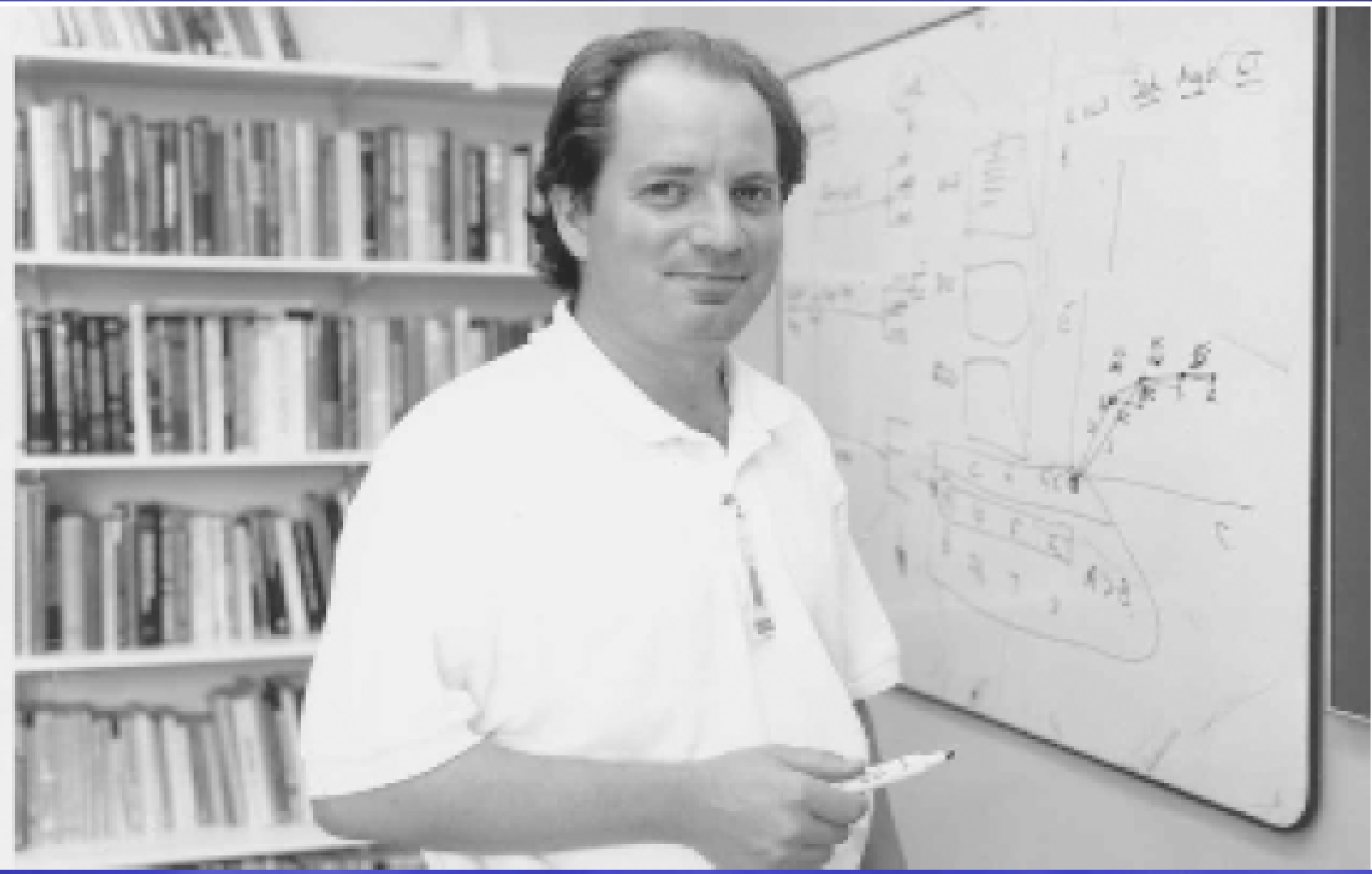


Judging the gift from the Box: Reflections on the power and significance of Bernie O'Brien's “Power and Significance”

Judging the gift from the Box: Reflections on the power and significance of Bernie O'Brien's "Power and Significance"

Jeffrey S. Hoch, PhD

I will be expressing ***my*** thoughts and not the official positions of any people or groups with whom I work.

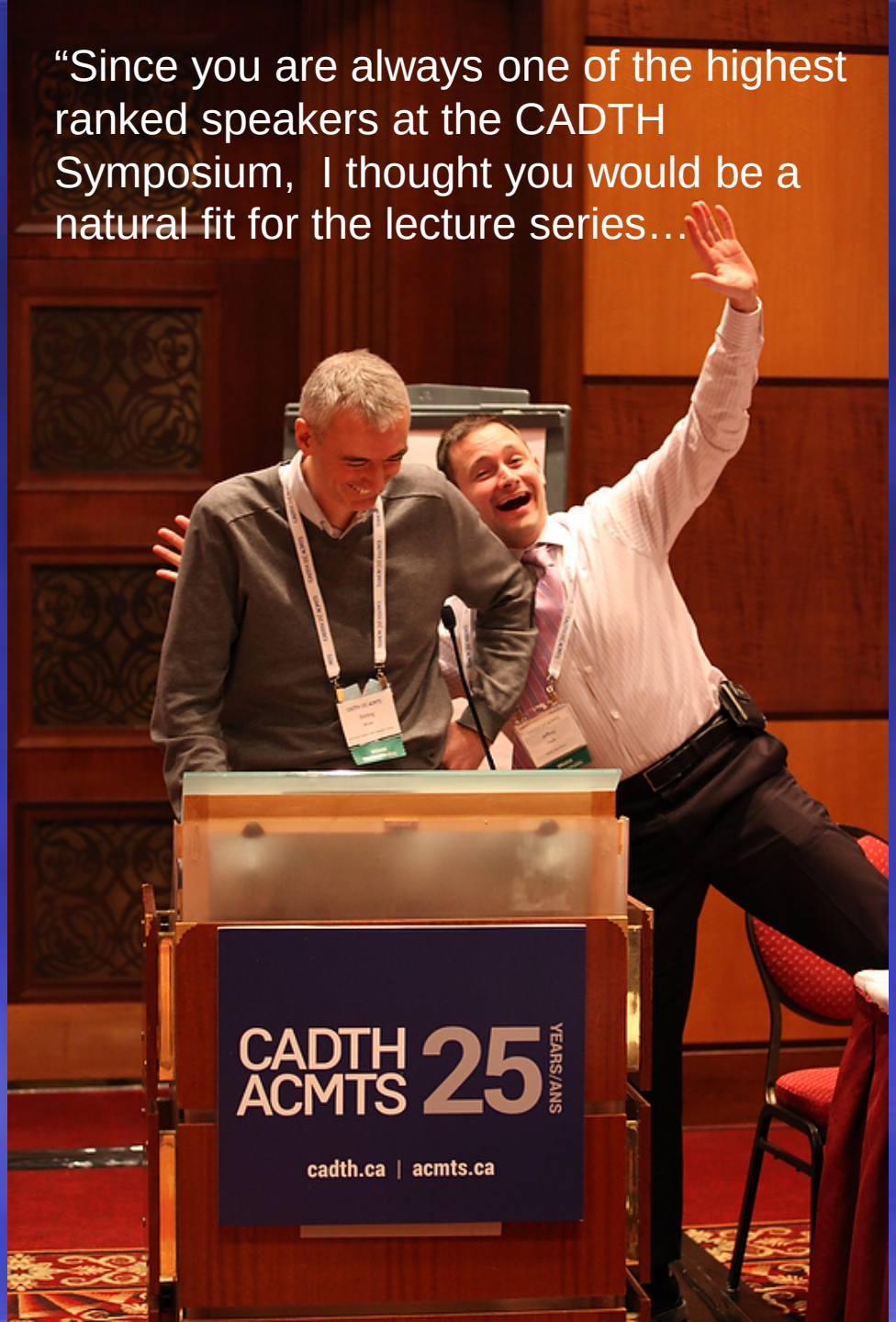
CLEAR

The Centre of Excellence in Economic Analysis Research

St. Michael's

Inspired Care.
Inspiring Science.

“Since you are always one of the highest ranked speakers at the CADTH Symposium, I thought you would be a natural fit for the lecture series…



Tributes to Bernie's contributions…

Unfinished Symphony: A Tribute to the Life and Career of Bernie O'Brien (1959–2004)

Andrew Briggs, DPhil, Martin Buxton, BA, Mike Drummond, DPhil, Ron Goeree, MA, Mark J. Sculpher, PhD, Andrew R. Willan, PhD

The death of Bernie O'Brien in February 2004 brought a premature end to one of the most productive and influential careers in the area of health technology assessment and economic evaluation. A long-term member of the Society for Medical Decision Making, Bernie will be remembered for his research contributions in areas including outcome valuation, decision modeling, statistical methods in economic evaluation, and applied cost-effectiveness studies. He was also an excellent communicator and teacher and, above all, a fun guy to work with. In this article, the authors provide a review of Bernie's academic contributions. **(Med Decis Making 2004;24:538–544)**

Pharmacoeconomics 2004; 22 (6): 343
1170-7690/04/0006-0343/$31.00/0

Bernard J. O'Brien, BA, MSc, PhD

Professor, Department of Clinical Epidemiology and Biostatistics, and Associate, Centre for Health Economics and Policy Analysis, McMaster University, Ontario, Canada, and Co-director, Centre for Evaluation of Medicines, St Joseph's Healthcare, Hamilton, Ontario, Canada

vincial health system. His most recent projects included work on health technology assessment for Canada's Ministry of Health and Long Term Care.

Bernie O'Brien received his bachelors and masters degrees in economics from the University of York, England and his PhD in economics from Brunel University, England before moving to Canada in 1990. In addition to his professorship at McMaster University, he was co-director of the Centre for Evaluation of Medicines at St Joseph's Hospital and an Associate of the Centre for Health Economics and Policy Analysis at McMaster University.

While at McMaster University, Bernie established and directed a world-class research team to study the cost effectiveness and cost utility of health care interventions. A pioneer in the emerging field of medical decision making, he will be remembered for his ground-breaking work in assessing the benefits and costs of health technology. His work in this area brought him much acclaim, including the Senior Investigator Award from the Canadian Institutes of Health Research.

Bernie published more than 100 peer-reviewed journal papers and co-authored a widely cited text-

Appl Health Econ Health Policy 2004; 3 (1): 57-60
1175-5652/04/0001-0057/$31.00/0

A Tribute to the Life and Work of Bernie O'Brien

1959–2004

John F.P. Bridges

The Junior Group, International Health Economics and Outcome Research, Department of Tropical Hygiene and Public Health, University of Heidelberg Medical School, Heidelberg, Germany

The discipline of health economics recently lost one of its most productive and well liked members, Bernie O'Brien. Dr O'Brien has left a lasting impression on many health economists around the globe. He worked with many of the established names, and he inspired and trained a new generation of health economists. It is into this latter category that I fall. Unfortunately, I did not have an opportunity to work closely with Dr O'Brien, but his work has had a profound impact on me. During my career, one or more of Dr O'Brien's papers has always been either on my desk or in close proximity for quick reference. Like many, I corresponded with him on a number of topics, including the area of portfolio theory in health evaluation. Those who knew Dr O'Brien received, with

reports, mainly through the Office of Health Economics in London (see O'Brien[1,2]), as well as articles in journals such as *Social Science and Medicine*,[3] *Journal of Health Economics*[4] and the *BMJ*.[5]

Rise to Full Professor

In 1990, Dr O'Brien immigrated to Canada to serve as an Assistant Professor in the Department of Clinical Epidemiology and Biostatistics in the Faculty of Health Sciences at McMaster University in Hamilton, Ontario. During his first decade at McMaster, he quietly rose through the academic ranks to Full Profes-

Volume 7 • Number 4 • 2004
VALUE IN HEALTH

In Memoriam: Bernie O'Brien (1959–2004)

Martin J. Buxton, PhD

Brunel University, Uxbridge, Middlesex, UK

Bernie O'Brien died tragically on the morning of February 13, while out jogging. He was 44 years old.

turer's Association of Canada, a Career Award in Health Sciences (1995–2000), and from the Canadian Institutes of Health Research, a Senior Investigator Award (2002–2007).

This brief summary clearly shows that with Bernie's death the world lost a first-rate researcher, and an internationally respected academic and teacher. When one recalls the details of his research, his contribution becomes all the more impressive, not least in the range of topics on which he worked. He was not an academic who had discovered a small area of comparative advantage and who kept mining that narrow seam of research. Rather, his research covered a remarkably broad range of applied topics and methodological issues. He undertook trial-based and modeling studies in fields as diverse as deep-vein thrombosis, helicobacter pylori, implantable defibrillators, atrial fibrillation,

Bernie O'Brien is recognized posthumously with The CADTH Anniversary Medal

Awards to honour Bernie…

ISPOR Bernie O'Brien New Investigator Award

ISPOR Bernie J. O'Brien New Investigator Award Chair

Description: The ISPOR Bernie O'Brien New Investigator Award was established in 2004 to honor the long-standing commitment of Bernie J. O'Brien, PhD to training and mentoring new scientists in the fields of outcomes research and pharmacoeconomics.

Criteria: The recipient of the ISPOR Bernie O'Brien New Investigator Award is selected by the O'Brien New Investigator Award Committee. The recipient shall be a member of ISPOR on the date of nomination and be nominated by an individual who has been an ISPOR member in good standing for at least two consecutive years prior to the date of nomination. Evidence of exceptional promise shall be assessed by evaluating the nominee's emerging body of technical and scholarly work in the fields of pharmacoeconomics and outcomes research. The emerging body of work may include research publications, technical reports and papers, books and book chapters, and other scholarly activities that establish the importance of the nominee's early contributions. The nominees shall be no more than 7 years from the receipt of their terminal degree (i.e. doctoral or master's degree) and no more than 10 years from their first full-time position in outcomes research or related field.

Selection Process: A call for nominations from the membership and the award selection criteria will be are published in November-December ISPOR CONNECTIONS. The New Investigator Committee Core Group meets via teleconference in March to discuss each of the nominees and

The Bernie O'Brien Post-Doctoral Fellowship

Department of Clinical Epidemiology and Biostatistics

Faculty of Health Sciences

McMaster University

To honour Bernie O'Brien and his enthusiasm for mentoring young researchers, the *Bernie O'Brien Fellowship* will be awarded annually to exceptional post-doctoral fellows in health economics, health technology assessment, health policy analysis or related fields of research at McMaster University.

Conferences in honour of Bernie

June 16, 2006

Better analysis for better decisions

By Sue Johnston, Faculty of Health Sciences

Some of the world's leading researchers who specialize in assessing the costs and benefits of health interventions ranging from pacemakers to diagnostic imaging to new drug therapies will gather at McMaster University next week for a two-day conference.

Founder and director of PATH - Bernard J. O'Brien, BA, MSc, PhD (1959 - 2004).

"It would be difficult to find this collection of speakers anywhere else," said Greg Stoddart, a McMaster professor and co-chair of the conference. "These are the best people in their fields in the world."

Judging the gift from the Box: Reflections on the power and significance of Bernie O'Brien's "Power and Significance"

In Search of Power and Significance: Issues in the Design and Analysis of Stochastic Cost-Effectiveness Studies in Health Care

BERNIE J. O'BRIEN, PHD,* MICHAEL F. DRUMMOND, PHD,†
ROBERTA J. LABELLE, PHD,‡ AND ANDREW WILLAN, PHD*

Application of techniques such as cost-effectiveness analysis (CEA) is growing rapidly in health care. There are two general approaches to analysis: deterministic models based upon assumptions and secondary analysis of retrospective data, and prospective stochastic analyses in which the design of a clinical experiment such as randomised controlled trial is adapted to collect patient-specific data on costs and effects. An important methodological difference between these two approaches is in the quantification and analysis of uncertainty. Whereas the traditional CEA model utilizes sensitivity analysis, the mean-variance data on costs and effects from a prospective trial presents the opportunity to analyze cost-effectiveness using conventional inferential statistical methods. In this study we explored some of the implications of moving economic appraisal away from deterministic models and toward the experimental paradigm. Our specific focus was on the feasibility and desirability of constructing statistical tests of economic hypotheses and estimation of cost-effectiveness ratios with associated 95% confidence intervals. We show how relevant variances can be estimated for this task and discuss the implications for the design and analysis of prospective economic studies. Key words: cost-effectiveness; statistics; confidence intervals; clinical trials. (Med Care 1994; 32:150–163)

O'Brien et al., 1994

Outline

- Review the paper
  - Main points
- Give examples of the main points
  - Empirical situations where this matters
- Bernie's impact on me
  - Take home messages

Outline

- Review the paper
- Give examples of the main points
- Bernie's impact on me

Best paper…

SOCIETY FOR MEDICAL DECISION MAKING

Winner of the Fifth Annual Award
for Outstanding Paper by a
Young Investigator

The winner of this award is BERNIE O'BRIEN, PHD, Department of Epidemiology and Biostatistics, McMaster University, and Centre for Evaluation of Medicines, St. Joseph's Hospital, for the paper:

O'Brien BJ, Drummond MF, Labelle RJ, Willan A. In search of power and significance: issues in the design and analysis of stochastic cost-effectiveness studies in health care. Med Care. 1994;32:150-163.

Main points, part I

- "there is obvious appeal in measuring cost and effect data on the same patients"
  - ! Analyze cost in studies of effectiveness !

- "the use of statistical inference and hypothesis testing in the analysis of costs, effects and cost-effectiveness when variables are sampled rather than approximated or assumed."
  - ! Analysis of cost-effectiveness data !
    - Estimation and uncertainty

> $200 million over the last decade

Canadian Research Information System

Search Criteria

Agency: Canadian Institutes of Health Research

Program: Randomized Controlled Trials

Funding Year: 2005-06 to2013-14

Search Results

Principal Investigator	Institution	Agency	Program	Project Title	Amount/ Year(s)
DOSCH, Hans-Michael ; DUPRE, John ; FRASER, William Donald; LAWSON, Margaret Lloyd; MAHON, Jeffrey Lewis; SERMER, Mathew ; TABACK, Shayne Philip	University of Western Ontario	Canadian Institutes of Health Research	Randomized Controlled Trials	Trial to Reduce IDDM in the Genetically at Risk (TRIGR) Details...	$7,080,466 2005-06 to 2013-14
				Page total:	$7,080,466

The total dollar amount for the specified search criteria is $202,974,274.

Your search returned 161 matches.

|< <<< Previous Page 17 of

$203 million / 161 trials ≈ 1.3 MILLION per Study!

More opportunities for person-level CEA

- Drug Safety and Effectiveness Network (DSEN)
- Mental Health Commission of Canada
  - Will they budget for CEA?
  - Will the CEA budget be used for CEA?

Idea in the background

- Clinical studies with results that researchers hope to use to influence clinical practice should be accompanied by economic evidence.

- If the clinical outcome from a trial is sufficient, so might the economic evidence from a trial, *and vice versa*.

Main points, part I cont.

- "there is obvious appeal in measuring cost and effect data on the same patients"
  - ! Analyze cost in studies of effectiveness !

- "the use of statistical inference and hypothesis testing in the analysis of costs, effects and cost-effectiveness when variables are sampled rather than approximated or assumed."
  - ! Analysis of cost-effectiveness data !
    - Estimation and uncertainty

Analysis, circa 1990

- CEA methods when
  - 1) cost and effect data reported for each person
    - Analyze data from one source
  - 2) person-level data are not available
    - Analyze data from many sources
      - Markov model / Decision tree
  - In both cases, mainly
    - Estimate = Incremental Cost-Effectiveness Ratio (ICER)
    - Uncertainty = Sensitivity Analysis

3 Problems with Sensitivity Analysis

- 1) The analyst has discretion as to which variables and what alternative values are included in the sensitivity analysis.
- 2) Interpretation is arbitrary as there are no standards for what degree of variation in results is acceptable proof that the analysis is 'robust'.
- 3) Variation of uncertain parameters one at a time carries a risk that interactions between parameters may not be captured.

Sampling variability in effect data

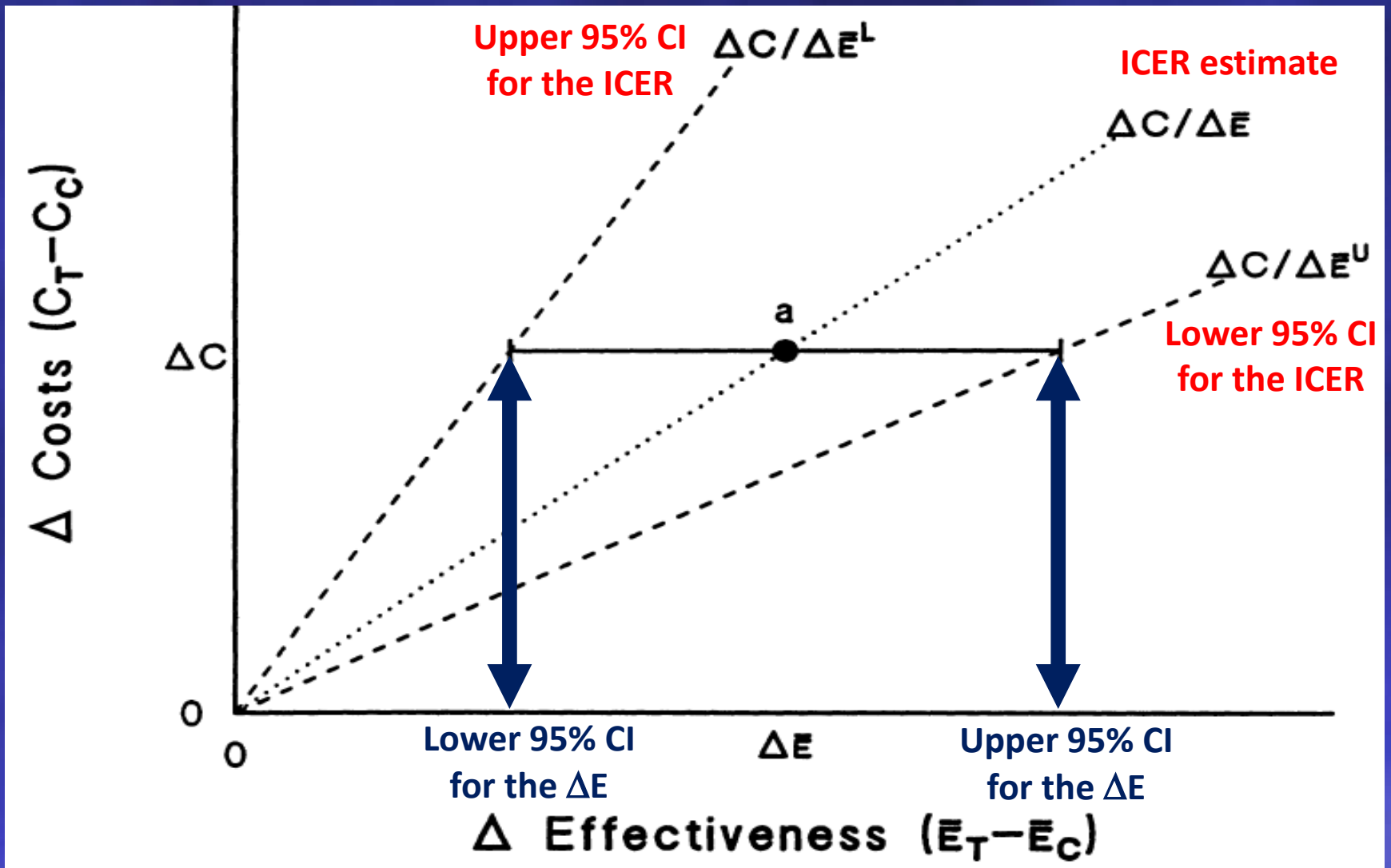


FIG. 1. Cost-effectiveness quasi-confidence interval I: deterministic analysis of cost differences and stochastic analysis of effectiveness differences.

