Probabilistic bias analysis of epidemiological results

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Second Nordic and Baltic countries
Stata Users Group meeting

Stockholm, 7 September, 2007

Outline

- Background of the methods
- Application to epidemiology
- Deterministic sensitivity analysis
- Probabilistic sensitivity analysis
- Strengths and limitations

Background

Sensitivity analysis is the study of how the variation in the output of a model can be attributed to different sources of variation.

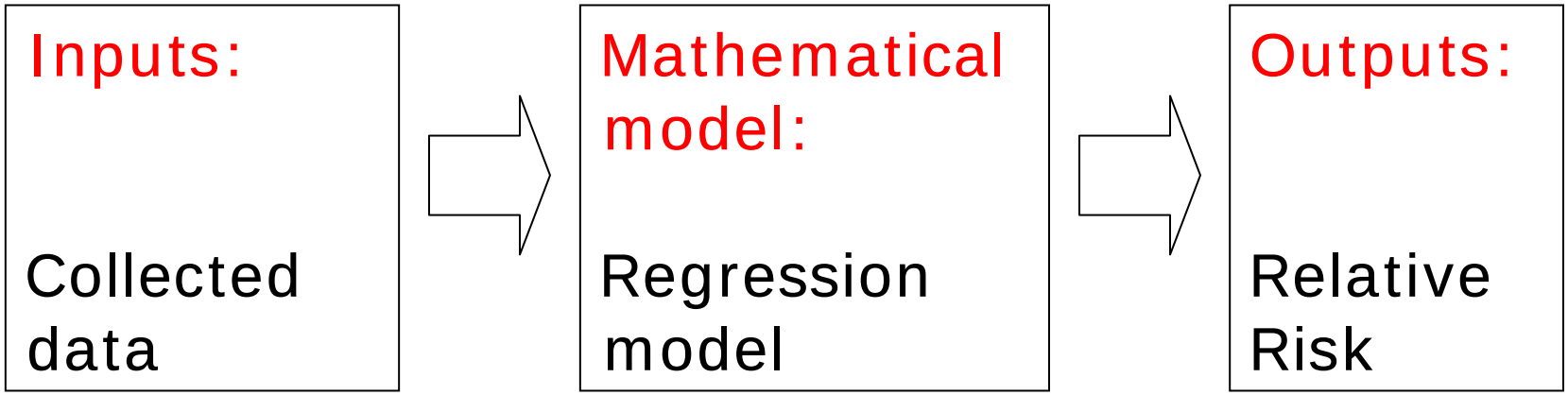
Methods dealing with uncertainty in model outputs are well known in

- Decision modeling
- Risk analysis

and applied in a variety of industries and applications

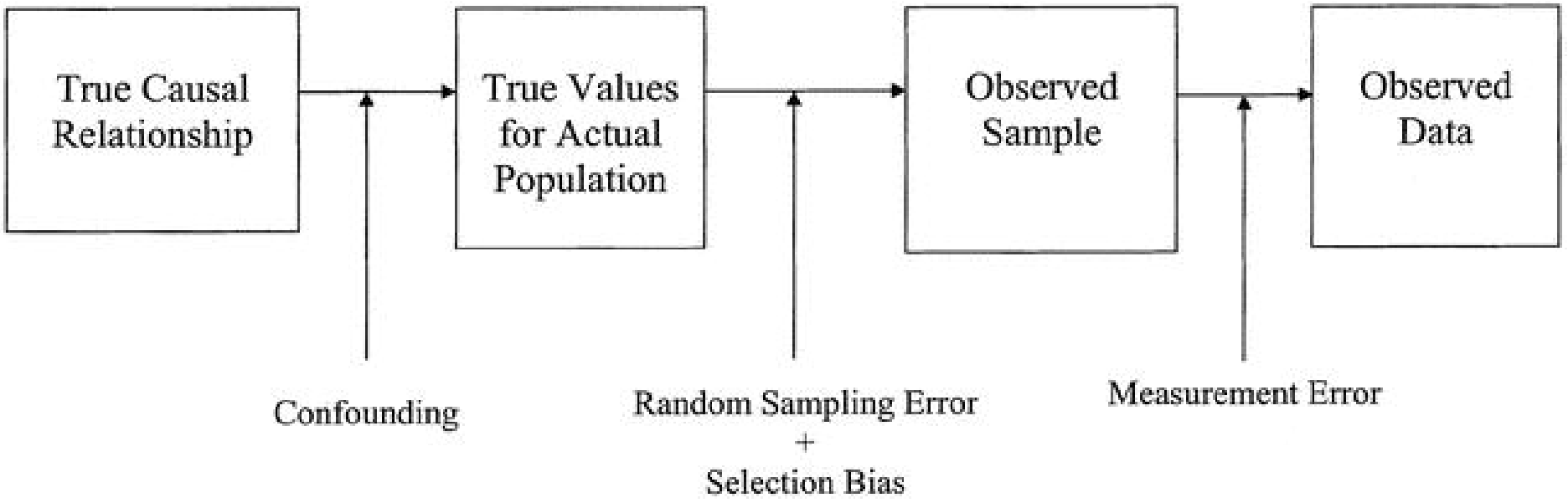
Engineering
Financial Planning
Project Management
Government
Health Care
Pharmaceuticals
Consulting
Insurance

Application to epidemiology



The collection of observational data is subject to many sources of uncertainty including errors of measurement, absence of information, and poor or partial understanding of the driving forces and mechanisms.

Causation of Bias



Generation of observed data.

Moving from left to right shows the introduction of errors as we move from what we are trying to measure to what we actually measure (Phillips 2003).

The two steps of a conventional analysis

Step 1) Use standard statistical methods based on the following not testable assumptions:

1. No unmeasured confounders

2. Random selection, participation, and missing

3. No mismeasurement

Step 2) address possible violations of assumption 1-3 with speculative discussions.

In practice, the assumptions of Step 1) may be grossly violated, and the Step 2) is often skipped (Greenland 2005).

Various approaches to bias

1. Ignore biases (or hope that they cancel out)
2. Mention something about potential biases
3. Address qualitatively the effect of bias
4. Address quantitatively the effect of bias

Based on a recent study, it seems that the majority of published papers on the major epidemiological journals follow the approaches 1 to 3 (Jurek, et al. 2006).

Why quantitative methods are rarely used?

1. Lack of training in epidemiology and biostatistics courses

2. No request from the reviewers

3. Lack of user-friendly packaged software

The problem is that

- A conventional confidence interval reflect only uncertainty due to random error and
- fail to consider uncertainty due to systematic errors.
- The confidence interval is too narrow.

Deterministic sensitivity analysis

- It estimates what the true measure of effect (Relative Risk) would be in light of the observed data and some hypothetical level of bias.

- The idea is to back-calculate the data that would have been observed without bias, assuming particular values for the bias parameters.

- Deterministic (traditional or classical) sensitivity analysis can be seen as a series of educated guesses about the bias parameters (Greenland 1996).

2 by 2 tables for epidemiologists

	Exposed	Unexposed	Total
Cases	a_1	a_0	m_1
Non-Cases	b_1	b_0	m_0

Case-control data (odds ratio)
Cohort - Cumulative incidence data (risk ratio)
Cohort - Incidence rate date (rate ratio) (Non-cases would be person-time at risk)

Misclassification of the exposure

- Sensitivity (Se) = probability someone exposed is classified as exposed

- Specificity (Sp) = probability someone unexposed is classified as unexposed

Misclassification of the exposure

The relative risk RR_a adjusted for misclassification is a function of the sensitivity and specificity specified for cases and non-cases.

	Non-differential	Differential
Cases	**Se Sp**	**Se Sp**
Non-cases		**Se Sp**

The bias parameters are Se and Sp

Misclassification of the exposure

$$RR_a = RR_o / K$$

$$K = \text{function}(Se, Sp)$$

RR_a is the misclassified-adjusted relative risk

RR_o is the observed relative risk

K is a factor that govern magnitude and direction of bias.

If Se = Sp = 1 there is no misclassification.

Selection bias

$$RR_a = RR_o / K$$

$$K = (Sa_1, Sb_0, Sa_0, Sb_1)$$

where Sa_1 , Sb_0 , Sa_0 , Sb_1 are the probabilities of case and non-cases selection among exposed and unexposed.

RR_a is the selection-bias adjusted relative risk

RR_o is the observed relative risk

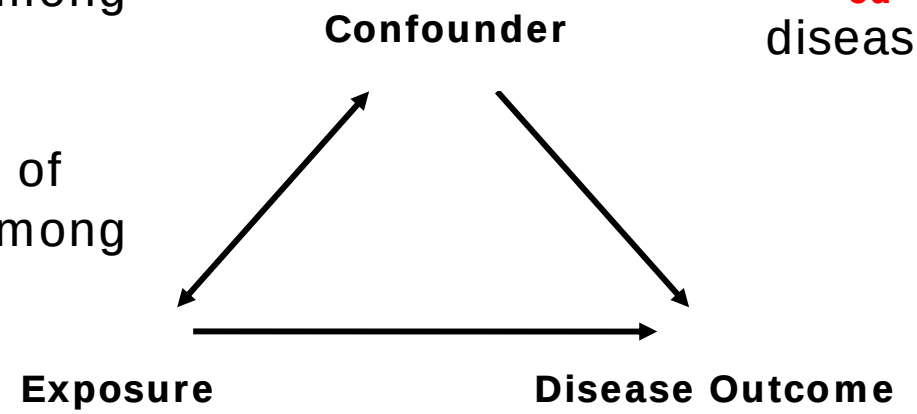
K is a factor that govern magnitude and direction of bias.

If Sa_1 , Sb_0 , Sa_0 , Sb_1 =1 there is no bias.

