals. We chose the Mantel-Haenszel test to assess heterogeneity, and sensitivity and subgroup analyses and fixed effects weighted regression techniques to explore causes of heterogeneity. We selected a funnel plot to assess publication bias visually and Egger's and Begg's tests to test it quantitatively. Stata software, version 7.0, was the tool for all statistical analyses.

Results

Our search strategy did not find any randomised controlled trials of the parachute.

Discussion

Evidence based pride and observational prejudice. It is a truth universally acknowledged that a medical intervention justified by observational data must be in want of verification through a randomised controlled

Department of
Ophthalmology and
Gynaecology,
Cambridge
University,
Cambridge
CB2 3QQ

Gordon C S Smith
professor

Department of
Public Health,
Greater Glasgow
MHS Board,
Glasgow G5 0YU

Jill P Pell

consultant

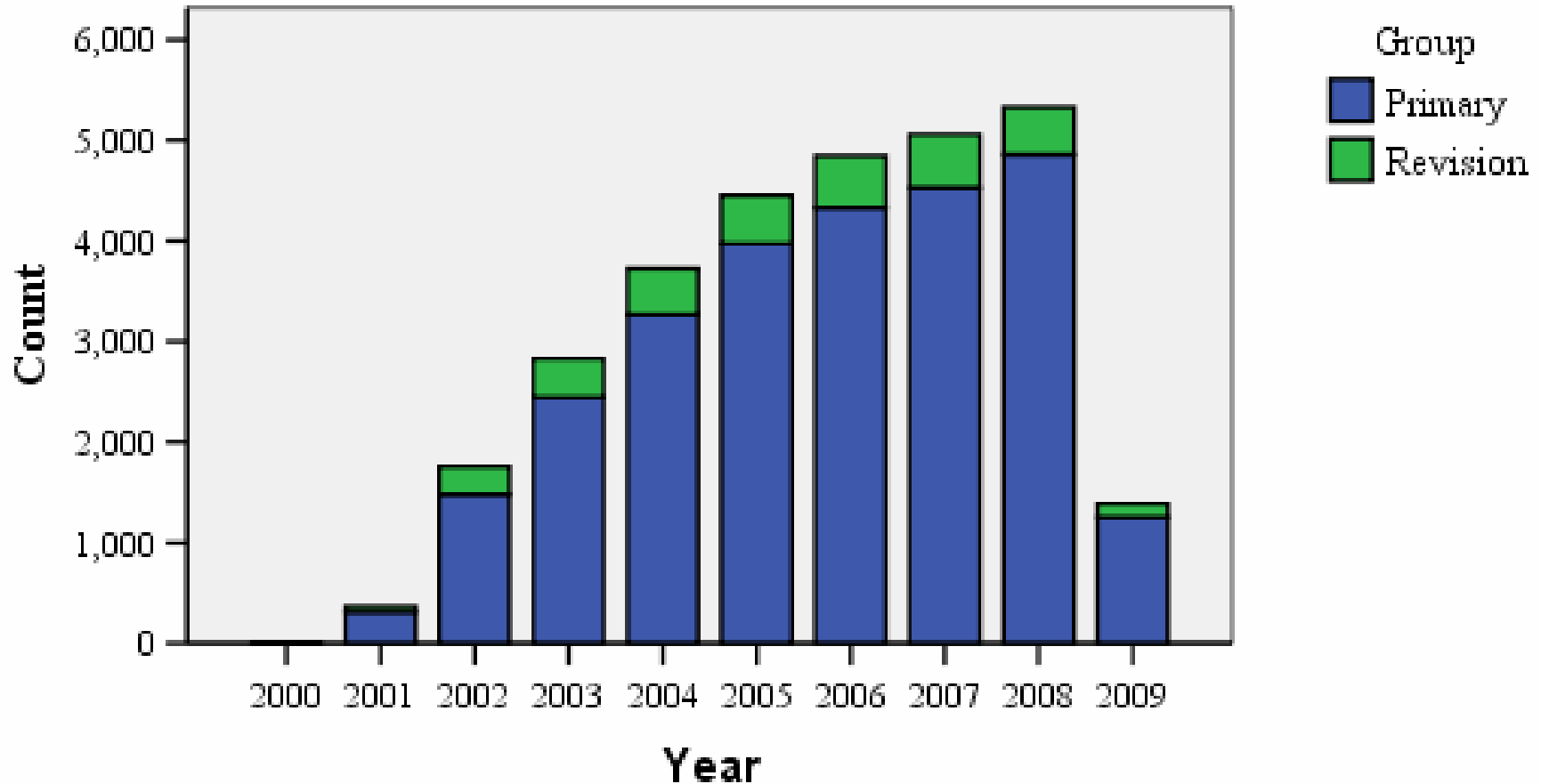
Correspondence to:
G C S Smith
gcs@cam.ac.uk