Sampling variability in C and E

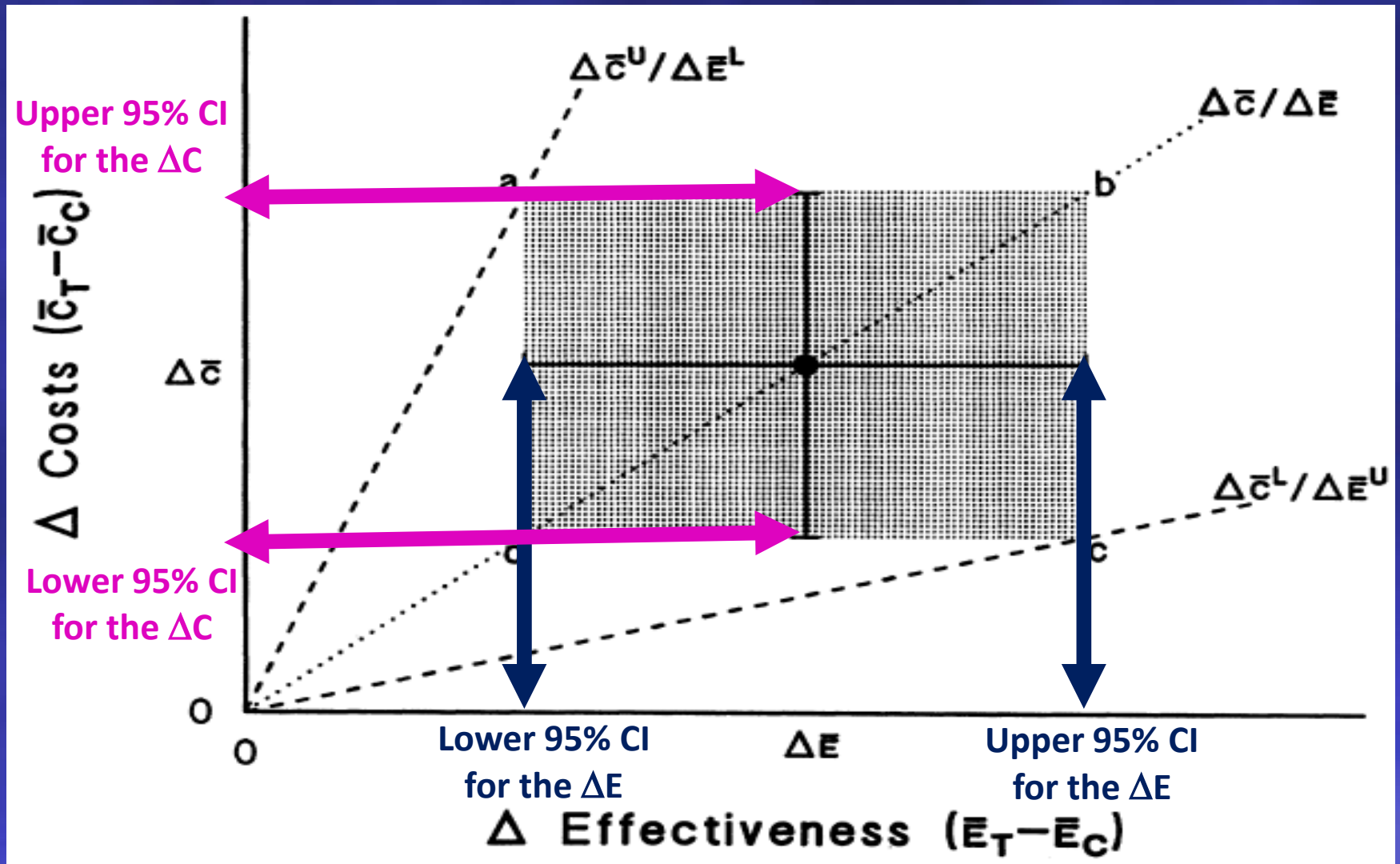


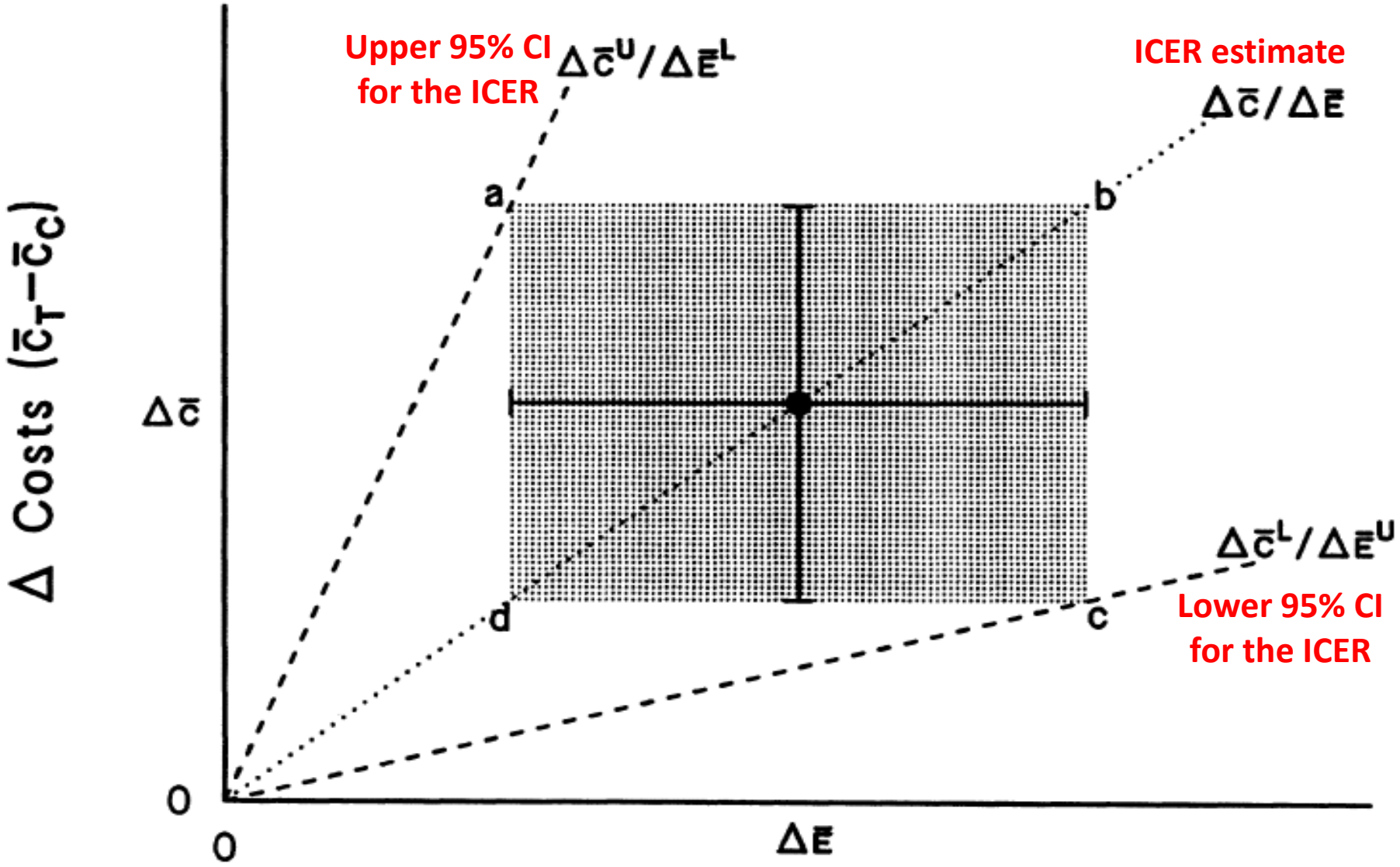
FIG. 2. Cost-effectiveness quasi-confidence interval II: stochastic analysis of both cost and effectiveness differences but assumption of zero covariance.

this region.

There are two problems with this line of reasoning. The first is that the depiction of

The second problem is the implicit assumption that costs and effects vary independently (i.e., have zero covariance). In

Estimates of ΔC and ΔE are made from Cost and Effect data that are likely correlated



Eggs are more likely than boxes

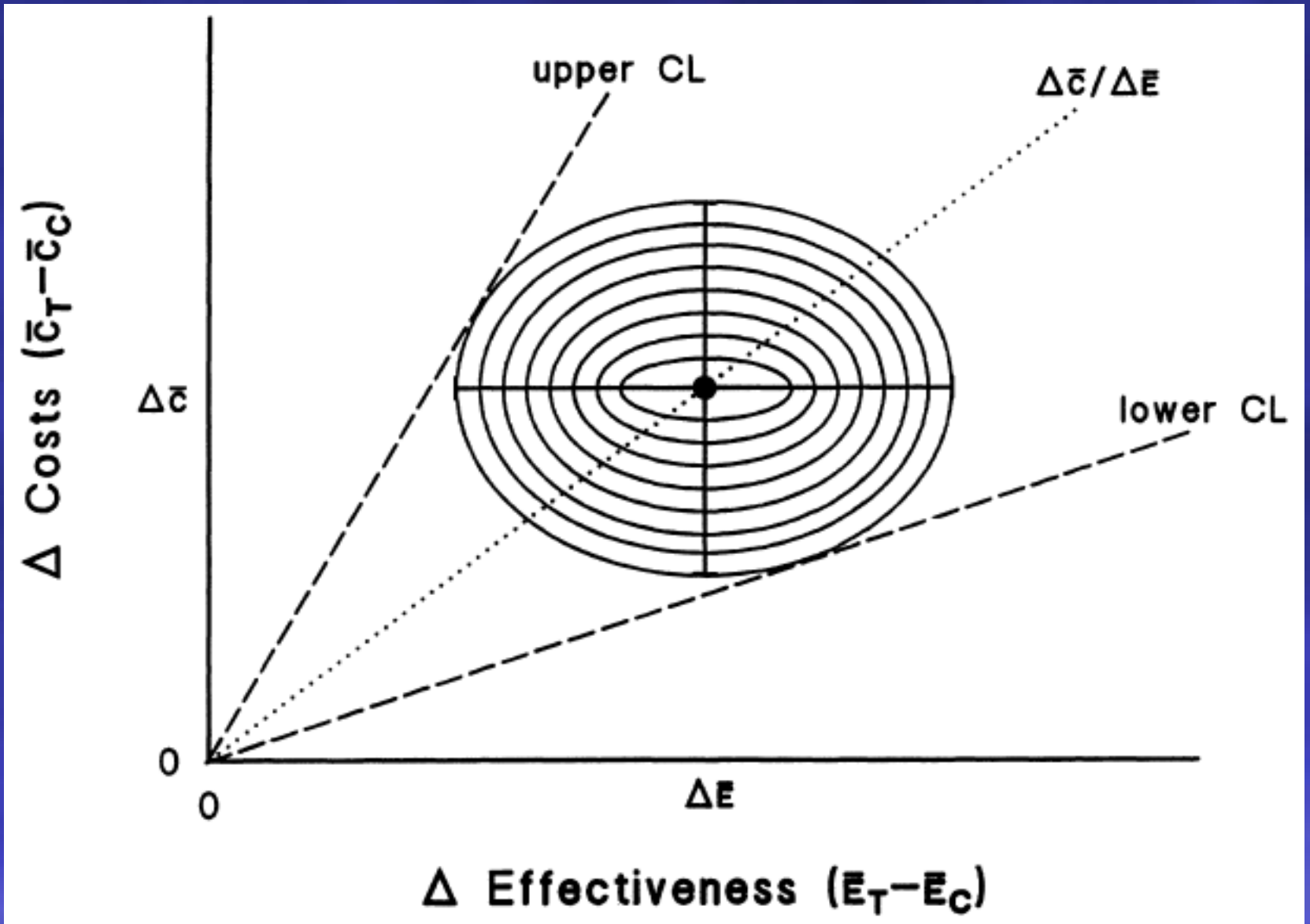


FIG. 3. Hypothetical probability density function around maximum likelihood point-estimate for cost-effectiveness.

The birth of "statistical CEA"…

- GOAL: Create a 95% CI for the ICER ($\Delta C/\Delta E$),
  - not the parts (ΔC and ΔE)
- 2 options:
  - Taylor's Approximation
  - Bootstrapping

pling variation. The challenge is whether a method exists for estimating the sampling distribution for the ratio of two random variables which may have non-zero covariance.

Two Ways Forward: Taylor Series Versus Bootstrapping

Taylor Series Method

Although no exact method exists for determining the variance of the ratio of two random variables it is possible to derive a

y in terms of the sum of partial derivatives of y with respect to x_1 and x_2, weighted by the variances of x_1 and x_2 and the covariance between x_1 and x_2:

$$var(y) \approx \left(\frac{\delta y}{\delta x_1}\right)^2 var(x_1) + \left(\frac{\delta y}{\delta x_2}\right)^2 var(x_2)$$

$$+ 2\left(\frac{\delta y}{\delta x_1}\right)\left(\frac{\delta y}{\delta x_2}\right) cov(x_1, x_2)$$

Taylor series method

- Calculate the variance of the ICER and then…

Knowing the variance around the estimated cost-effectiveness ratio (R) we could construct a 95% confidence using the general form:

$$\hat{R} \pm ? \sqrt{var(\hat{R})}$$

such that in 95% of repeated samples this range would contain the true value of R.

Bootstrapping

My sample:

Bootstrap sample #1

Bootstrap sample #2

Bootstrap sample #3

Bootstrap sample #4

Bootstrap sample #5

Bootstrap sample #B

(c) Jeffrey Hoch, PhD

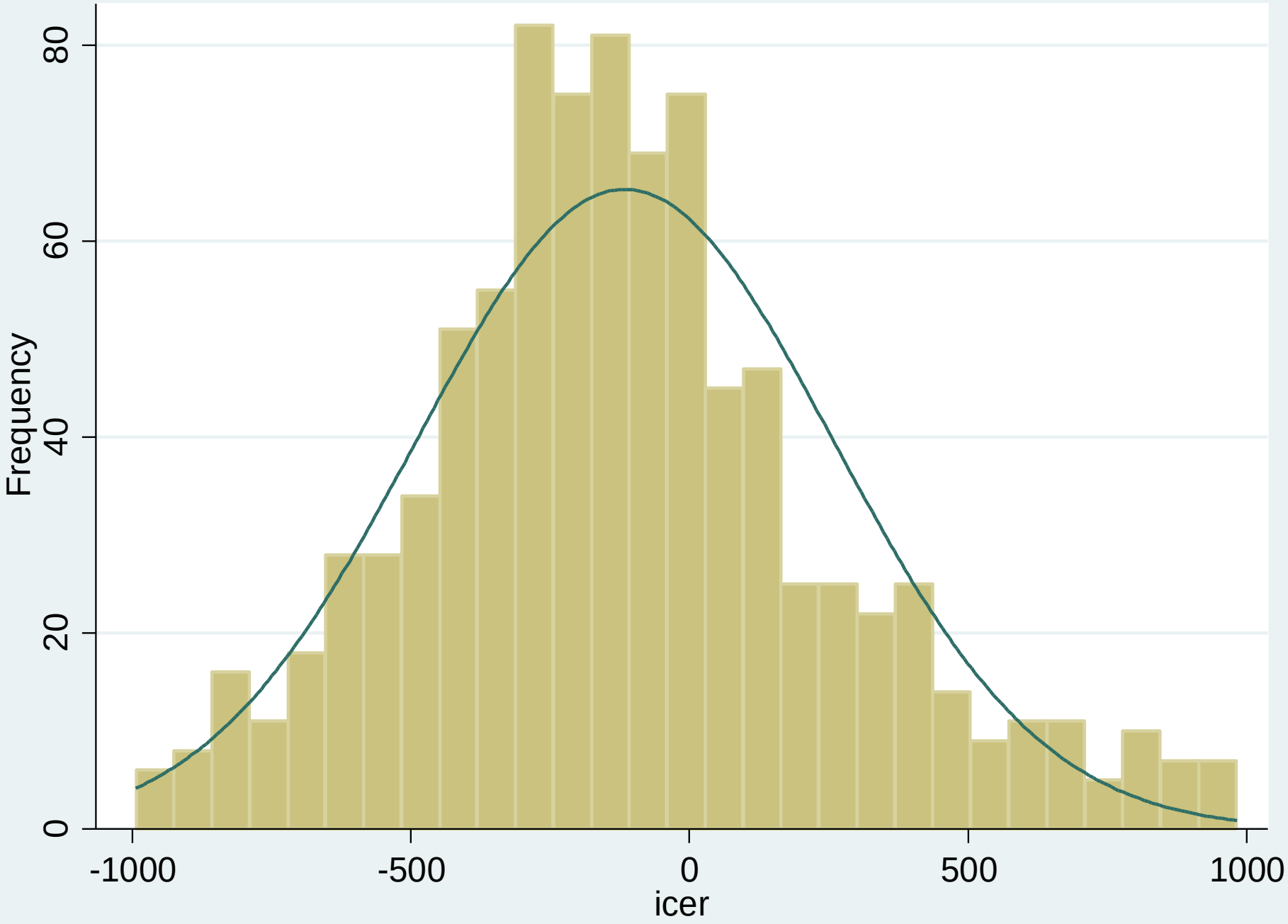
Non-Parametric Bootstrapping

Confidence intervals and tests of hypotheses for R can be derived using non-parametric bootstrapping methods.[18,19] The observed data for costs and effects are treated as an empirical probability distribution that is resampled with replacement many times. Each resampling is used to provide an estimate of R. The many estimates of R are used to establish an empirical distribution of R from which confidence intervals and tests of hypotheses are constructed.

An important advantage of the bootstrap approach is that, unlike the Taylor series method, it is of no consequence whether R is a well-behaved distribution because it forms its own probability density distribution. The historical limitation on this method has been computing power for resampli rithms; but given the capacity and modern computers this is no longe

Main idea

- Sample from your sample (bootstrap)
- Look at the resulting distribution of ICERs
- “trap” the middle 95%

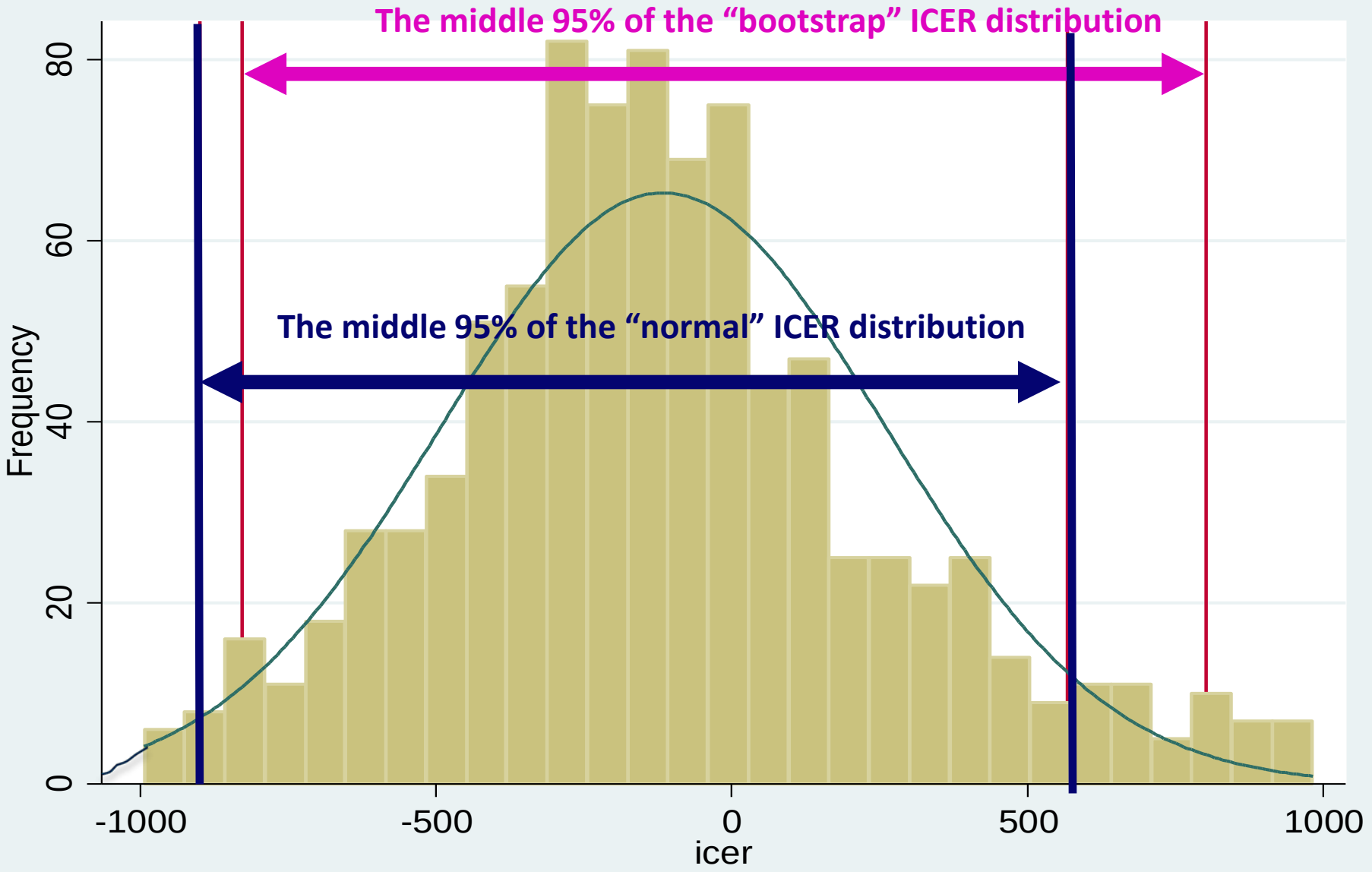

Frequency
0
20
40
60
80
-1000
-500
0
500
1000
icer

Between the 2.5% and the 97.5% lies 95%

icer	Freq.	Percent	Cum.
-993.8018	1	0.11	0.1
-979.9256	1	0.11	0.2
-966.0487	1	0.11	0.3
-959.8277	1	0.11	0.4
-958.7526	1	0.11	0.5
-939.3558	1	0.11	0.6
-897.7859	1	0.11	0.7
-895.5593	1	0.11	0.8
-887.9271	1	0.11	1.0
-886.0725	1	0.11	1.1
-880.817	1	0.11	1.2
-876.7219	1	0.11	1.3
-865.6255	1	0.11	1.4
-863.2797	1	0.11	1.5
-854.0043	1	0.11	1.6
-853.9956	1	0.11	1.7
-847.7708	1	0.11	1.8
-846.5762	1	0.11	2.0
-843.2885	1	0.11	2.1
-838.2949	1	0.11	2.2
-830.6065	1	0.11	2.3
-829.2341	1	0.11	2.4
-828.7919	1	0.11	2.5
-828.7231	1	0.11	2.6
-817.7943	1	0.11	2.7
-810.8395	1	0.11	2.8

725.0397	1	0.11	97.0
726.016	1	0.11	97.1
759.5393	1	0.11	97.2
766.4498	1	0.11	97.3
781.3801	1	0.11	97.4
803.7295	1	0.11	97.5
810.1152	1	0.11	97.6
810.6283	1	0.11	97.7
814.0504	1	0.11	97.8
814.9971	1	0.11	98.0
815.6007	1	0.11	98.1
827.8044	1	0.11	98.2
833.5886	1	0.11	98.3
843.6336	1	0.11	98.4
847.8884	1	0.11	98.5
858.65	1	0.11	98.6
870.8182	1	0.11	98.7
874.6653	1	0.11	98.8
878.6324	1	0.11	99.0
892.4974	1	0.11	99.1
900.1661	1	0.11	99.2
932.6655	1	0.11	99.3
945.9769	1	0.11	99.4
962.5139	1	0.11	99.5
962.9263	1	0.11	99.6
964.3281	1	0.11	99.7
980.2561	1	0.11	99.8
982.4378	1	0.11	100.0

95% CIs for the ICER



Invitation to inquiry…

mate. We conclude that more empirical work on these issues is urgently needed: 1) to explore the feasibility of the Taylor series method versus non-parametric bootstrapping; and 2) to assess the appropriate mix of inferential statistics and sensitivity analysis when reporting data.

1	In search of power and significance: issues in the design and analysis of stochastic cost-effectiveness studies in health care.	O'Brien, B.J., Drummond, M.F., Labelle, R.J., Willan, A.	1994 Medical Care 32 (2), pp. 150-163	287 Cited by

Full Text | Show abstract

In search of power and significance: issues in the design and analysis of stochastic cost-effectiveness studies in health care

BJ O'Brien, MF Drummond, RJ Labelle, A Willan - Medical care, 1994 - JSTOR

Application of techniques such as **cost-effectiveness analysis** (CEA) is growing rapidly in **health care**. There are two general approaches to **analysis**: deterministic models based upon assumptions and secondary **analysis** of retrospective data, and prospective **...**

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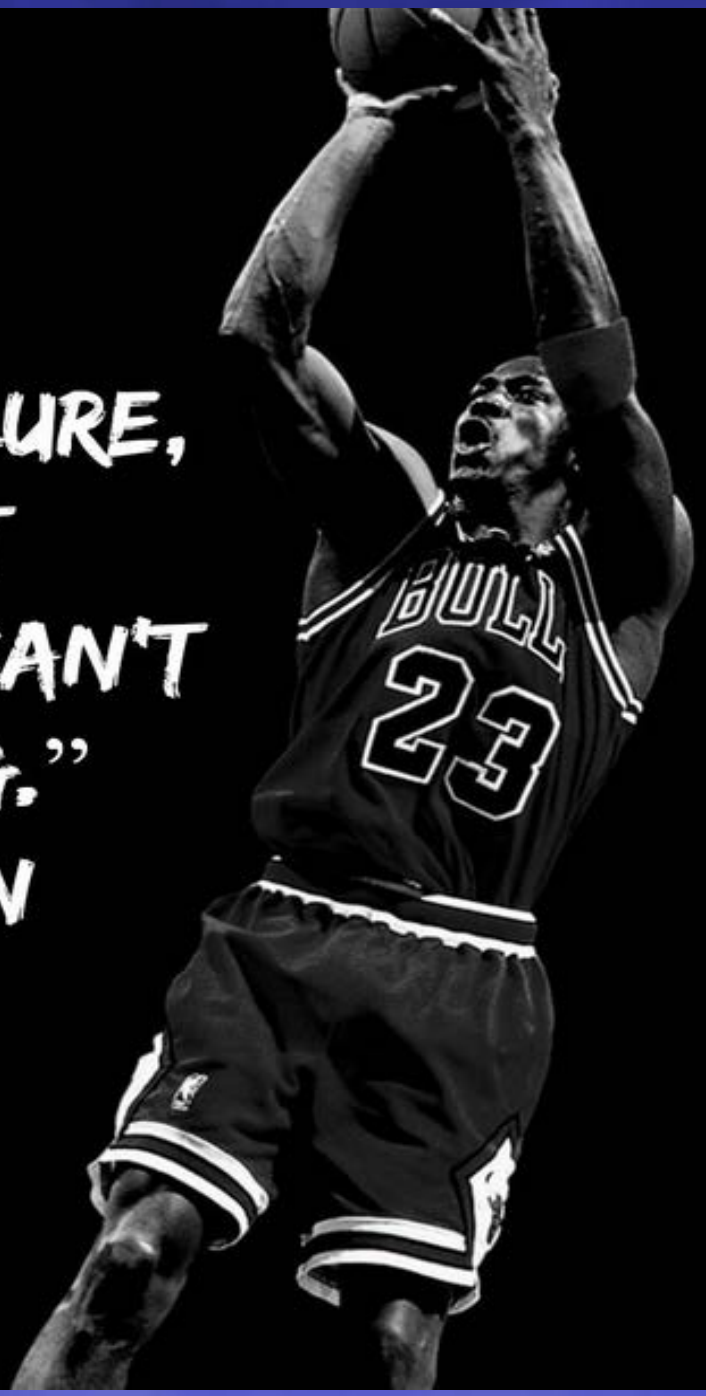
"I CAN ACCEPT FAILURE, EVERYONE FAILS AT SOMETHING. BUT I CAN'T ACCEPT NOT TRYING."
— MICHAEL JORDAN



HEALTH ECONOMICS, VOL. 5: 297–305 (1996)

ECONOMIC EVALUATION

CONFIDENCE INTERVALS FOR COST-EFFECTIVENESS RATIOS: AN APPLICATION OF FIELLER'S THEOREM

The aim of this paper is to explore some of the statistical issues arising in the movement from deterministic cost-effectiveness models towards stochastic models in studies where cost and effectiveness data are sampled rather than approximated or assumed. A brief review of cost-effectiveness analysis in health care is given in the next section. In an earlier paper, we used a Taylor's series approximation for estimating the variance[9] to calculate a confidence interval for the incremental cost-effectiveness ratio. This method was criticised in a recent publication by van Hout *et al.*,[10] who proposed an approximate solution as an alternative. We use Fieller's Theorem to develop a more accurate method, which we illustrate using the example from van Hout *et al.*[10] A summary of some simulations is also given.