Unmeasured or uncontrolled confounder

P_{c1} = Prevalence of the confounder among the exposed

P_{c0} = Prevalence of the confounder among the unexposed



RR_{cd} = confounder-disease relative risk

A confounder is associated with the exposure and is also an independent risk factor of the disease outcome.

If either association is non-existent, there is no confounding.

The bias parameters are P_{c1} , P_{c0} , and RR_{cd}

Unmeasured or uncontrolled confounder

$$RR_a = RR_o / K$$

$$K = (P_{c0}, P_{c1}, RR_{cd})$$

RR_a is the confounder-adjusted relative risk

RR_o is the observed relative risk

K is a factor that govern magnitude and direction of bias

If $P_{c1} = P_{c0}$ there is no confounding

If $RR_{cd} = 1$ there is no confounding

New Stata commands

Name	Description
episens	It requires the original data.
episensi	Original data not available. Immediate version of episens. It requires the cell counts.

Example – Case-control study about occupational exposure to resins and lung cancer mortality

```
. cci 45 94 257 945 , woolf
```

	Exposed	Unexposed	Total	Proportion Exposed
Cases	45	94	139	0.3237
Controls	257	945	1202	0.2138
Total	302	1039	1341	0.2252
	Point estimate		[95% Conf.	Interval]
Odds ratio	**1.760286**		**1.202457**	**2.576898**
Attr. frac. ex.	.4319106		.1683693	.6119365
Attr. frac. pop	.1398272			

chi2(1) = 8.63 Pr>chi2 = 0.0033

Non-differential misclassification of the exposure

```
. episensi 45 94 257 945 , st(cc) dseca(c(.9)) dspca(c(.9)) ///
dsenc(c(.9)) dspnc(c(.9))

Se|Cases   : Constant(.9)
Sp|Cases   : Constant(.9)
Se|No-Cases: Constant(.9)
Sp|No-Cases: Constant(.9)

Observed Odds Ratio [95% Conf. Interval]= 1.76 [1.20, 2.58]

Deterministic sensitivity analysis for
misclassification of the exposure
   External adjusted Odds Ratio = 2.34
   Percent bias = -25%
```

Differential misclassification of the exposure

```
. episensi 45 94 257 945, st(cc) dseca(c(.9)) dspca(c(.8)) ///
dsenc(c(.8)) dspnc(c(.8))

Se|Cases   : Constant(.9)
Sp|Cases   : Constant(.8)
Se|No-Cases: Constant(.8)
Sp|No-Cases: Constant(.8)

Observed Odds Ratio [95% Conf. Interval]= 1.76 [1.20, 2.58]

Deterministic sensitivity analysis for
misclassification of the exposure
   External adjusted Odds Ratio = 9.11
   Percent bias = -81%
```

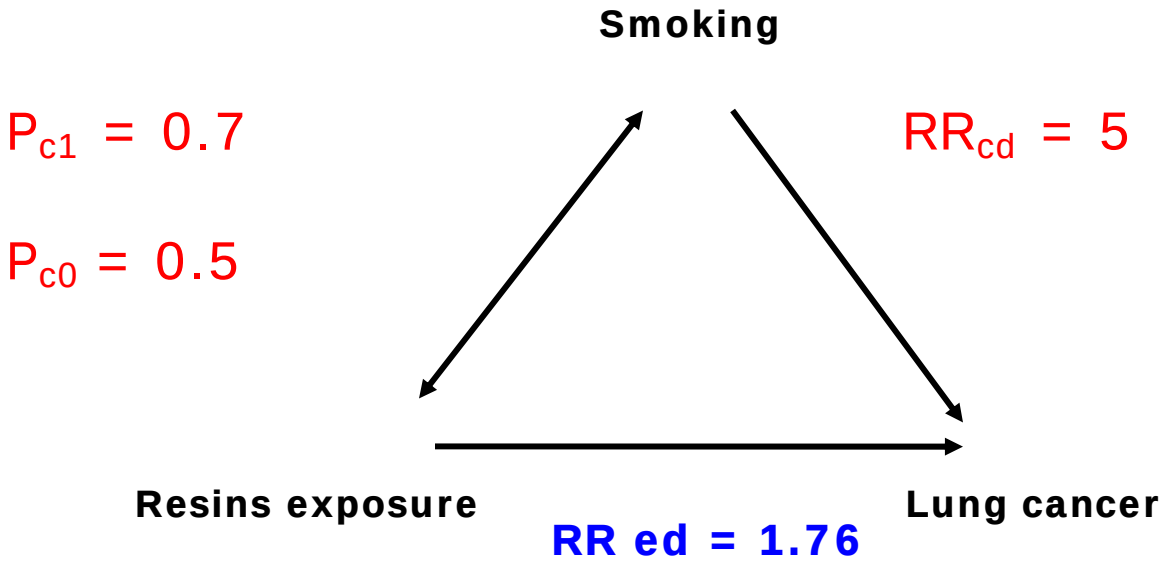
Table. Deterministic sensitivity analysis of the resins-lung cancer odds ratios under various assumptions about the exposure sensitivity (Se) and specificity (Sp) among cases and controls.

Cases			Controls			
Se	Sp	Se	0.9	0.8	0.9	0.8
		Sp	0.9	0.9	0.8	0.8
0.9	0.9		2.3	2.0	19	16
0.8	0.9		2.8	2.4	23	20
0.9	0.8		1.3	1.1	11	9
0.8	0.8		1.6	1.3	13	11

Under non-differential misclassification (yellow cells) bias-corrected relative risks are always further away from the null.

The uncertainty in the corrected RR (range 2.3 up to 11) overwhelms the uncertainty suggested by conventional limits 95% CI, 1.2-2.6).

Unmeasured confounder



Binary outcome: Lung cancer death

Binary exposure: Resins exposure, yes vs no

Binary unmeasured confounder: Smoking, yes vs no

Case-control data

```
. episensi 45 94 257 945, dpexp(c(.7)) dpunexp(c(.5))
drrcd(c(5))

Pr(c=1|e=1): Constant(.7)
Pr(c=1|e=0): Constant(.5)
RR_cd      : Constant(5)

Observed Odds Ratio [95% Conf. Interval]= 1.76 [1.20, 2.58]

Deterministic sensitivity analysis for unmeasured
confounding
   External adjusted Odds Ratio = 1.39
   Percent bias =  27%
```

Table. Deterministic sensitivity analysis of the resins-cancer odds ratios to choice of different values for the bias parameters: smoking prevalences among exposed (P_{c1}) and unexposed (P_{c0}), and the smoking-lung cancer relative risk (RR_{cd}).

P_{c1}	P_{c0}	OR_{ce}	RR_{cd}		
			5	10	15
0.40	0.30	1.56	1.49	1.42	1.39
0.55	0.45	1.49	1.54	1.49	1.48
0.70	0.60	1.56	1.57	1.54	1.53
0.45	0.25	2.45	1.26	1.13	1.09
0.60	0.40	2.25	1.35	1.27	1.24
0.75	0.55	2.45	1.41	1.35	1.33

The observed unadjusted resins-lung cancer odds ratio is 1.8 (95% CI, 1.2-2.6).

OR_{ce} is the confounder-exposure OR, calculated from the prevalences P_{c1} and P_{c0}.

Limitation of deterministic sensitivity analysis

- Lack probability structure for the bias parameters
- Fail to discriminate among the different scenarios in terms of their likelihood
- It is not easy to summarize results

Probabilistic sensitivity analysis

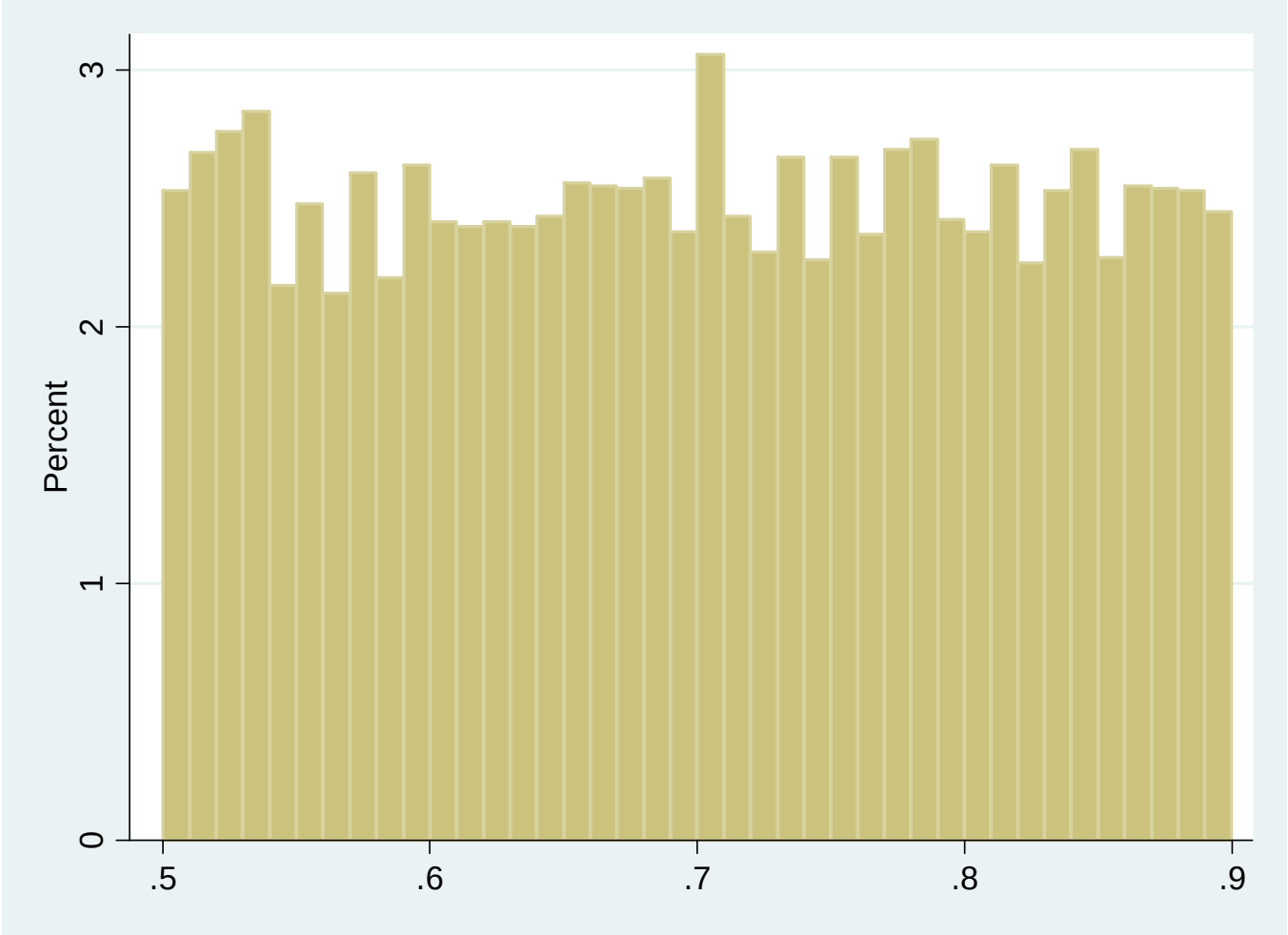
A more realistic approach allows for uncertainty in the bias parameters.