BMJ 2005;327:1459-61

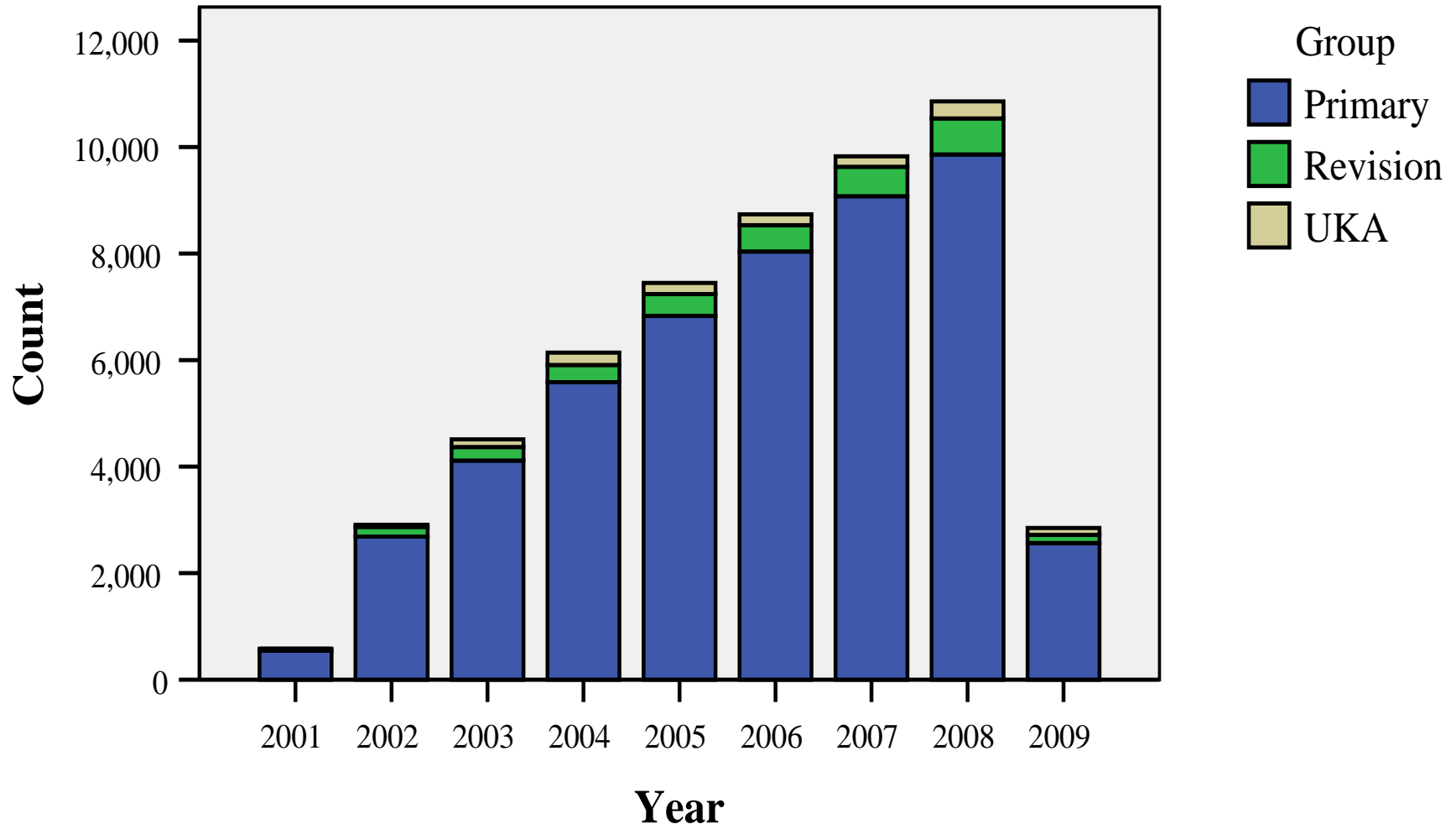


Parachutes reduce the risk of injury after gravitational challenge, but their effectiveness has not been proved with randomised controlled trials

Total Joint Registries: Hips



Total Joint Registries: Knees



Registry Data: Variables



Demographics: *Age, Gender, Race/Ethnicity*

Comorbidities: *Diabetes, types of Arthritis*

Patient Characteristics: *BMI*

Surgeon, Site, Region, Op Date

Follow-up Time

Outcomes: *Revision, Infection, DVT*

Procedure Characteristics: *Prophylaxis, Fixation*

Implant Characteristics: *Cup Category, Bearing Surface, Femoral Component*

Registry goals



- 1) Monitor revision, failure, and rates of key complications (e.g., infection, venous thromboembolic disease such as blood clots and embolism, and mortality)
- 2) Identify patients at risk for poor clinical outcomes following TJA
- 3) Identify the most effective techniques and implant devices (best practices and implant constructs)
- 4) Track implant usage and costs
- 5) Monitor and support implant recalls and advisories in cooperation with FDA

Improving Care and Survival Analysis



For first three goals (monitor revisions, identify patients at risk, identify best practices), analyze :

1.who gets a revision

2.who gets one sooner rather than later

and

3. take account of how long everybody else has gone without a revision

Best method: survival analysis

Two Versions of SA: KM and PH



- Univariate survival analysis
 - relation of a single variable to outcome
 - graphically: Kaplan-Meier curves
- Multivariate survival analysis
 - can look at how any number of risk factors work together
 - most widely used: Proportional Hazards regression (=PH regression, Cox regression)