Fieller's theorem in 2 steps

Step 1: Compute the formula below

Step 2: Hope you did not make a mistake

$$\hat{R} \cdot \frac{1 - z_{\alpha/2}^2 \rho \ \mathrm{cv}(\Delta\bar{C})\,\mathrm{cv}(\Delta\bar{E})}{1 - z_{\alpha/2}^2\,\mathrm{cv}(\Delta\bar{E})^2}$$

$$\pm \hat{R} \cdot \frac{z_{\alpha/2}\sqrt{\mathrm{cv}(\Delta\bar{C})^2 + \mathrm{cv}(\Delta\bar{E})^2 - 2\rho\ \mathrm{cv}(\Delta\bar{C})\,\mathrm{cv}(\Delta\bar{E}) - z_{\alpha/2}^2(1-\rho^2)\,\mathrm{cv}(\Delta\bar{C})^2\,\mathrm{cv}(\Delta\bar{E})^2}}{1 - z_{\alpha/2}^2\,\mathrm{cv}(\Delta\bar{E})^2}$$

Outline

- Review the paper
- Give examples of the main points
- Bernie's impact on me

My experience with these concepts

- P = Homeless people with mental illness
- I = Assertive community treatment (ACT)
- C = Usual care (walk it off therapy)
- O = Days of stable housing

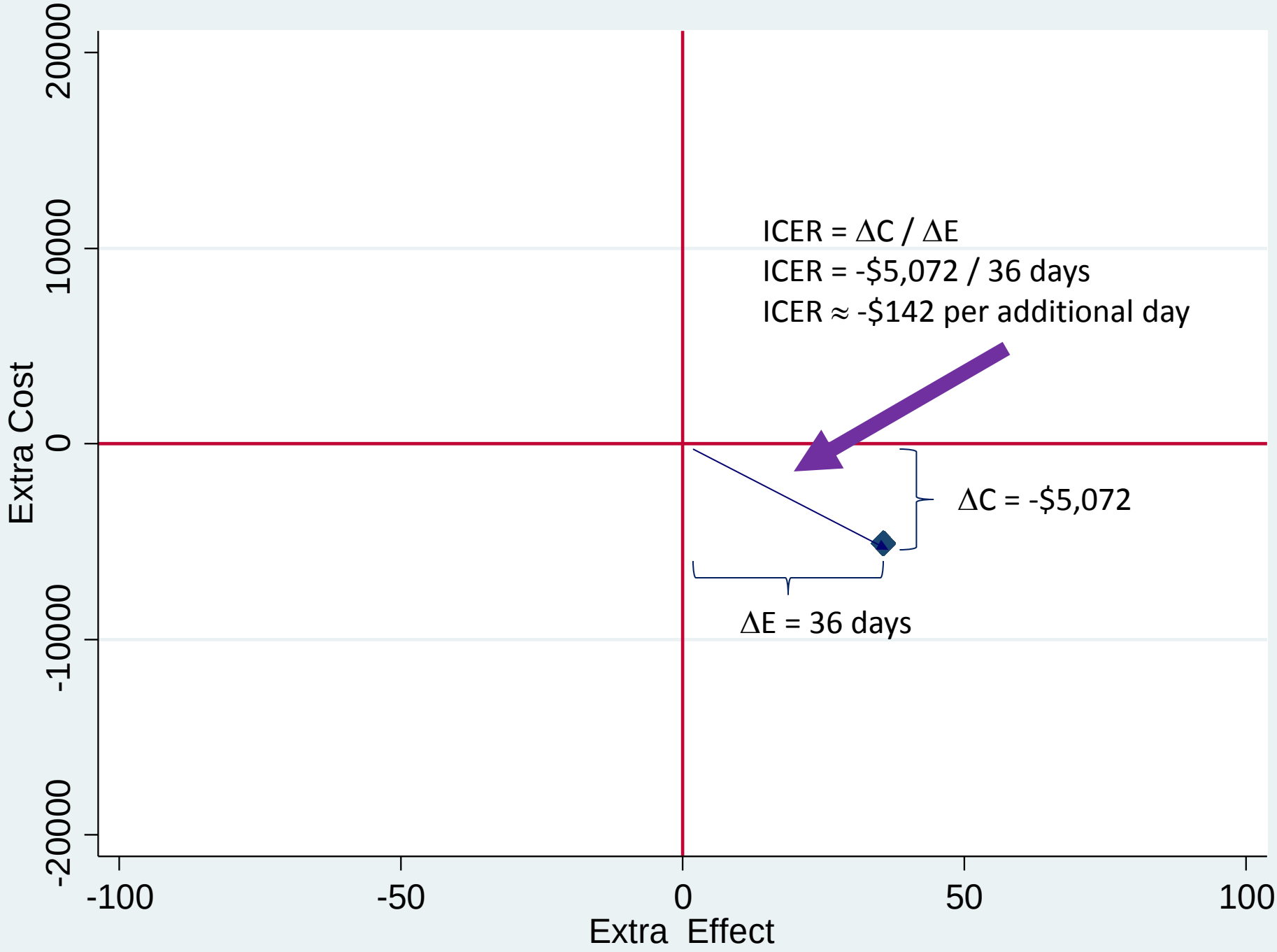
- Major research project
  - "Over the past 3 years, funding for these 5 projects totaled $26.8 million in gov't funds"

Background

Example: empirical data from a randomised trial

Background

The Program in Assertive Community Treatment (PACT) is one of the most studied models of care for persons with severe and persistent mental illnesses (SPMI) [18–21]. Lehman *et al*. [22] found that an assertive community treatment (ACT) program, relative to usual community services, reduced psychiatric inpatient days, emergency room visits, days homeless, and days in jail for *homeless* persons with SPMI in Baltimore, Maryland (USA). The study's rationale was that by providing potentially more expensive but coordinated, community-based care through the ACT programme, homeless persons with severe mental illnesses would spend more days in stable community housing with savings realized by shifting the patterns of care from higher cost crisis-oriented inpatient and emergency services to lower cost, ongoing ambulatory services. The results suggest that in the city of Baltimore, ACT was effective in achieving important outcomes warranting an examination of the cost-effect trade-off. Lehman *et al*. [23] conducted an economic evaluation of the ACT programme as it was implemented. Their analysis employed ICERs and provides an empirical example of the simplifying and unifying nature of the net-benefit framework.


ICER = ΔC / ΔE
ICER = -$5,072 / 36 days
ICER ≈ -$142 per additional day
ΔC = -$5,072
ΔE = 36 days
Extra Cost
20000
10000
0
-10000
-20000
-100
-50
0
50
100
Extra Effect

Sampling variability in effect data

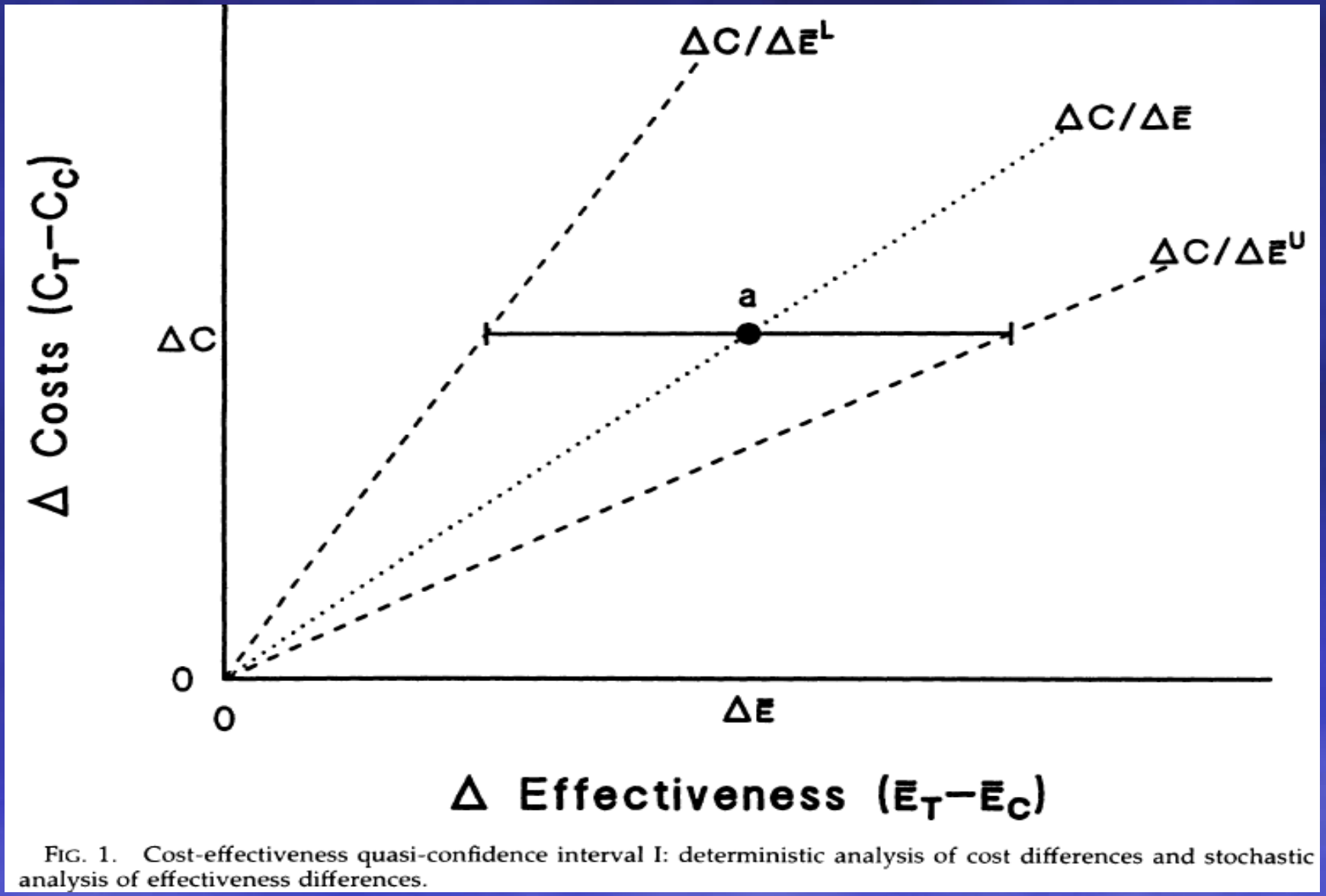
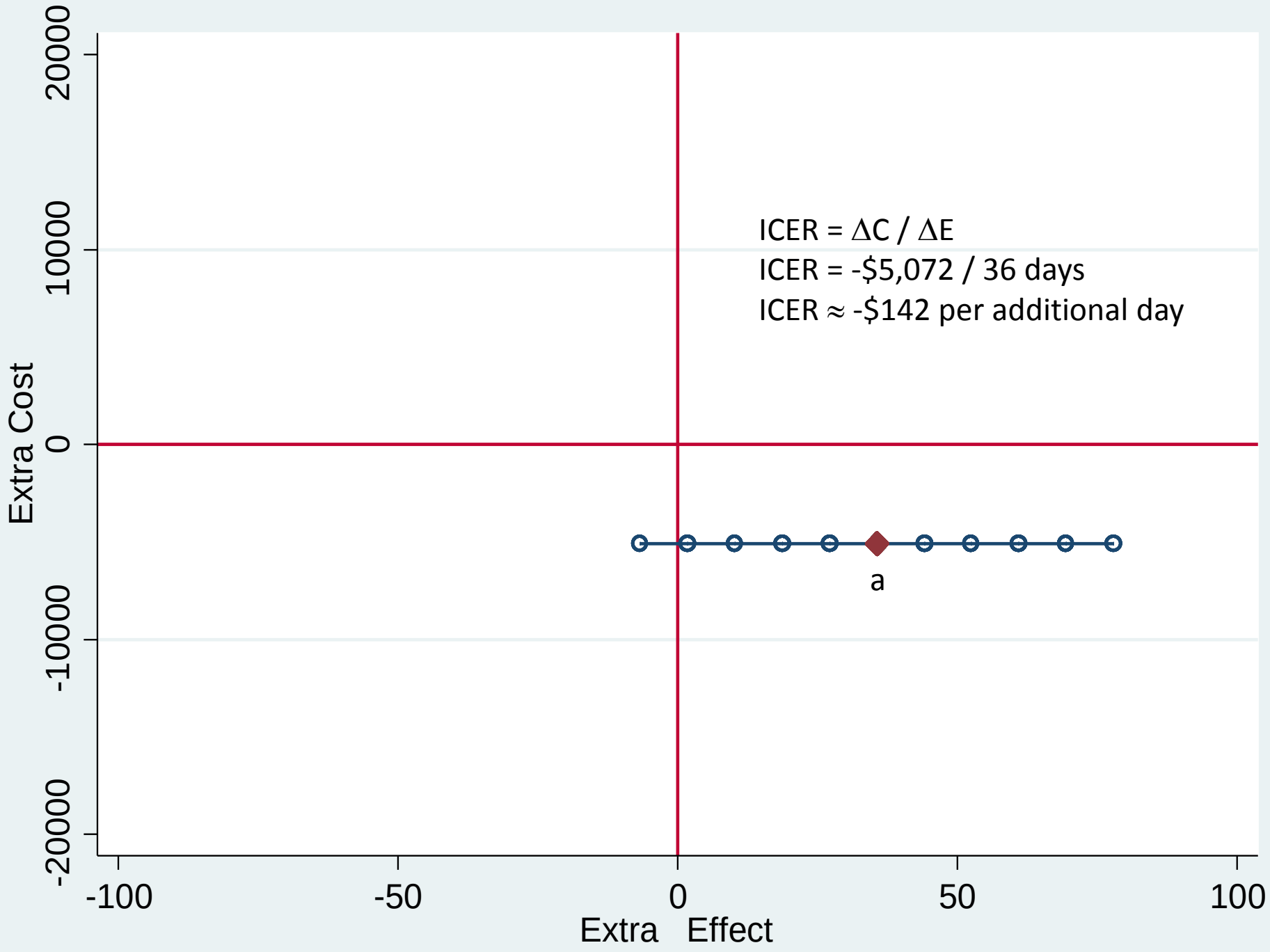
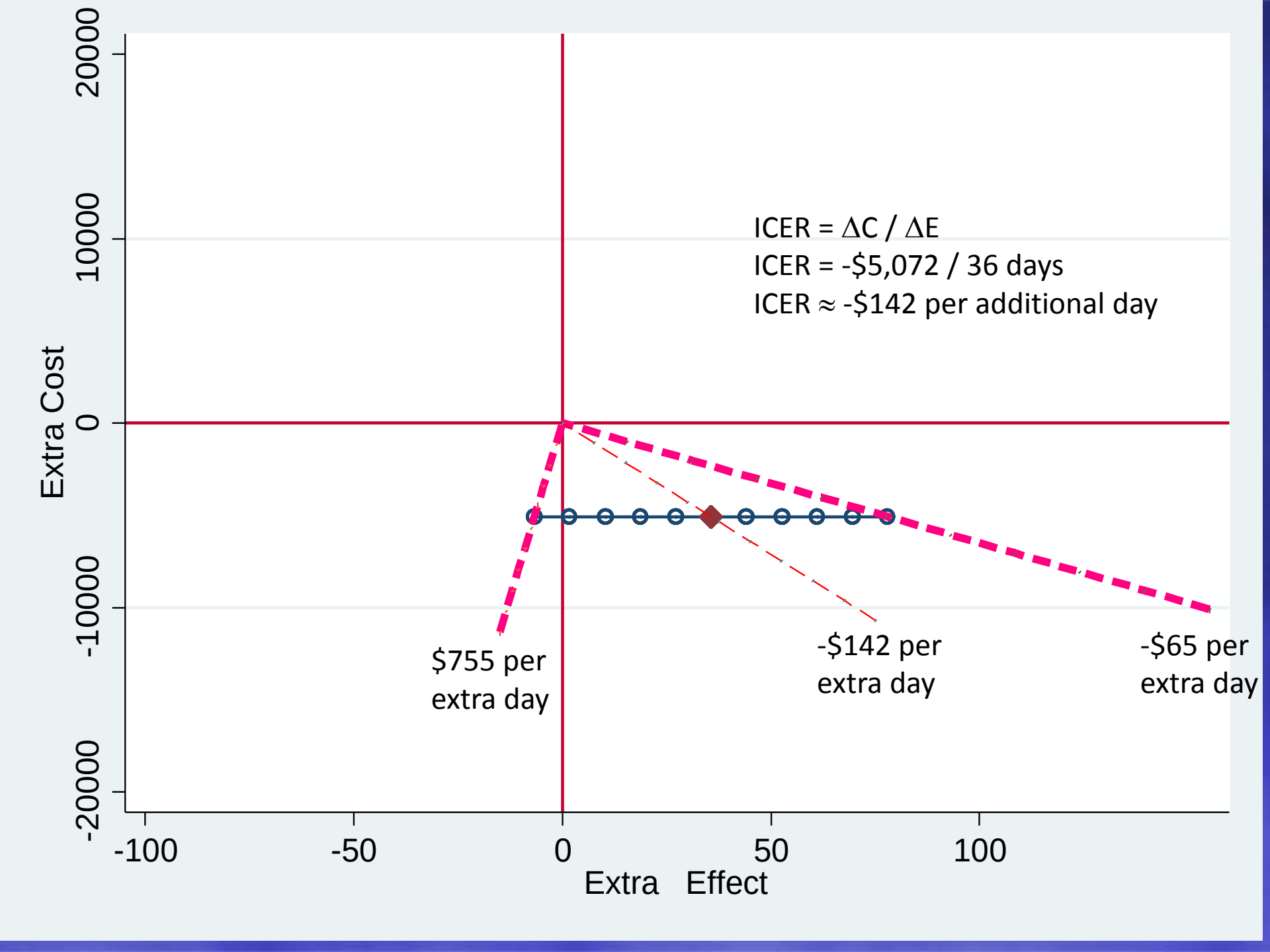


FIG. 1. Cost-effectiveness quasi-confidence interval I: deterministic analysis of cost differences and stochastic analysis of effectiveness differences.


ICER = ΔC / ΔE
ICER = -$5,072 / 36 days
ICER ≈ -$142 per additional day
a
Extra Cost
20000
10000
0
-10000
-20000
-100
-50
0
50
100
Extra Effect


ICER = ΔC / ΔE
ICER = -$5,072 / 36 days
ICER ≈ -$142 per additional day
$755 per extra day
-$142 per extra day
-$65 per extra day
Extra Cost
Extra Effect
20000
10000
0
-10000
-20000
-100
-50
0
50
100

Reporting back…

- "I'm pretty sure that the true value is between

- And my best guess is that the ICER is -142.

Oops

- ΔE not $p < 0.05$
- 95% CI for ICER doesn't make sense
- Haven't accounted for uncertainty in ΔC yet

Sampling variability in C and E

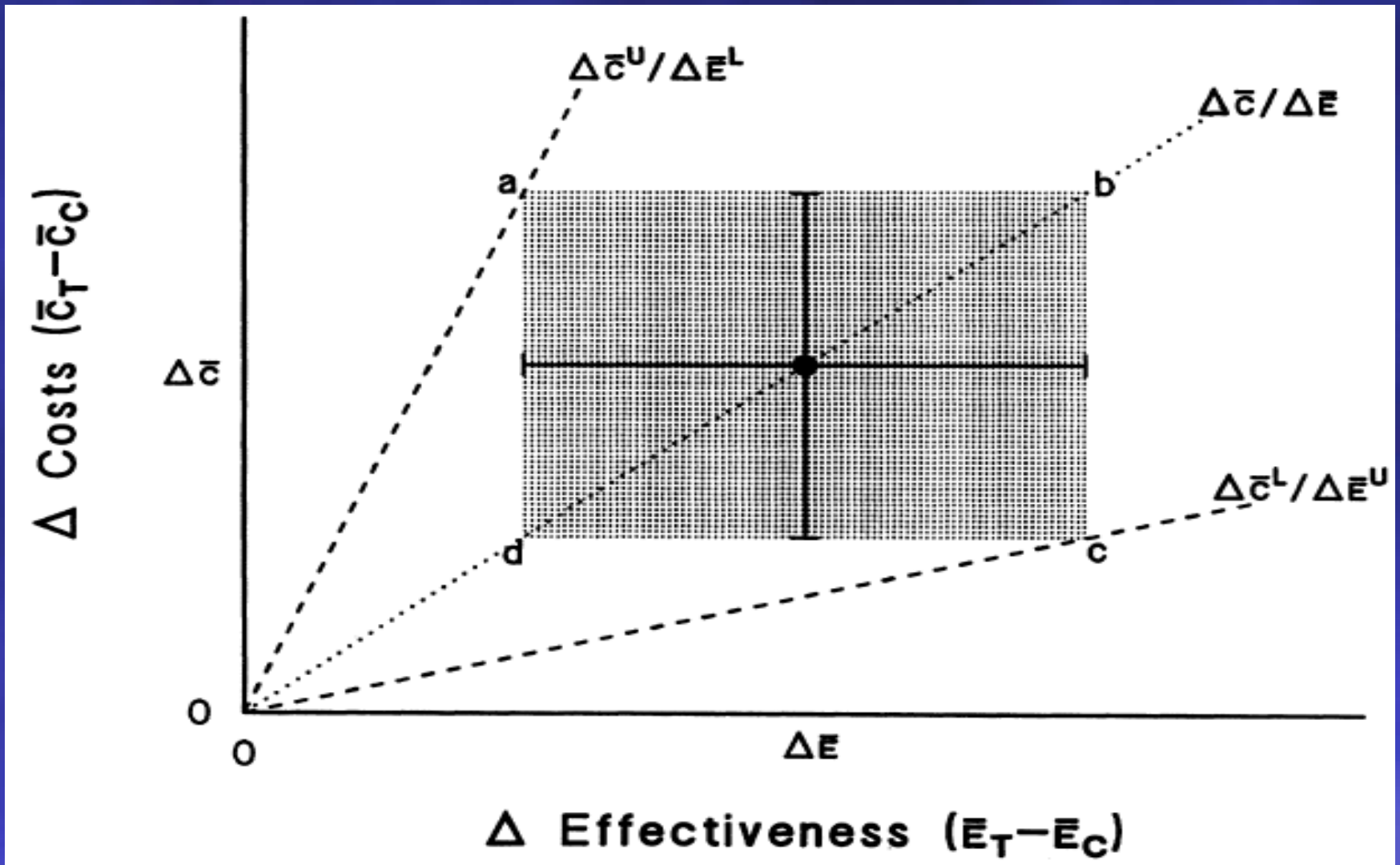
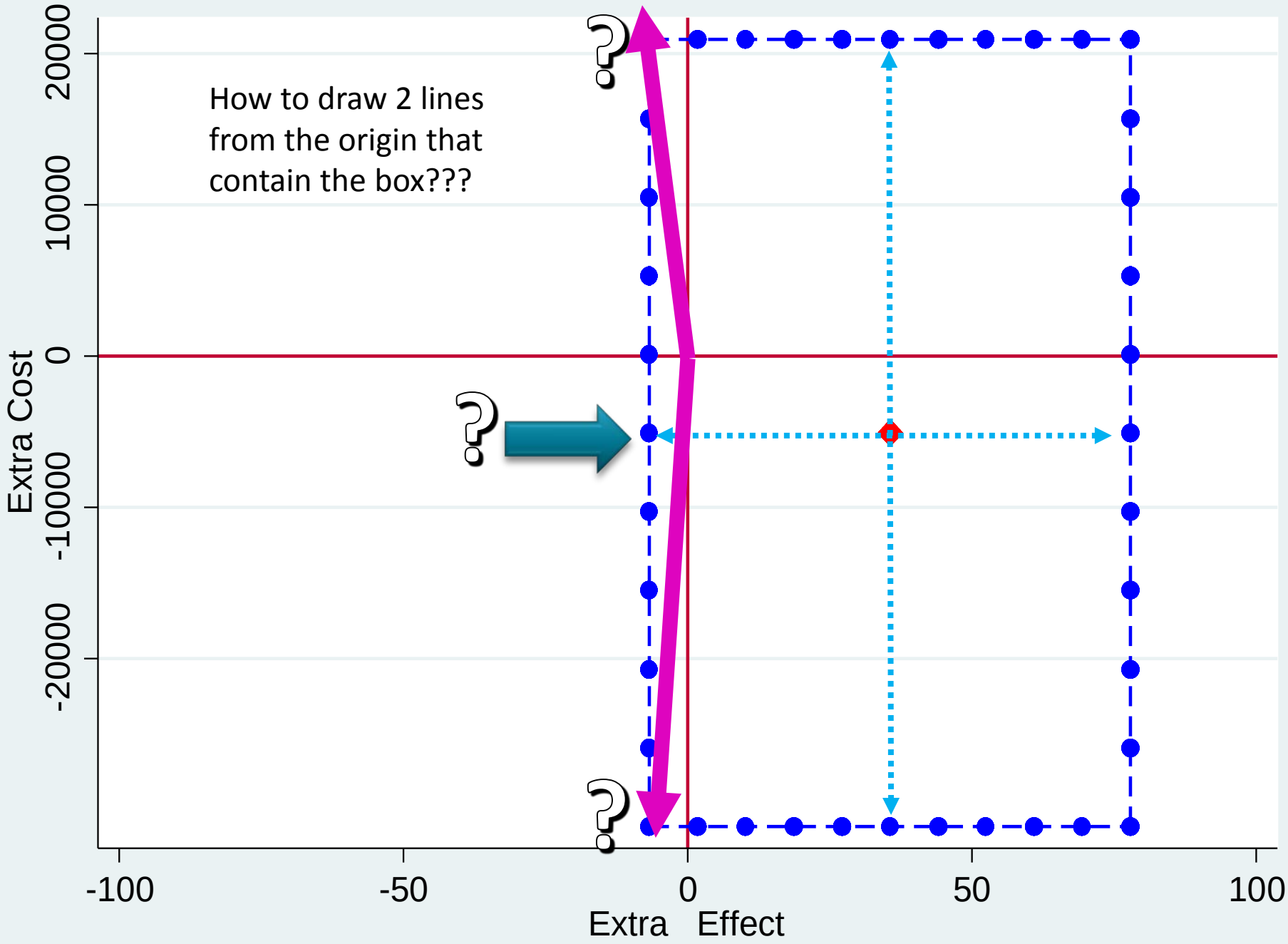
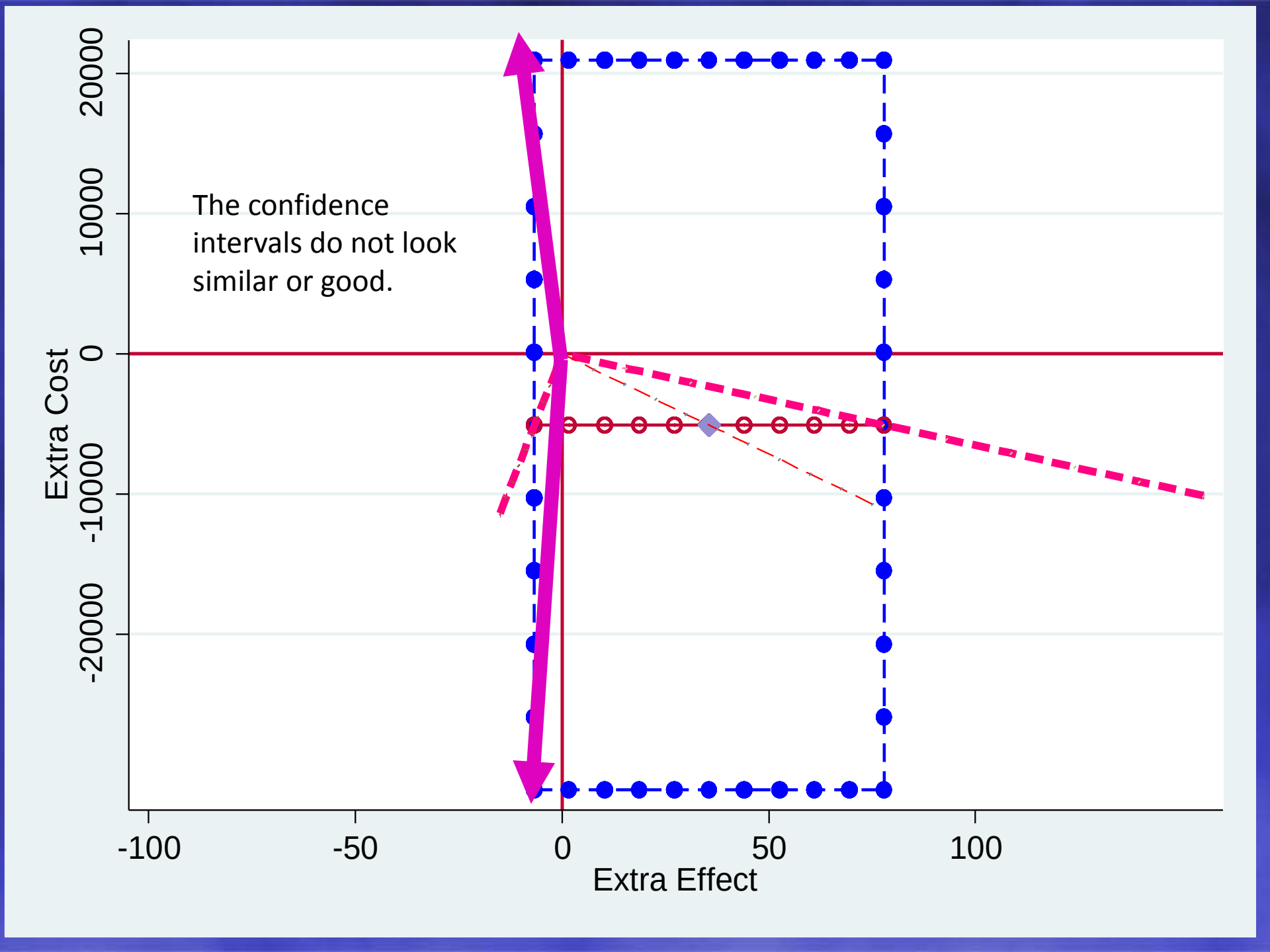


FIG. 2. Cost-effectiveness quasi-confidence interval II: stochastic analysis of both cost and effectiveness differences but assumption of zero covariance.


