

# Clarifying and Contextualizing Sensitivity to Unmeasured Confounding Tipping Point Analyses

Lucy D'Agostino McGowan  
Robert Greevy, Jr

[https://ryan-j-apps.shinyapps.io/  
seminarSurvival/](https://ryan-j-apps.shinyapps.io/seminarSurvival/)

motivation



\* review of 90 observational  
studies 2015

- \* review of 90 observational studies 2015
- \* 45.6% mentioned unmeasured confounding as a limitation

- \* review of 90 observational studies 2015
- \* 45.6% mentioned unmeasured confounding as a limitation
- \* 4.4% included a quantitative sensitivity analysis 😐

"In a study with binary outcomes and binary exposures the relative risk may be off by a factor of 2, but unlikely to be off more than that."

*van Belle, G. (2011). Statistical Rules of Thumb. Wiley.*



# Estrogen Replacement Therapy and Coronary Heart Disease: A Quantitative Assessment of the Epidemiologic Evidence<sup>1,2</sup>

MEIR J. STAMPFER, M.D., \*†,‡ AND GRAHAM A. COLDITZ, M.D.\*‡

\*The Channing Laboratory, Department of Medicine, Harvard Medical School and Brigham and Women's Hospital, Boston, Massachusetts; †Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts; and ‡Technology Assessment Group, Department of Health Policy and Management, Harvard School of Public Health, Boston, Massachusetts

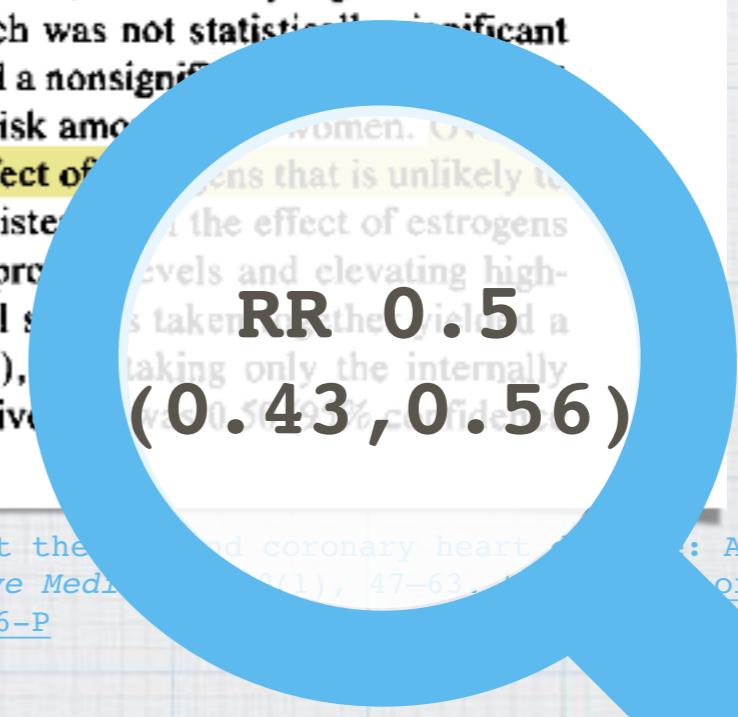
Considerable epidemiological evidence has accumulated regarding the effect of postmenopausal estrogens on coronary heart disease risk. Five hospital-based case-control studies yielded inconsistent but generally null results; however, these are difficult to interpret due to the problems in selecting appropriate controls. Six population-based case-control studies found decreased relative risks among estrogen users, though only 1 was statistically significant. Three cross-sectional studies of women with or without stenosis on coronary angiography each showed markedly less atherosclerosis among estrogen users. Of 16 prospective studies, 15 found decreased relative risks, in most instances, statistically significant. The Framingham study alone observed an elevated risk, which was not statistically significant when angina was omitted. A reanalysis of the data showed a nonsignificant protective effect among younger women and a nonsignificant increase in risk among older women. Overall, the bulk of the evidence strongly supports a protective effect of estrogens that is unlikely to be explained by confounding factors. This benefit is consistent with the effect of estrogens on lipoprotein subfractions (decreasing low-density lipoprotein levels and elevating high-density lipoprotein levels). A quantitative overview of all studies taken together yielded a relative risk of 0.56 (95% confidence interval 0.50–0.61), and taking only the internally controlled prospective and angiographic studies, the relative risk was 0.50 (95% confidence interval 0.43–0.56). © 1991 Academic Press, Inc.

# Estrogen Replacement Therapy and Coronary Heart Disease: A Quantitative Assessment of the Epidemiologic Evidence<sup>1,2</sup>

MEIR J. STAMPFER, M.D., \*†,‡ AND GRAHAM A. COLDITZ, M.D.\*‡

\*The Channing Laboratory, Department of Medicine, Harvard Medical School and Brigham and Women's Hospital, Boston, Massachusetts; †Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts; and ‡Technology Assessment Group, Department of Health Policy and Management, Harvard School of Public Health, Boston, Massachusetts

Considerable epidemiological evidence has accumulated regarding the effect of postmenopausal estrogens on coronary heart disease risk. Five hospital-based case-control studies yielded inconsistent but generally null results; however, these are difficult to interpret due to the problems in selecting appropriate controls. Six population-based case-control studies found decreased relative risks among estrogen users, though only 1 was statistically significant. Three cross-sectional studies of women with or without stenosis on coronary angiography each showed markedly less atherosclerosis among estrogen users. Of 16 prospective studies, 15 found decreased relative risks, in most instances, statistically significant. The Framingham study alone observed an elevated risk, which was not statistically significant when angina was omitted. A reanalysis of the data showed a nonsignificant increase in risk among younger women and a nonsignificant increase in risk among older women. Overall, the bulk of the evidence strongly supports a protective effect of estrogen. This benefit is consistent with the known effects of estrogens on lipoprotein subfractions (decreasing low-density lipoprotein levels and elevating high-density lipoprotein levels). A quantitative overview of all studies, including hospital-based case-control prospective and angiographic studies, the relative risk was 0.56 (95% confidence interval 0.50–0.61), while for population-based case-control prospective studies, the relative risk was 0.43 (95% confidence interval 0.43–0.56). © 1991 Academic Press, Inc.



RR 0.5  
(0.43, 0.56)

# Estrogen Replacement Therapy and Coronary Heart Disease: A Quantitative Assessment of the Epidemiologic Evidence<sup>1,2</sup>

MEIR J. STAMPFER, M.D., \*†,‡ AND GRAHAM A. COLDITZ, M.D.\*‡

\*The Channing Laboratory, Department of Medicine, Harvard Medical School and Brigham and Women's Hospital, Boston, Massachusetts; †Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts; and ‡Technology Assessment Group, Department of Health Policy and Management, Harvard School of Public Health, Boston, Massachusetts

Considerable epidemiological evidence has accumulated regarding the effect of postmenopausal estrogens on coronary heart disease risk. Five hospital-based case-control studies yielded inconsistent but generally null results; however, these are difficult to interpret due to the problems in selecting appropriate controls. Six population-based case-control studies found decreased relative risks among estrogen users, though only 1 was statistically significant. Three cross-sectional studies of women with or without stenosis on coronary angiography each showed markedly less atherosclerosis among estrogen users. Of 16 prospective studies, 15 found decreased relative risks, in most instances, statistically significant. The Framingham study alone observed an elevated risk, which was not statistically significant when angina was omitted. A reanalysis of the data showed a nonsignificant protective effect among younger women and a nonsignificant increase in risk among older women. Overall, the bulk of the evidence strongly supports a protective effect of estrogens that is unlikely to be explained by confounding factors. This benefit is consistent with the effect of estrogens on lipoprotein subfractions (decreasing low-density lipoprotein levels and elevating high-density lipoprotein levels). A quantitative overview of all studies taken together yielded a relative risk of 0.56 (95% confidence interval 0.50–0.61), and taking only the internally controlled prospective and angiographic studies, the relative risk was 0.50 (95% confidence interval 0.43–0.56). © 1991 Academic Press, Inc.

\*The Channing Laboratory, Department of Medicine, Harvard Medical School and Brigham and Women's Hospital, Boston, Massachusetts; †Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts; and ‡Technology Assessment Group, Department of Health Policy and Management, Harvard School of Public Health, Boston, Massachusetts

Considerable epidemiological evidence has accumulated regarding the effect of postmenopausal estrogens on coronary heart disease risk. Five hospital-based case-control studies yielded inconsistent but generally null results; however, these are difficult to interpret due to the problems in selecting appropriate controls. Six population-based case-control studies found decreased relative risks among estrogen users, though only 1 was statistically significant. Three cross-sectional studies of women with or without stenosis on coronary angiography each showed markedly less atherosclerosis among estrogen users. Of 16 prospective studies, 15 found decreased relative risks, in most instances, statistically significant. The Framingham study alone observed an elevated risk, which was not statistically significant when angina was omitted. A reanalysis of the data showed a nonsignificant protective effect among younger women and a nonsignificant increase in risk among older women. Overall, the bulk of the evidence strongly supports a protective effect of estrogens that is unlikely to be explained by confounding factors. This benefit is consistent with the effect of estrogens on lipoprotein subfractions (decreasing low-density lipoprotein levels and elevating high-density lipoprotein levels). A quantitative overview of all studies taken together yielded a relative risk of 0.56 (95% confidence interval 0.50–0.61), and taking only the internally controlled prospective and angiographic studies, the relative risk was 0.50 (95% confidence interval 0.43–0.56).