Kaplan-Meier Curves



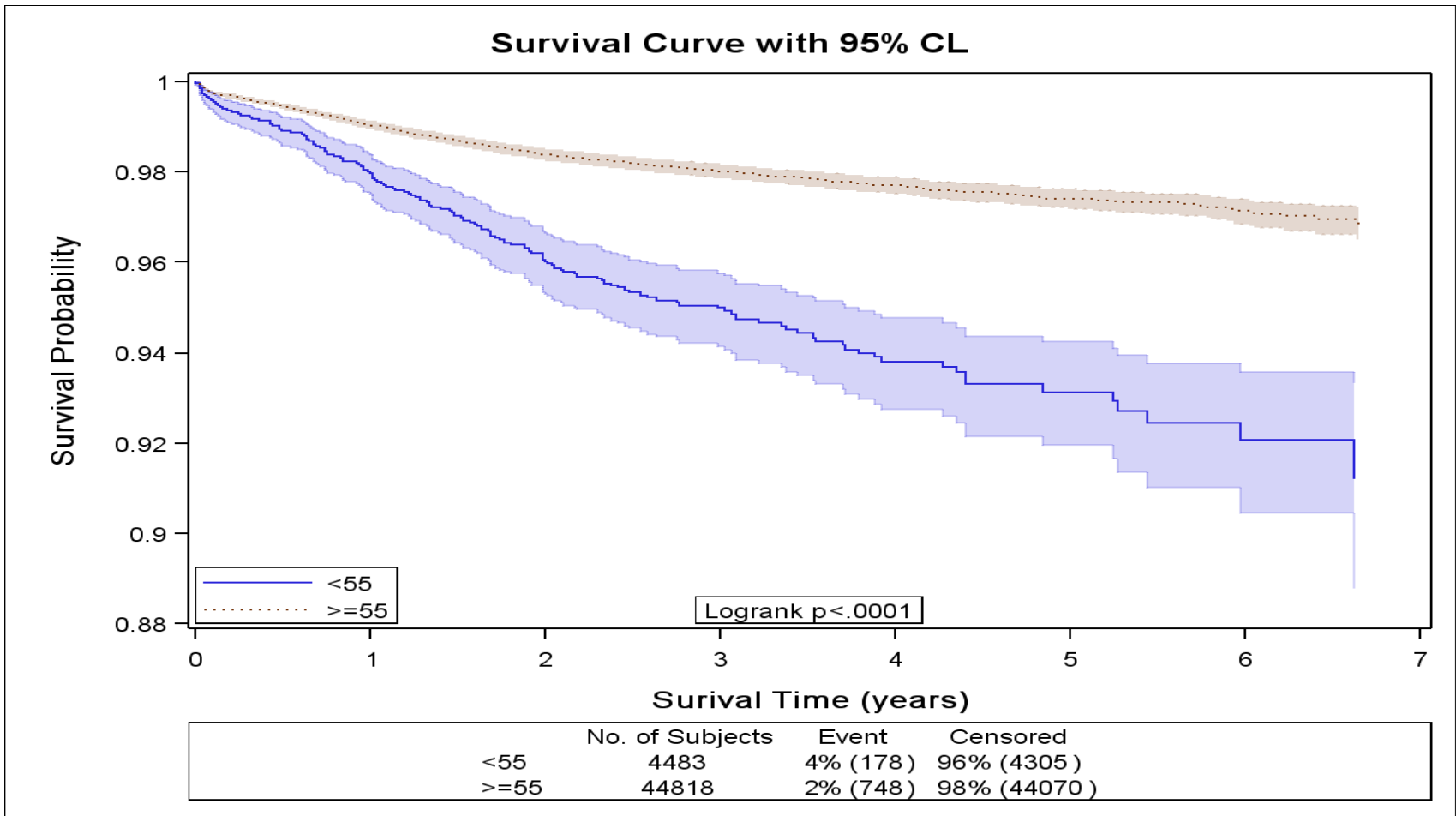
One variable -> subgroups

Survival curve for each subgroup -- each time point shows chance person in the subgroup would go that long without outcome

Statistically test: subgroups have different survival experience?

Non-parametric – no assumptions or models needed

Example: TKA 2009 – Age Group



Terminology

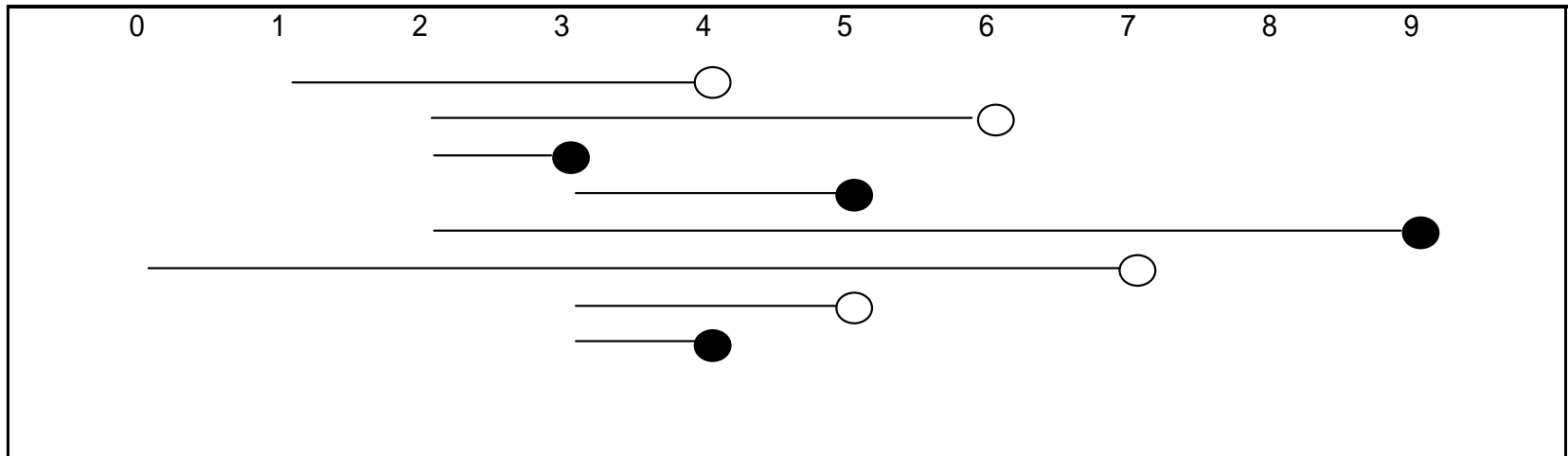


- Event: Occurrence of outcome under study, e.g., a revision.
- Censoring: Observation for that event ending without one having occurred. When revision is the outcome, a case would be censored when the patient dies or ends their KP membership, for example.
- Failure=Having an event
- Survival=Going without failure