How to draw 2 lines
from the origin that
contain the box???
?
?
?
Extra Cost
20000
10000
0
-10000
-20000
-100
-50
0
50
100
Extra Effect


The confidence intervals do not look similar or good.
Extra Cost
20000
10000
0
-10000
-20000
-100
-50
0
50
100
Extra Effect

Oops, part II

- The "ΔE 95% CI" does not contain the box
- The box CI does not contain the box
- All I can say about the ICER's uncertainty is that I am uncertain about how to express it

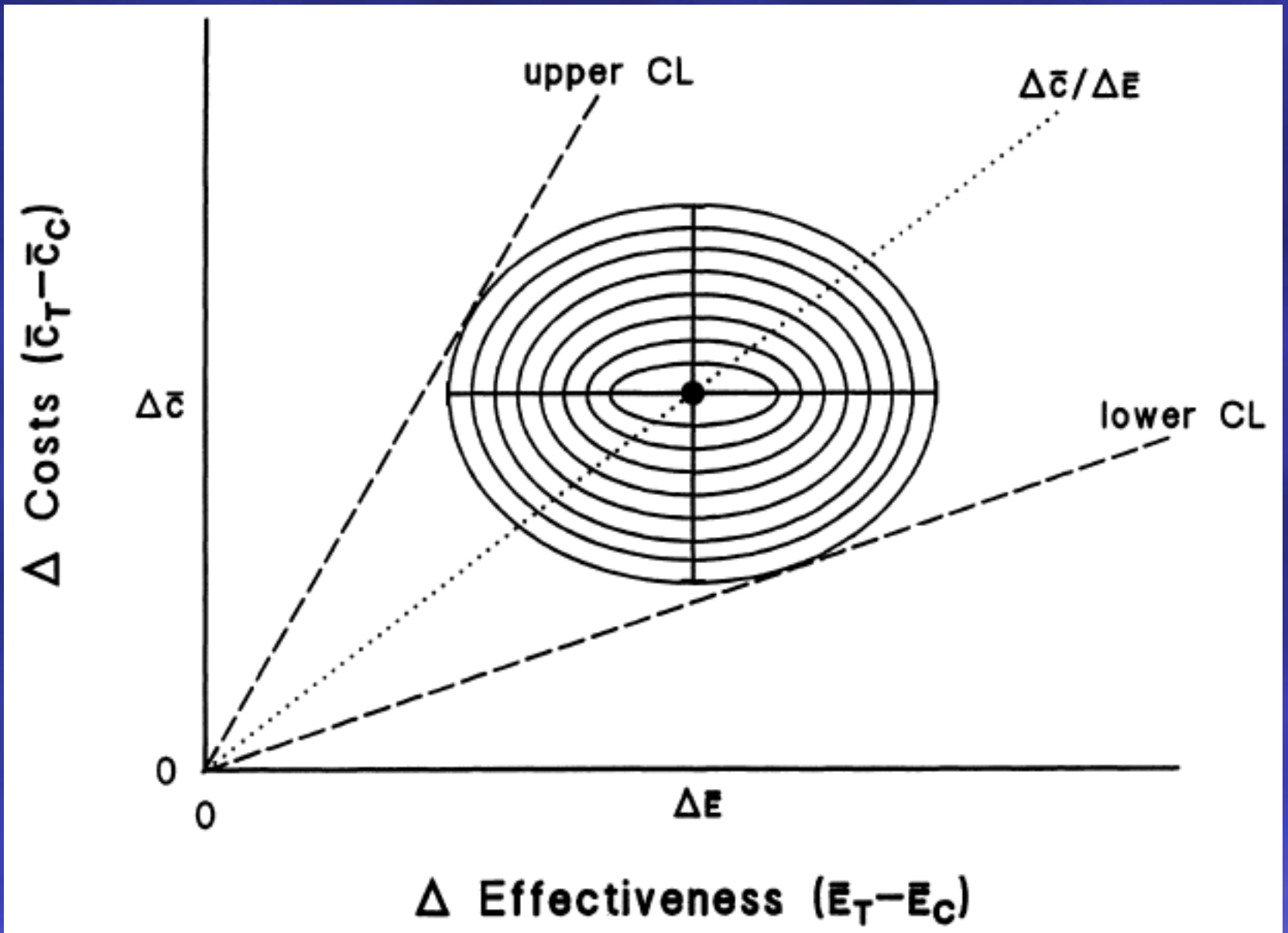
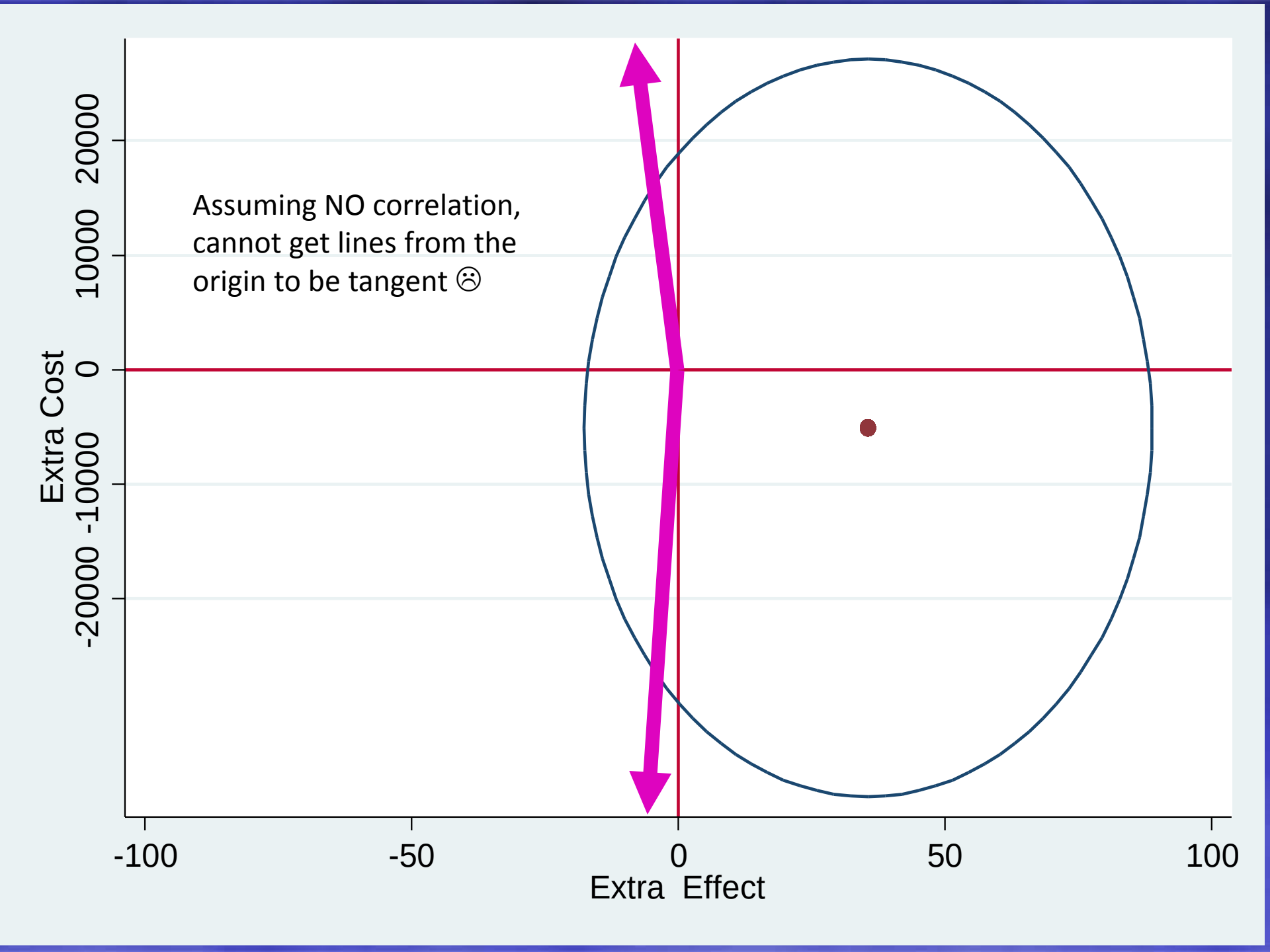
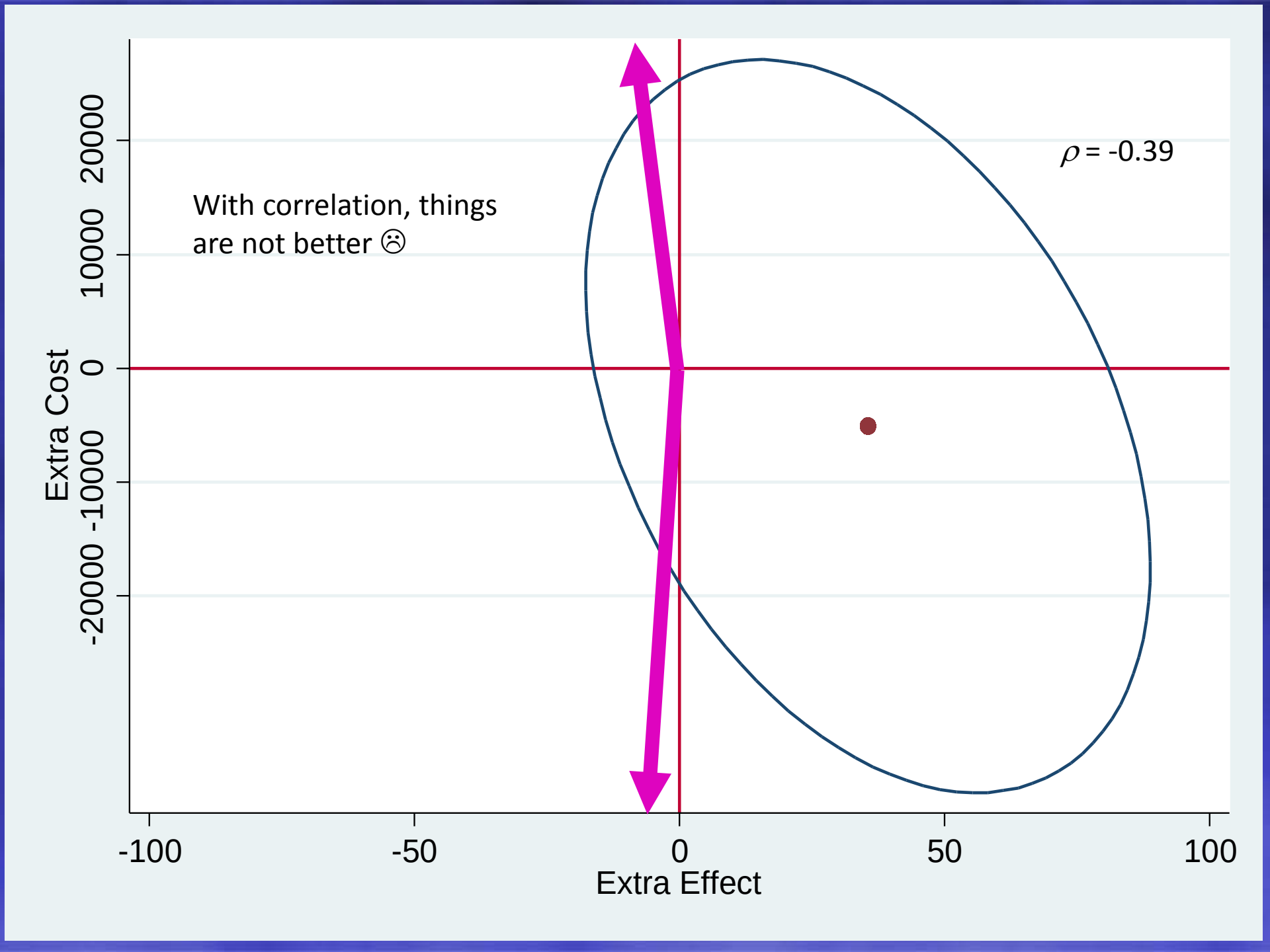
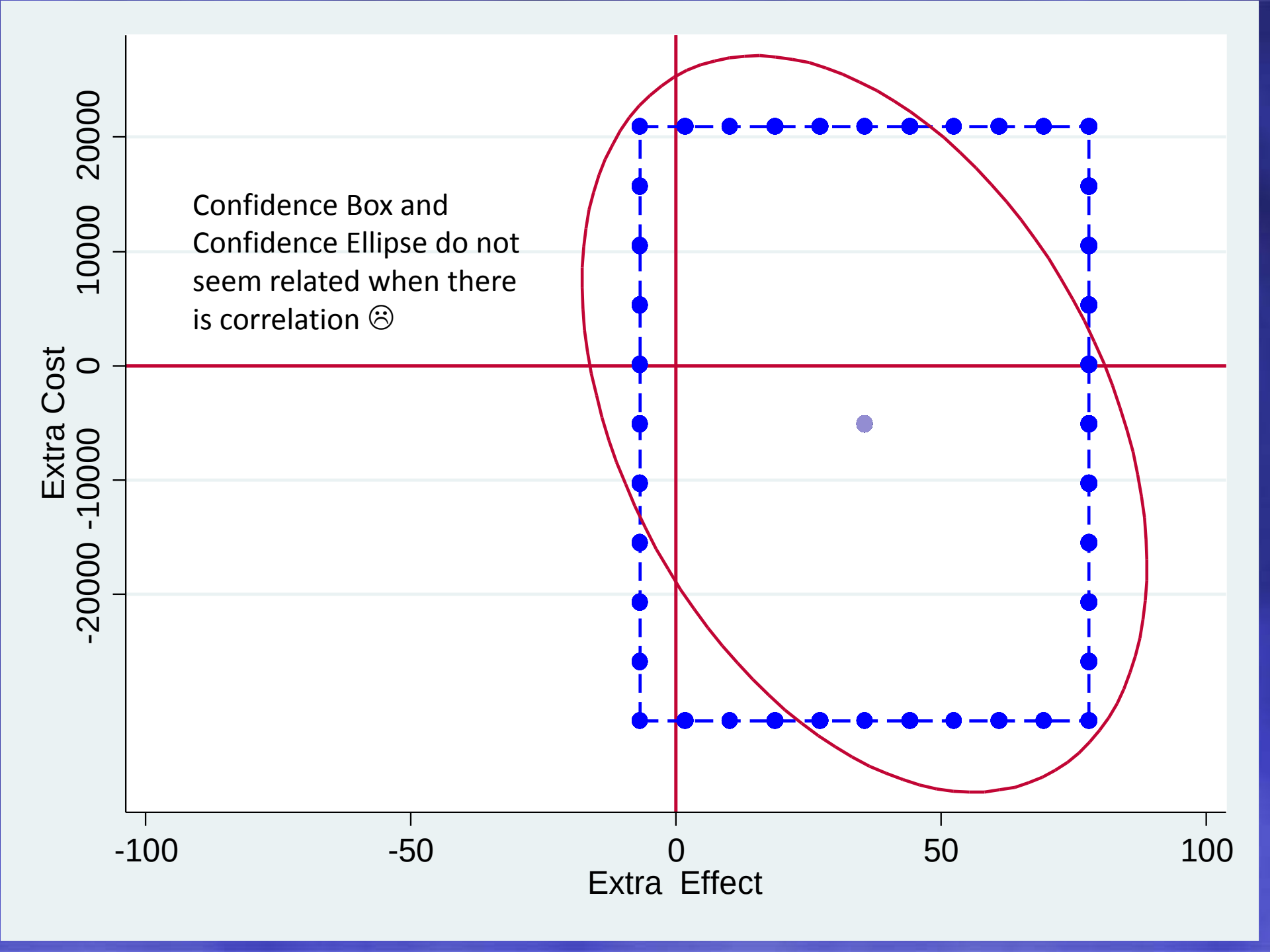
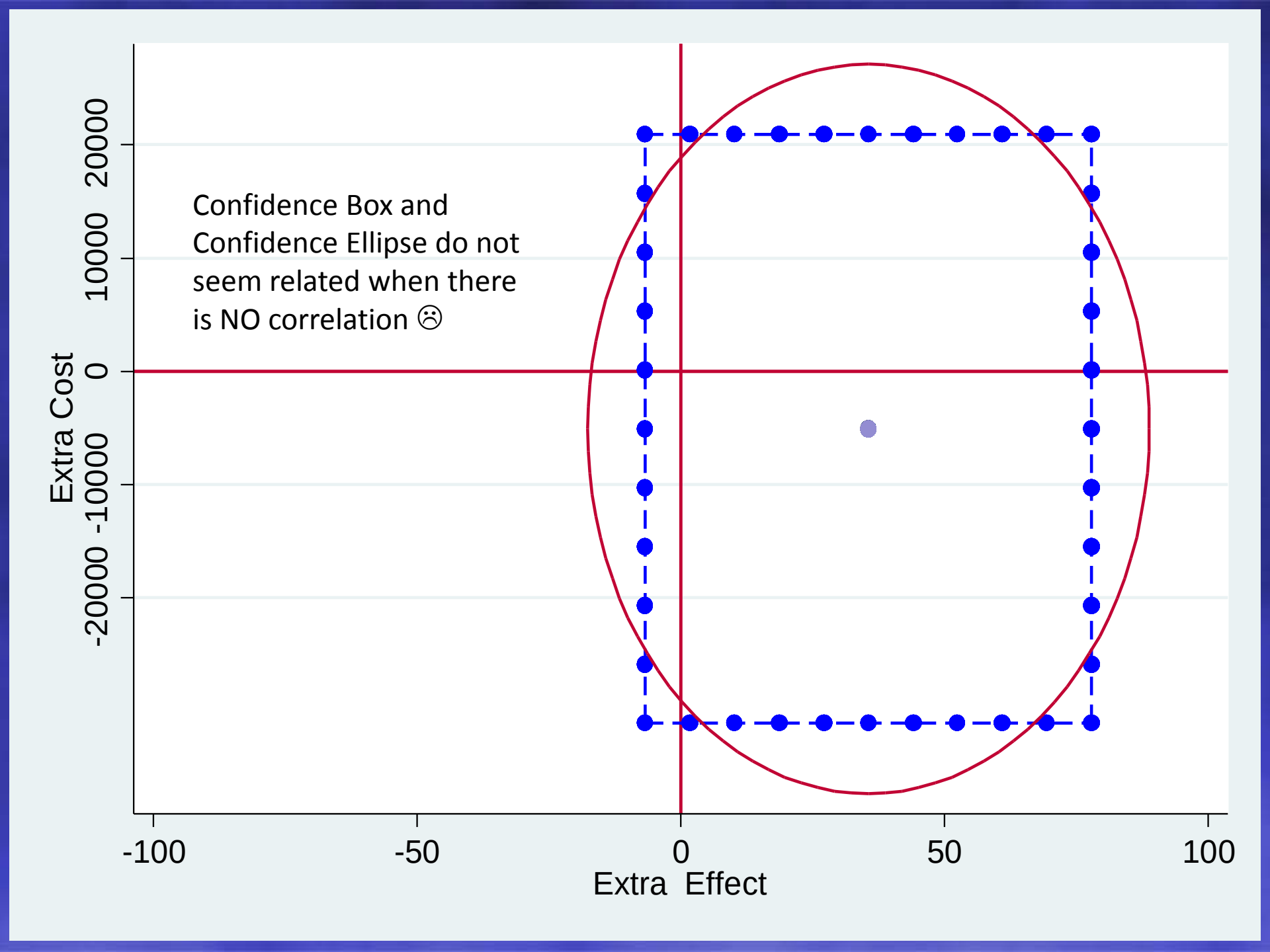


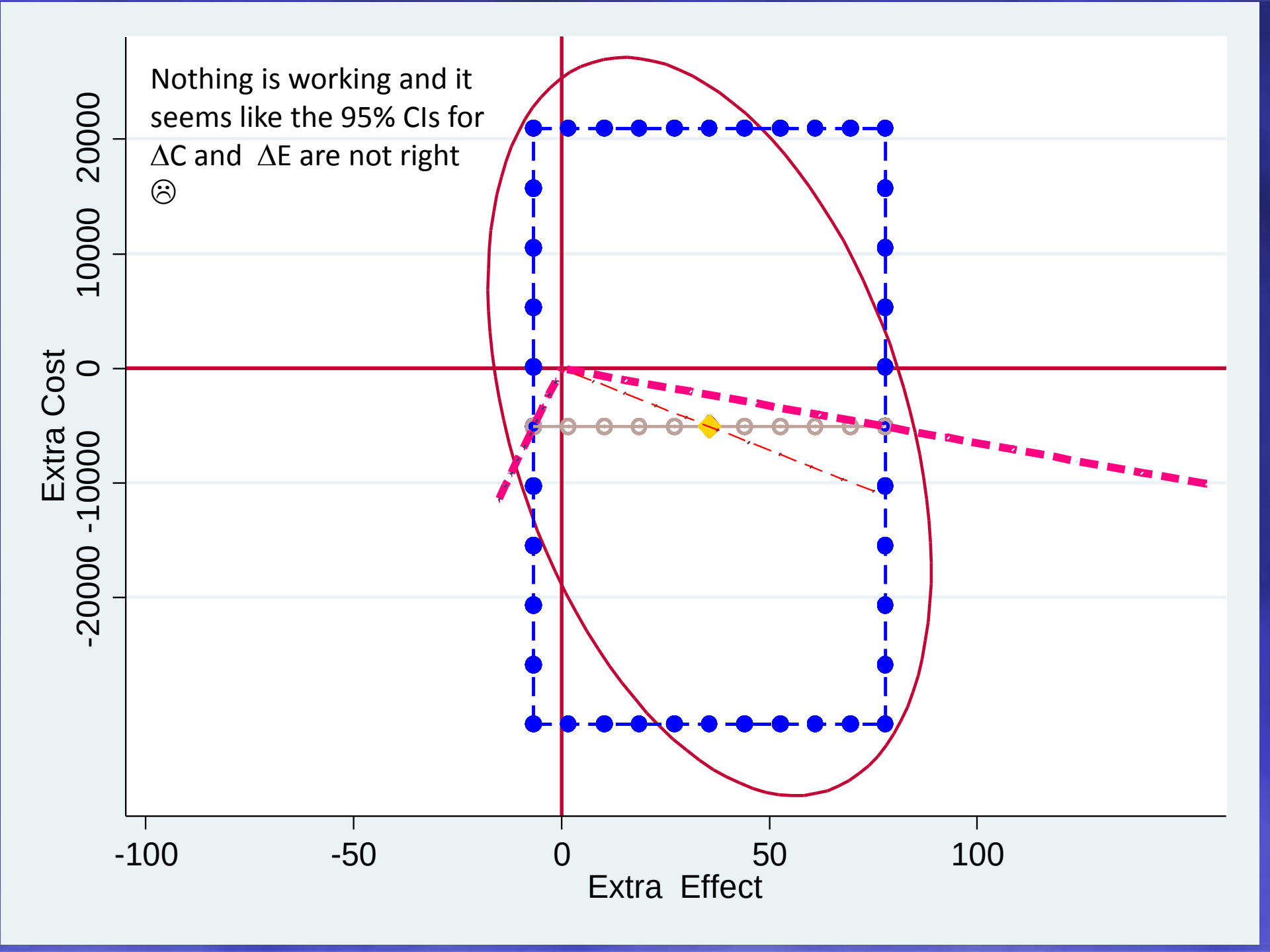
FIG. 3. Hypothetical probability density function around maximum likelihood point-estimate for cost-effectiveness.


Assuming NO correlation,
cannot get lines from the
origin to be tangent ☹
Extra Cost
20000
10000
0
-10000
-20000
-100
-50
0
50
100
Extra Effect


With correlation, things
are not better ☹
ρ = -0.39
Extra Cost
20000
10000
0
-10000
-20000
-100
-50
0
50
100
Extra Effect


Confidence Box and
Confidence Ellipse do not
seem related when there
is correlation ☹
Extra Cost
20000
10000
0
-10000
-20000
-100
-50
0
50
100
Extra Effect


Confidence Box and
Confidence Ellipse do not
seem related when there
is NO correlation ☹
Extra Cost
20000
10000
0
-10000
-20000
-100
-50
0
50
100
Extra Effect


Nothing is working and it seems like the 95% CIs for ΔC and ΔE are not right ☹
Extra Cost
20000
10000
0
-10000
-20000
-100
-50
0
50
100
Extra Effect

Lesson #1 from the paper

We are not after a 95% CI for ΔE, ΔC or both; we seek a 95% CI for a ***function*** of ΔC and ΔE

ICER $\equiv \Delta C / \Delta E$ and INB $\equiv \Delta E \lambda - \Delta C$

Options for the 95% CI for the ICER

- Taylor's approximation
- Bootstrapping
- Fieller's theorem

mally, the ratio of two normal distributed variables has neither a finite mean nor a finite variance.[12] This is a well known problem to statisticians and publications about this go back to 1928 (eg[13,14,12]). One of the consequences is that using a Taylor approximation to calculate 95% confidence limits (as proposed by O'Brien *et al.*[5]) is formally incorrect. Therefore, another approach has to be followed. One may propose

ECONOMIC EVALUATION

COSTS, EFFECTS AND C/E-RATIOS ALONGSIDE A CLINICAL TRIAL

BEN A. VAN HOUT[1], MAIWENN J. AL[1], GILAD S. GORDON[2] AND FRANS F. H. RUTTEN[1]
[1] *Institute for Medical Technology Assessment, Erasmus University Rotterdam, The Netherlands;* [2] *Health Sciences Center, University of Colorado and Synergen Inc. Boulder, Colorado, USA*

THE C/E-ACCEPTABILITY CURVE

Building further on ideas of O'Brien *et al.* a more general approach can be followed. Here, the central argument is that the probability that the C/E-ratio is under a certain acceptable limit, say R. To calculate this probability we may devise the $\Delta C/\Delta E$ plane in two surfaces: above and under the $\Delta C/\Delta E = R$ line (see Figure 3).