By specifying a probability distribution for the bias parameters, the bias-adjusted relative risk reflects the uncertainty in the bias parameters.

The command **episens** allows the user to specify a variety of probability densities for the bias parameters, and use these densities to obtain simulation limits for the bias adjusted exposure-disease measure of effect.

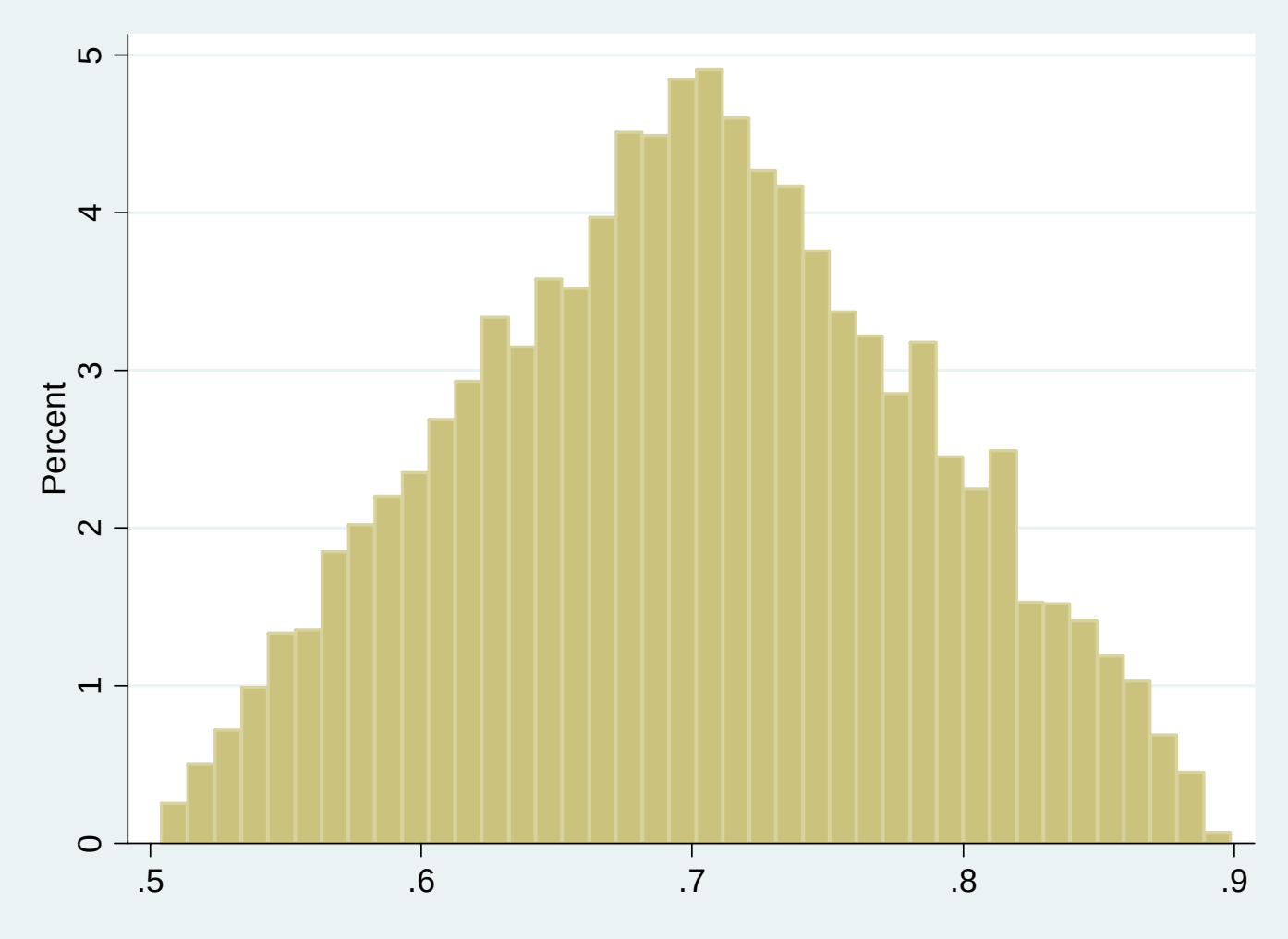
Type of systematic error and bias parameters	Description	Probability density functions
Misclassification of the exposure		
dseca	Sensitivity cases	constant(k) uniform(a b) triangular(a b c) trapezoidal(a b c d) logit-logistic(m s [lb ub]) logit-normal(m s [lb ub])
dspca	Specificity cases	
dsenc	Sensitivity non-cases	
dspnc	Specificity non-cases	
Selection bias		
dpscex	Pr selection cases exposed	constant(k) uniform(a b) triangular(a b c) trapezoidal(a b c d) logit-logistic(m s [lb ub]) logit-normal(m s [lb ub])
dpscun	Pr selection cases unexposed	
dpsnex	Pr selection non cases exposed	
dpsnun	Pr selection non case sunexposed	
dsbfactor	Selection bias factor	constant(k) log-normal(m s) log-logistic(m s)
Unmeasured confounding		
dpexp	Pr confounder exposed	constant(k) uniform(a b) triangular(a b c) trapezoidal(a b c d) logit-logistic(m s [lb ub]) logit-normal(m s [lb ub])
dpunexp	Pr confounder unexposed	
drrcd	RR confounder-disease	constant(k) log-normal(m s) log-logistic(m s)
dorce	OR confounder-exposure	

Uniform distribution



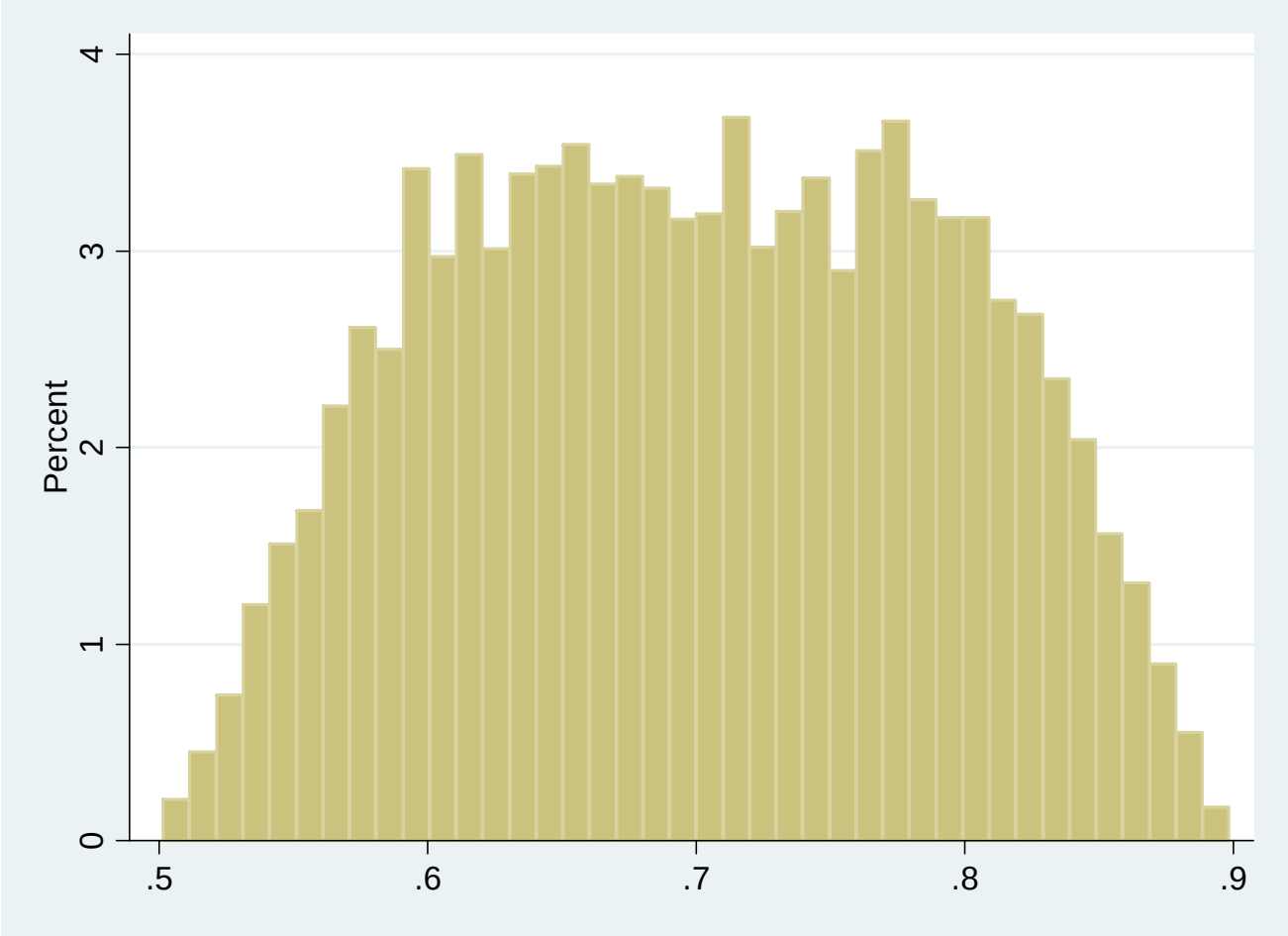
All the values within the specified bounds (a=.5, b=.9) are equally probable