© 1991 Academic Press, Inc.



## Comparative Safety of Sulfonylurea and Metformin Monotherapy on the Risk of Heart Failure: A Cohort Study

Christianne L. Roumie, MD, MPH; Jea Young Min, PharmD, MPH; Lucy D'Agostino McGowan, MS; Caroline Presley, MD; Carlos G. Grijalva, MD, MPH; Amber J. Hackstadt, PhD; Adriana M. Hung, MD, MPH; Robert A. Greevy, PhD; Tom Elasy, MD, MPH; Marie R. Griffin, MD, MPH

**Background**—Medications that impact insulin sensitivity or cause weight gain may increase heart failure risk. Our aim was to compare heart failure and cardiovascular death outcomes among patients initiating sulfonylureas for diabetes mellitus treatment versus metformin.

**Methods and Results**—National Veterans Health Administration databases were linked to Medicare, Medicaid, and National Death Index data. Veterans aged  $\geq 18$  years who initiated metformin or sulfonylureas between 2001 and 2011 and whose creatinine was  $<1.4$  (females) or  $1.5$  mg/dL (males) were included. Each metformin patient was propensity score-matched to a sulfonylurea initiator. The outcome was hospitalization for acute decompensated heart failure as the primary reason for admission or a cardiovascular death. There were 126 867 and 79 192 new users of metformin and sulfonylurea, respectively. Propensity score matching yielded 65 986 per group. Median age was 66 years, and 97% of patients were male; hemoglobin A<sub>1c</sub> 6.9% (6.3, 7.7); body mass index 30.7 kg/m<sup>2</sup> (27.4, 34.6); and 6% had heart failure history. There were 1236 events (1184 heart failure hospitalizations and 52 cardiovascular deaths) among sulfonylurea initiators and 1078 events (1043 heart failure hospitalizations and 35 cardiovascular deaths) among metformin initiators. There were 12.4 versus 8.9 events per 1000 person-years of use (adjusted hazard ratio 1.32, 95%CI 1.21, 1.43). The rate difference was 4 heart failure hospitalizations or cardiovascular deaths per 1000 users of sulfonylureas versus metformin annually.

**Conclusions**—Predominantly male patients initiating treatment for diabetes mellitus with sulfonylurea had a higher risk of heart failure and cardiovascular death compared to similar patients initiating metformin. (*J Am Heart Assoc.* 2017;6:e005379. DOI: 10.1161/JAHA.116.005379.)

**Key Words:** acute heart failure • comparative effectiveness • diabetes mellitus • pharmacoepidemiology

## Comparative Safety of Sulfonylurea and Metformin Monotherapy on the Risk of Heart Failure: A Cohort Study

Christianne L. Roumic, MD, MPH; Jea Young Min, PharmD, MPH; Lucy D'Agostino McGowan, MS; Caroline Presley, MD; Carlos G. Grijalva, MD, MPH; Amber J. Hackstadt, PhD; Adriana M. Hung, MD, MPH; Robert A. Greevy, PhD; Tom Elasy, MD, MPH; Marie R. Griffin, MD, MPH

**Background**—Medications that impact insulin sensitivity or cause weight gain may increase heart failure risk. Our aim was to compare heart failure and cardiovascular death outcomes among patients initiating sulfonylureas for diabetes mellitus treatment versus metformin.

**Methods and Results**—National Veterans Health Administration databases were linked to Medicare, Medicaid, and National Death Index data. Veterans aged  $\geq 18$  years who initiated metformin or sulfonylureas between 2001 and 2011 and whose creatinine was  $< 1.4$  (females) or  $1.5$  mg/dL (males) were included. Each metformin patient was propensity score-matched to a sulfonylurea initiator. The outcome was hospitalization for acute decompensated heart failure as the primary reason for admission or a cardiovascular death. There were 79 986 new users of metformin and 79 192 new users of sulfonylurea, respectively. Propensity score matching resulted in 39 986 per group. Mean age was 66 years, and 97% of patients were male; hemoglobin A<sub>1c</sub> 6.9% (6.3, 7.7); body mass index 30.7 kg/m<sup>2</sup> (27.4, 34.0); and 6% had heart failure history. There were 1236 events (1184 heart failure hospitalizations and 52 cardiovascular deaths) among sulfonylurea initiators and 1078 events (1043 heart failure hospitalizations and 35 cardiovascular deaths) among metformin initiators. There were 12.4 versus 8.9 events per 1000 person-years of use (absolute difference was 4 heart failure hospitalizations or cardiovascular deaths per 1000 person-years).  
**Conclusion**—Initiating treatment for diabetes mellitus with sulfonylurea had a higher risk of heart failure hospitalization or cardiovascular death compared with patients initiating metformin. (*J Am Heart Assoc.* 2017;6:e005379. DOI: 10.1161/JAHA.116.005379.)

HR 1.32  
(1.21, 1.43)

effectiveness • diabetes mellitus • pharmacoepidemiology

background

# Cornfield 1959



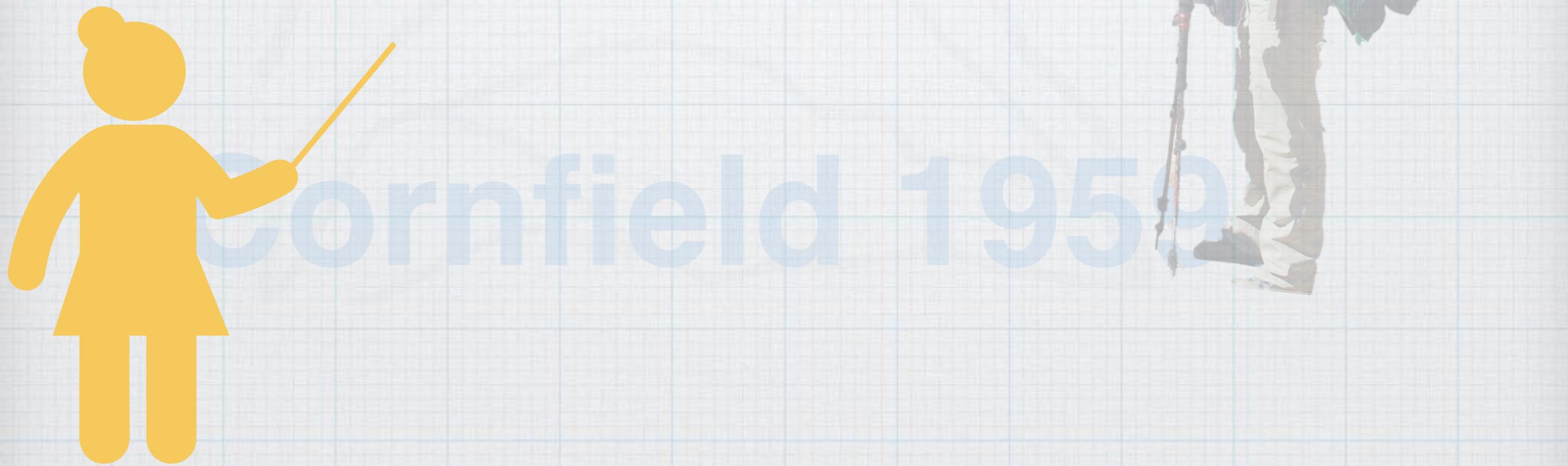
$$\frac{R_1}{R_0} = \frac{p_1 R_U + (1 - p_1) R_{\bar{U}}}{p_0 R_U + (1 - p_0) R_{\bar{U}}}$$



cornfield 1959



$$\frac{R_1}{R_0} = \frac{p_1 R_U + (1 - p_1) R_{\bar{U}}}{p_0 R_U + (1 - p_0) R_{\bar{U}}}$$



$$\frac{R_1}{R_0} = \frac{p_1 R_U + (1 - p_1) R_{\bar{U}}}{p_0 R_U + (1 - p_0) R_{\bar{U}}}$$



cornfield 1959



$$\frac{R_1}{R_0} = \frac{p_1 R_U + (1 - p_1) R_{\bar{U}}}{p_0 R_U + (1 - p_0) R_{\bar{U}}}$$