HEALTH ECONOMICS, VOL. 3: 309–319 (1994)

ECONOMIC EVALUATION

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Options for the 95% CI for the ICER

- Taylor's approximation
- Bootstrapping
- Fieller's theorem

Options for the 95% CI for the ICER

- ~~Taylor's approximation~~
- Bootstrapping
- Fieller's theorem
- Cost-effectiveness acceptability curve (CEAC)

Bootstrapping

	icer
1.	-208959.2
2.	-10148.99
3.	-9818.279
4.	-8697.708
5.	-8104.338
6.	-5711.276
7.	-4590.097
8.	-4487.878
9.	-4071.302
10.	-4035.07
11.	-3990.472
12.	-3977.136
13.	-3727.241
14.	-3178.251
15.	-3074.219
16.	-2970.422
17.	-2878.403
18.	-2772.987
19.	-2615.952
20.	-2407.651
21.	-2125.95
22.	-2118.703
23.	-2100.793
24.	-2032.782
25.	-2010.856

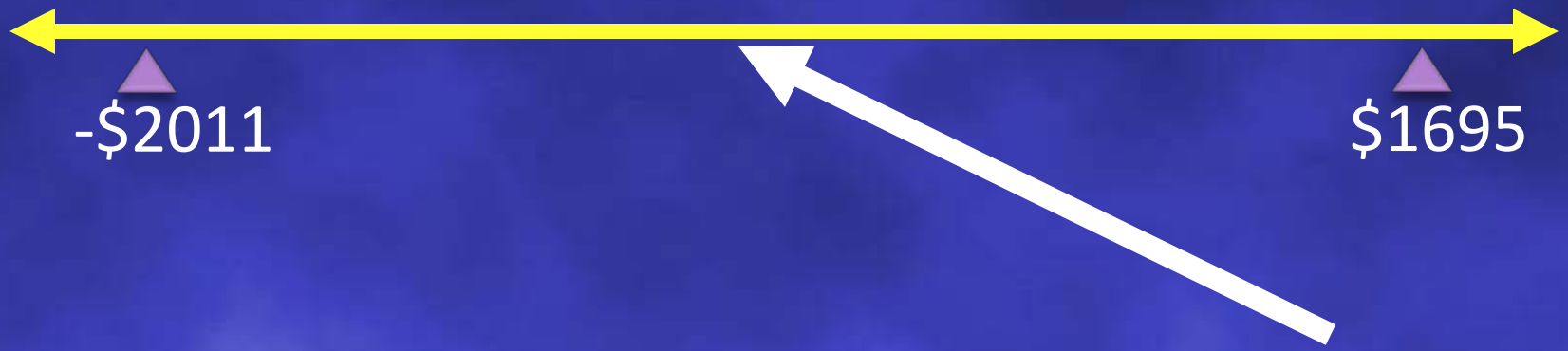
1) Sort the 1,000 bootstrapped replicates from smallest to largest →

2) Pick the 2.5% and the 97.5% from the list

975.	1694.685
976.	1710.733
977.	1736.83
978.	1908.611
979.	2022.328
980.	2276.893
981.	2395.489
982.	2509.087
983.	2557.764
984.	2662.646
985.	2723.05
986.	2834.105
987.	2875.642
988.	3260.172
989.	3309.066
990.	3514.609
991.	3699.1
992.	5198.82
993.	5467.617
994.	5555.38
995.	5670.703
996.	6047.626
997.	15219.27
998.	15479.27
999.	16808.19
1000.	79008.77

Reporting back…

- "I'm pretty sure that the true value is between



- And my best guess is that the ICER is -142.

Options for the 95% CI for the ICER

- ~~Taylor's approximation~~
- Bootstrapping (-2011, 1695)
- Fieller's theorem
- Cost-effectiveness acceptability curve (CEAC)

$$\hat{R} \cdot \frac{1 - z_{\alpha/2}^2 \rho \ \mathrm{cv}(\Delta\bar{C})\,\mathrm{cv}(\Delta\bar{E})}{1 - z_{\alpha/2}^2\,\mathrm{cv}(\Delta\bar{E})^2}$$

$$\pm \hat{R} \cdot \frac{z_{\alpha/2}\sqrt{\mathrm{cv}(\Delta\bar{C})^2 + \mathrm{cv}(\Delta\bar{E})^2 - 2\rho\ \mathrm{cv}(\Delta\bar{C})\,\mathrm{cv}(\Delta\bar{E}) - z_{\alpha/2}^2(1-\rho^2)\,\mathrm{cv}(\Delta\bar{C})^2\,\mathrm{cv}(\Delta\bar{E})^2}}{1 - z_{\alpha/2}^2\,\mathrm{cv}(\Delta\bar{E})^2}$$

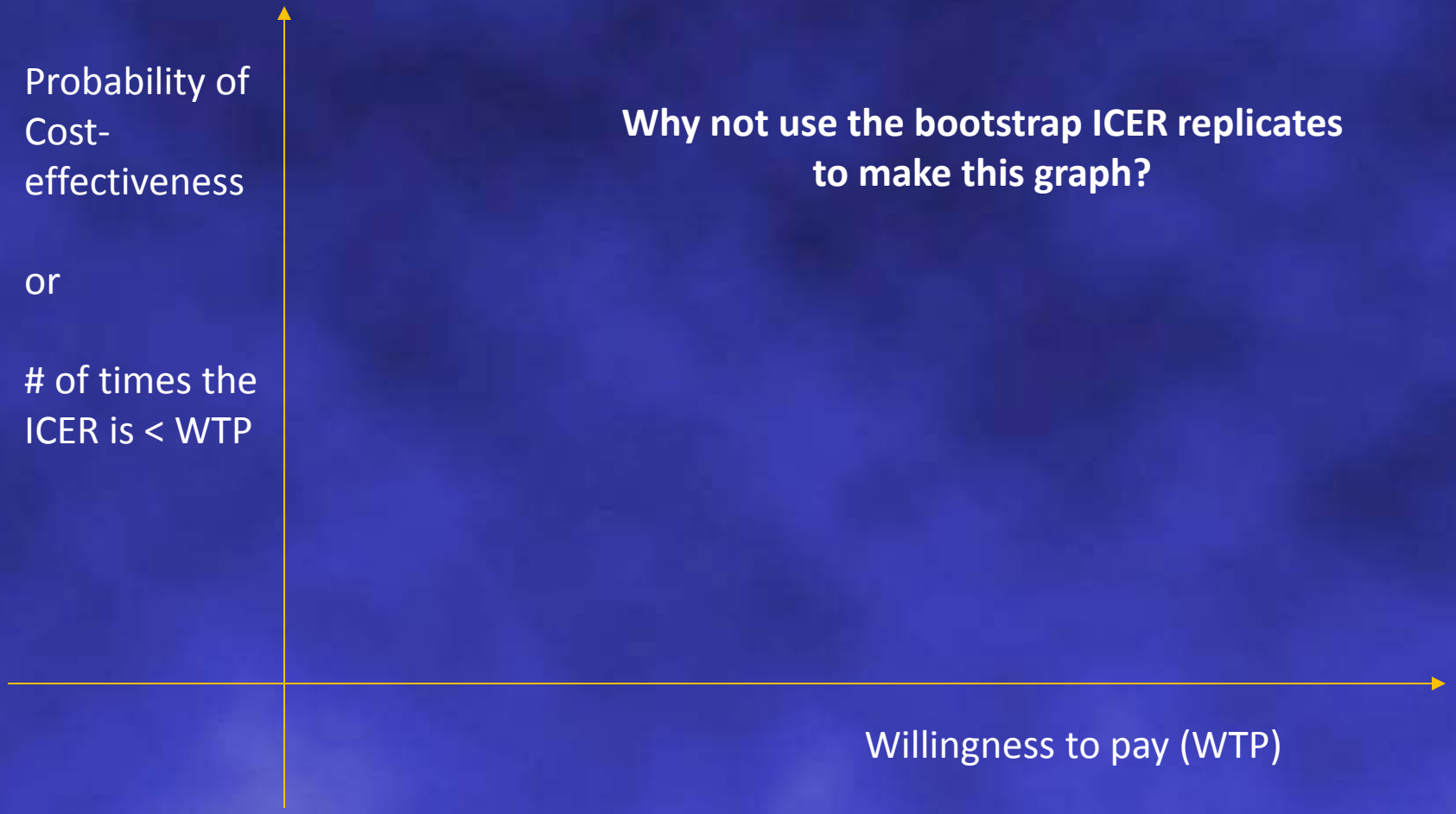
Fieller's Theorem

- $\sqrt{}$ [big (+) – bigger (+)] = $\sqrt{}$ [(– #)] = ?
- Confidence is imaginary?
- Oops.
  - Did I do it wrong or is the universe out to get me?
- Oh well, on to the next option…

Options for the 95% CI for the ICER

- ~~Taylor's approximation~~
- Bootstrapping (-2011, 1695)
- Fieller's theorem
- Cost-effectiveness acceptability curve (CEAC)

CEAC main idea



Why not use the bootstrap ICER replicates to make this graph?

```
-> tabulation of icer0k → Is the ICER < $0

     icer0k |      Freq.     Percent        Cum.
------------+-----------------------------------
          0 |        333       33.30       33.30
          1 |        667       66.70      100.00
------------+-----------------------------------
      Total |      1,000      100.00
```

What % of the bootstrap replicates are < WTP?

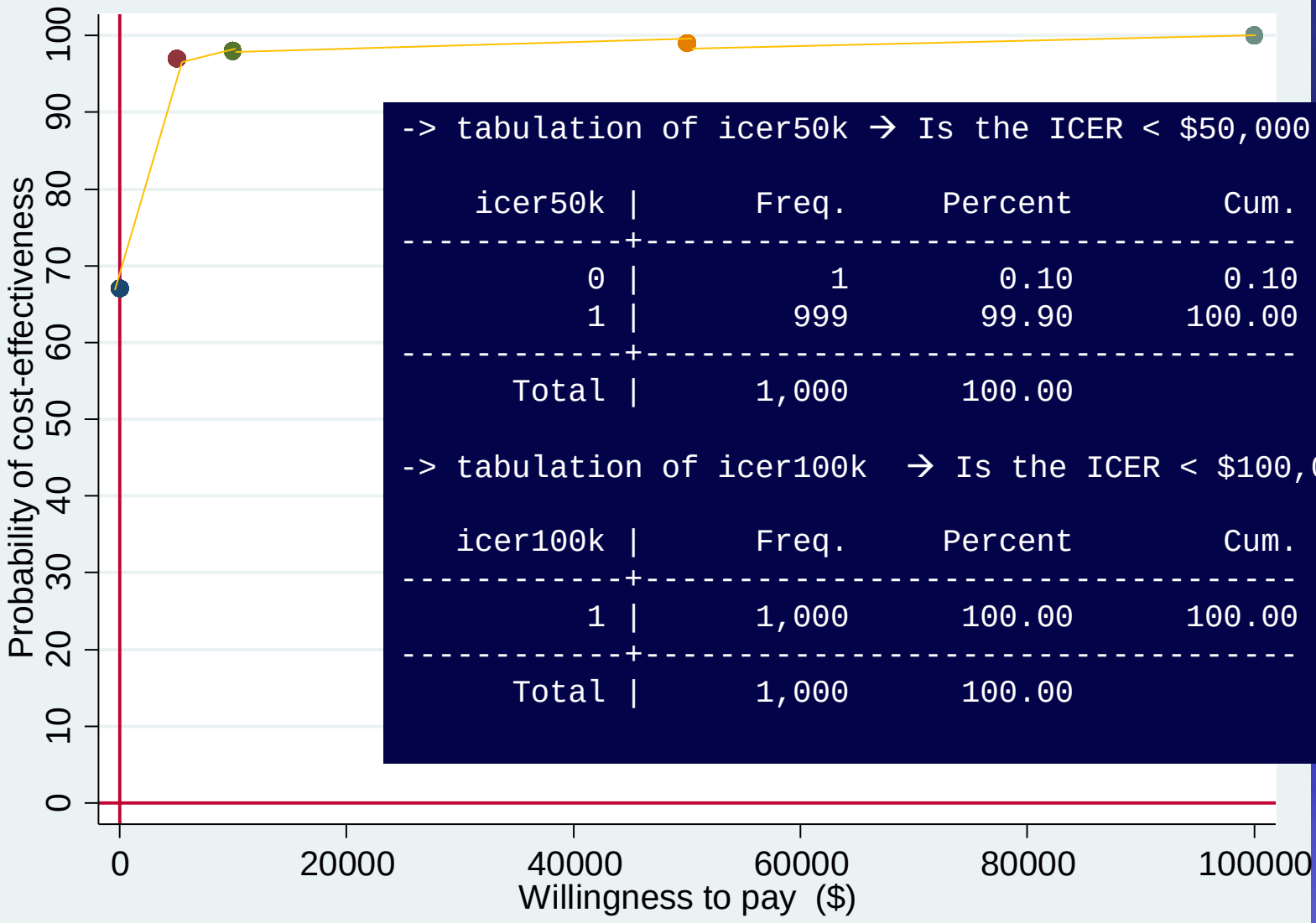
```
-> tabulation of icer5k → Is the ICER < $5,000

     icer5k |      Freq.     Percent        Cum.
------------+-----------------------------------
          0 |          9        0.90        0.90
          1 |        991       99.10      100.00
------------+-----------------------------------
      Total |      1,000      100.0
```

```
-> tabulation of icer10k

    icer10k |      Freq.     Percen
------------+-----------------------
          0 |          4        0.4
          1 |        996       99.6
------------+-----------------------
      Total |      1,000      100.0
```

```
-> tabulation of icer50k

    icer50k |      Freq.     Percent        Cum.
------------+-----------------------------------
          0 |          1        0.10        0.10
          1 |        999       99.90      100.00
------------+-----------------------------------
      Total |      1,000      100.00
```

```
-> tabulation of icer100k

   icer100k |      Freq.     Percent        Cum.
------------+-----------------------------------
          1 |      1,000      100.00      100.00
------------+-----------------------------------
      Total |      1,000      100.00
```

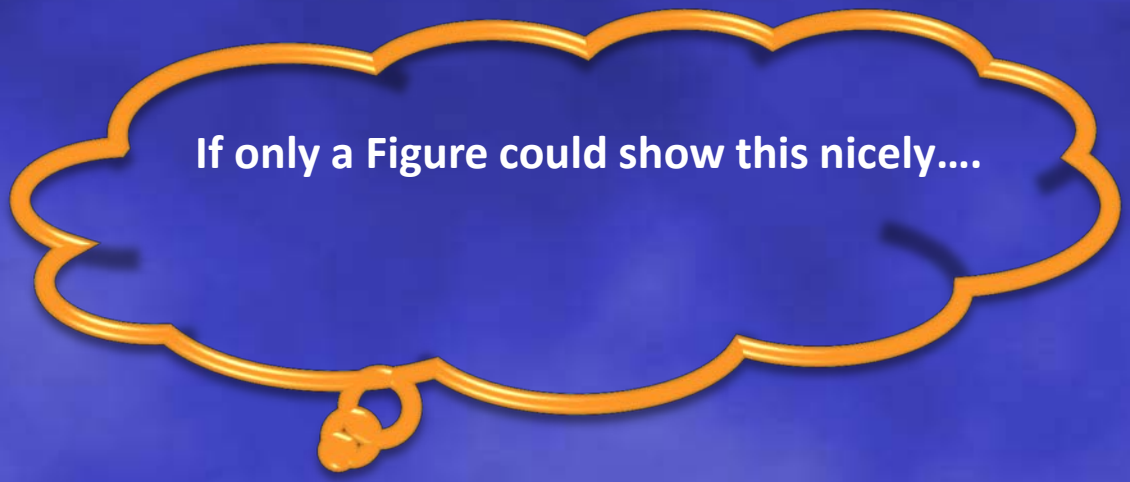
CEAC says, "100% CE at $100k"




```
-> tabulation of icer50k → Is the ICER < $50,000

    icer50k |      Freq.     Percent        Cum.
------------+-----------------------------------
          0 |          1        0.10        0.10
          1 |        999       99.90      100.00
------------+-----------------------------------
      Total |      1,000      100.00

-> tabulation of icer100k  → Is the ICER < $100,000

   icer100k |      Freq.     Percent        Cum.
------------+-----------------------------------
          1 |      1,000      100.00      100.00
------------+-----------------------------------
      Total |      1,000      100.00
```

Options for the 95% CI for the ICER

- ~~Taylor's approximation~~
- Bootstrapping (-2011, 1695)
- Fieller's theorem
- Cost-effectiveness acceptability curve (CEAC)
  - All of the ICERs are below $100,000



HEALTH ECONOMICS
Health Econ. 7: 723–740 (1998)

STUDENT CORNER

CONFIDENCE INTERVALS OR SURFACES? UNCERTAINTY ON THE COST-EFFECTIVENESS PLANE

ANDREW BRIGGS[a,*] AND PAUL FENN[b]
[a] *Health Economics Research Centre, Institute of Health Sciences, University of Oxford, UK*
[b] *School of Management and Finance, University of Nottingham, UK*

SUMMARY

Although cost-effectiveness analysis is not new, it is only recently that economic analysis has been conducted alongside clinical trials. Whereas in the past economic analysts most often used sensitivity analysis to examine the implications of uncertainty for their results, the existence of patient-level data on costs and effects opens up the possibility of statistical analysis of uncertainty.

Unfortunately, ratio statistics can cause problems for standard statistical methods of confidence interval estimation. The recent health economics literature contains a number of suggestions for estimating confidence limits for ratios. In this paper, we begin by reviewing the different methods of confidence interval estimation with a view to providing guidance concerning the most appropriate method.

Figure 6 and Table 2 emphasize the differences in confidence intervals that can be obtained for

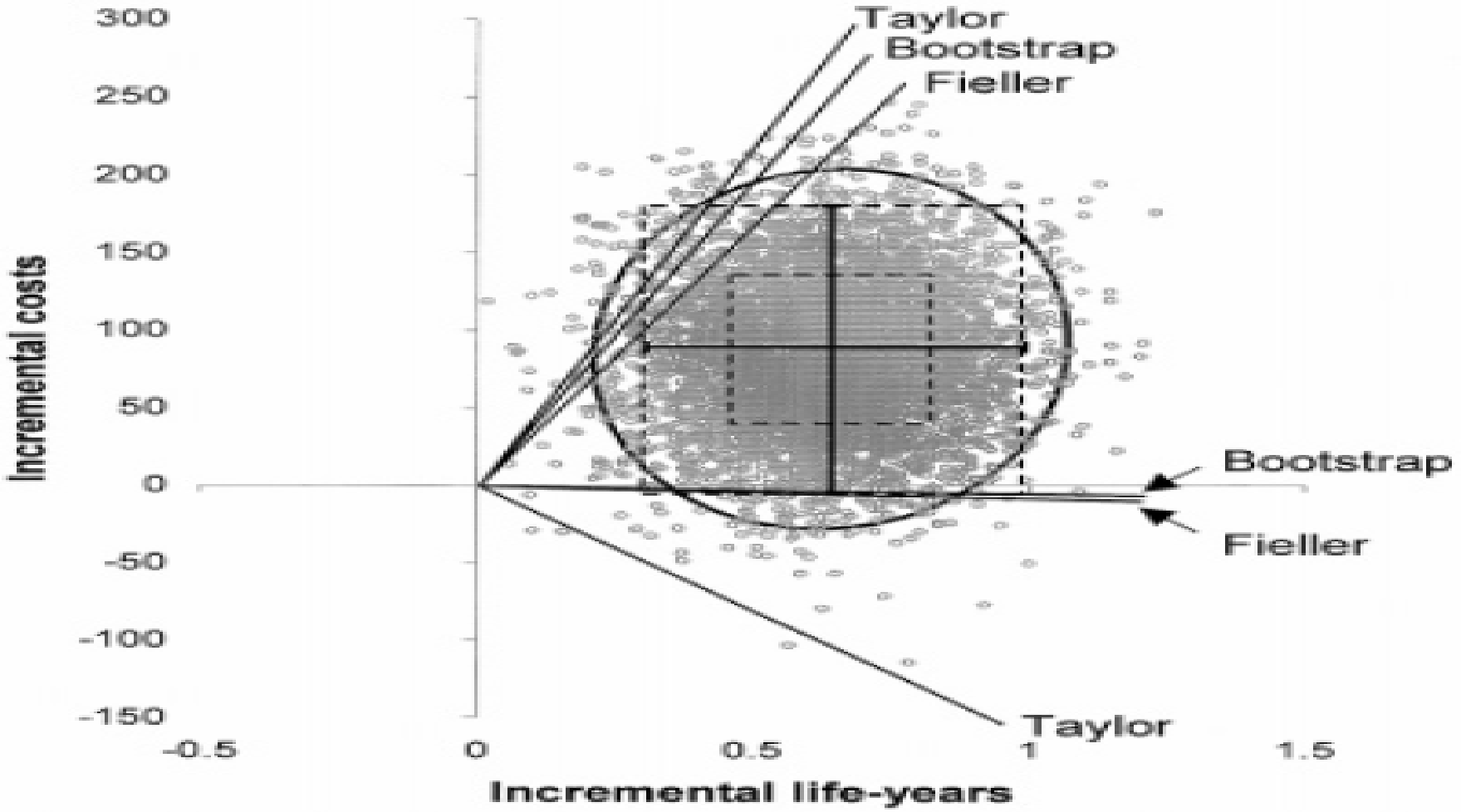
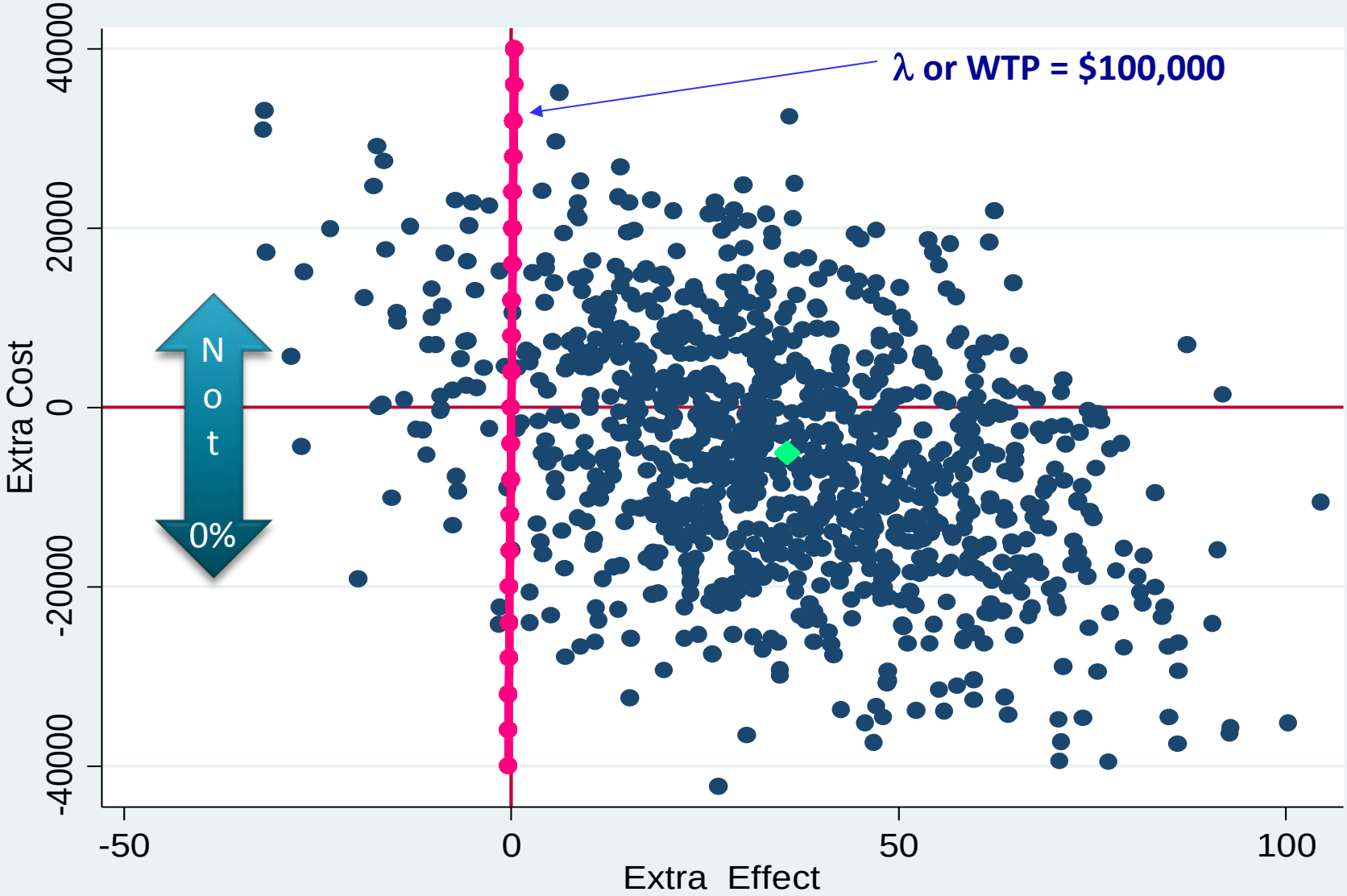


Figure 6. Confidence surfaces and intervals on the cost-effectiveness plane: example from a clinical trial. (Rays from the origin represent intervals for Taylor, Fieller and bootstrap methods—rays representing confidence intervals for ellipse method and box methods are not shown in order to avoid cluttering the figure.)

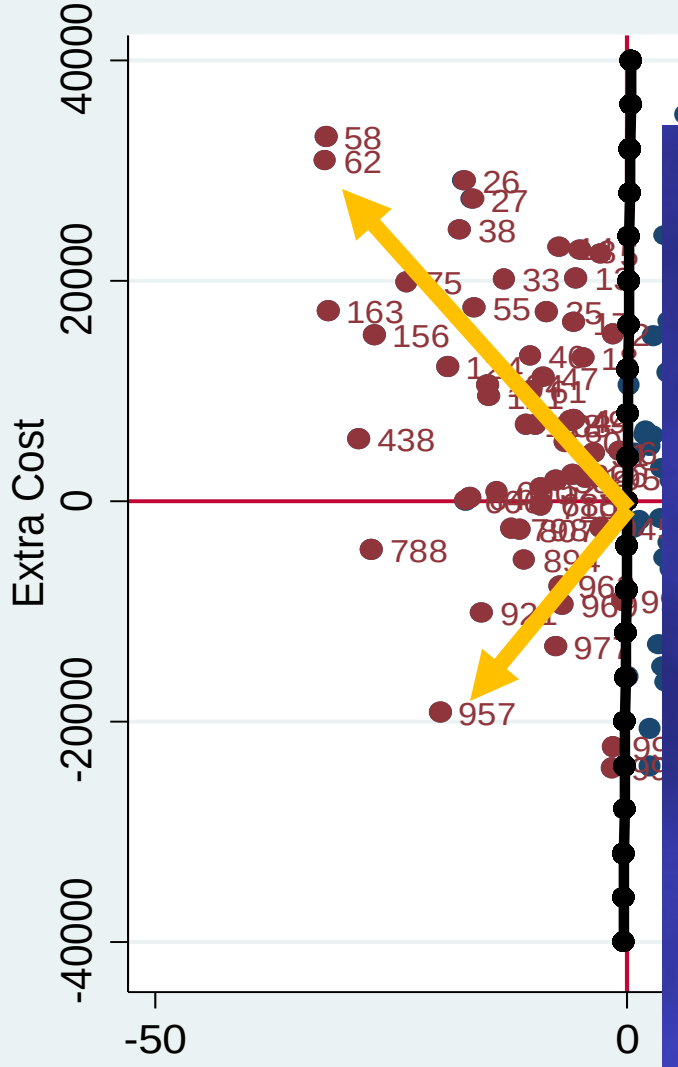
All of the ICERs are below the λ = $100,000 line?