Triangular distribution



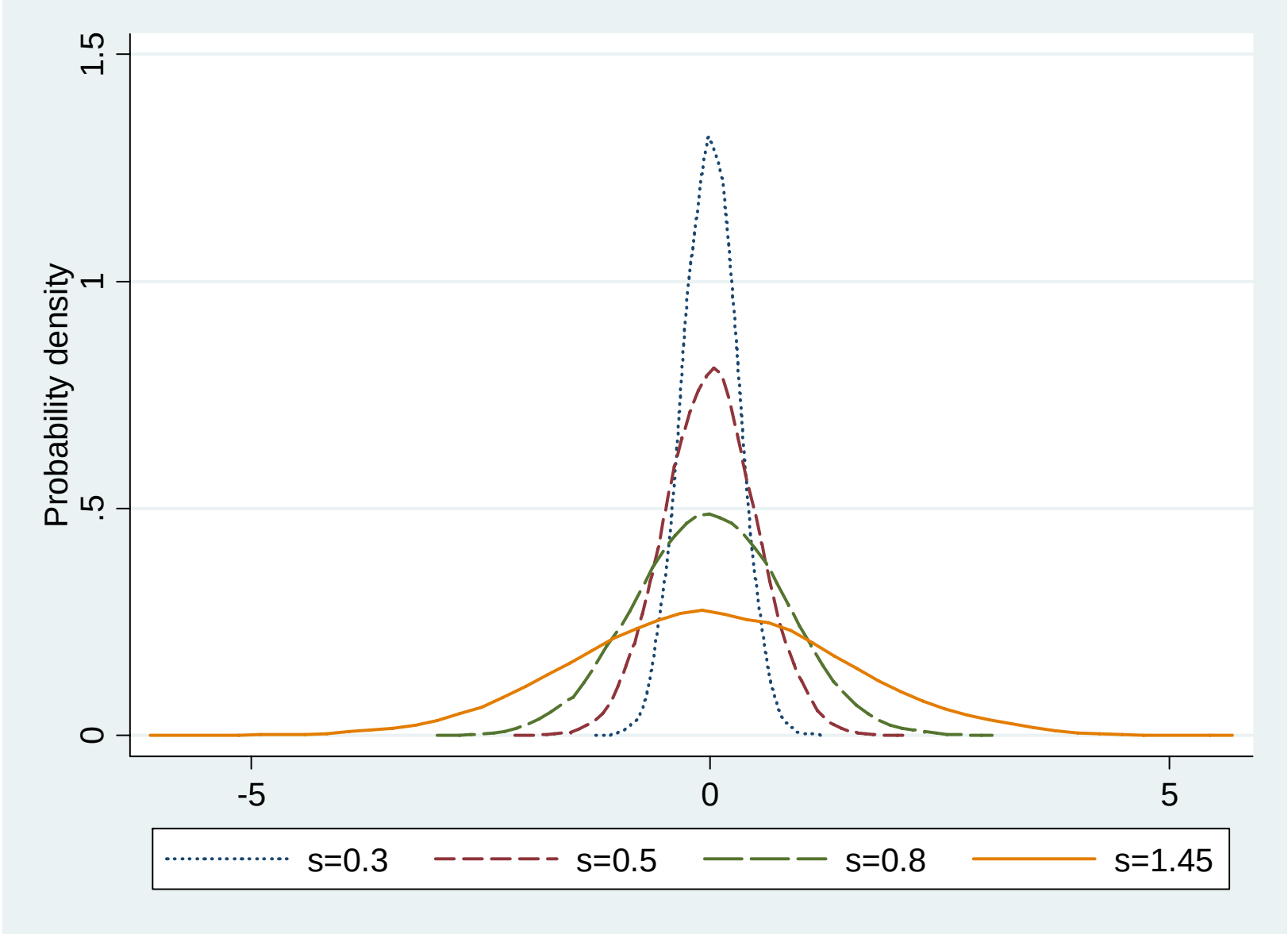
There is a mode (most likely value, b=.7) within the specified bounds (a=.5, c=.9)

Trapezoidal distribution

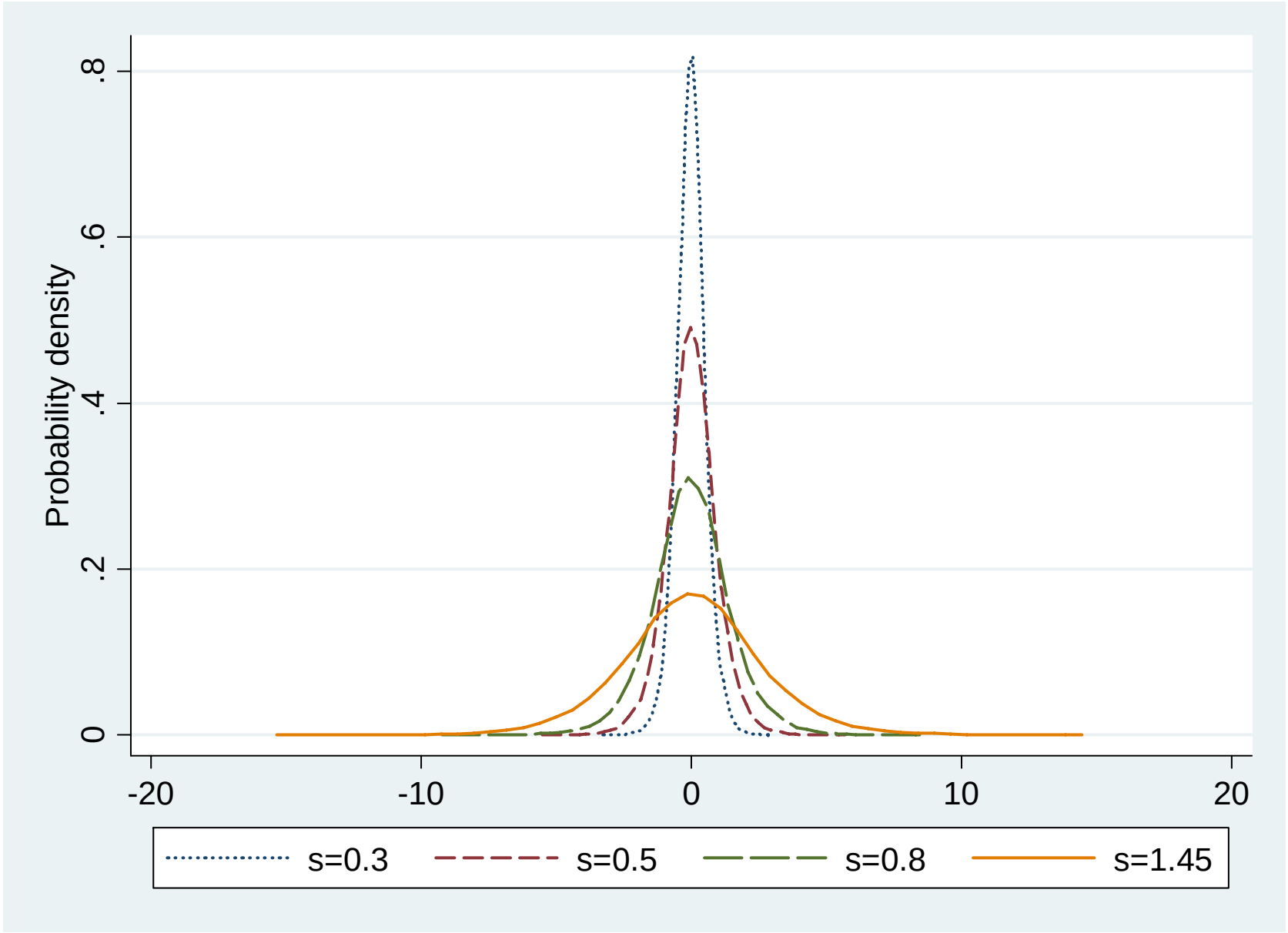


There is an interval of equally probable values between .6 and .8, within specified bounds (.5, .9).