cornfield 1959



$$\frac{R_1}{R_0} = \frac{p_1 R_U + (1 - p_1) R_{\bar{U}}}{p_0 R_U + (1 - p_0) R_{\bar{U}}}$$



cornfield 1959



$$\frac{R_1}{R_0} = \frac{p_1 R_U + (1 - p_1) R_{\bar{U}}}{p_0 R_U + (1 - p_0) R_{\bar{U}}}$$



$$\frac{R_1}{R_0} = \frac{p_1 R_U + (1 - p_1) R_{\bar{U}}}{p_0 R_U + (1 - p_0) R_{\bar{U}}}$$



cornfield 1959



$$\frac{R_1}{R_0} = \frac{p_1 R_U + (1 - p_1) R_{\bar{U}}}{p_0 R_U + (1 - p_0) R_{\bar{U}}}$$



cornfield 1959



$$\frac{R_1}{R_0} = \frac{p_1 R_U + (1 - p_1) R_{\bar{U}}}{p_0 R_U + (1 - p_0) R_{\bar{U}}}$$



cornfield 1959



$$\frac{R_1}{R_0} = \frac{p_1 R_U + (1 - p_1) \boxed{R_{\bar{U}}}}{p_0 R_U + (1 - p_0) \boxed{R_{\bar{U}}}}$$



cornfield 1959



$$\frac{R_1}{R_0} = \frac{p_1 R_U + (1 - p_1) R_{\bar{U}}}{p_0 R_U + (1 - p_0) R_{\bar{U}}}$$



cornfield 1959



9

$$\frac{R_1}{R_0} = \frac{p_1 R_U + (1 - p_1) R_{\bar{U}}}{p_0 R_U + (1 - p_0) R_{\bar{U}}}$$



cornfield 1959



$$\frac{p_1}{p_0} = \frac{R_1}{R_0} + \frac{1}{p_0} \frac{R_{\bar{U}}}{R_U} \left[ (1 - p_0) \frac{R_1}{R_0} - (1 - p_1) \right]$$

Cornfield 1959

+

$$\frac{p_1}{p_0} = \frac{R_1}{R_0} + \frac{1}{p_0} \frac{R_{\bar{U}}}{R_U} \left[ (1 - p_0) \frac{R_1}{R_0} - (1 - p_1) \right]$$



Cornfield 1959



$$\frac{p_1}{p_0} > \frac{R_1}{R_0}$$

Cornfield 1959

$$\frac{p_1}{p_0} > 9$$

Cornfield 1959

the proportion of hormone-X-producers among cigarette smokers must be at least **9 times greater** than that of nonsmokers...

Cornfield 1959

Bross 1966  
Cornfield 1959





Schlesselman 1978  
Bross 1966  
Cornfield 1959

$$RR_{obs} = RR_{adj} \frac{\Gamma p_1 + (1 - p_1)}{\Gamma p_0 + (1 - p_0)}$$

Bross 1966  
Cornfield 1959

$$RR_{obs} = RR_{adj} \frac{\Gamma p_1 + (1 - p_1)}{\Gamma p_0 + (1 - p_0)}$$

$$\frac{R_1}{R_0}$$

Bross 1966  
Cornfield 1959

$$RR_{obs} = RR_{adj} \frac{\Gamma p_1 + (1 - p_1)}{\Gamma p_0 + (1 - p_0)}$$

Bross 1966  
Cornfield 1959

$$RR_{obs} = RR_{adj} \frac{\Gamma_{p_1} + (1 - p_1)}{\Gamma_{p_0} + (1 - p_0)}$$

$$\frac{\text{Br}_{R_U} \text{ 1966}}{\overline{R}_{\bar{U}}} \text{ 1959}$$

$$RR_{obs} = RR_{adj} \frac{\Gamma p_1 + (1 - p_1)}{\Gamma p_0 + (1 - p_0)}$$

Bross 1966  
Cornfield 1959

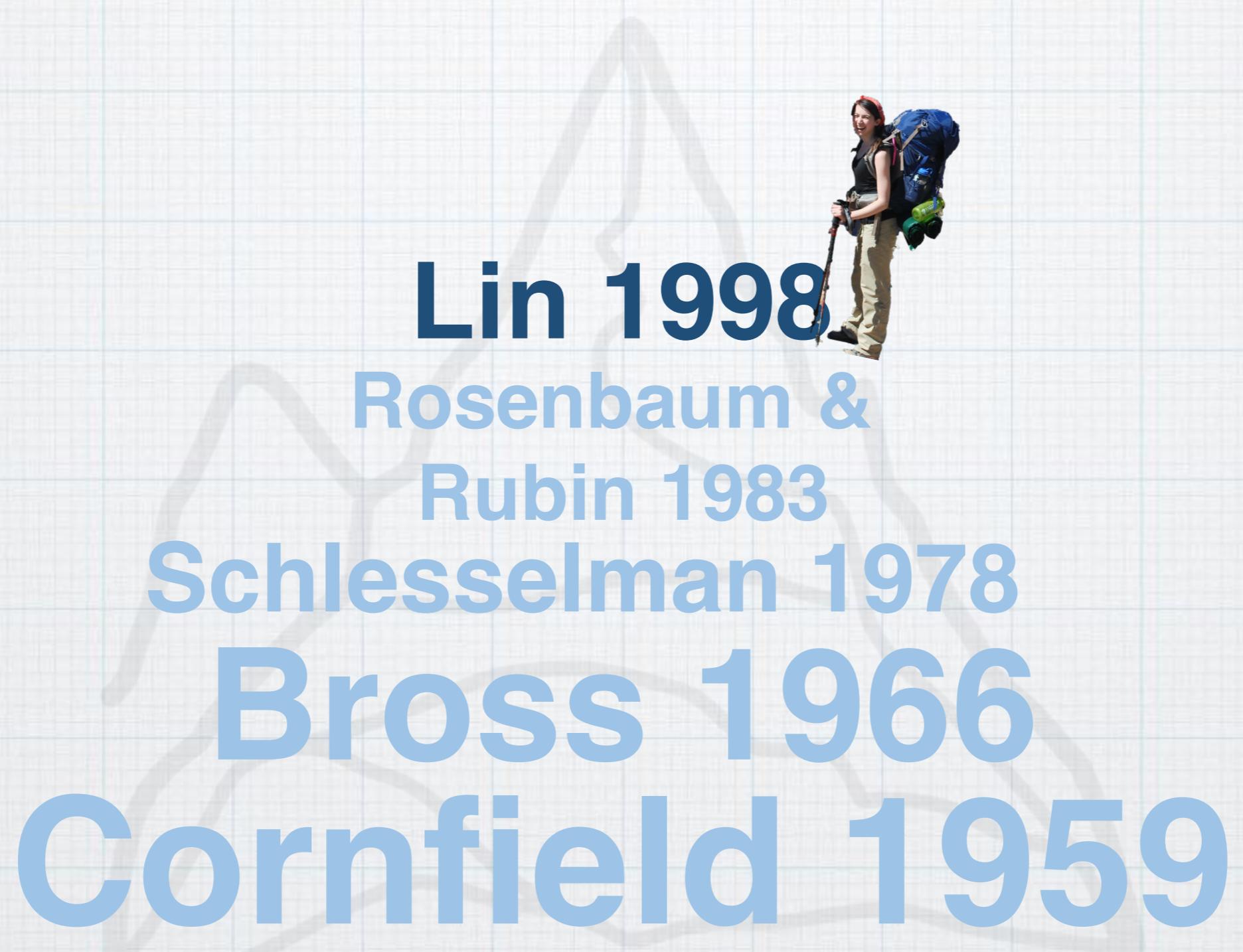


Rosenbaum &  
Rubin 1983

Schlesselman 1978

Bross 1966

Cornfield 1959



**Lin 1998**  
**Rosenbaum &**  
**Rubin 1983**  
**Schlesselman 1978**  
**Bross 1966**  
**Cornfield 1959**

$$RR_{adj} = RR_{obs} \frac{\Gamma p_0 + (1 - p_0)}{\Gamma p_1 + (1 - p_1)}$$

Bross 1966  
Cornfield 1959

$$RR_{adj} = RR_{obs} \frac{\Gamma p_0 + (1 - p_0)}{\Gamma p_1 + (1 - p_1)}$$

Bross 1966  
Cornfield 1959

$$RR_{adj} = RR_{obs} \frac{\Gamma p_0 + (1 - p_0)}{\Gamma p_1 + (1 - p_1)}$$

Bross 1966  
Cornfield 1959

$$HR_{adj} = HR_{obs} \frac{\Gamma p_0 + (1 - p_0)}{\Gamma p_1 + (1 - p_1)}$$

Bross 1966  
Cornfield 1959

$$HR_{adj} = \frac{HR_{obs}}{\Gamma p_0 + (1 - p_0)} \frac{\Gamma p_1 + (1 - p_1)}{\Gamma p_1 + (1 - p_1)}$$