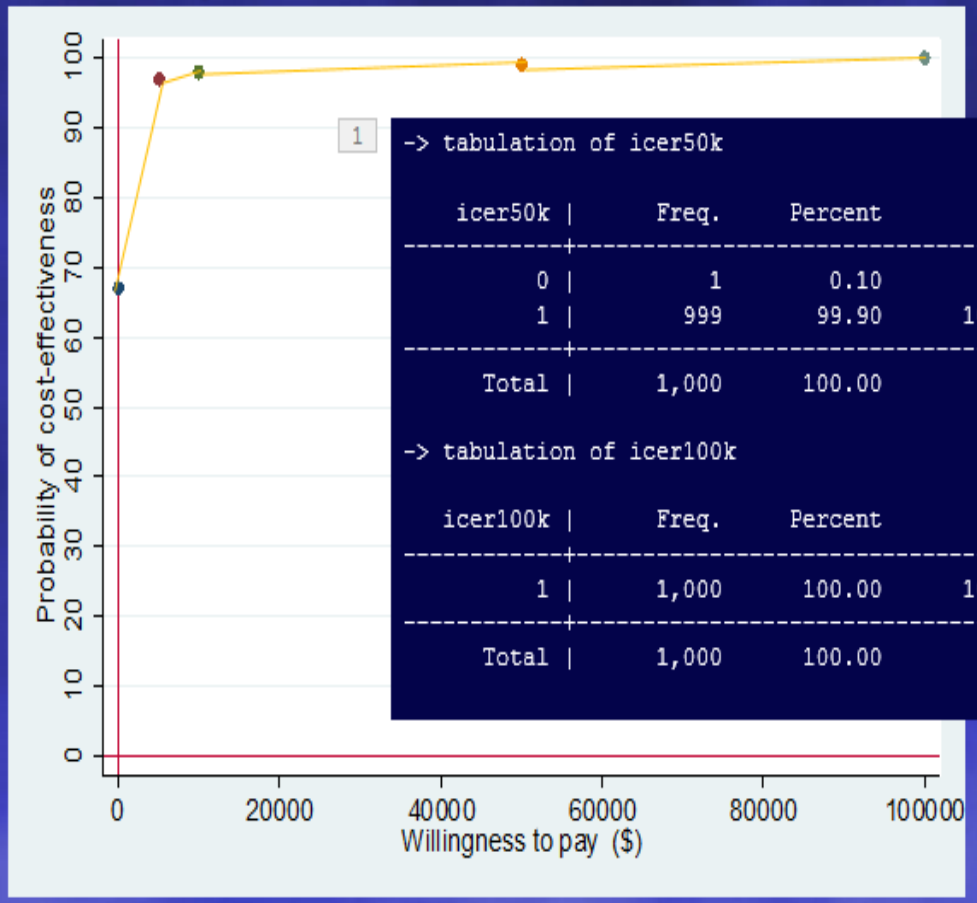
ICERs < $100,000, but not cost-effective!

Lesson #1: Negative ICER can be bad.

Lesson #2: Smaller ICER can be bad.

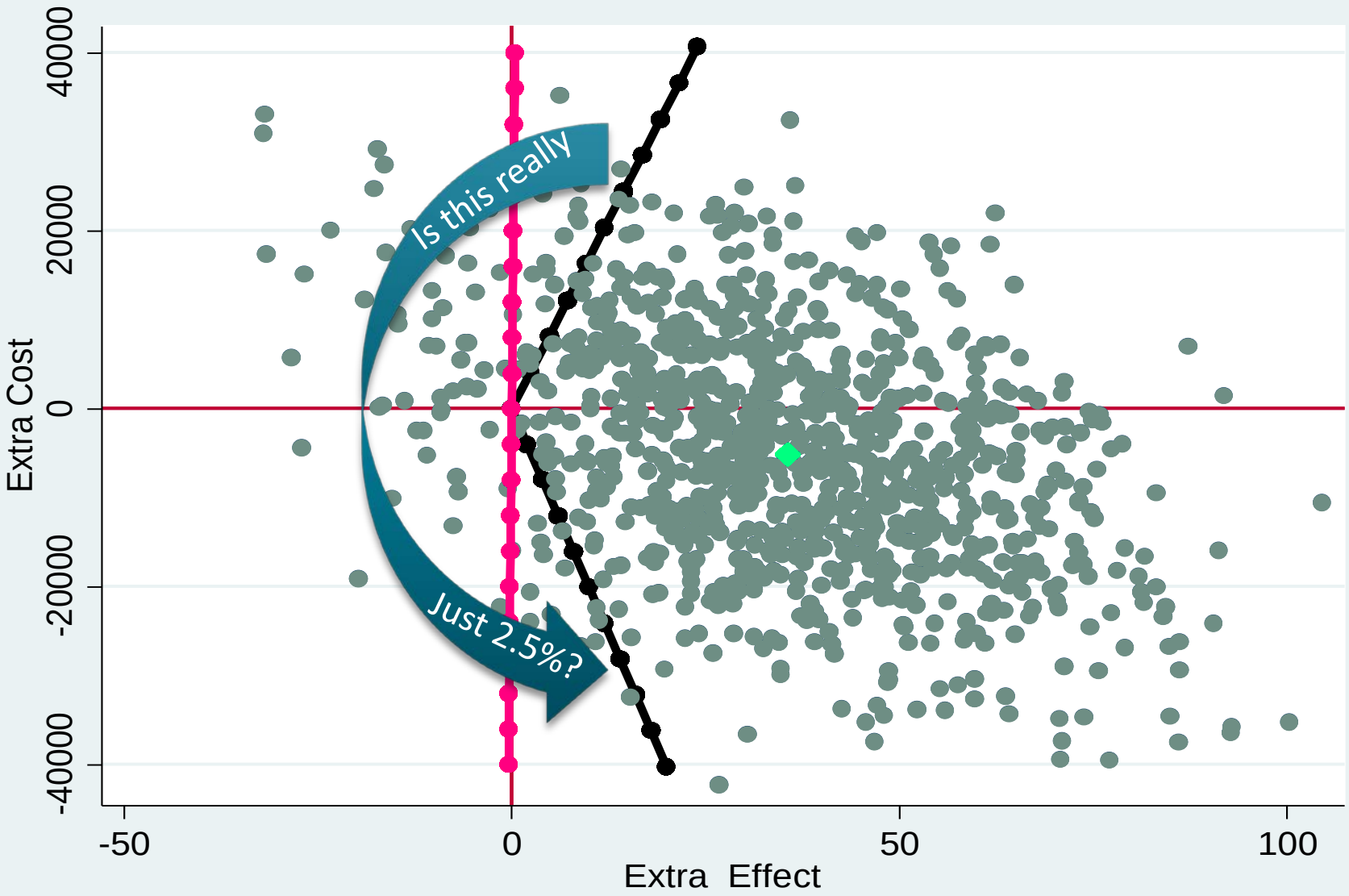


CEAC says, "100% CE at $100k"

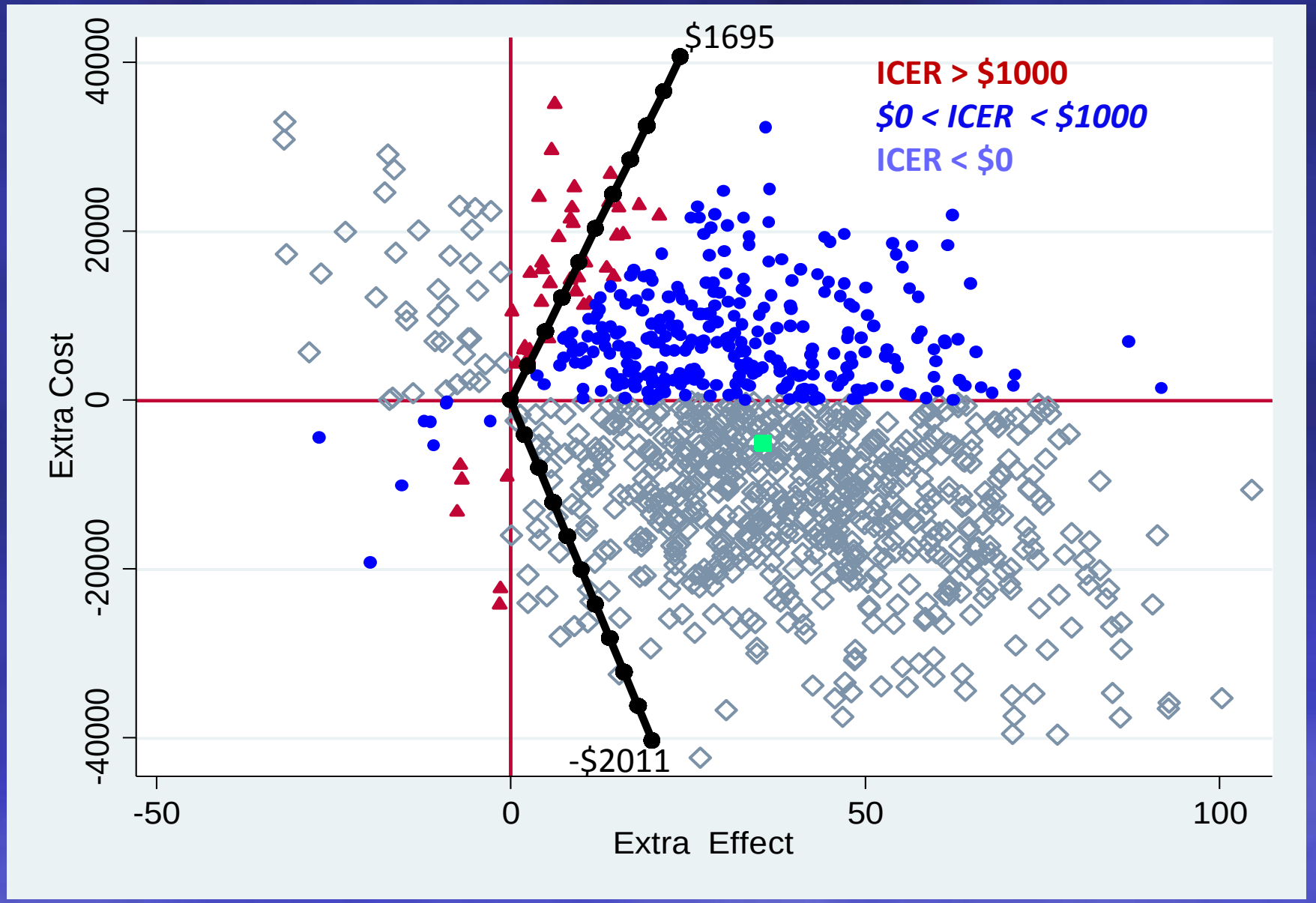



```
-> tabulation of icer50k

    icer50k |      Freq.     Percent        Cum.
------------+-----------------------------------
          0 |          1        0.10        0.10
          1 |        999       99.90      100.00
------------+-----------------------------------
      Total |      1,000      100.00

-> tabulation of icer100k

   icer100k |      Freq.     Percent        Cum.
------------+-----------------------------------
          1 |      1,000      100.00      100.00
------------+-----------------------------------
      Total |      1,000      100.00
```

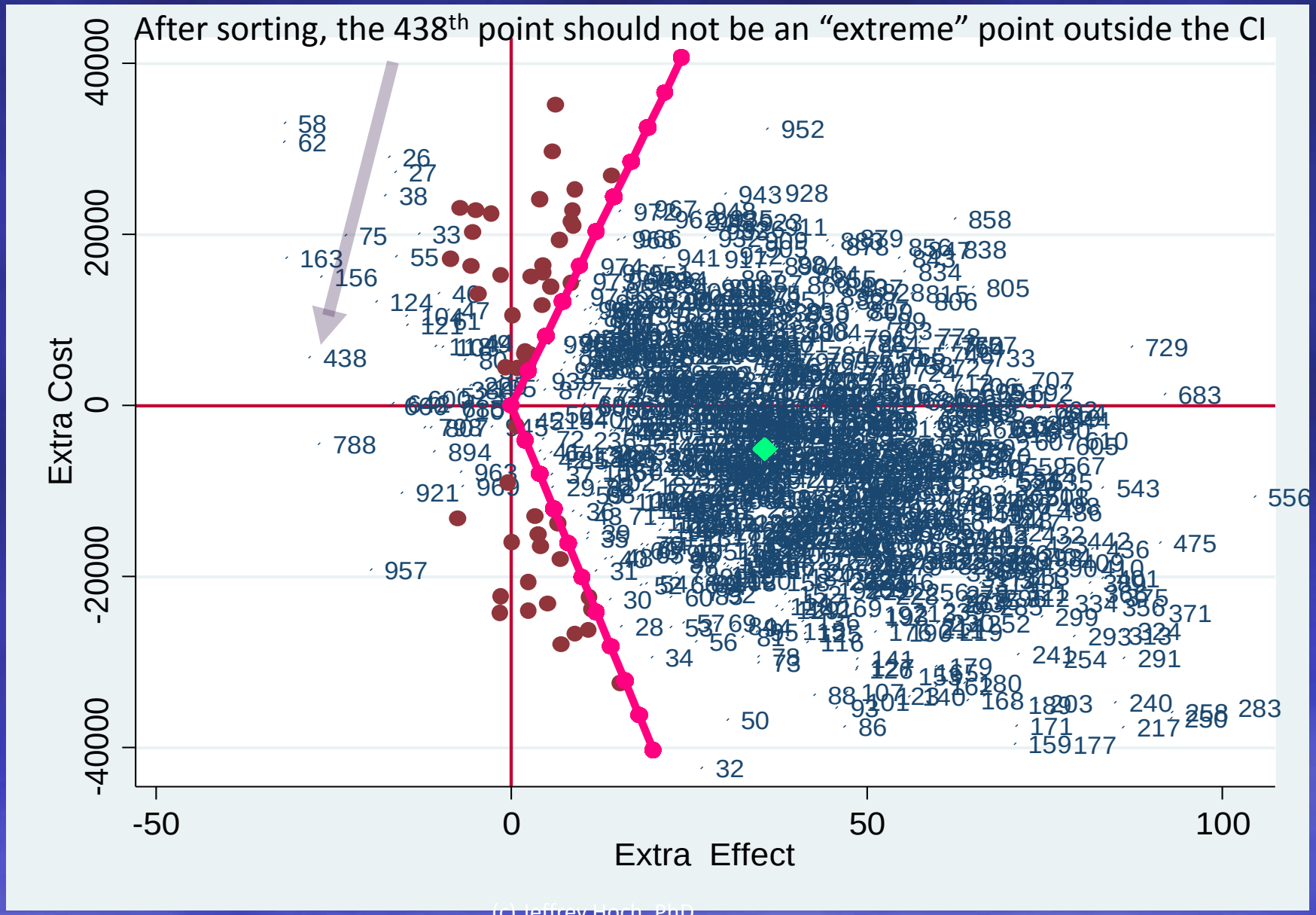
Bootstrap vs. CEAC: could both be wrong?



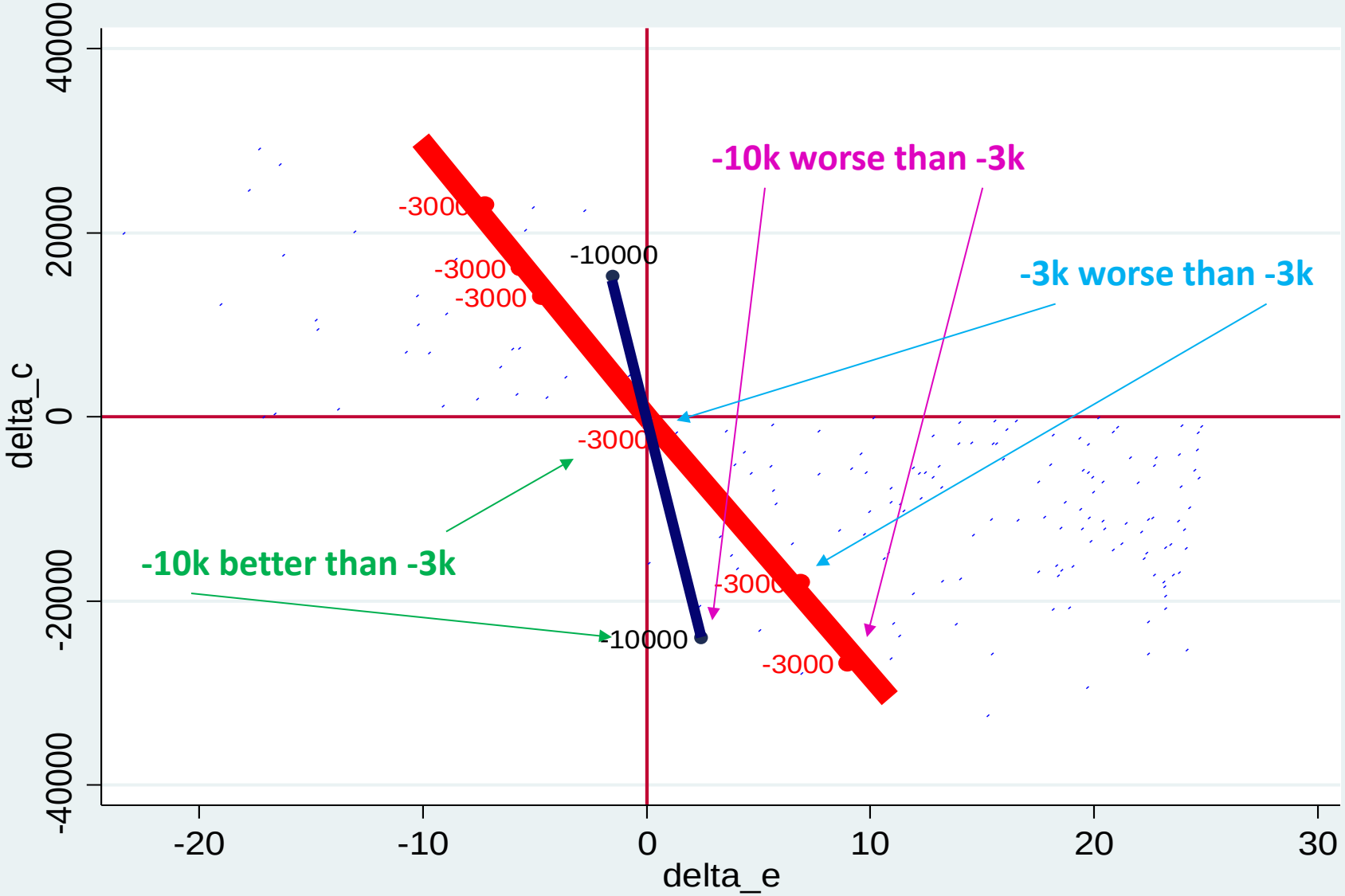
Shouldn't (-2011, 1695) contain all ICER values ($0, $1000)?



#'s 26 – 974 are supposed to be "good"



What's going on? Better is worse?



Take home lessons

- Negative ICERs are tricky!
- ICERs with both ΔC and $\Delta E < 0$ must be $> \lambda$ for CE
- Looking at things with graphs can help

Outline

- Review the paper
- Give examples of the main points
- Bernie's impact on me

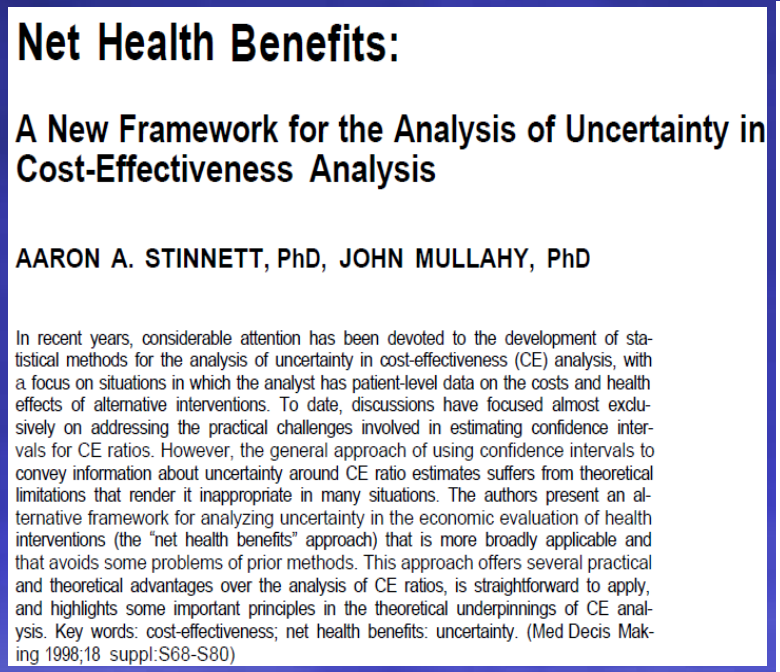
1998 and the discovery of INB

Incremental net MONETARY benefit

- $INMB = \lambda \Delta E - \Delta C$
- If $INMB > 0$ then $\lambda \Delta E - \Delta C > 0$, so $\lambda > \Delta C / \Delta E$

Incremental net HEALTH benefit

- $INHB = \Delta E - \Delta C / \lambda$
- If $INHB > 0$ then $\Delta E - \Delta C / \lambda > 0$, so $\lambda > \Delta C / \Delta E$

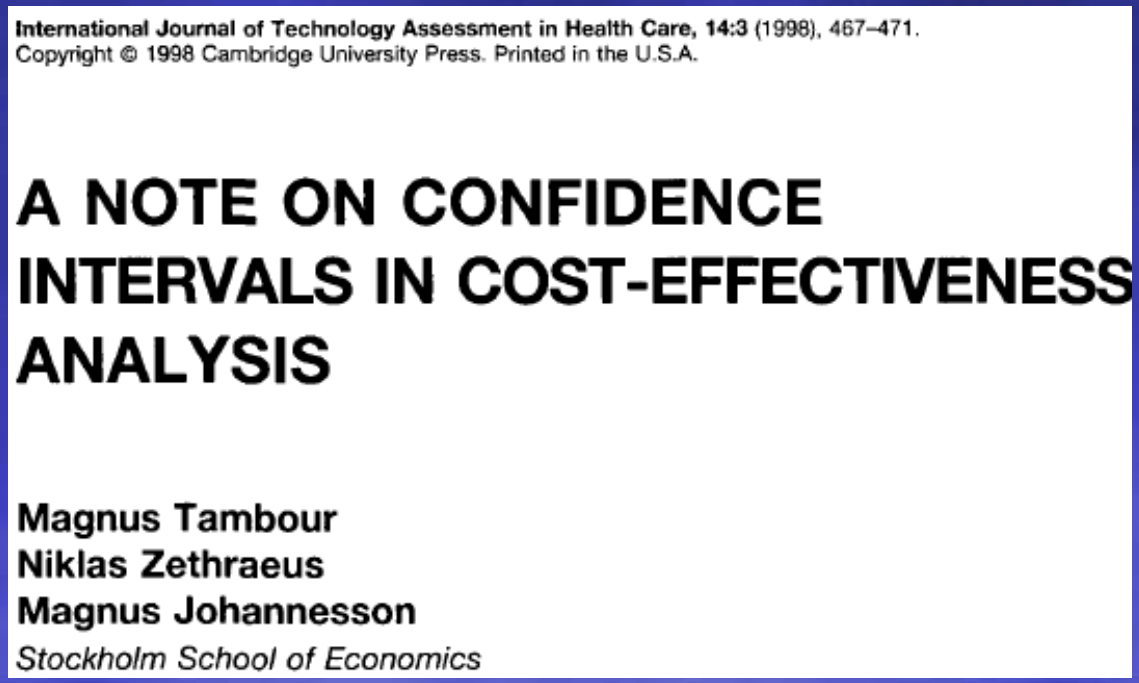


Net Health Benefits:

A New Framework for the Analysis of Uncertainty in Cost-Effectiveness Analysis

AARON A. STINNETT, PhD, JOHN MULLAHY, PhD

In recent years, considerable attention has been devoted to the development of statistical methods for the analysis of uncertainty in cost-effectiveness (CE) analysis, with a focus on situations in which the analyst has patient-level data on the costs and health effects of alternative interventions. To date, discussions have focused almost exclusively on addressing the practical challenges involved in estimating confidence intervals for CE ratios. However, the general approach of using confidence intervals to convey information about uncertainty around CE ratio estimates suffers from theoretical limitations that render it inappropriate in many situations. The authors present an alternative framework for analyzing uncertainty in the economic evaluation of health interventions (the "net health benefits" approach) that is more broadly applicable and that avoids some problems of prior methods. This approach offers several practical and theoretical advantages over the analysis of CE ratios, is straightforward to apply, and highlights some important principles in the theoretical underpinnings of CE analysis. Key words: cost-effectiveness; net health benefits: uncertainty. (Med Decis Making 1998;18 suppl:S68-S80)



International Journal of Technology Assessment in Health Care, 14:3 (1998), 467–471.

A NOTE ON CONFIDENCE INTERVALS IN COST-EFFECTIVENESS ANALYSIS

Magnus Tambour
Niklas Zethraeus
Magnus Johannesson
Stockholm School of Economics

Growth of the field....

In recent years, considerable attention has been devoted to the development of statistical methods for the analysis of uncertainty in cost-effectiveness (CE) analysis, with a focus on situations in which the analyst has patient-level data on the costs and health effects of alternative interventions. To date, discussions have focused almost exclusively on addressing the practical challenges involved in estimating confidence intervals for CE ratios. However, the general approach of using confidence intervals to convey information about uncertainty around CE ratio estimates suffers from theoretical limitations that render it inappropriate in many situations. The authors present an alternative framework for analyzing uncertainty in the economic evaluation of health interventions (the "net health benefits" approach) that is more broadly applicable and that avoids some problems of prior methods. This approach offers several practical and theoretical advantages over the analysis of CE ratios, is straightforward to apply, and highlights some important principles in the theoretical underpinnings of CE analysis.

Abstract

How to obtain confidence intervals for cost-effectiveness ratios is complicated by the statistical problems of obtaining a confidence interval for a ratio of random variables. Different approaches have been suggested in the literature, but no consensus has been reached. We propose an alternative simple solution to this problem. By multiplying the effectiveness units by the price per effectiveness unit, both costs and benefits can be expressed in monetary terms and standard statistical techniques can be used to estimate a confidence interval for net benefits. This approach avoids the ratio estimation problem and explicitly recognizes that the price per effectiveness unit has to be known to provide cost-effectiveness analysis with a useful decision rule.