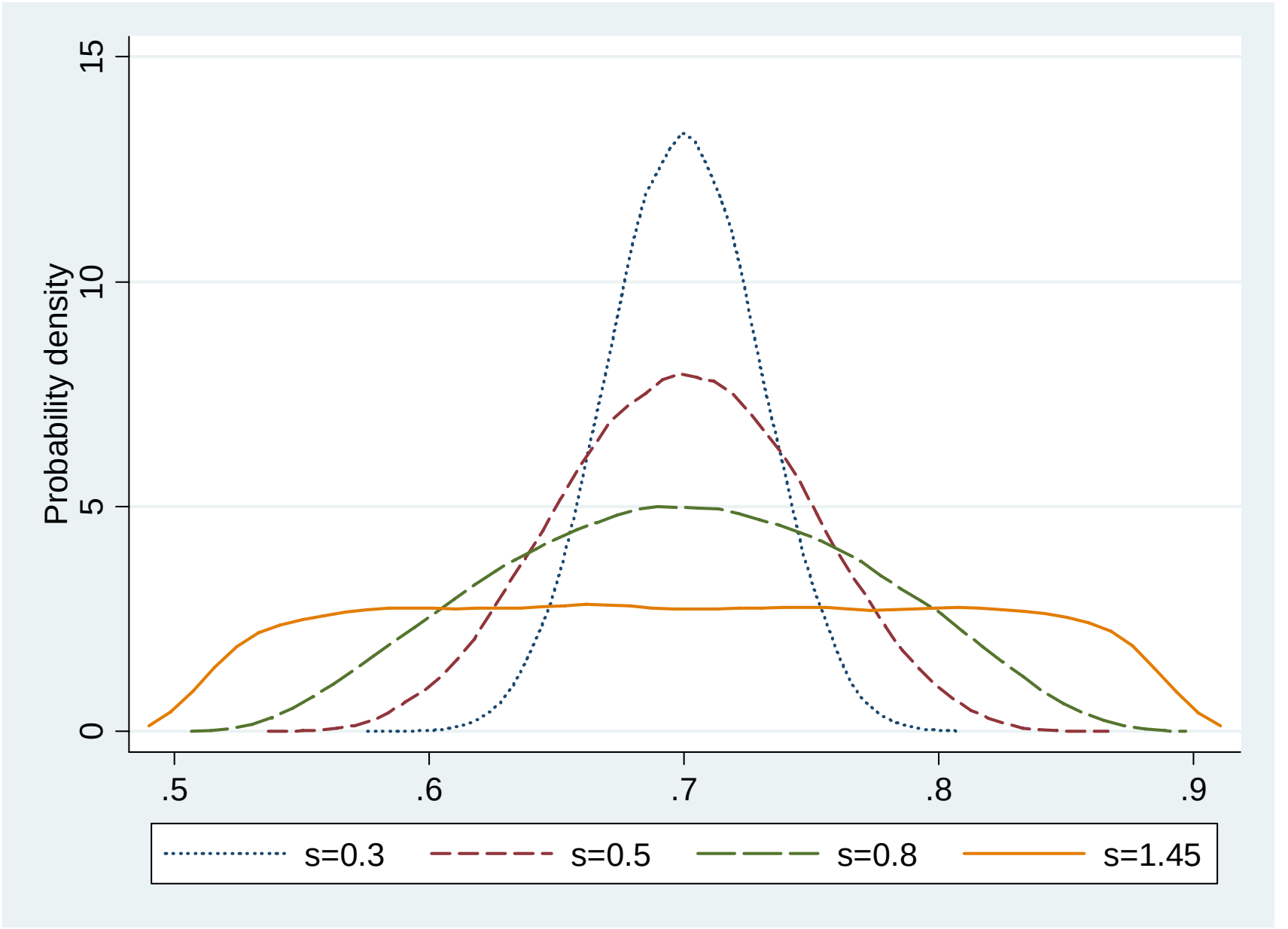
Log-normal distribution (m=0)



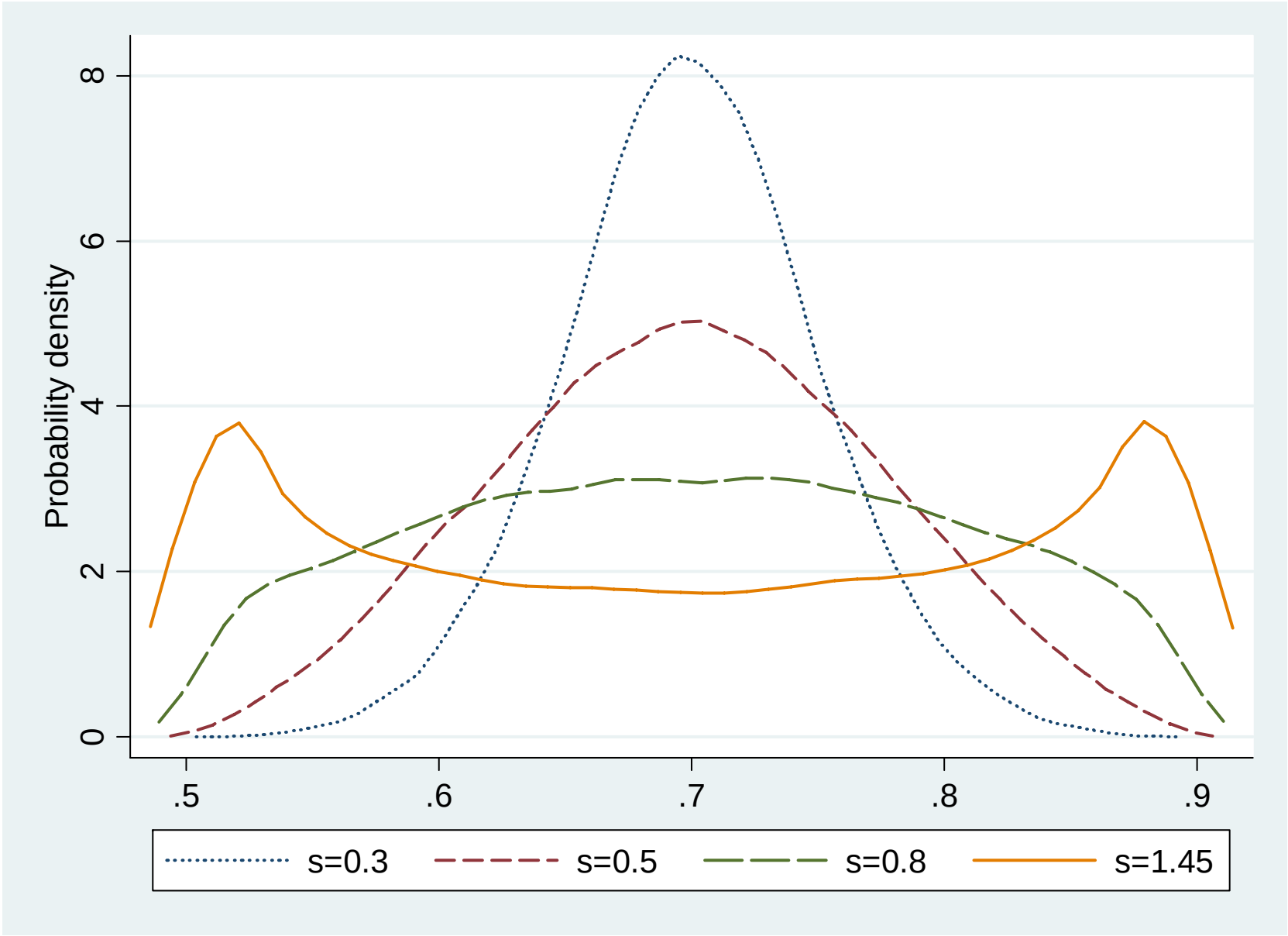
Log-logistic distribution (m=0)



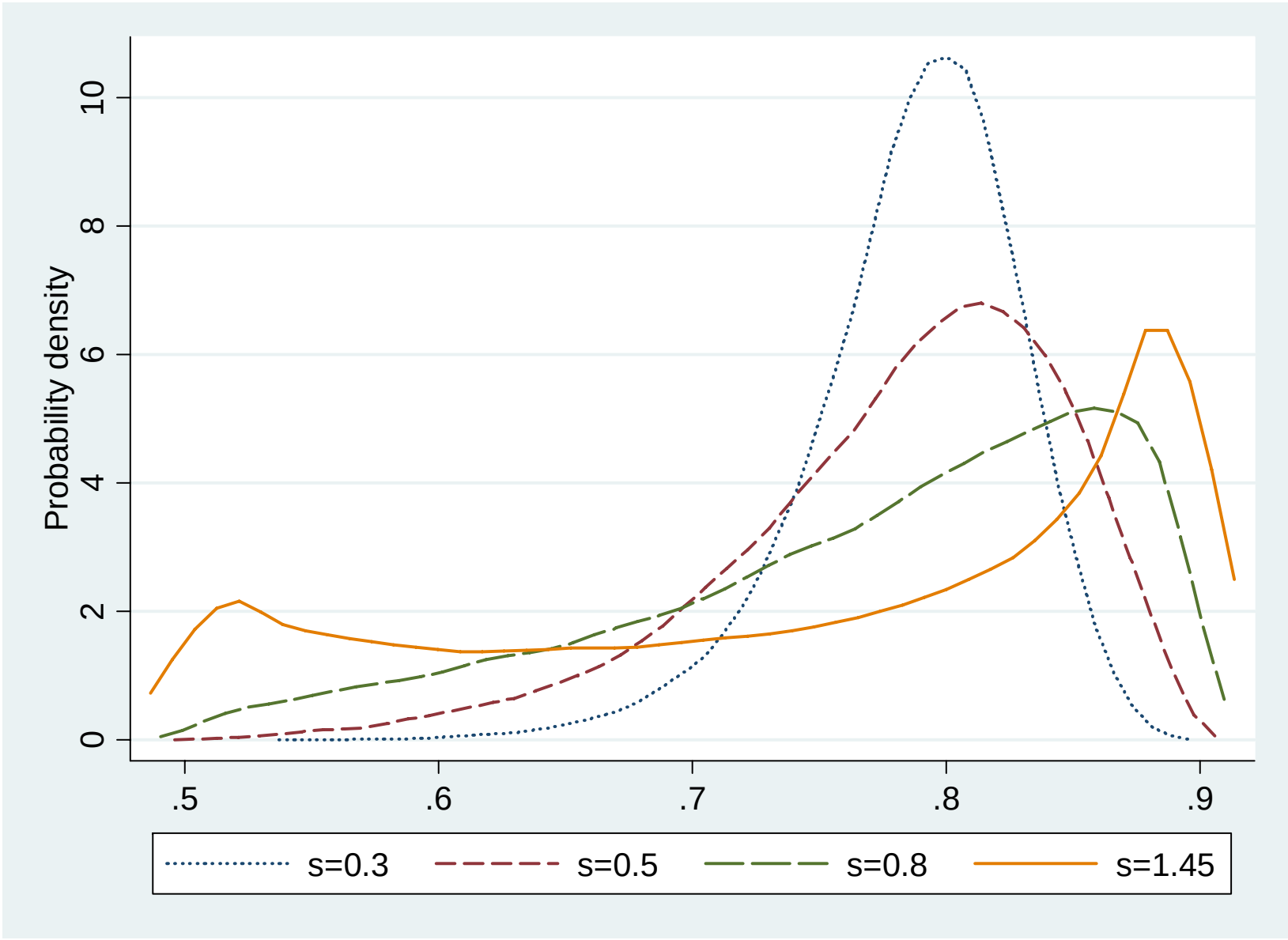
Logit-normal distribution (m=0, lb=.5, ub=.9)