Bross 1966  
Cornfield 1959

$$HR_{adj} = \frac{HR_{obs}}{\frac{\Gamma p_0 + (1 - p_0)}{\Gamma p_1 + (1 - p_1)}}$$

Table 39: Adjusted Effect (PER90)

	Low	High	$\Delta$	Effect	S.E.	Lower 0.95	Upper 0.95
Sulfonylurea	0	1	1	0.27655	0.04195	0.19433	0.35877
<i>Hazard Ratio</i>	0	1	1	1.31860		1.21450	1.43160

$$P(Y = 1 | X, \mathbf{Z}) =$$

$$\exp\{\alpha^* + \beta^* X + \theta^{*\prime} \mathbf{Z}\}$$

what we fit

$$\exp\{\alpha + \beta X + \boldsymbol{\theta}' \mathbf{Z}\}(\exp\{\gamma_X\} p_{X,\mathbf{Z}} + (1 - p_{X,\mathbf{Z}}))$$



what we wish we fit

$$\exp\{\alpha + \beta X + \theta' \mathbf{Z}\}(\exp\{\gamma_X\} p_{X,\mathbf{Z}} + (1 - p_{X,\mathbf{Z}}))$$

what we wish we fit

$$\exp\{\alpha + \beta X + \theta' \mathbf{Z}\}(\exp\{\gamma_X P_X + (1 - P_X)\})$$

what we wish we fit

$$\exp \left\{ \alpha + \log \{ e^{\gamma_0} p_0 + (1 - p_0) \} \right. \\ \left. + \left( \beta + \log \frac{e^{\gamma_1} p_1 + (1 - p_1)}{e^{\gamma_0} p_0 + (1 - p_0)} \right) X + \theta' \mathbf{Z} \right\}$$

what we wish we fit

$$\exp \left\{ \alpha + \log \{ e^{\gamma_0} p_0 + (1 - p_0) \} \right. \\ \left. + \left( \beta + \log \frac{e^{\gamma_1} p_1 + (1 - p_1)}{e^{\gamma_0} p_0 + (1 - p_0)} \right) X + \theta' \mathbf{Z} \right\}$$

what we wish we fit

$$\beta = \beta^* - \log \frac{e^{\gamma_1} p_1 + (1 - p_1)}{e^{\gamma_0} p_0 + (1 - p_0)}$$

solving for  
what we wish we fit

$$RR_{adj} = RR_{obs} \frac{\Gamma p_0 + (1 - p_0)}{\Gamma p_1 + (1 - p_1)}$$

Ding &  
VanderWeele  
2016



Lin 1998  
Rosenbaum &  
Rubin 1983  
Schlesselman 1978  
Bross 1966  
Cornfield 1959

tipping point





- \* what will tip our confidence bound to cross 1



- \* what will tip our confidence bound to cross 1
- \* assuming the **sensitivity parameters are fixed and known**, we can extend these methods to confidence bounds

$$RR_{adj} = RR_{obs} \frac{\Gamma p_0 + (1 - p_0)}{\Gamma p_1 + (1 - p_1)}$$

$$LB_{adj} = LB_{obs}\frac{\Gamma p_0 + (1-p_0)}{\Gamma p_1 + (1-p_1)}$$

$$LB_{adj} = LB_{obs} \frac{\Gamma p_0 + (1 - p_0)}{\Gamma p_1 + (1 - p_1)}$$

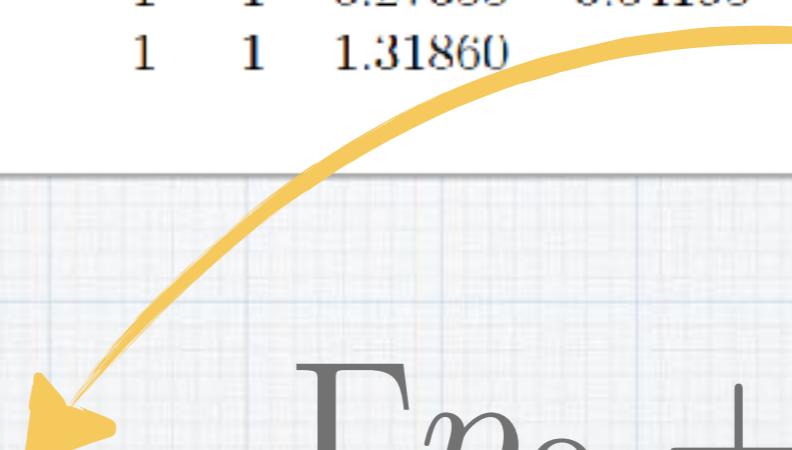


1

Table 39: Adjusted Effect (PER90)

	Low	High	$\Delta$	Effect	S.E.	Lower 0.95	Upper 0.95
Sulfonylurea	0	1	1	0.27655	0.04195	0.19433	0.35877
<i>Hazard Ratio</i>	0	1	1	1.31860		1.21450	1.43160

$$LB_{adj} = LB_{obs} \frac{\Gamma p_0 + (1 - p_0)}{\Gamma p_1 + (1 - p_1)}$$





$$\Gamma(LB_{obs}, p_0, p_1) = \frac{LB_{obs}(1-p_0)-(1-p_1)}{p_1-LB_{obs}p_0}$$

Table 39: Adjusted Effect (PER90)

	Low	High	$\Delta$	Effect	S.E.	Lower 0.95	Upper 0.95
Sulfonylurea	0	1	1	0.27655	0.04195	0.19433	0.35877
<i>Hazard Ratio</i>	0	1	1	1.31860		1.21450	1.43160

$$\Gamma(LB_{obs}, p_0, p_1) = \frac{LB_{obs}(1 - p_0)}{p_1 - LB_{obs}p_0} \cdot (1 - p_1)$$

"in order for our association to no longer be significant, there would need to exist an unmeasured confounder of size  $\Gamma$  that is prevalent in  $p_1$  of the exposed population and  $p_0$  of the unexposed population"

"in order for our association to no longer be significant, there would need to exist an unmeasured confounder of size  $\Gamma$  that is prevalent in  $p_1$  of the exposed population and  $p_0$  of the unexposed population"

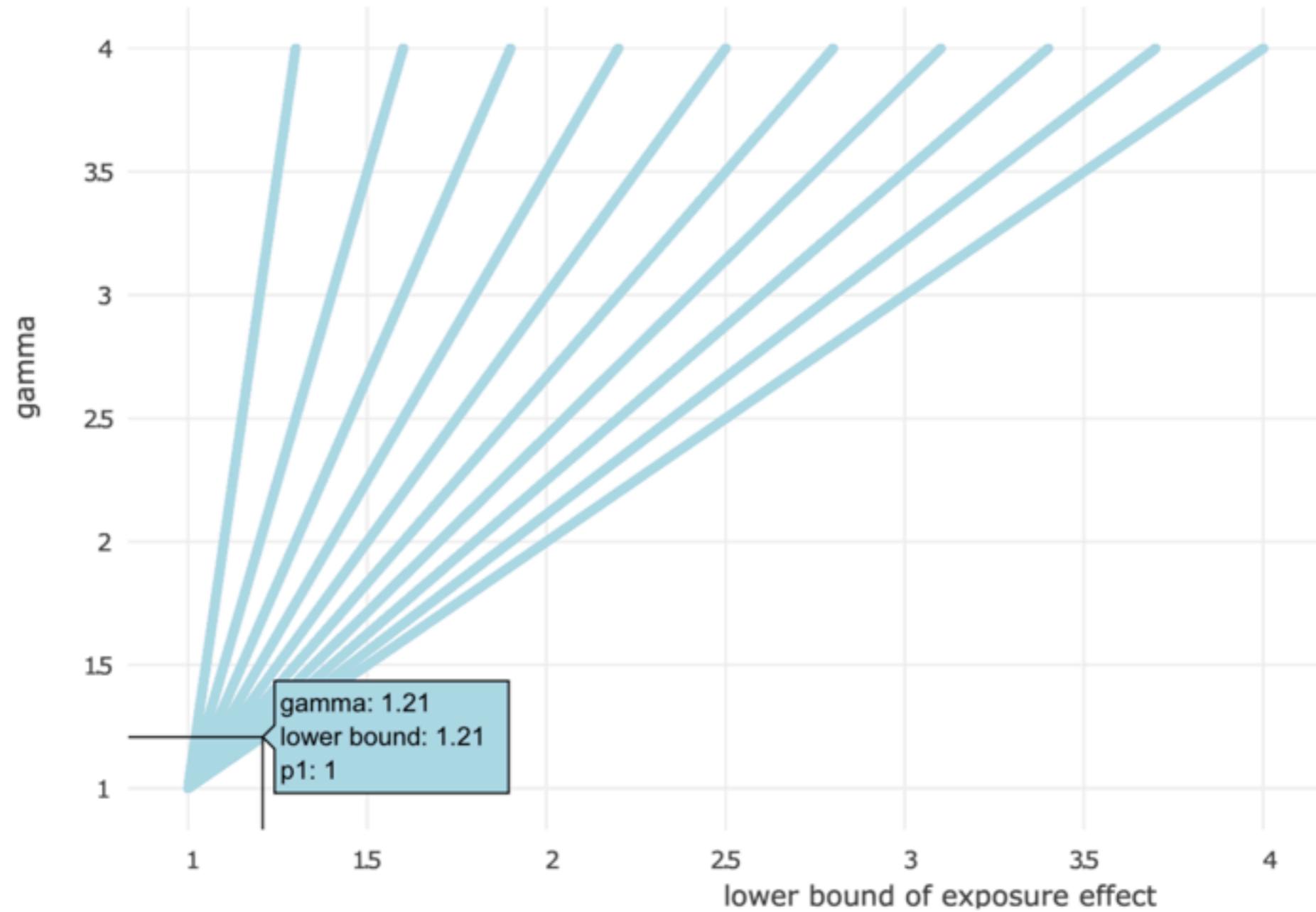
$$\Gamma(LB_{obs}, p_0, p_1) = \frac{LB_{obs}(1-p_0)-(1-p_1)}{p_1-LB_{obs}p_0}$$