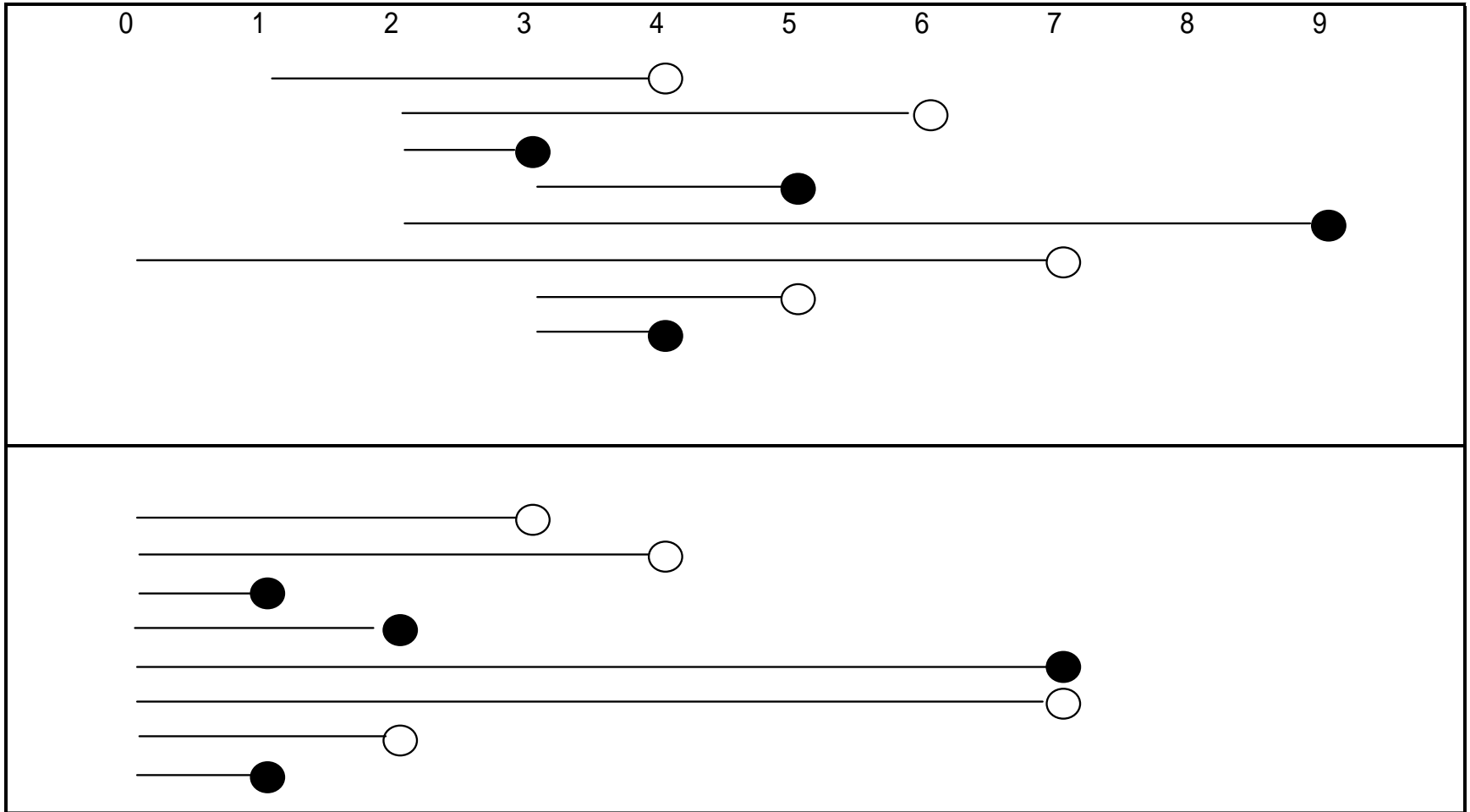
Example Data



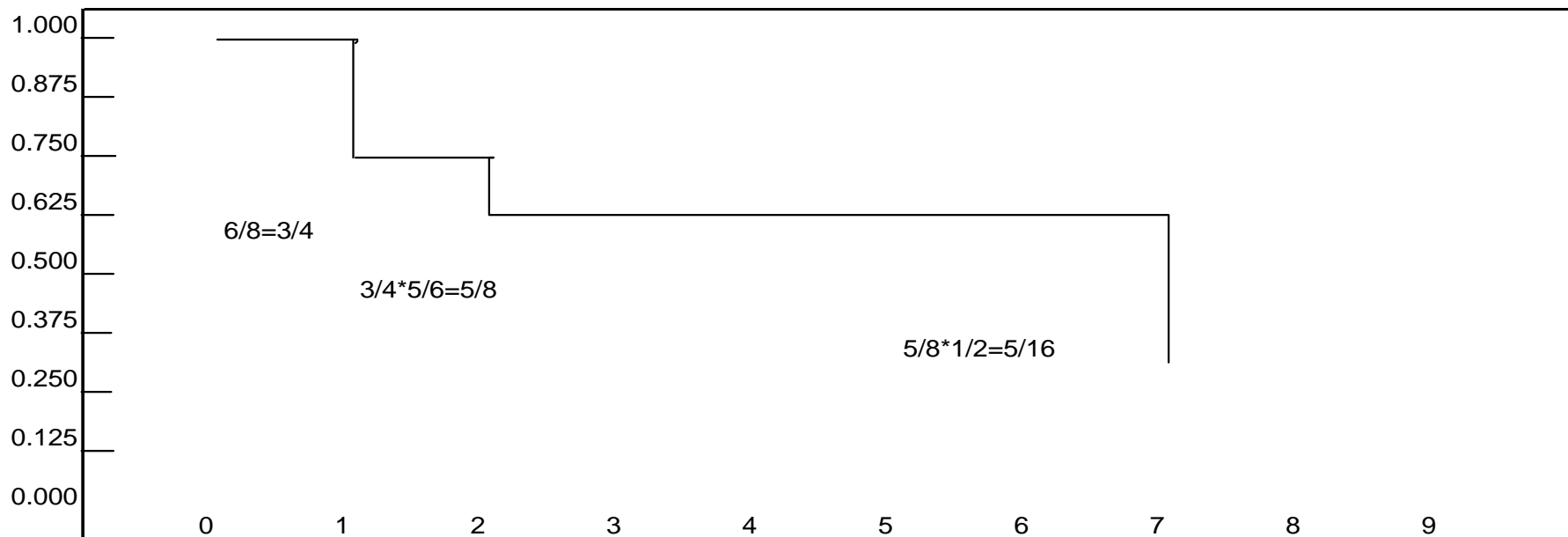
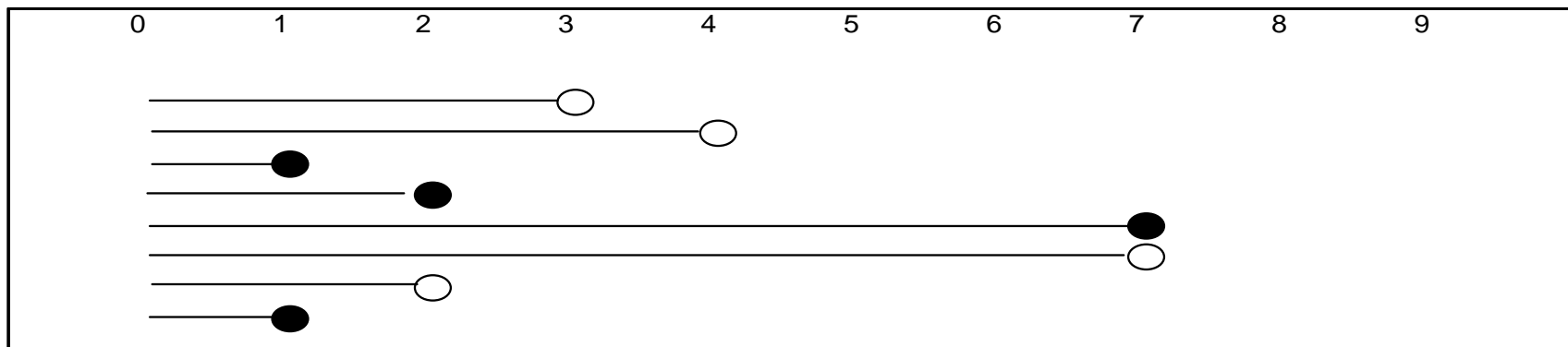
	OpDate	RevDate	LftKP	DthDate
1	1-Jan	.	1-Apr	.
2	1-Feb	.	1-Jun	.
3	1-Feb	1-Mar	.	.
4	1-Mar	1-May	.	.
5	1-Feb	1-Sep	.	.
6	1-Dec	.	.	1-Jul
7	1-Mar	.	1-May	.
8	1-Mar	1-Apr	1-May	.