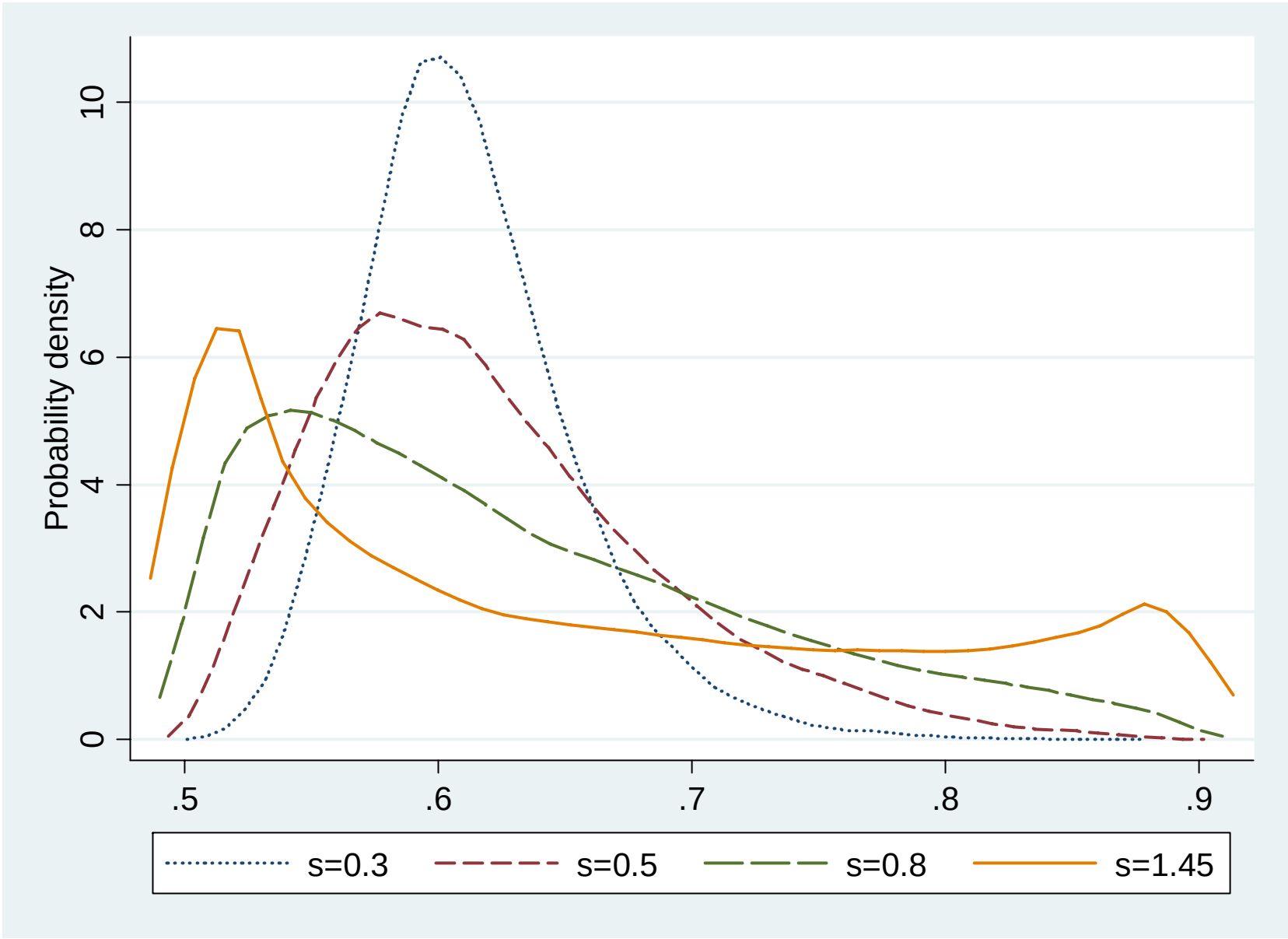
Logit-logistic distribution (m=0, lb=.5, ub=.9)



Logit-logistic distribution (m=1, lb=.5, ub=.9)



Logit-logistic distribution (m=-1, lb=.5, ub=.9)



Monte Carlo-type simulations

Monte Carlo (random number-based) simulations involve two steps:

step 1) generate a dataset containing observations from the user specified probability density functions of the bias parameters

step 2) draw a random sample (one set of likely bias parameters) from this dataset to back-calculate the relative risk

We repeat steps 1 and 2 a large number of times to obtain a distribution of bias-corrected estimates.

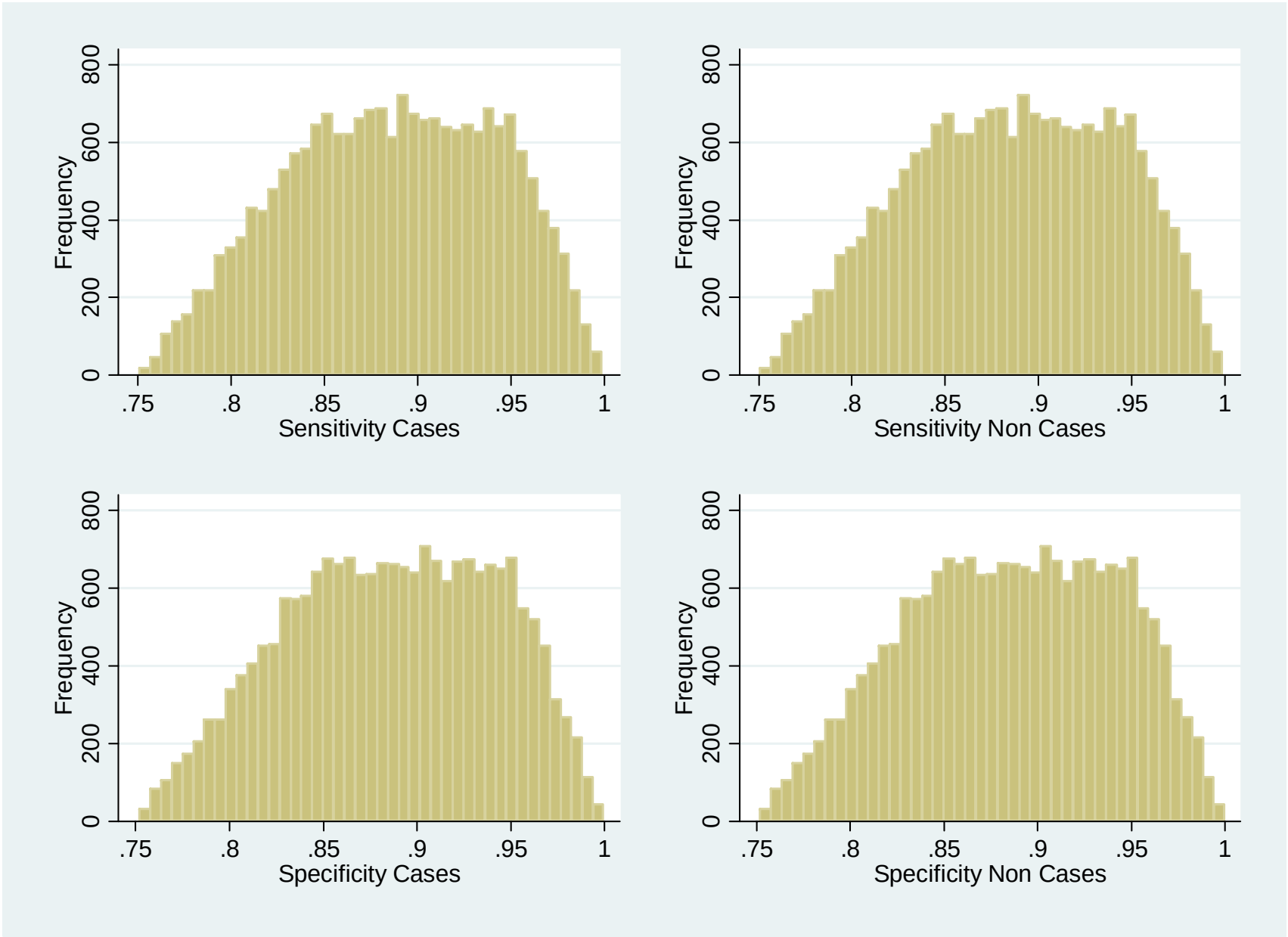
Non-differential misclassification of the exposure (a=.75, b=.85, c=.95, 1)

```
. episensi  45 94 257 945 , st(cc) reps(20000)  nodots    ///
dseca(trap(.75  .85 .95  1) )   dspca(trap(.75  .85 .95  1) )  ///
dsenc(trap(.75  .85 .95  1) )   dspnc(trap(.75  .85 .95  1))
grpriors

Se|Cases   : Trapezoidal(.75,.85,.95,1)
Sp|Cases   : Trapezoidal(.75,.85,.95,1)
Se|No-Cases: Trapezoidal(.75,.85,.95,1)
Sp|No-Cases: Trapezoidal(.75,.85,.95,1)

Probabilistic sensitivity analysis for misclassification of the
exposure
```