Table 39: Adjusted Effect (PER90)

	Low	High	$\Delta$	Effect	S.E.	Lower 0.95	Upper 0.95
Sulfonylurea	0	1	1	0.27655	0.04195	0.19433	0.35877
<i>Hazard Ratio</i>	0	1	1	1.31860		1.21450	1.43160

$$\Gamma(LB_{obs}, p_0, p_1) = \frac{LB_{obs}(1 - p_0) - (1 - p_1)}{p_1 - LB_{obs}p_0}$$

p0 is 0 varying p1 from 0.1 to 1



p0 is 0 varying p1 from 0.1 to 1

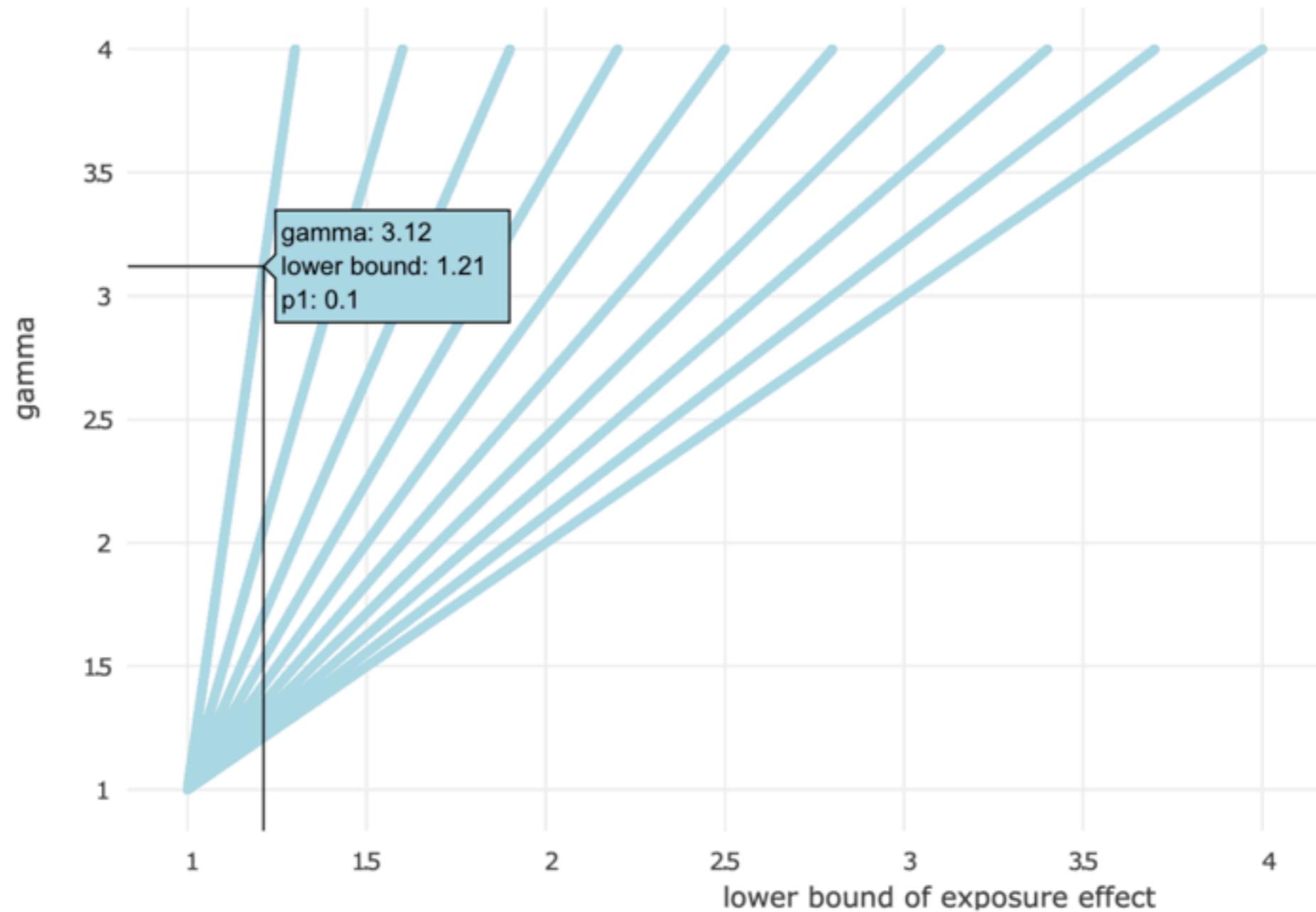


Table 1: Descriptive Statistics.  $a$ ,  $b$ ,  $c$  represent the lower quartile  $a$ , the median  $b$ , and the upper quartile  $c$  for continuous variables.  $x \pm s$  represents  $X \pm 1$  SD.

	Sulfonylurea <i>N</i> = 79192	Metformin <i>N</i> = 126867
Liver	1.86%	0.83%
CHF	9.6%	3.8%
CVD history	28%	22%
Mental Disease	16%	17%
Cardiac Valve	2.3%	1.2%
Arrhythmias	11.1%	6.5%
Smoking diseases	11%	12%
COPD	15%	12%
Any cancer	6.6%	5.0%
Race (Black)	14%	13%
Race (Other)	4.6%	4.4%
Gender (female)	2.6%	5.0%

Model Tests	Discrimination Indexes			
	Obs	LR $\chi^2$	$R^2$	0.091
Events	2314	d.f.	72	$D_{xy}$ 0.688
Center	1.9756	Pr(> $\chi^2$ )	0.0000	$g$ 1.305
		Score $\chi^2$	6155.14	$g_r$ 3.687
		Pr(> $\chi^2$ )	0.0000	

	Coef	S.E.	Wald Z	Pr(>  Z )
sulfon	0.2766	0.0420	6.59	< 0.0001
d9Liver	0.2574	0.2121	1.21	0.2249
d9chf	0.8503	0.0580	14.65	< 0.0001
CvdHistory	0.3665	0.0516	7.10	< 0.0001
MentalDisease	-0.0864	0.0694	-1.24	0.2132
d9cardiacValve	0.2338	0.0889	2.63	0.0085
d9arrhythmias	0.3802	0.0586	6.49	< 0.0001
d9SmokingDiseases	0.1526	0.0687	2.22	0.0263
d9copd	0.2367	0.0538	4.40	< 0.0001
d9Ca_Any	-0.2565	0.0859	-2.99	0.0028
RaceBlack	0.2514	0.0817	3.08	0.0021
RaceOther	-0.0898	0.1368	-0.66	0.5117

Table 1: Descriptive Statistics.  $a$ ,  $b$ ,  $c$  represent the lower quartile  $a$ , the median  $b$ , and the upper quartile  $c$  for continuous variables.  $x \pm s$  represents  $X \pm 1$  SD.