Key moments for me

1. **Hoch J**. “Characterizing Uncertainty in the Economic Evaluation of an Assertive Community Treatment Program: Incremental Cost-Effectiveness Ratios, Net Health Benefits, and Policy Implications” presented at the Centre for Evaluation of Medicines, McMaster University, Hamilton, Ontario, March 2000.
2. “beer” afterwards
3. Working on the paper
4. Recognition afterwards
5. Mentorship

Resulting article…

HEALTH ECONOMICS
Health Econ. **11**: 415–430 (2002)
Published online 31 January 2002 in Wiley InterScience (www.interscience.wiley.com). **DOI:**10.1002/hec.678

ECONOMETRICS AND HEALTH ECONOMICS

Regression INB λ or WTP

Something old, something new, something borrowed, something blue: a framework for the marriage of health econometrics and cost-effectiveness analysis

Jeffrey S. Hoch[a,*], Andrew H. Briggs[b] and Andrew R. Willan[c]

Gauss–Markov theorem

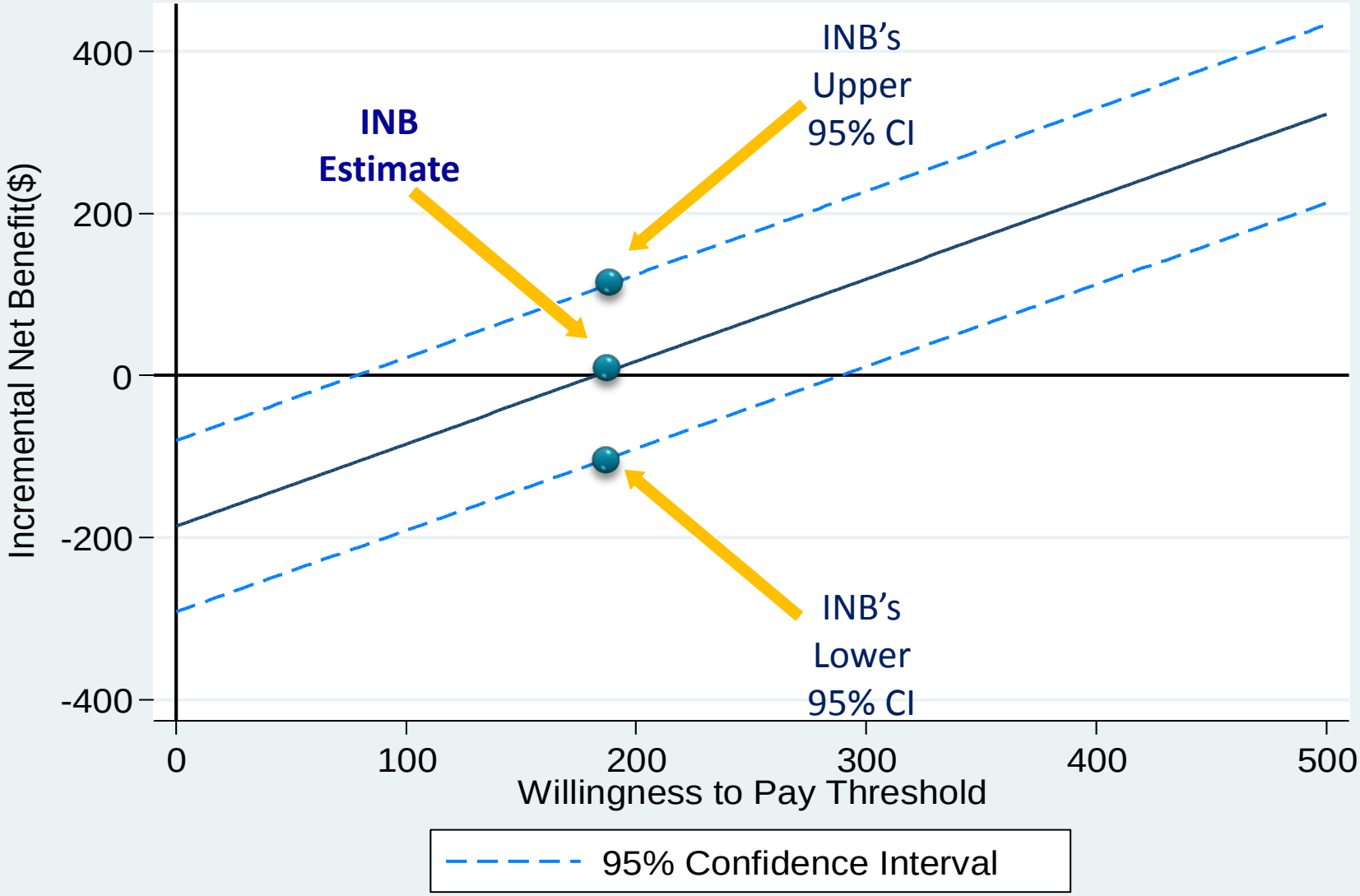
OLS estimates are BLUE

From Wikipedia, the free encyclopedia

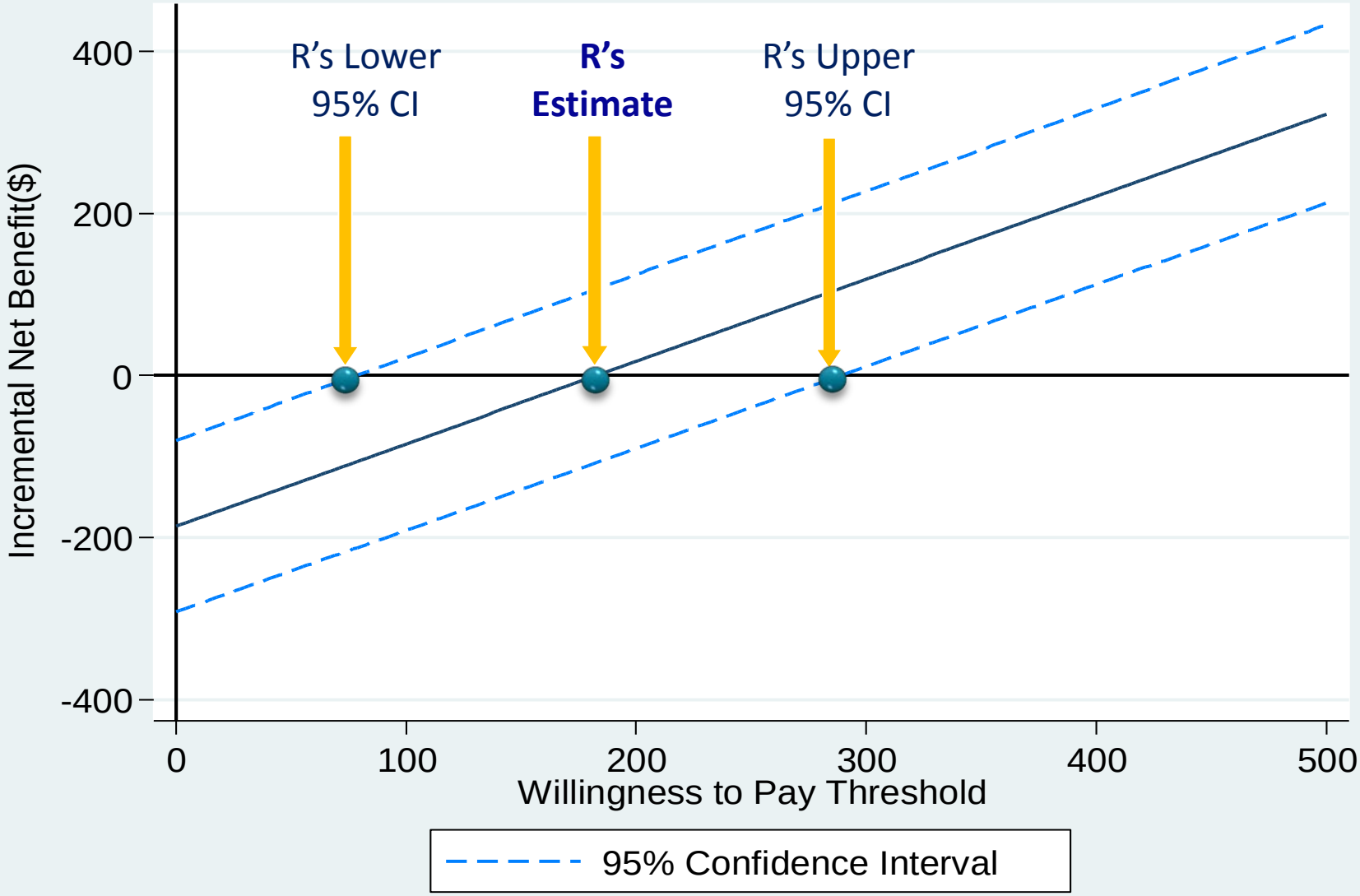
Not to be confused with Gauss–Markov process.
"BLUE" redirects here. For queue management algorithm, see Blue (queue management algorithm).

In statistics, the **Gauss–Markov theorem**, named after Carl Friedrich Gauss and Andrey Markov, states that in a linear regression model in which the errors have expectation zero and are uncorrelated and have equal variances, the **best linear unbiased estimator** (**BLUE**) of the coefficients is given by the ordinary least squares (OLS) estimator. Here "best" means giving the lowest variance of the estimate, as compared to other unbiased, linear estimators. The errors don't need to be normal, nor do they need to

Net benefit regression



Net benefit regression, cont.



Key moments for me

1. **Hoch J**. “Characterizing Uncertainty in the Economic Evaluation of an Assertive Community Treatment Program: Incremental Cost-Effectiveness Ratios, Net Health Benefits, and Policy Implications” presented at the Centre for Evaluation of Medicines, McMaster University, Hamilton, Ontario, March 2000.
2. “beer” afterwards
3. Working on the paper
4. Recognition afterwards
5. Mentorship

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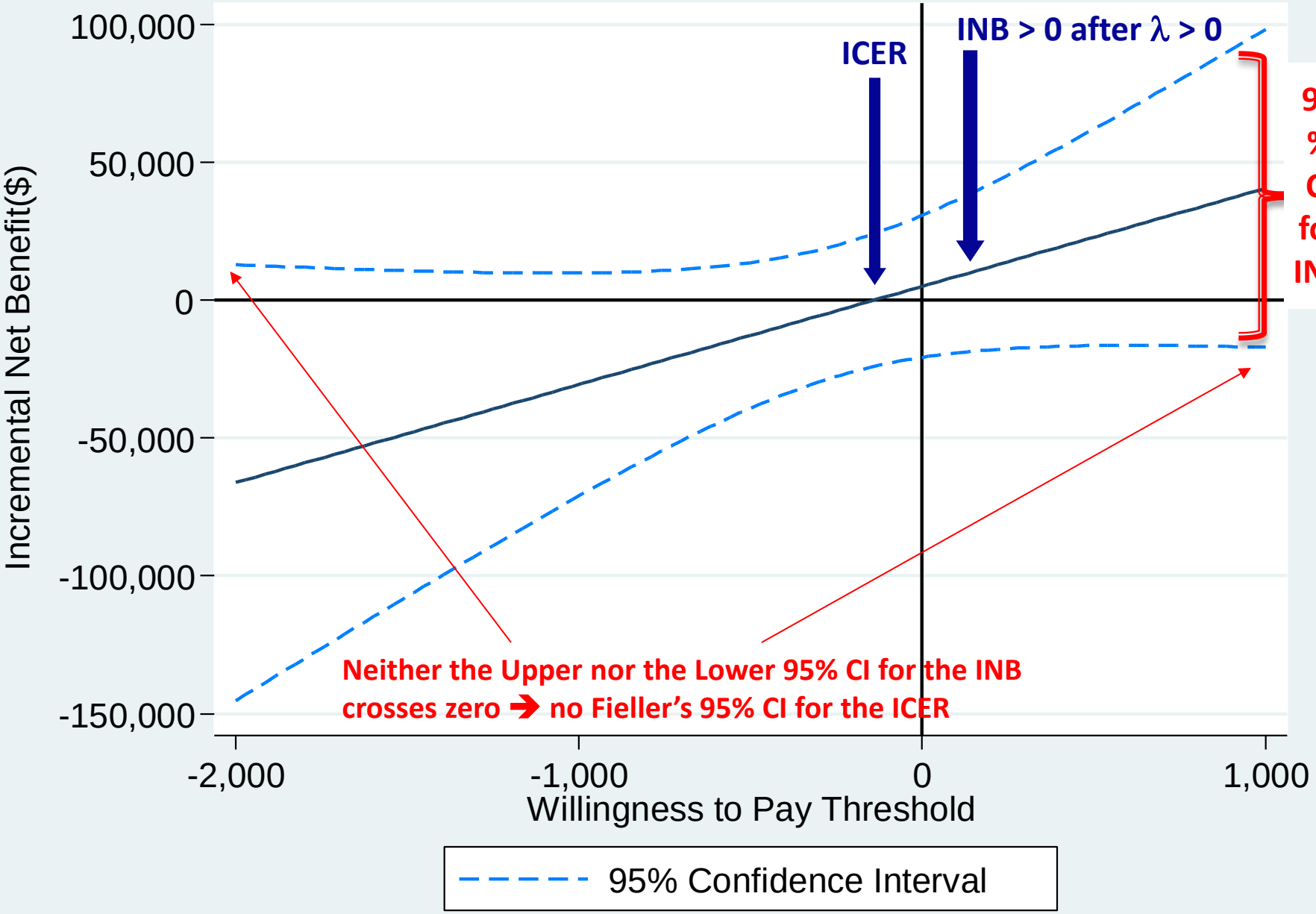
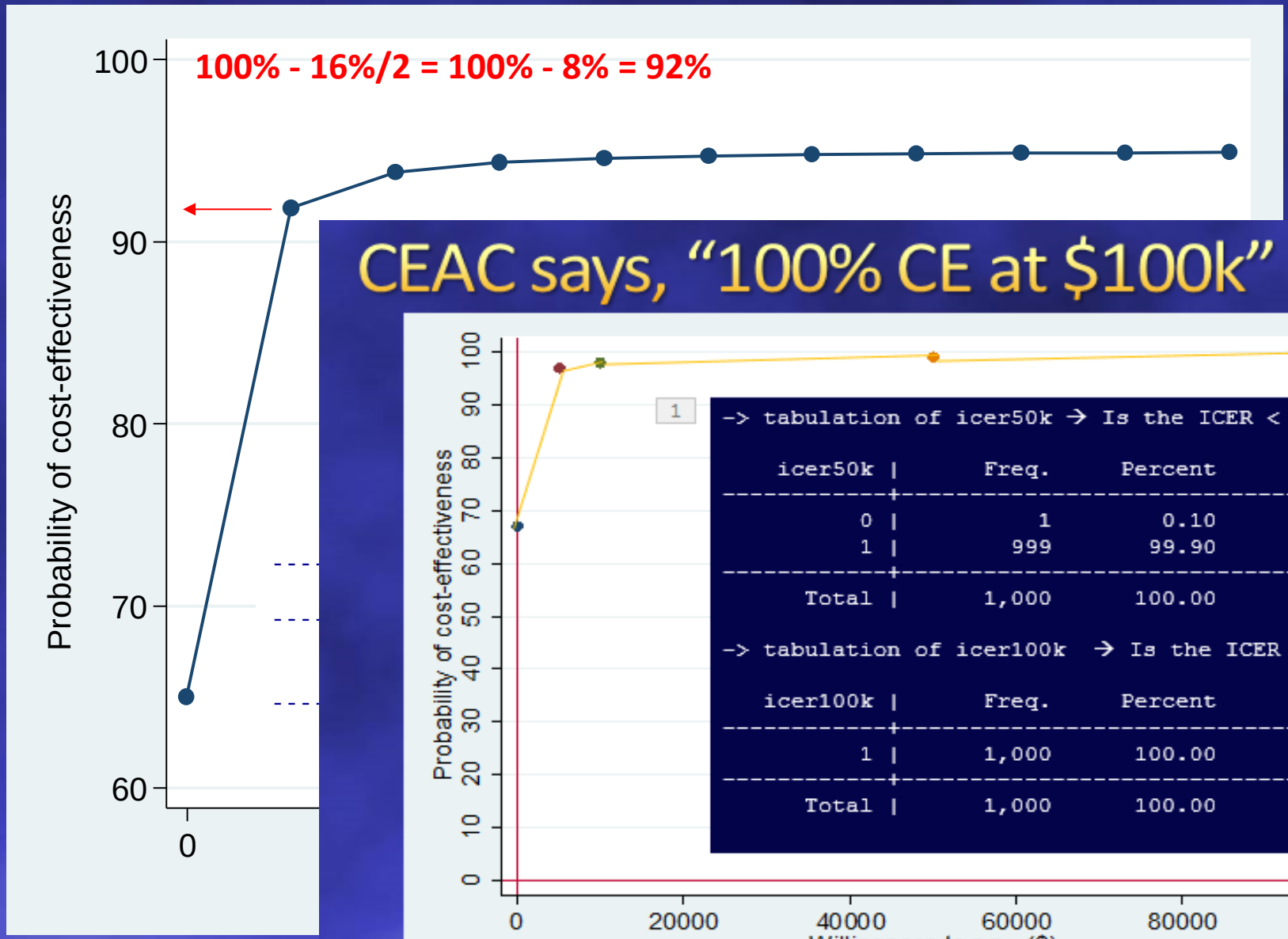
Net benefit regression can answer

- Estimate issues
  - What is the ICER?
  - What is the INB?
- Uncertainty issues
  - Why can't I compute Fieller's 95% CI?
  - How can I create a CEAC?



CEAC can be made from p-value



CEAC says, "100% CE at $100k"


```
-> tabulation of icer50k → Is the ICER < $50,000

    icer50k |      Freq.     Percent        Cum.
------------+-----------------------------------
          0 |          1        0.10        0.10
          1 |        999       99.90      100.00
------------+-----------------------------------
      Total |      1,000      100.00

-> tabulation of icer100k  → Is the ICER < $100,000

   icer100k |      Freq.     Percent        Cum.
------------+-----------------------------------
          1 |      1,000      100.00      100.00
------------+-----------------------------------
      Total |      1,000      100.00
```

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Nomination leads to Recognition

2003 ISPOR Research Excellence Awards

The recipients of the 2003 ISPOR Research Excellence Award (one for Methodology Excellence and one for Practical Application Excellence) are selected by the Awards Committee based upon publications that have appeared in respected peer-review journals and other communication venues (e.g., books, reports) during the preceding eighteen months from January 1 of the year awarded. The award selection is based upon the publicationï¿½s clear description of methods, along with the appropriate and creative applications (or proposal thereof in conceptual methodology work) of techniques to answer important questions in the field of pharmacoeconomics and outcomes research. Such publications will be expected to have much impact on the field, due to their acceptance and application by others.

ISPOR Research Excellence Award for Methodology Excellence
Jeffrey S. Hoch PhD,

The 2003 recipient of the ISPOR Research Excellence Award for Methodology Excellence

Jeffrey S. Hoch, BA, MA, PhD as the senior author of the research paper:
ï¿½Something Old, Something New, Something Borrowed, Something BLUE: A Framework for the Marriage of Health Econometrics and Cost-effectiveness Analysis.ï¿½ Health Economics 2002; 11:415-430

Methods for the Economic Evaluation of Health Care Programmes

THIRD EDITION

Michael F. Drummond
Mark J. Sculpher
George W. Torrance
Bernie J. O'Brien
Greg L. Stoddart

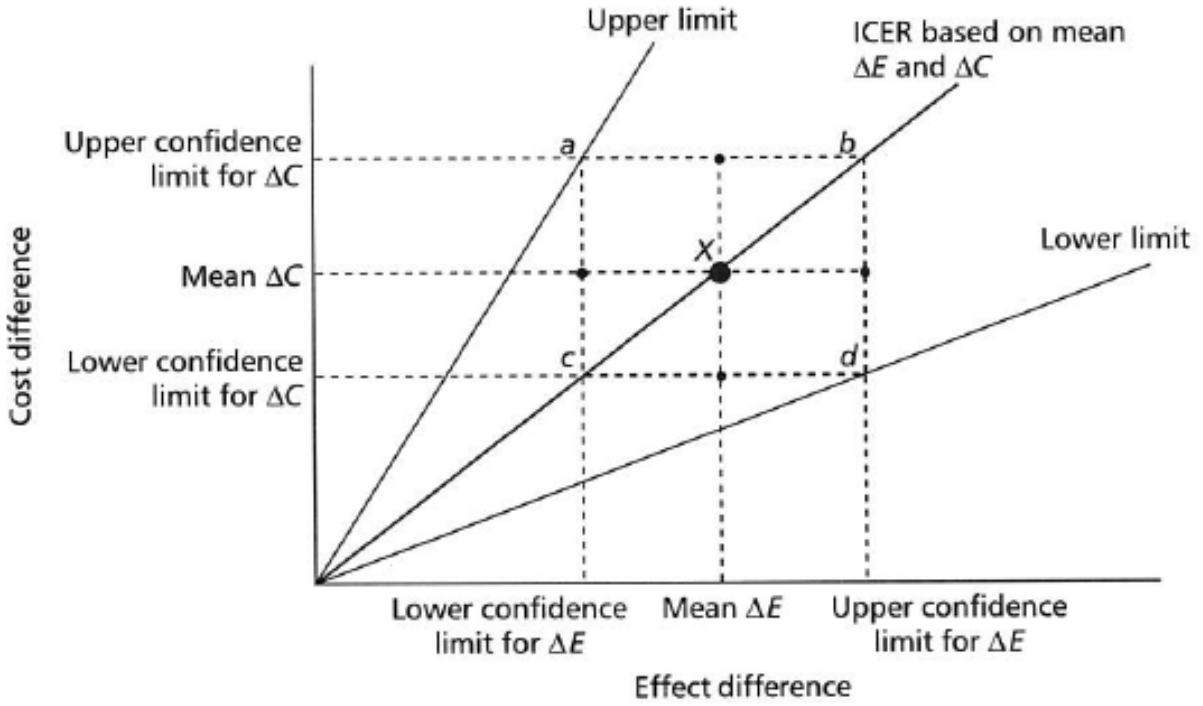


Fig. 8.2 The top right ('north-east') quadrant of the cost-effectiveness plane. This shows mean cost and effect differences (of treatment compared to control) at point X and the associated incremental cost-effectiveness ratio (ICER) represented by the bold line from the origin through that point. The 'confidence box' *abcd* is the combination of confidence intervals in cost and effect differences.

The combination of these simple 95% CIs for cost and effect differences can be portrayed as two-dimensional confidence regions for cost-effectiveness as in Fig. 8.2 (O'Brien *et al.* 1994*b*, *c*). The most simple definition of the confidence region is the 'confidence box' bounded by *abcd*. Rays from the origin passing through points *a* and *d* define a slice of pie based on the upper limits of each CI. The box approach assumes that the difference in costs is independent of (uncorrelated with) the difference in effects which would be unlikely in most situations. It is also the case that, when costs and effects are independent, the confidence box will represent 90% CIs although

8.3.3. Explaining variability in cost-effectiveness analysis

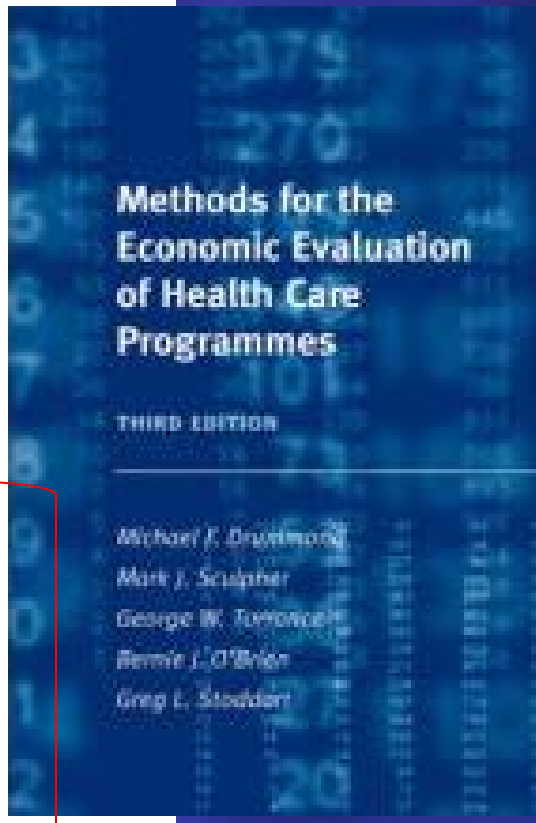
As mentioned in Section 8.3.2, in analysing patient-level data on costs and effects, explaining variability in cost-effectiveness can be very important. Whilst cost-effectiveness analysis was based on deterministic measures of the ICER, formal regression analysis to quantify variability was not possible. One of the implications of moving to stochastic methods in the analysis of patient-level economic data is that regression methods are now feasible. Regression analysis for costs is widely undertaken, although it is complicated by the features of cost data described in Section 8.3.1 (Manning and Mullahy 2001), but this has conventionally not been the case with cost-effectiveness. Hoch *et al.* (2002) made a major contribution to this development by introducing the concept of net benefit regression. When individual patient data on costs and effects exist, as in trial-based studies, NMB can be calculated for each individual (i) in the trial as shown in the equation below where the subscript i indicates that the relevant measure can relate to the individual patient:

$$NMB_i = (E_i \times R_T) - C_i$$

Using a model regressing this patient-level NMB_i against the treatment arm dummy variable (t_i), Hoch *et al.* (2002) demonstrated the equivalence of a regression-based approach to CEA with a 'standard' stochastic cost-effectiveness analysis. Their regression framework is illustrated in the equation below:

$$NMB_i = \alpha + \beta t_i + e_i$$

In this formulation, the NMB for the i-th patient in the trial is the patient-level net-benefit defined above and t_i represents a treatment dummy taking the value 0 for 'standard' or comparator therapy and 1 for the new intervention. In the context of



p. 267 of the "blue" book

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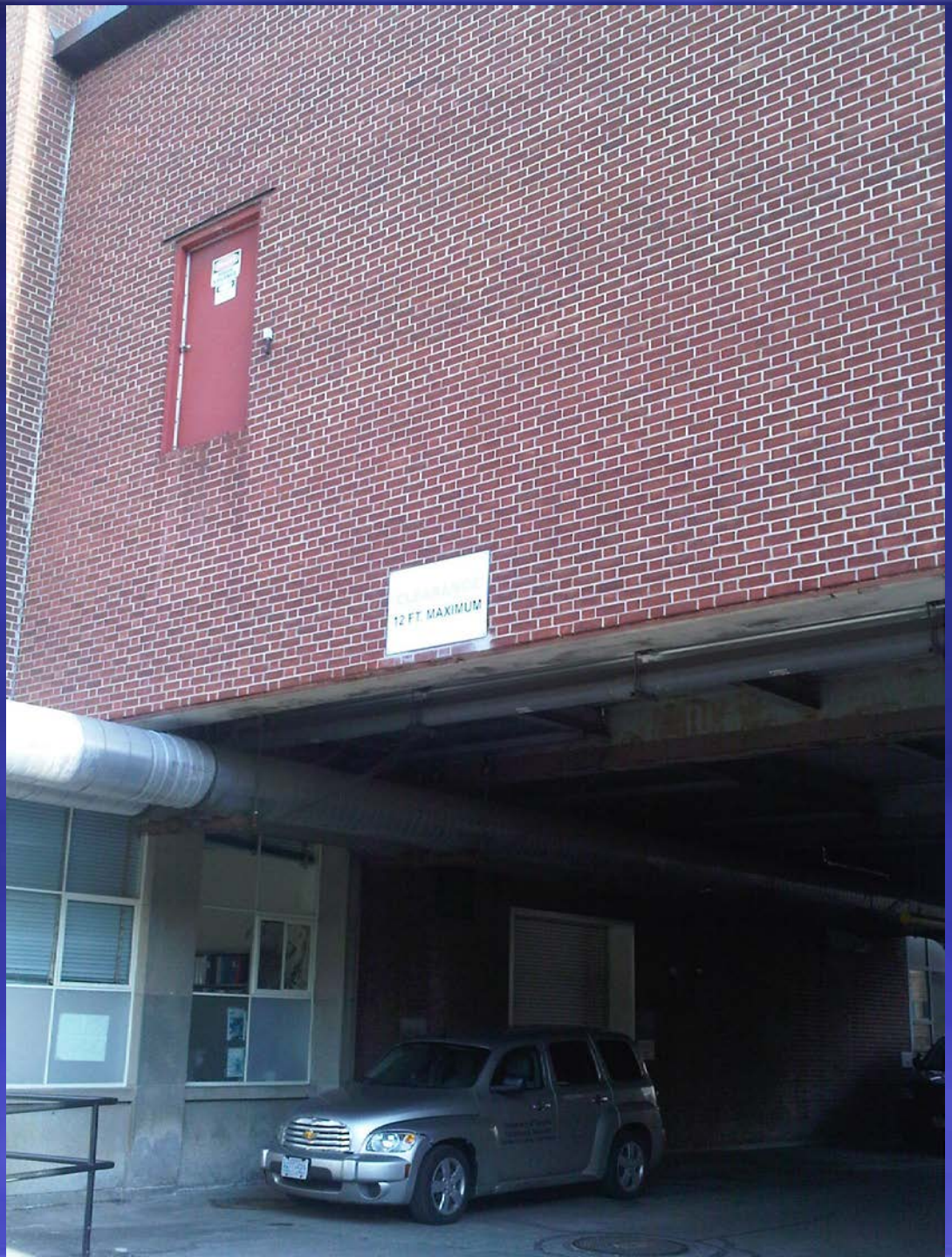
There is tension in HTA between doing work that is theoretically correct versus practically useful.