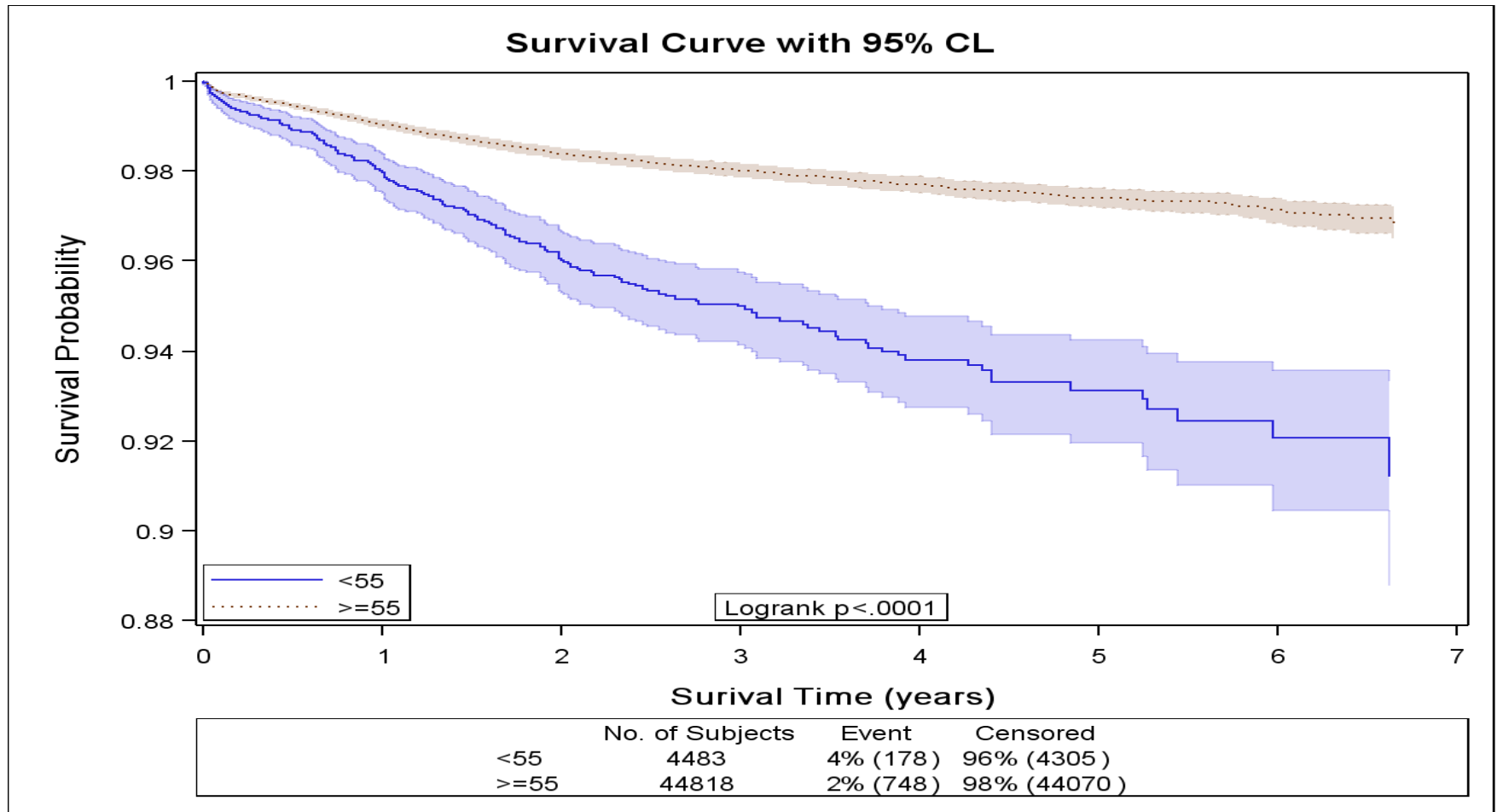
K-M Curves: Numerator and Denominator



Generating the K-M Curve



Example: TKA 2009 – Age Group



Multivariate Survival Analysis



Univariate: only that risk factor

p-value, direction

Multivariate: look at all risk factors together

p-value, direction, magnitude of relative risk (hazard)

No necessary connection:

From univariate result, can't get

- 1) magnitude
- 2) statistical significance
- 3) direction

of multivariate result

Univariate Risk Factors: Knee

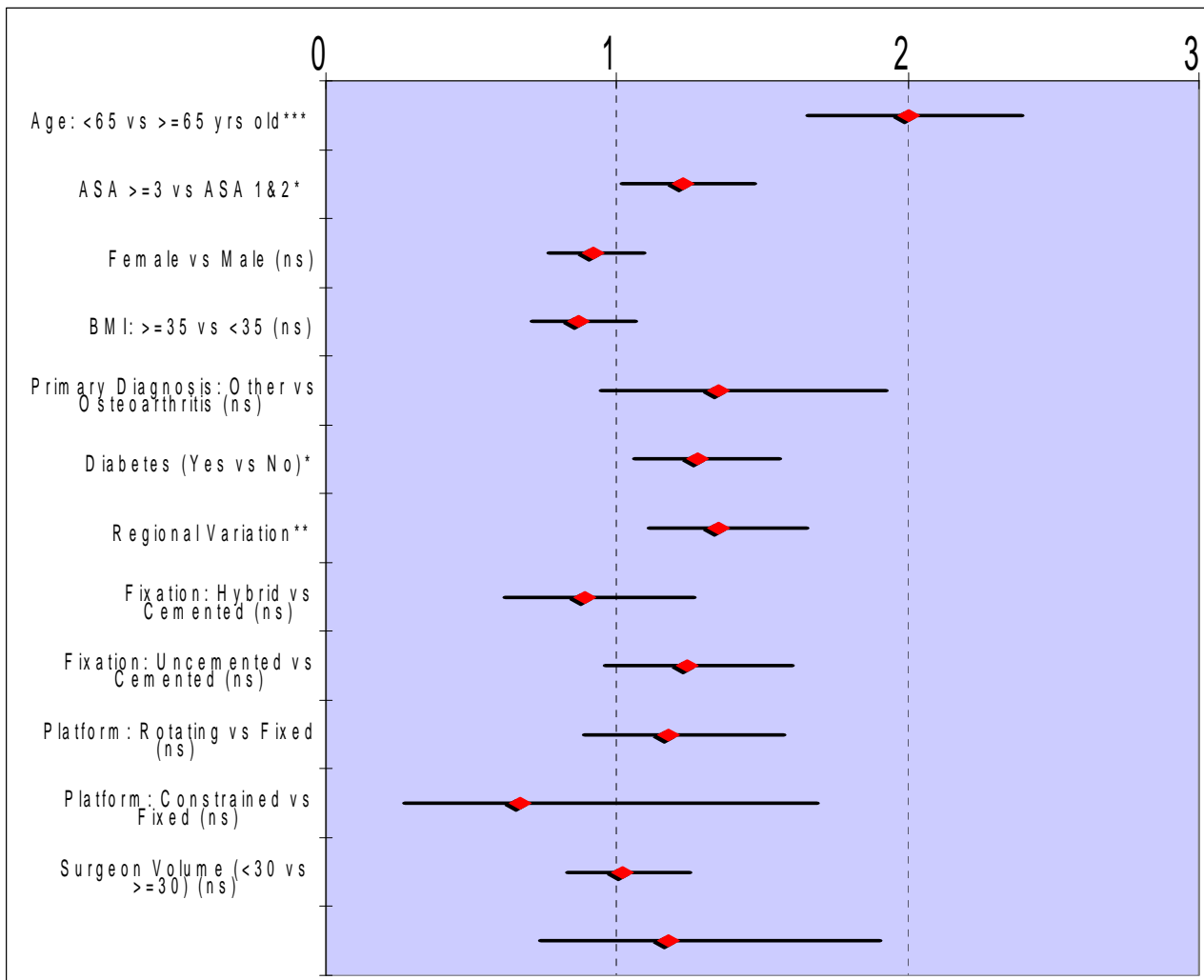


Variable	Comparison Groups	Log-Rank P Value**
<i>Patient</i>		
Age Group	<55/>=55 yrs old	<0.001
ASA Category	1&2/>=3/Unknown	<0.001
BMI Category	< 35/>=35/Unknown	<0.001
Diabetes	Yes/No	<0.001
Primary Diagnosis	Osteoarthritis/Other	<0.001
Gender	Male/Female	<0.001
<i>Hospital</i>		
Region		0.013
Hospital Volume	Small:<50; Medium:50-199; Large:200>	0.606
Surgeon Volume	Small:<10; Medium:9-49; Large:50> annual cases	0.607
<i>Implant</i>		
Fixation (Cement)	Cemented/Cementless/Hybrid	0.013