	Sulfonylurea <i>N</i> = 79192	Metformin <i>N</i> = 126867
Liver	1.86%	0.83%
CHF	9.6%	3.8%
CVD history	28%	22%
Mental Disease	16%	17%
Cardiac Valve	2.3%	1.2%
Arrhythmias	11.1%	6.5%
Smoking diseases	11%	12%
COPD	15%	12%
Any cancer	6.6%	5.0%
Race (Black)	14%	13%
Race (Other)	4.6%	4.4%
Gender (female)	2.6%	5.0%

$$p_1 = 0.096$$

$$p_0 = 0.038$$

Model Tests	Discrimination Indexes		
	Obs	LR $\chi^2$	$R^2$
Events	131972	3843.50	0.091
Center	2314	d.f. 72	$D_{xy}$ 0.688
	1.9756	Pr(> $\chi^2$ ) 0.0000	$g$ 1.305
		Score $\chi^2$ 6155.14	$g_r$ 3.687
		Pr(> $\chi^2$ ) 0.0000	

	Coef	S.E.	Wald Z	Pr(>  Z )
sulfon	0.2766	0.0420	6.59	< 0.0001
d9Liver	0.2574	0.2121	1.21	0.2249
d9chf	0.8503	0.0580	14.65	< 0.0001
CvdHistory	0.3665	0.0516	7.10	< 0.0001
MentalDisease	-0.0864	0.0694	-1.24	0.2132
d9cardiacValve	0.2338	0.0889	2.63	0.0085
d9arrhythmias	0.3802	0.0586	6.49	< 0.0001
d9SmokingDiseases	0.1526	0.0687	2.22	0.0263
d9copd	0.2367	0.0538	4.40	< 0.0001
d9Ca_Any	-0.2565	0.0859	-2.99	0.0028
RaceBlack	0.2514	0.0817	3.08	0.0021
RaceOther	-0.0898	0.1368	-0.66	0.5117

Table 1: Descriptive Statistics.  $a$ ,  $b$ ,  $c$  represent the lower quartile  $a$ , the median  $b$ , and the upper quartile  $c$  for continuous variables.  $x \pm s$  represents  $X \pm 1$  SD.

	Sulfonylurea <i>N</i> = 79192	Metformin <i>N</i> = 126867
Liver CII	1.86% 0.6%	0.83% 3.8%
CVD history	28%	22%
Mental Disease	16%	17%
Cardiac Valve	2.3%	1.2%
Arrhythmias	11.1%	6.5%
Smoking diseases	11%	12%
COPD	15%	12%
Any cancer	6.6%	5.0%
Race (Black)	14%	13%
Race (Other)	4.6%	4.4%
Gender (female)	2.6%	5.0%

$$p_1 = 0.096$$

$$p_0 = 0.038$$

$$\Gamma = 2.34$$

Model Tests	Discrimination Indexes		
	Obs	LR $\chi^2$	$R^2$
Events	131972	3843.50	0.091
Center	2314	d.f. 72	$D_{xy}$ 0.688
	1.9756	Pr(> $\chi^2$ ) 0.0000	$g$ 1.305
		Score $\chi^2$ 6155.14	$g_r$ 3.687
		Pr(> $\chi^2$ ) 0.0000	

	Coef	S.E.	Wald Z	Pr(>  Z )
sulfon	0.2766	0.0420	6.59	< 0.0001
d9Liver	0.2574	0.2121	1.21	0.2249
<b>d9chf</b>	<b>0.8503</b>	<b>0.0580</b>	<b>14.65</b>	<b>&lt; 0.0001</b>
CvdHistory	0.3665	0.0516	7.10	< 0.0001
MentalDisease	-0.0864	0.0694	-1.24	0.2132
d9cardiacValve	0.2338	0.0889	2.63	0.0085
d9arrhythmias	0.3802	0.0586	6.49	< 0.0001
d9SmokingDiseases	0.1526	0.0687	2.22	0.0263
d9copd	0.2367	0.0538	4.40	< 0.0001
d9Ca_Any	-0.2565	0.0859	-2.99	0.0028
RaceBlack	0.2514	0.0817	3.08	0.0021
RaceOther	-0.0898	0.1368	-0.66	0.5117

calculate it

$$\Gamma(LB_{obs}, p_0, p_1) = \frac{LB_{obs}(1 - p_0) - (1 - p_1)}{p_1 - LB_{obs}p_0}$$

LB = 1.21

p<sub>1</sub> = 0.096

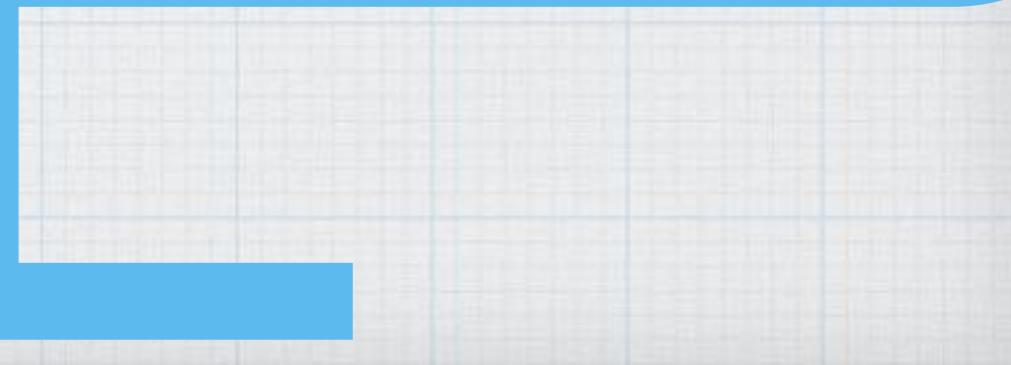
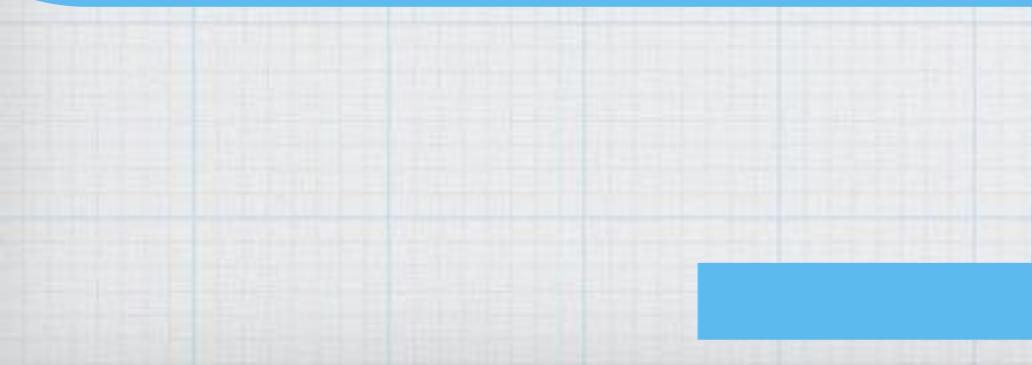
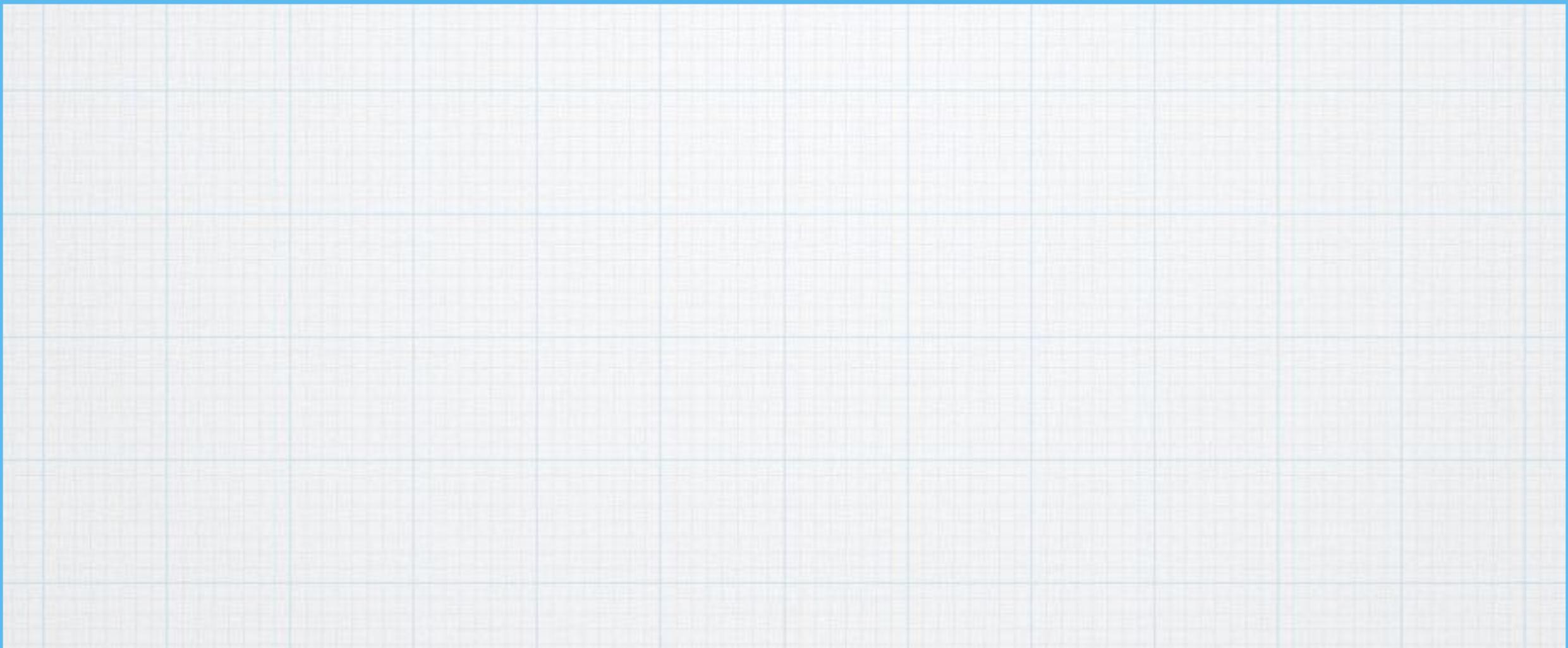
p<sub>0</sub> = 0.038

$$\Gamma(LB_{obs}, p_0, p_1) = \frac{LB_{obs}(1 - p_0) - (1 - p_1)}{p_1 - LB_{obs}p_0}$$