	Percentiles			Ratio
	2.5	50	97.5	97.5/2.5
Conventional	1.20	1.76	2.58	2.14
Systematic error	**1.87**	**2.46**	**14.70**	**7.86**
Systematic and random error	**1.49**	**2.57**	**15.07**	**10.10**


Frequency
0
200
400
600
800
.75
.8
.85
.9
.95
1
Sensitivity Cases
Sensitivity Non Cases
Specificity Cases
Specificity Non Cases

Differential misclassification of the exposure (a=.75, b=.85, c=.95, 1)

```
. episensi  45 94 257 945  , st(cc) reps(20000) nodots ///
 dseca(trap(.75  .85 .95  1)  )  dspca(trap(.75  .85 .95  1) )  ///
 dsenc(trap(.7   .8  .9  .95) )  dspnc(trap(.7   .8  .9  .95) )
 corrsens(.8)  corrspec(.8)
```

```
Se|Cases   : Trapezoidal(.75,.85,.95,1)
Sp|Cases   : Trapezoidal(.75,.85,.95,1)
Se|No-Cases: Trapezoidal(.7,.8,.9,.95)
Sp|No-Cases: Trapezoidal(.7,.8,.9,.95)
Corr Se|Cases and Se|No-Cases : .8
Corr Sp|Cases and Sp|No-Cases : .8

Probabilistic sensitivity analysis for misclassification of the
exposure
```

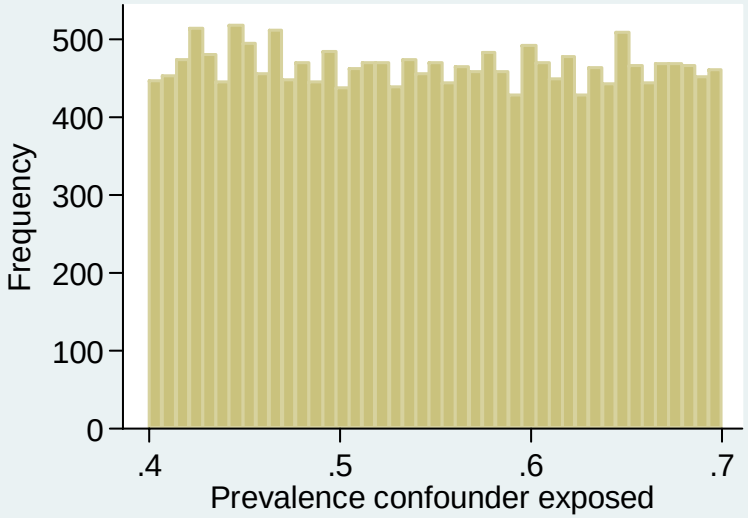
	Percentiles			Ratio
	2.5	50	97.5	97.5/2.5
Conventional	1.20	1.76	2.58	2.14
Systematic error	**1.81**	**3.48**	**48.19**	**26.57**
Systematic and random error	**1.61**	**3.60**	**48.92**	**30.47**

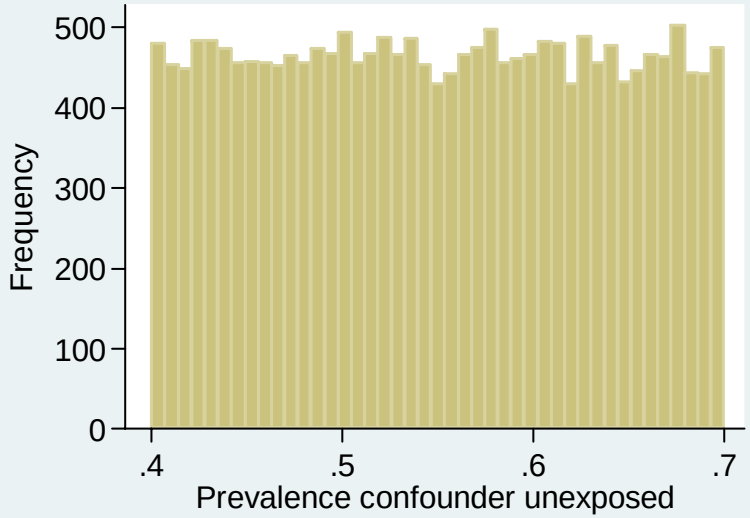
Unmeasured confounder

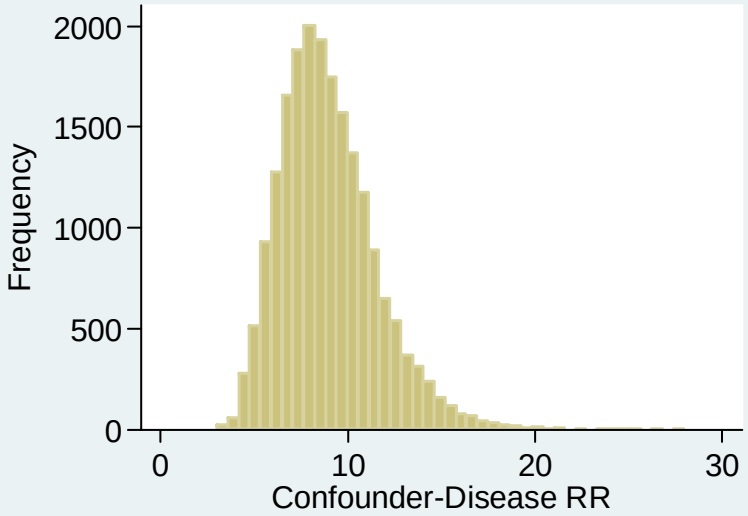
Two uniform distributions for the smoking prevalences among exposed and unexposed between 0.4 and 0.7.

The probability density function of the smoking-lung cancer mortality RR is assumed to be log-normal with 95% confidence limits of log(5) and log(15).

The limits imply that the mean of this distribution is [(log(15)-log(5)]/2=2.159 with standard deviation [log(15)-log(5)]/2*1.96=0.280.