Lessons I learned

- I learned from Bernie that it is ok to
  - Have funny titles
  - Address a problem (even if the 1st attempt is not perfect)
  - Help others, especially new researchers

Honour Humour

- "Health care cost matters for homeless people: An example of costing mental health and addiction services in homeless shelters in Canada"
- "All dressed up and know where to go: An example of how to use net benefit regression to do a cost-effectiveness analysis with person-level data (The 'A' in CEA)"
- "Something old, something new, something borrowed, something BLUE: A framework for the marriage of health econometrics and cost effectiveness analysis"

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Lessons I learned

- I learned from Bernie that it is ok to
  - Have funny titles
  - Address a problem (even if the 1st attempt is not perfect)
  - Help others, especially new researchers

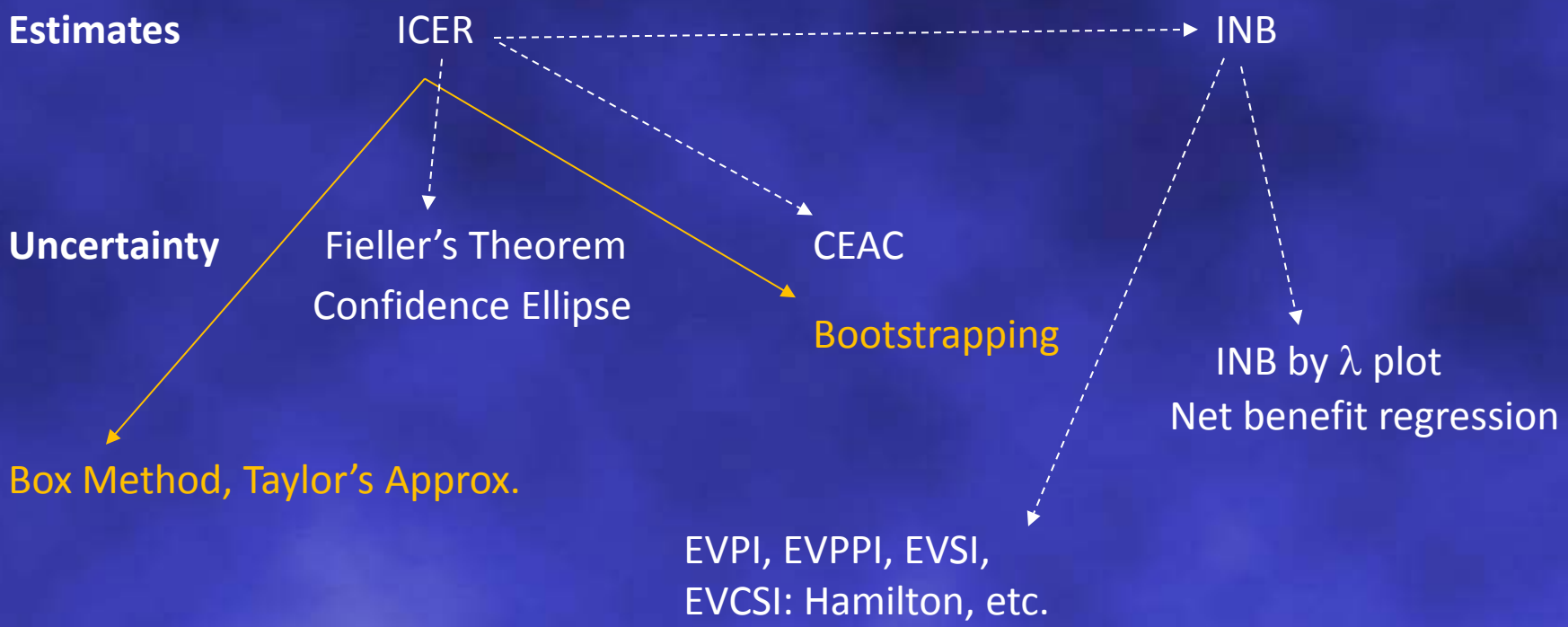
- Are we training people to replace the people we will miss?

- How can we reward behavior that helps us all?

Main messages for the HTA field

- Even with all of the data (from a trial), there is still uncertainty.
- Uncertainty in CEA is more than just a 95% CI for ΔC and one for ΔE. You need one for a f().
- It is ok to be understandable and to make a first attempt at solving a problem.

The power and significance of the "power and significance" paper

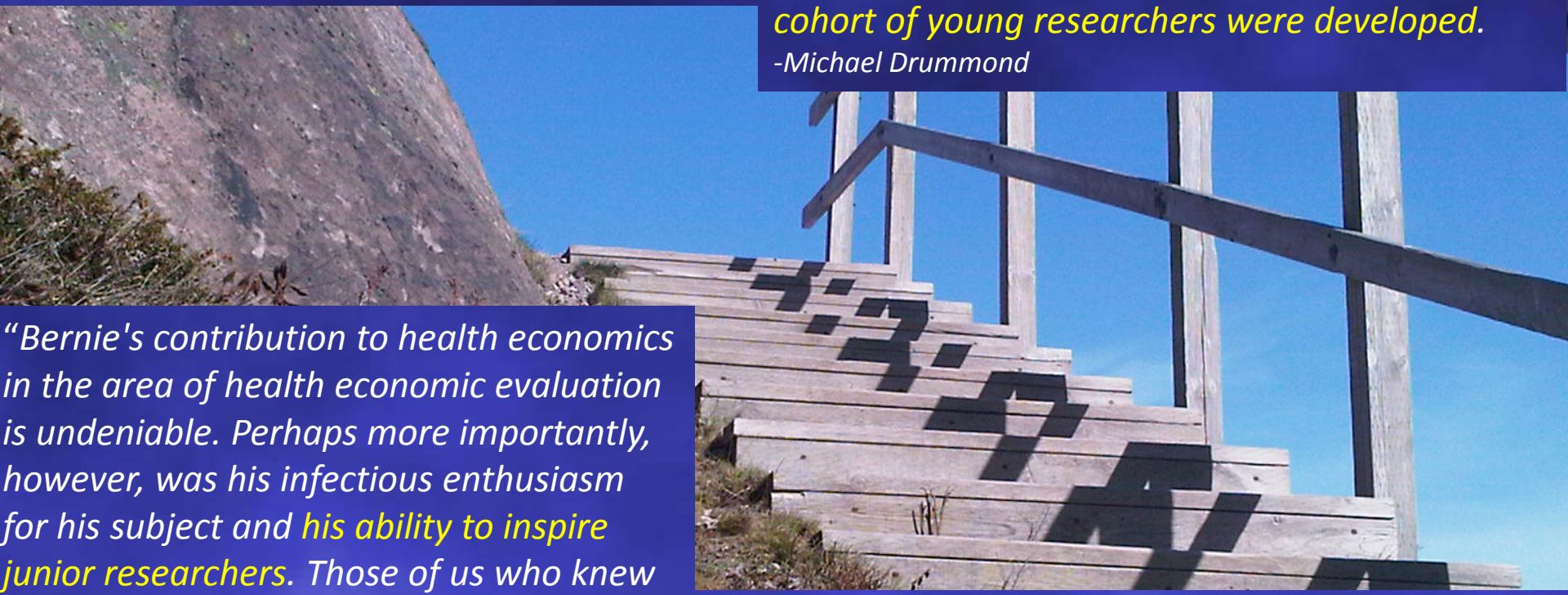


Michael Jordan

"Some people want it to happen some wish it would happen others make it happen".

Bernie "never lost sight of the fact the main role of economic evaluation was to help doctors and health agencies, facing inevitable resource constraints, make cost effective choices under uncertainty."
- Martin Buxton

"Bernie was obviously destined for a top leadership position in health economics. I imagine that he would have developed new ways to merge theory and practice. He would have also accomplished this whilst establishing a learning environment where the skills of a new cohort of young researchers were developed.
-Michael Drummond



"Bernie's contribution to health economics in the area of health economic evaluation is undeniable. Perhaps more importantly, however, was his infectious enthusiasm for his subject and his ability to inspire junior researchers. Those of us who knew Bernie will miss him terribly, yet it is the coming generation of health economists who have really lost out. Without Bernie, health economics will just be a little less fun."
-Andrew Briggs

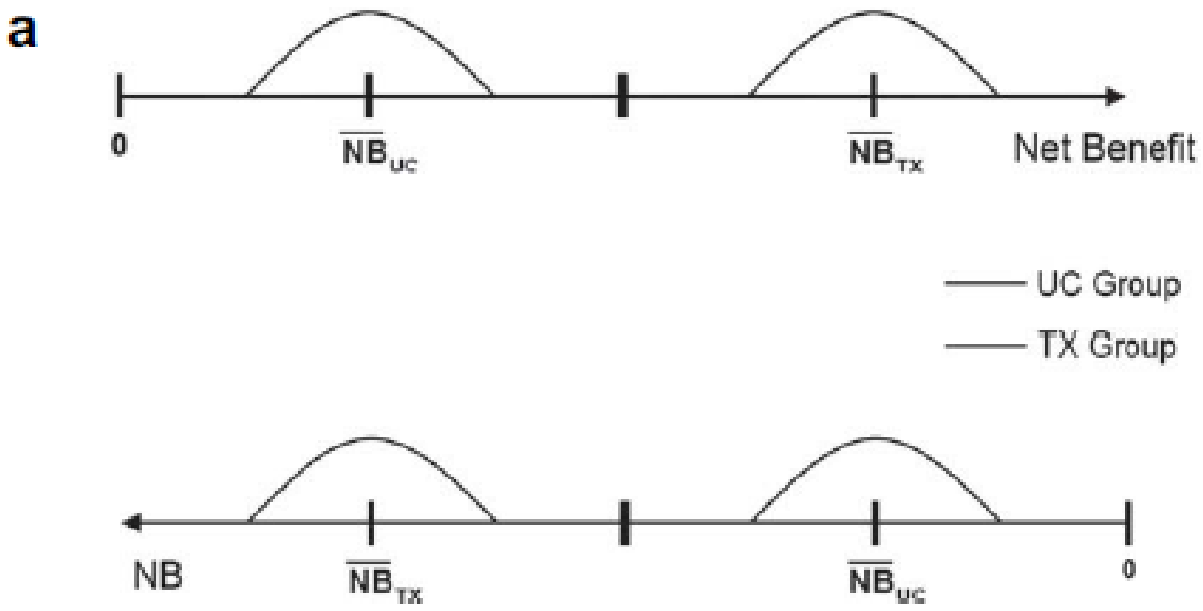
"Bernie was deeply respected by all who had the privilege of working with him, not only for his brilliance and expertise, but also for his open manner, warmth, enthusiasm and constant pursuit of excellence."
-Les Levin

Questions?

jeffrey.hoch@utoronto.ca

Extra slides

Going *from* person-level data *to* group means

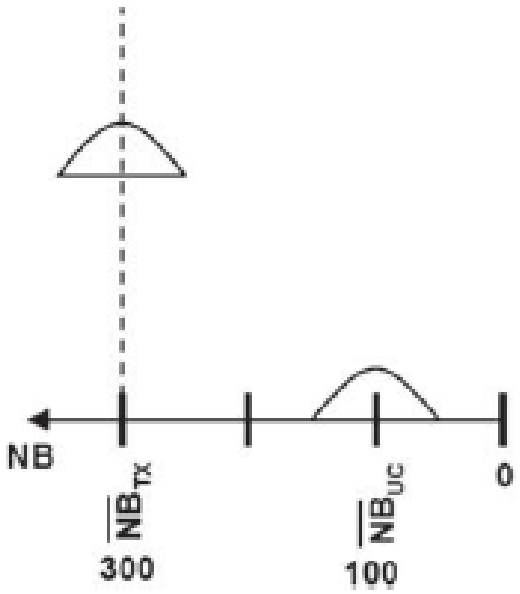


Net benefits are measured on a scale from small (on the left) to large (on the right).

Net benefits are reverse scaled from large (on the left) to small (on the right).

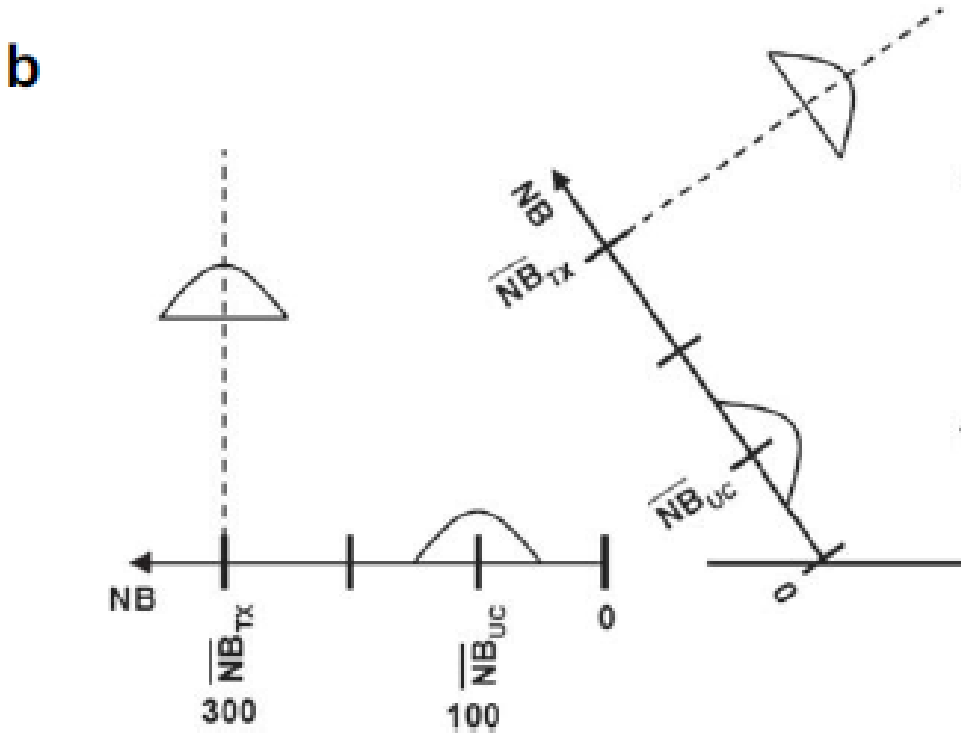
The idea behind NBR

b



Average net benefit for TX is levitated…

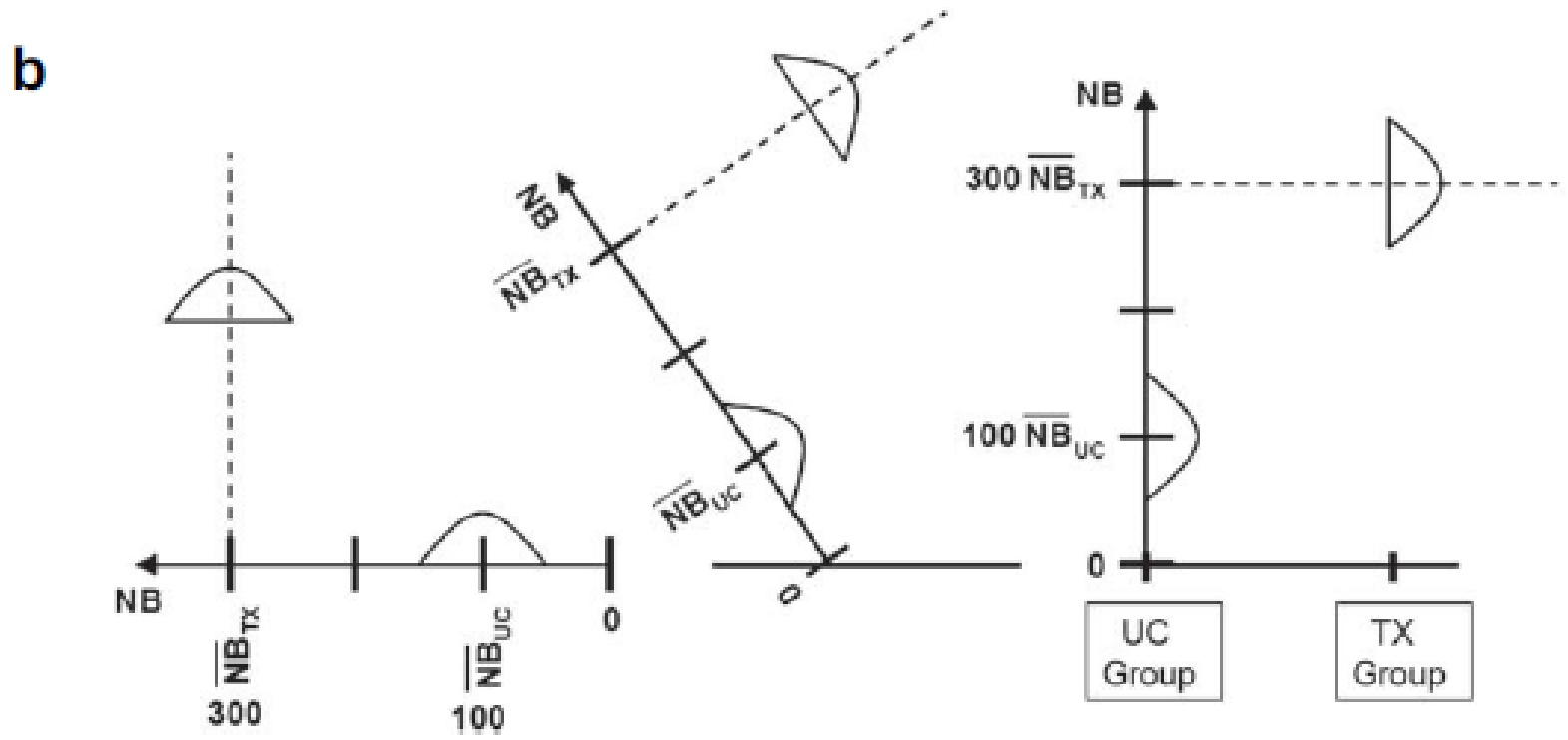
The idea behind NBR



Average net benefit for TX is levitated…

the graph rotates…

The idea behind NBR

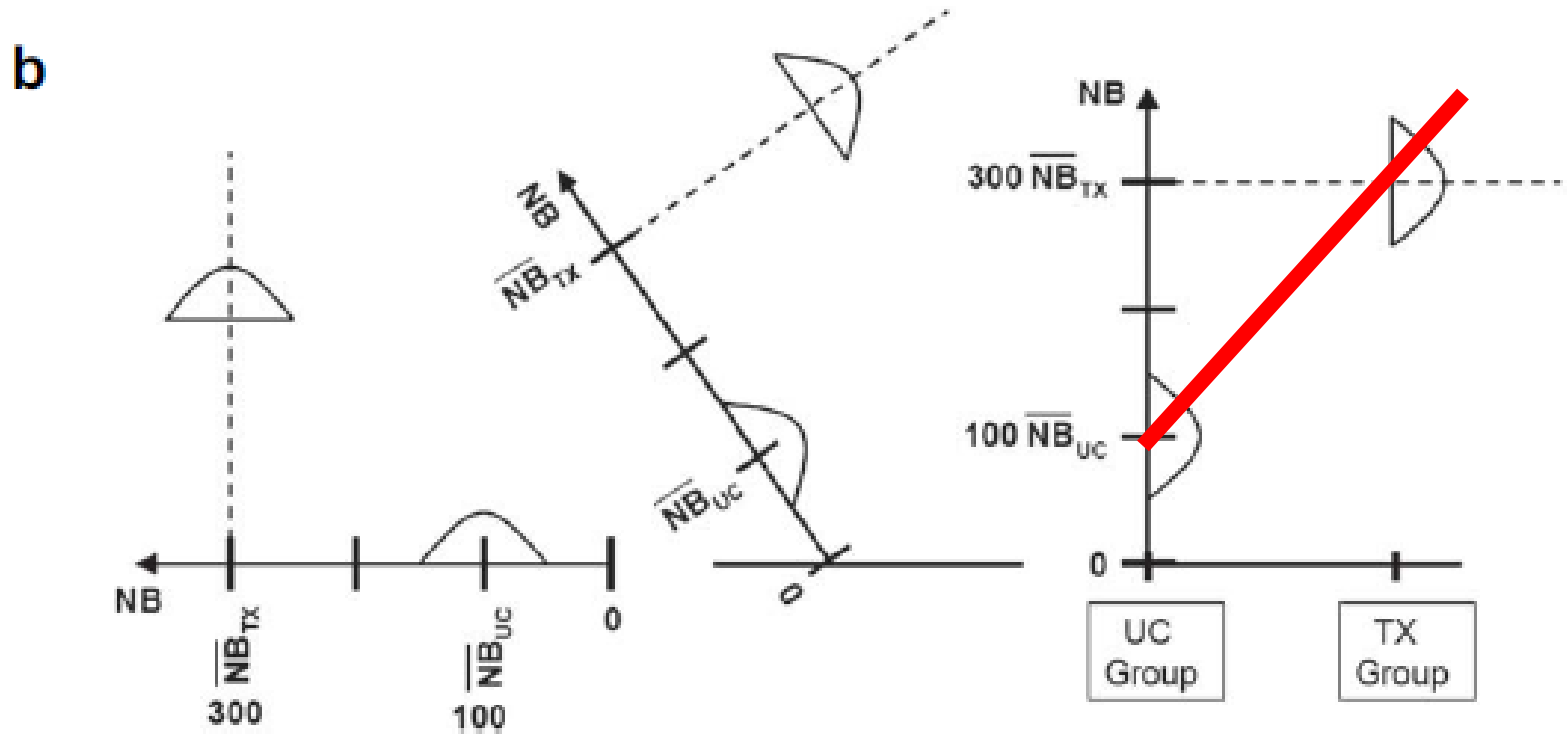


Average net benefit for TX is levitated…

the graph rotates…

and regression will fit a line with a slope equal to the difference in the average net benefits for the UC and TX groups. The y-intercept term equals the average net benefit for UC, the slope equals the incremental net benefit and the sum of the intercept and the slope equals the average net benefit for TX

What are b_0 and b_1 in $NB = b_0 + b_1 TX$?



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Published: November 14, 2003

With the increasing costs of the healthcare system, making decisions about which equipment and technologies are funded is a tough call.

At McMaster University, a team of researchers has been assembled to provide direction in assessing health technologies by Bernie O'Brien, a professor of clinical epidemiology and biostatistics. The team's work is being assisted by a $3-million grant over three years from the Ministry of Health and Long-Term Care (MOHLTC).

O'Brien is associate director of the Centre for Evaluation of Medicines located at St. Joseph's Hospital in Hamilton, and director of PATH (Program for Assessment of Technology in Health). He and his colleagues will assess the benefits and the costs of new health technologies through a series of research studies.

The resulting health economic evaluations will provide evidence to enable the government to make well-informed judgments as they relate to purchasing decisions.

"The delicate balance between cost and effectiveness of healthcare technologies places a heavy burden on decision makers," said O'Brien. "Whereas pharmaceutical products undergo a rigorous assessment process, the same standards do not exist when evaluating the cost effectiveness of emerging healthcare technologies."

With the PATH program, O'Brien and his team will assess several new therapeutic interventions, including drug-eluting stents, positron emission tomography (PET) scanning and endovascular aneurysm repair (EVAR).

An aortic aneurysm is a dilation of the aorta that will eventually rupture and result in death unless surgically repaired. Standard treatment for aortic aneurysms involves directly replacing that portion of the aorta with a synthetic graft by opening the chest or abdomen.

EVAR repair is a much less-invasive technique, which is safer and therefore the preferred method for the high-risk patients, because it involves excluding the aneurysm from the circulation by introducing a 'stent-graft' into the aorta through an artery in the groin. The costs associated with the stent device and its insertion in patients who are deemed non-surgical candidates creates a financial burden for hospitals. PATH will conduct a formal economic analysis of the costs, including outcomes, which will be used to inform the ministry's future funding policy on EVAR.

The team of researchers will also evaluate drug-coated stents used in angioplasty procedures to open clogged arteries. The stents release drugs that inhibit tissue growth in narrowed coronary arteries in an effort to prevent a re-narrowing of the artery. The ministry has provided $12 million for the new drug-eluting stents provided that the centres agree to participate in O'Brien's studies.

PATH is also assessing the economics of PET scanners, of which the MOHLTC will fund at least two randomized controlled trials. This sophisticated technology allows doctors to assess organs, muscle tissue

HEALTH ECONOMICS
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Regression methods for covariate adjustment and subgroup analysis for non-censored cost-effectiveness data

Andrew R. Willan[a,b,*], Andrew H. Briggs[c] and Jeffrey S. Hoch[d]
[a] *Program in Population Health Sciences, Hospital for Sick Children, Toronto, Canada*
[b] *Department of Public Health Sciences, University of Toronto, Canada*
[c] *Health Economics Research Centre, University of Oxford, UK*
[d] *Department of Epidemiology and Biostatistics, University of Western Ontario, Canada*

when cost data are log-normal and the total sample size is as small as 100. The results of this experiment agree with other recent analyses of this problem that have also concluded that least squares methods are generally robust to skewed data [36,37]. However, a potential area of for future research is whether the use of other techniques, such as generalized linear models, can offer efficiency gains for modeling cost data.

Abstract