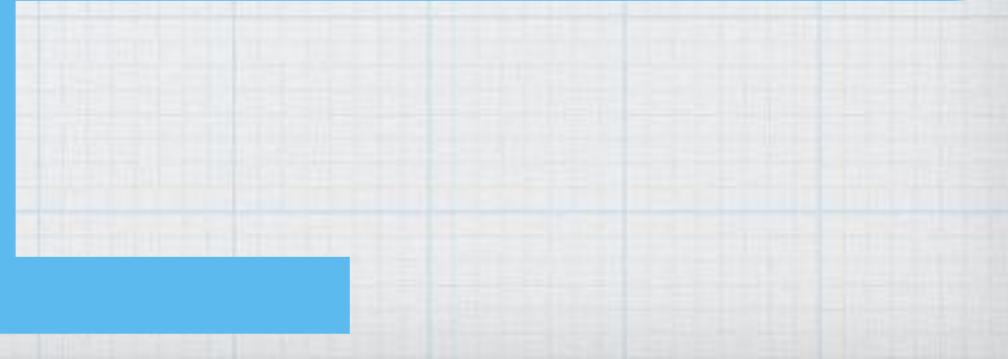
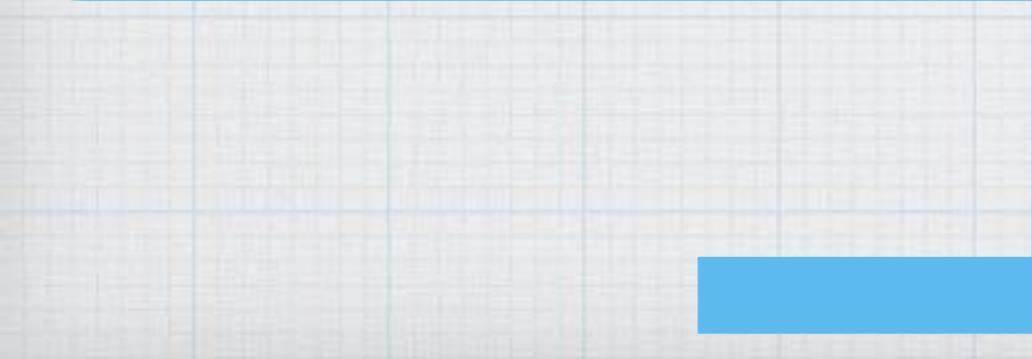
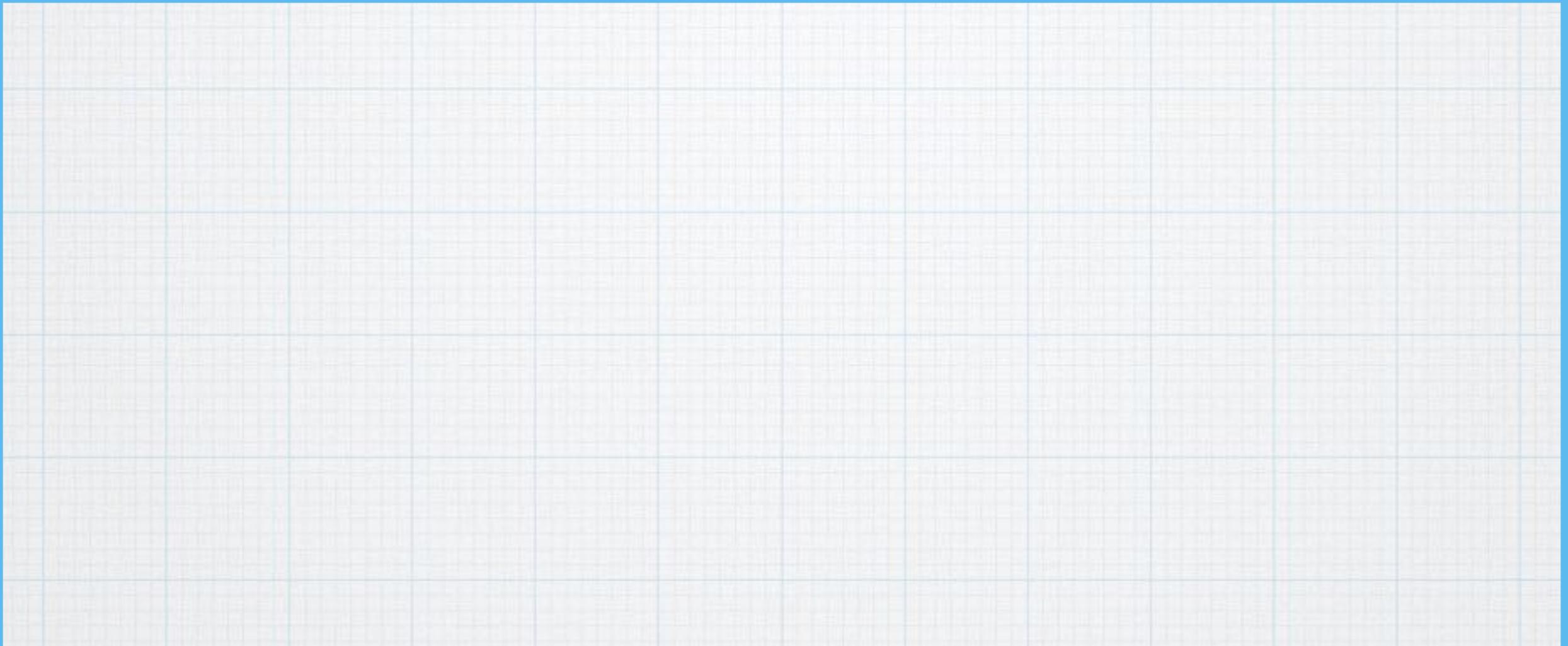
$$\begin{aligned} LB &= 1.21 \\ p_1 &= 0.1 \\ p_0 &= 0.038 \end{aligned}$$

$$\Gamma(LB_{obs}, p_0, p_1) = \frac{LB_{obs}(1 - p_0) - (1 - p_1)}{p_1 - LB_{obs}p_0}$$

LB = 1.21  
p<sub>1</sub> = 0.1  
p<sub>0</sub> = 0



```
> devtools::install_github("LucyMcGowan/tipr")
> library('tipr')
> tip(p1 = 0.1,
      p0 = 0,
      lb = 1.21,
      ub = 1.43)
[1] 3.1
```



```
> tip(p1 = 0.1, p0 = 0, lb = 1.21, ub = 1.43,  
  explanation = TRUE)
```

[1] "An unmeasured confounder of size 3.1  
with a prevalence of 0.1 in the exposed  
**population** and 0 in the unexposed population  
would tip your (1.21,1.43) result to  
nonsignificance."

[lucy.shinyapps.io/tipr](http://lucy.shinyapps.io/tipr)

**SENSITIVITY TO UNMEASURED CONFOUNDER**

**Input from your Study**

**Explore Plots**

Fill in the following with your information or examine the plots to the left to determine how an unmeasured confounder would tip your analysis.

Prevalence in the exposed group

.1

Prevalence in the unexposed group

0

Lower bound (95% CI) of observed effect

1.21

Upper bound (95% CI) of observed effect

1.43

An unmeasured confounder of size 3.1 with a prevalence of 0.1 in the exposed population would need a prevalence of 0 in the unexposed population to tip your (1.21,1.43) result to nonsignificance.

anchor it

Table 1: Descriptive Statistics.  $a$ ,  $b$ ,  $c$  represent the lower quartile  $a$ , the median  $b$ , and the upper quartile  $c$  for continuous variables.  $x \pm s$  represents  $X \pm 1$  SD.