Frequency
0
100
200
300
400
500
.4
.5
.6
.7
Prevalence confounder exposed


Frequency
0
100
200
300
400
500
.4
.5
.6
.7
Prevalence confounder unexposed


Frequency
0
500
1000
1500
2000
0
10
20
30
Confounder-Disease RR

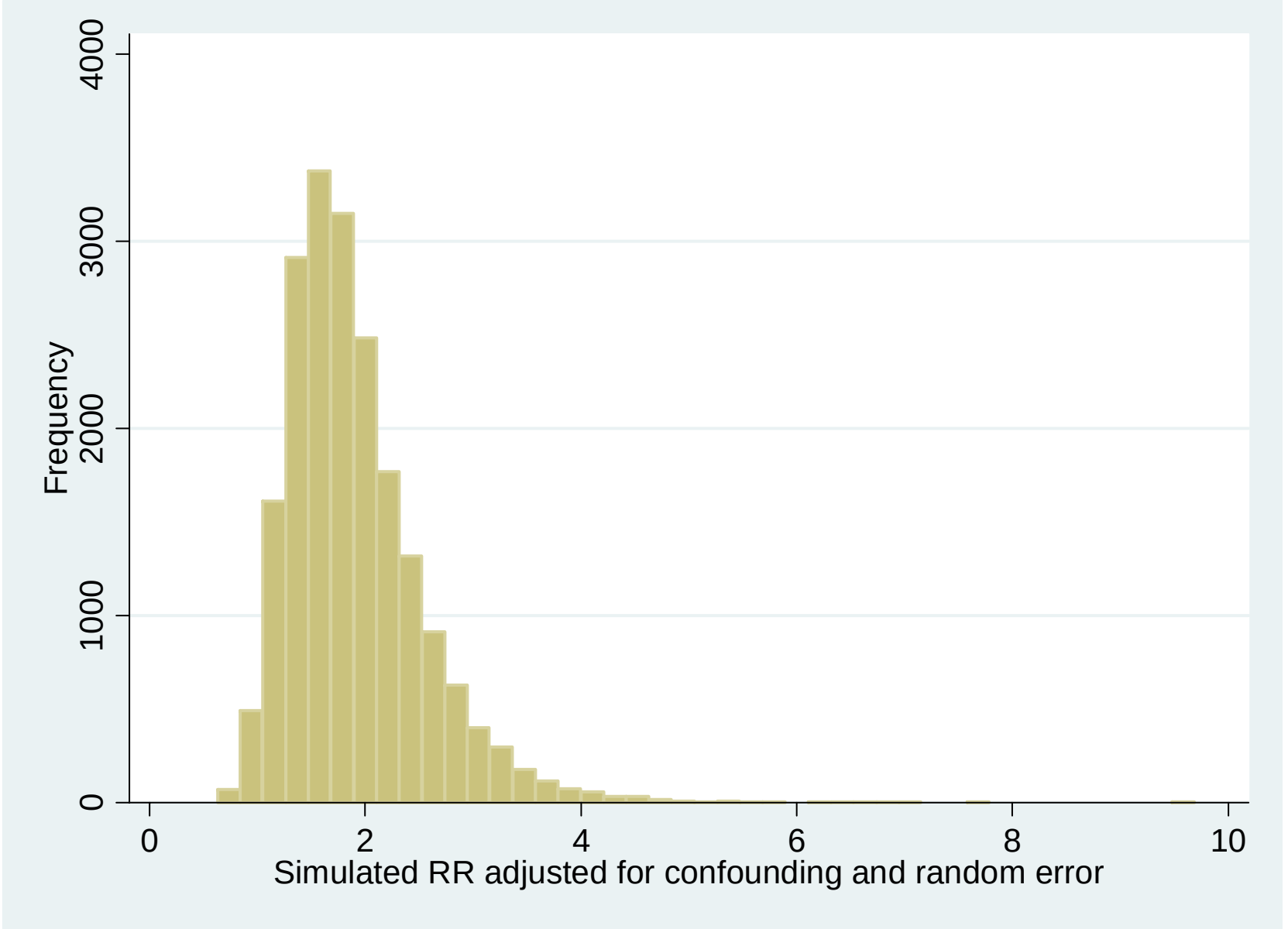
```
. episensi  45 94 257 945 , st(cc) reps(20000) nodots
dpexp(uni(.4 .7)) dpunexp(uni(.4 .7)) drrcd(log-n(2.159 .280))
grarrsys grarrtot grprior

Pr(c=1|e=1): Uniform(.4,.7)
Pr(c=1|e=0): Uniform(.4,.7)
RR_cd      : Log-Normal(2.16,0.28)

Probabilistic sensitivity analysis for unmeasured confounding

                                          Percentiles          Ratio
                                 2.5          50          97.5      97.5/2.5
                                 ----------------------------------------
Conventional                     1.17         1.76        2.61      2.23
Systematic error                 1.24         1.76        2.49      2.00
Systematic and random error      1.04         1.76        3.01      2.90
```

The median smoking-adjusted resins-lung cancer OR is 1.76 with 95% simulation limits of 1.04 and 3.01. As expected, the ratio of the smoking-adjusted simulation limits (2.9) is higher than the ratio of the conventional limits (2.2).

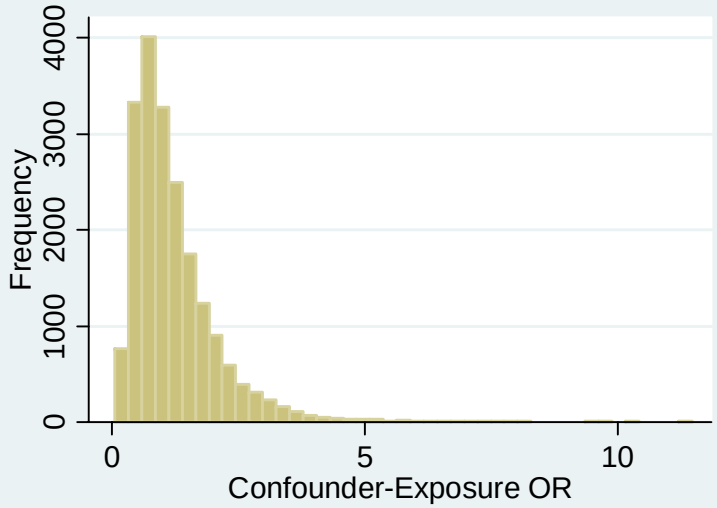

Frequency
0
1000
2000
3000
4000
0
2
4
6
8
10
Simulated RR adjusted for confounding and random error

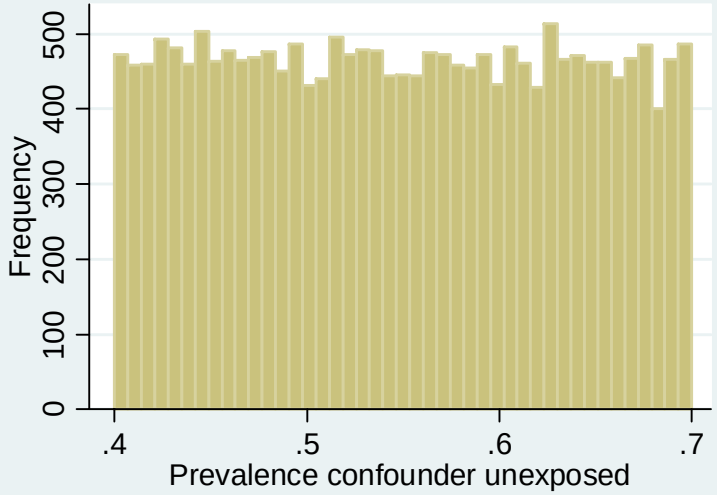
More reasonable priors

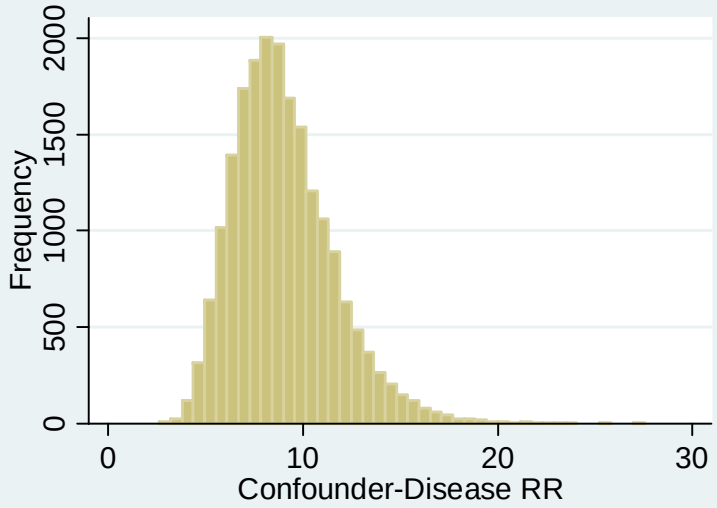
Given that there is no reason to expect great differences in the prevalence of smoking among resins exposed and unexposed, small differences are more likely than large ones.

One way to address non independent distributions of the confounder-exposure specific prevalences is to specify a probability density function for the confounder-exposure OR (option **dorce**) instead of the prevalence of the confounder among the exposed (option **dpexp**).

Assuming independent priors for the confounder-exposure OR and the prevalence of the confounder among the unexposed is not unreasonable.


Frequency
0
1000
2000
3000
4000
0
5
10
Confounder-Exposure OR


Frequency
0
100
200
300
400
500
.4
.5
.6
.7
Prevalence confounder unexposed


Frequency
0
500
1000
1500
2000
0
10
20
30
Confounder-Disease RR

```
. episensi  45 94 257 945 , st(cc) reps(20000) nodots    ///
dpunexp(uni(.4 .7)) drrcd(log-n(2.159 .280))
dorce(log-normal(0 .639))

Pr(c=1|e=0): Uniform(.4,.7)
RR_cd      : Log-Normal(2.16,0.28)
OR_ce      : Log-Normal(0.00,0.64)

Probabilistic sensitivity analysis for unmeasured confounding

                                        Percentiles         Ratio
                              2.5       50        97.5      97.5/2.5
                              ------------------------------------
Conventional                  1.20      1.76      2.58      2.14
Systematic error              1.24      1.76      3.04      2.45
Systematic and random error   1.04      1.77      3.44      3.30
```

Table. Percentiles of Monte Carlo simulated distribution of the smoking-adjusted resins-lung cancer odds ratio.

Type of analysis	Percentiles		
	2.5th	Median	97.5th
Conventional	1.2	1.8	2.6
Systematic error			
Adjusted Odds Ratio	1.2	1.8	3.0
Systematic and random-sampling error			
Adjusted Odds Ratio	1.0	1.8	3.4

Summary

Conventional statistical methods to estimate exposure-disease associations from observational studies are based on several assumptions.

When such assumptions are not met, however, the point and interval estimates for the association between exposure and disease are likely to be biased and fail to capture the uncertainty around them.

Deterministic (traditional) sensitivity analysis provides a range of bias-adjusted exposure-disease OR, based on observed data and some hypothetical level of bias.

In more realistic scenario, probabilistic sensitivity analysis provides a distribution of bias-adjusted exposure-disease OR.

Strengths

- Sensitivity analysis helps the investigator to make explicit the location and shape of the distribution of the bias parameters.

- The distributions of the bias parameters reflect the knowledge and judgment of the investigator about the potential systematic errors that may affect the observed findings.

- Probabilistic sensitivity analysis provides a wider confidence interval that includes both systematic and random error, which conventional analysis fails to consider (too narrow).

Limitations

- Concerns have been raised by some about the arbitrariness in the particular distributions assumed for the bias parameters, which can lead to different distributions of the adjusted exposure-disease RR.

- However, it should be emphasized that in order to make a shared and meaningful bias correction of the exposure-disease RR, the distributions of the bias parameters should be based on the best available evidence and by careful judgment.

- Informed sensitivity analysis is therefore limited by lack of data and/or scientific knowledge about the role of bias in a specific exposure-disease association.

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Acknowledgments

I would like to thank co-authors and project collaborators

- Rino Bellocco
- Matteo Bottai
- Alicja Wolk
- Sander Greenland

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