Platform Type	Rotating/Fixed	<0.001
Bearing Surface*	Cocr on X-link/Cocr on Conventional/ Cocr-Oxi on Constr/Oxi on Conventional	0.570
<i>Total</i>	<i>12</i>	

* Categories with no revisions excluded

**Log rank test compares survival curves between 2 or more groups of the same variable. P Values <0.05 indicate difference in survival between comparison groups

Multivariate Risk factors: Knee



Proportional Hazards regression



Multivariate survival analysis:

other techniques available

Why is PH regression so popular?

No need to assume any particular form of distribution for survival times

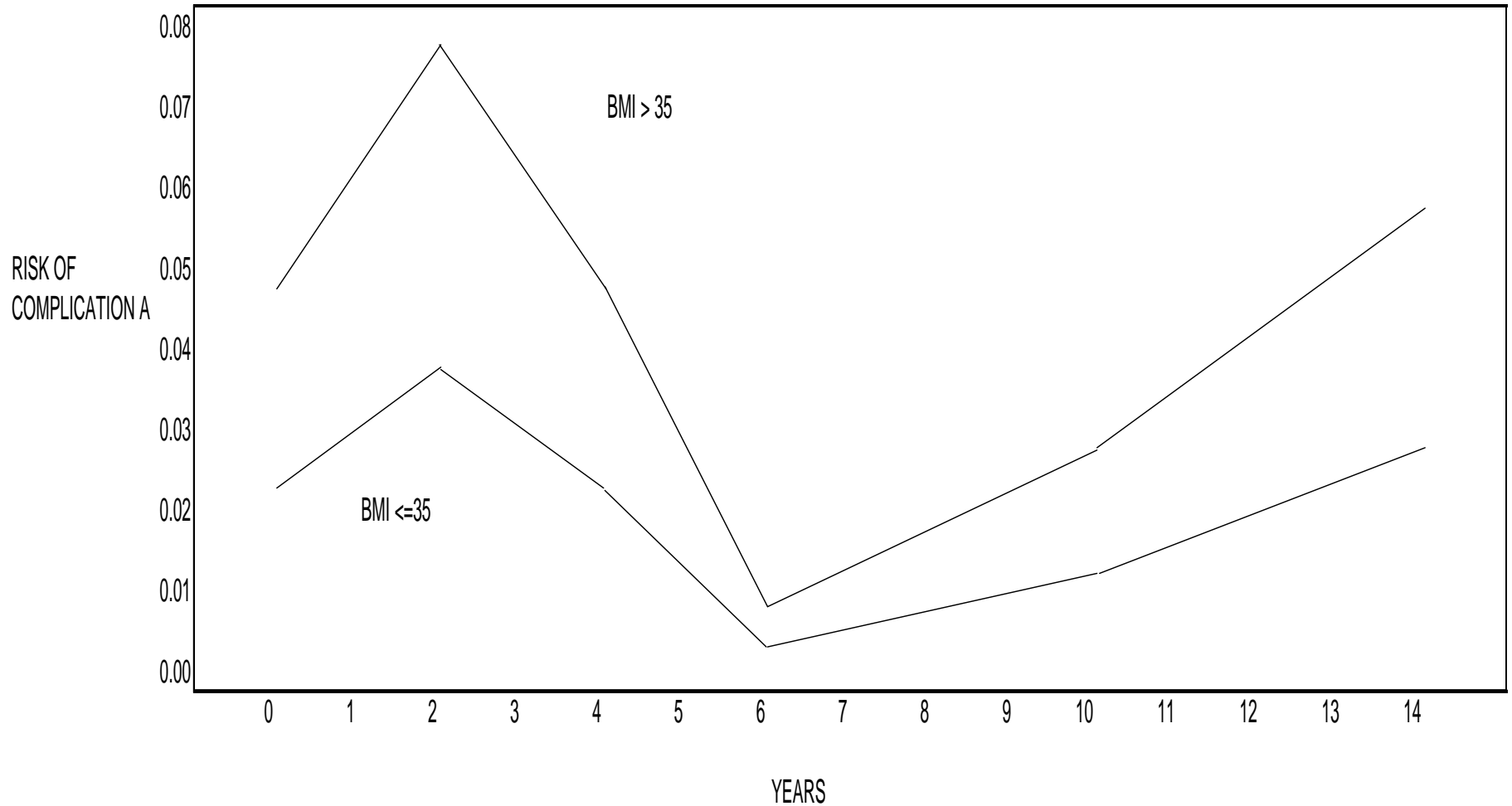
The price you pay:

just get *relative* risks

Actually, *can* get an estimate of absolute risks, but:

extra work, and must specify particular point in time and values for all covariates

Proportional Hazards (Risks)



Missing Data



	KNEES (N=52386)		HIPS (N=29744)	
Gender	2	<0.1%	4	<0.1%
ASA	1263	2.4%	769	2.6%
Age	8	<0.1%	4	<0.1%
BMI	10454	20.0%	6603	22.2%

Missing Data in Registry Studies: Techniques



Bias? Other problems?

Older methods:

Complete case analysis; available case analysis;
last observation carried forward (LOCF)

Better: single imputation

Much better: multiple imputation

Can produce valid results: unbiased and correct
representation of uncertainty

Bottom line: studies must say what they did about missing
data; worst – just ignore

A Hierarchy of Evidence



From Petrie, A. Statistics in orthopaedic papers, J Bone Joint Surgery [Br] 2006, 88-B(9): 1121-1136.

Dimensions of Quality



- Dimensions of quality explored by different scales*

Scale and study	No. of levels	Study design	Quality of conduct
• Canadian Task Force, 1990	4	X	
• US Preventive Services Task Force, 1996	5	X	
• AHCPR, 19921	5	X	
• Guyatt et al., 1995	6	X	
• Eccles et al, 1996	6	X	
• Hadorn et al, 1996	7	X	X
• Ball et al, 1997	10	X	X
• Liddle et al, 1997	5	X	X
• Jovell et al, 1997	9	X	X

• AHCPR = Agency for Health Care Policy and Research.

- *An “X” indicates an area explored; a blank space indicates it was not addressed by the study.
- West J Med. 2001 April; 174(4): 262–265.

JBJS Levels of Evidence



Levels of Evidence for Primary Research Question

	Types of Studies			
	Therapeutic Studies— Investigating the Results of Treatment	Prognostic Studies— Investigating the Outcome of Disease	Diagnostic Studies— Investigating a Diagnostic Test	Economic and Decision Analyses— Developing an Economic or Decision Model
Level I	<ol style="list-style-type: none"> 1. Randomized controlled trial <ol style="list-style-type: none"> a. Significant difference b. No significant difference but narrow confidence intervals 2. Systematic review ² of Level-I randomized controlled trials (studies were homogeneous) 	<ol style="list-style-type: none"> 1. Prospective study ¹ 2. Systematic review ² of Level-I studies 	<ol style="list-style-type: none"> 1. Testing of previously developed diagnostic criteria in series of consecutive patients (with universally applied reference "gold" standard) 2. Systematic review ² of Level-I studies 	<ol style="list-style-type: none"> 1. Clinically sensible costs and alternatives; values obtained from many studies; multiway sensitivity analyses 2. Systematic review ² of Level-I studies
Level II	<ol style="list-style-type: none"> 1. Prospective cohort study ³ 2. Poor-quality randomized controlled trial (e.g., <80% follow-up) 3. Systematic review ² <ol style="list-style-type: none"> a. Level-II studies b. nonhomogeneous Level-I studies 	<ol style="list-style-type: none"> 1. Retrospective study ⁴ 2. Study of untreated controls from a previous randomized controlled trial 3. Systematic review ² of Level-II studies 	<ol style="list-style-type: none"> 1. Development of diagnostic criteria on basis of consecutive patients (with universally applied reference "gold" standard) 2. Systematic review ² of Level-II studies 	<ol style="list-style-type: none"> 1. Clinically sensible costs and alternatives; values obtained from limited studies; multiway sensitivity analyses 2. Systematic review ² of Level-II studies

JBJS Levels of Evidence, cont.



Level III	1. Case-control study ⁵ 2. Retrospective cohort study ⁴ 3. Systematic review ² of Level-III studies		1. Study of nonconsecutive patients (no consistently applied reference "gold" standard) 2. Systematic review ² of Level-III studies	1. Limited alternatives and costs; poor estimates 2. Systematic review ² of Level-III studies
Level IV	Case series (no, or historical, control group)	Case series	1. Case-control study 2. Poor reference standard	No sensitivity analyses
Level V	Expert opinion	Expert opinion	Expert opinion	Expert opinion

1. All patients were enrolled at the same point in their disease course (inception cohort) with ≥80% follow-up of enrolled patients.
2. A study of results from two or more previous studies.
3. Patients were compared with a control group of patients treated at the same time and institution.
4. The study was initiated after treatment was performed.
5. Patients with a particular outcome ("cases" with, for example, a failed total arthroplasty) were compared with those who did not have the outcome ("controls" with, for example, a total hip arthroplasty that did not fail).

Observational Data vs. Experimental



- RCTs as “the gold standard”
- The price of gold:
 - what size needed?
 - External validity
- Causal modeling with observational data:
 - 1: propensity scores
 - 2: instrumental variables
- Size of registries; registries as populations