	Sulfonylurea <i>N</i> = 79192	Metformin <i>N</i> = 126867
Liver	1.86%	0.83%
CHF	9.6%	3.8%
CVD history	28%	22%
Mental Disease	16%	17%
Cardiac Valve	2.3%	1.2%
Arrhythmias	11.1%	6.5%
Smoking diseases	11%	12%
COPD	15%	12%
Any cancer	6.6%	5.0%
Race (Black)	14%	13%
Race (Other)	4.6%	4.4%
Gender (female)	2.6%	5.0%

Model Tests	Discrimination Indexes			
	Obs	LR $\chi^2$	$R^2$	0.091
Events	2314	d.f.	72	$D_{xy}$ 0.688
Center	1.9756	Pr(> $\chi^2$ )	0.0000	$g$ 1.305
		Score $\chi^2$	6155.14	$g_r$ 3.687
		Pr(> $\chi^2$ )	0.0000	

	Coef	S.E.	Wald Z	Pr(>  Z )
sulfon	0.2766	0.0420	6.59	< 0.0001
d9Liver	0.2574	0.2121	1.21	0.2249
d9chf	0.8503	0.0580	14.65	< 0.0001
CvdHistory	0.3665	0.0516	7.10	< 0.0001
MentalDisease	-0.0864	0.0694	-1.24	0.2132
d9cardiacValve	0.2338	0.0889	2.63	0.0085
d9arrhythmias	0.3802	0.0586	6.49	< 0.0001
d9SmokingDiseases	0.1526	0.0687	2.22	0.0263
d9copd	0.2367	0.0538	4.40	< 0.0001
d9Ca_Any	-0.2565	0.0859	-2.99	0.0028
RaceBlack	0.2514	0.0817	3.08	0.0021
RaceOther	-0.0898	0.1368	-0.66	0.5117

Table 1: Descriptive Statistics.  $a$ ,  $b$ ,  $c$  represent the lower quartile  $a$ , the median  $b$ , and the upper quartile  $c$  for continuous variables.  $x \pm s$  represents  $X \pm 1$  SD.

	Sulfonylurea <i>N</i> = 79192	Metformin <i>N</i> = 126867
Liver	1.86%	0.83%
CHF	9.6%	3.8%
CVD history	28%	22%
Mental Disease	16%	17%
Cardiac Valve	2.3%	1.2%
Arrhythmias	11.1%	6.5%
Smoking diseases	11%	12%
COPD	15%	12%
Any cancer	6.6%	5.0%
Race (Black)	14%	13%
Race (Other)	4.6%	4.4%
Gender (female)	2.6%	5.0%

$$p_1 = 0.096$$

$$p_0 = 0.038$$

Model Tests	Discrimination Indexes		
	Obs	LR $\chi^2$	$R^2$
Events	131972	3843.50	0.091
Center	2314	d.f. 72	$D_{xy}$ 0.688
	1.9756	Pr(> $\chi^2$ ) 0.0000	$g$ 1.305
		Score $\chi^2$ 6155.14	$g_r$ 3.687
		Pr(> $\chi^2$ ) 0.0000	

	Coef	S.E.	Wald Z	Pr(>  Z )
sulfon	0.2766	0.0420	6.59	< 0.0001
d9Liver	0.2574	0.2121	1.21	0.2249
d9chf	0.8503	0.0580	14.65	< 0.0001
CvdHistory	0.3665	0.0516	7.10	< 0.0001
MentalDisease	-0.0864	0.0694	-1.24	0.2132
d9cardiacValve	0.2338	0.0889	2.63	0.0085
d9arrhythmias	0.3802	0.0586	6.49	< 0.0001
d9SmokingDiseases	0.1526	0.0687	2.22	0.0263
d9copd	0.2367	0.0538	4.40	< 0.0001
d9Ca_Any	-0.2565	0.0859	-2.99	0.0028
RaceBlack	0.2514	0.0817	3.08	0.0021
RaceOther	-0.0898	0.1368	-0.66	0.5117

Table 1: Descriptive Statistics.  $a$ ,  $b$ ,  $c$  represent the lower quartile  $a$ , the median  $b$ , and the upper quartile  $c$  for continuous variables.  $x \pm s$  represents  $X \pm 1$  SD.

	Sulfonylurea <i>N</i> = 79192	Metformin <i>N</i> = 126867
Liver CII	1.86% 0.6%	0.83% 3.8%
CVD history	28%	22%
Mental Disease	16%	17%
Cardiac Valve	2.3%	1.2%
Arrhythmias	11.1%	6.5%
Smoking diseases	11%	12%
COPD	15%	12%
Any cancer	6.6%	5.0%
Race (Black)	14%	13%
Race (Other)	4.6%	4.4%
Gender (female)	2.6%	5.0%

$$p_1 = 0.096$$

$$p_0 = 0.038$$

$$\Gamma = 2.34$$

Model Tests	Discrimination Indexes		
	Obs	LR $\chi^2$	$R^2$
Events	131972	3843.50	0.091
Center	2314	d.f. 72	$D_{xy}$ 0.688
	1.9756	Pr(> $\chi^2$ ) 0.0000	$g$ 1.305
		Score $\chi^2$ 6155.14	$g_r$ 3.687
		Pr(> $\chi^2$ ) 0.0000	

	Coef	S.E.	Wald Z	Pr(>  Z )
sulfon	0.2766	0.0420	6.59	< 0.0001
d9Liver	0.2574	0.2121	1.21	0.2249
d9chf	0.8503	0.0580	14.65	< 0.0001
CvdHistory	0.3665	0.0516	7.10	< 0.0001
MentalDisease	-0.0864	0.0694	-1.24	0.2132
d9cardiacValve	0.2338	0.0889	2.63	0.0085
d9arrhythmias	0.3802	0.0586	6.49	< 0.0001
d9SmokingDiseases	0.1526	0.0687	2.22	0.0263
d9copd	0.2367	0.0538	4.40	< 0.0001
d9Ca_Any	-0.2565	0.0859	-2.99	0.0028
RaceBlack	0.2514	0.0817	3.08	0.0021
RaceOther	-0.0898	0.1368	-0.66	0.5117

A hypothetical unobserved binary confounder with a 10% prevalence difference between the therapies would need to have an association with heart failure of  $HR=3.1$  to tip this analysis to nonsignificance at a 5% level.

For a comparison from the observed confounders, baseline heart failure history had a prevalence difference of 5.8% in the pre-matching cohort and an association with CHF of  $\text{HR}=2.34$ ; thus an unmeasured confounder of this magnitude would be insufficient to tip this analysis to statistical insignificance.

write up



1. state primary analysis  
result

1. state primary analysis  
result

1. **state** primary analysis result
2. **calculate** the size & prevalence of a hypothetical tipping point confounder

1. **state** primary analysis result
2. **calculate** the size & prevalence of a hypothetical tipping point confounder

1. **state** primary analysis result
2. **calculate** the size & prevalence of a hypothetical tipping point confounder
3. **anchor** this in an example from your data

conclusion



- \* we have presented a useful, **easily implemented**, and intuitively understood approach to allow researchers to assess the potential impact of unmeasured confounders in observational research

- \* we have presented a useful, **easily implemented**, and intuitively understood approach to allow researchers to assess the potential impact of unmeasured confounders in observational research
- \* can be applied to **both past and future research**, allowing readers to understand the sensitivity of studies that do not include such an analysis, and allowing future investigators to readily include such an analysis.

I FOUND A STUDY\* THAT SAID  
WATER IS GOOD FOR YOU,  
BUT YOU SHOULD JUST DRINK  
IT WHEN YOU FEEL THIRSTY  
AND NOT GO OVERBOARD.



\*DOI: 10.1097/JSM.0000000000000221

ANOTHER STUDY\* FOUND  
THAT PROLONGED SITTING  
ISN'T NECESSARILY BAD FOR  
YOU, AS LONG AS YOU'RE  
ALSO GETTING EXERCISE.



\*DOI: 10.1093/ije/dyv191

NOW A STUDY\* CLAIMS THAT  
HUMANS IN PRE-INDUSTRIAL  
SOCIETIES STAY UP LATE AND  
SLEEP 6 OR 7 HOURS A NIGHT,  
JUST LIKE MOST PEOPLE TODAY.



\*DOI: 10.1016/j.cub.2015.09.046

MAYBE WE'RE OVERTHINKING IT.  
BUT WHAT CAUSED OUR MODERN  
EPIDEMIC OF OVERTHINKING?  
PLUMBING? OR IS IT EMAIL?  
MODERN? I BET THE WHEEL  
WAS INVENTED BY SOMEONE  
OVERTHINKING "PUSHING."



*On the other hand, it took us embarrassingly long to clue in to the lung cancer/cigarette thing, so I guess the real lesson is "figuring out which ideas are true is hard."*

tid bits

what about multiple  
unmeasured  
confounders?

bias factors

design  
sensitivity

next steps



\* tutorial

- \* tutorial
- \* bias factors

- \* tutorial
- \* bias factors
- \* design sensitivity

- \* tutorial
- \* bias factors
- \* design sensitivity
- \* puppets