From Statistical Evidence to Evidence of Causality

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Case-Control Study

Frachon *et al.* (2010). *PLOS One* 5 (4), e10128

Benfluorex Use?	Valvular Heart Disease	Controls
Yes	19	3
No	8	51

Odds Ratio = (19/8)/(3/51) = 40.4

Adjusted Odds Ratio *(from logistic regression)* = 17.1

Hypothetical Toxic Tort Case

- **A woman with unexplained valvular heart disease sues the manufacturer of Benfluorex, claiming that it caused her illness**
- **Citing the Frachon study, an expert witness for the plaintiff claims that the medication causes valvular heart disease**
- **The manufacturer's expert testifies that their clinical trials did not suggest this as a side effect.**

How should the judge rule?

Causal Questions

- **Plaintiff's expert testified about the scientific question: "Can Benfluorex be shown to cause heart disease?"**
- **The judge wants to know the cause of this woman's heart disease**
- **What would have happened had the woman not taken Benfluorex?**

Effects of Causes versus Causes of Effects

- **Effects of Causes (EoC):** ***If she takes Benfluorex, is she more likely to develop valvular heart disease?***
  - **type causation?**
- **Causes of Effects (CoE):** ***Was it the Benfluorex she took that caused her valvular heart disease?***
  - **token causation?**

Is a question about CoE essentially the same as one about EoC?

If not, how do they differ?

Potential Responses

- *Binary exposure E*
- *Binary response R*

Model (E, R)

Introduce R_e = *"value of R if $E = e$"*

(so $R = R_E$)

Model (E, R_0, R_1) *jointly*

– ***but not jointly observable***

– R_0 *is* **counterfactual** *when* $E = 1$

Assessing Causes of Effects

- ***Was it the aspirin I took 30 minutes ago that caused my headache to disappear?***

- **Recovery rates (in large randomized trial):**
  - **No aspirin: 12%** $\Pr(R=1|E=0) = \Pr(R_0=1)$
  - **Aspirin: 30%** $\Pr(R=1|E=1) = \Pr(R_1=1)$

Probability of Causation

- ***Probability of Causation (via counterfactual contrast):***

  PC $= \Pr(R_0=0 \mid R_1=1)$

- **Requires JOINT DISTRIBUTION of** (R_0, R_1)
  - **Cannot estimate!**
    - ***At best, can only know marginal probabilities***

What can be said about PC?

Probability of Causation

R_1 \ R_0	0	1	Total
0	$88 - x$	$x - 18$	70
1	x	$30 - x$	30
Total	88	12	100

- PC = $\Pr(R_0=0 \mid R_1=1) = x/30$
- But must have $x \geq 18$
- So PC $\geq 18/30 = 60\%$

Probability of Causation

- **PC** $\geq$ **{Pr(R_0 = 1) −Pr(R_1 = 1)} / Pr(R_1 = 1)**

  = 1 − (1/RR)

  where RR = Pr(R_1 = 1)/Pr(R_0 = 1)

  is the (causal) *risk ratio*

- **In particular,**

  RR > 2 implies PC > ½

  –"proof on the balance of probabilities"

NB: converse is false! **Aetiological fallacy (Miller)**

A Bayesian Approach to Complex Clinical Diagnoses

A case-study in child abuse

Best et al., J. Roy. Statist. Soc. A (in Press)

- **Child c suffered *Acute Life-Threatening Event***
- **Also previous nose-bleed**
- **What is the evidence that c was physically abused?**

Literature search provided data relevant to:

- **Pr(abuse | ALTE)**
- **Pr(bleed | abuse, ALTE)**
- **Pr(bleed | no abuse, ALTE)**

+ *Bayes*

→ **Pr(abuse | bleed, ALTE)**

Table 1. Data extracted for the model to estimate Pr(abuse|ALTE, bleed)

Study	*d*	*n*	*Comments*
Pr(abuse|ALTE)			
Truman and Ayoub (2002)	138	11	Combines information on alive and dead children (Tables 2 and 3) 6 confirmed abuse in dead children (although another 7 possible cases of suspicious death) 4 reported abuse cases in live children and another identified later There is a possibility of 2 further cases, in the high risk group in Table 2; it is unclear whether they are a subset of the previous column
Pitetti *et al.* (2002)	128	3	1 further suspected case of abuse
Altman *et al.* (2003)	243	6	6 cases of confirmed abuse Another 4 possible cases of abuse, plus 35 further cases that are unlikely but cannot be ruled out
Davies and Gupta (2002)	65	2	2 confirmed cases of abuse 15 cases with unknown diagnosis that may be abuse, but unlikely
Pr(bleed|abuse,ALTE)			
Truman and Ayoub (2002)	6	1	Table 3, group V (confirmed abuse in children who died) Two cases of suspected abuse in group IV have not been included as either abuse or non-abused, but had experienced bleeding
Truman and Ayoub (2002)	5	0–4	Table 2 (4 reported abuse cases in live children and another identified later) It is not possible to determine exact numbers of abused children with bleeding in the live group, but the number must be between 0 and 4 of the 5 cases If the number of abused cases in this subgroup is as high as 7 (i.e. the 2 high risk cases identified on follow-up are *not* a subset of the previous column) then the number who had a bleed is between 0 and 6
Southall *et al.* (1997)	37	10	Cases 36 and 37 did not appear to have been abused, so were excluded from the denominator
Pr(bleed|no abuse, ALTE)			
Truman and Ayoub (2002)	29	0	Table 3, groups I–III (children who died and have confirmed diagnosis not involving abuse) Two cases of suspected abuse in group IV have not been included as either abuse or non abused but had experienced bleeding
Truman and Ayoub (2002)	98	5–9	Table 2, excluding 4 cases of reported abuse and 1 case of abuse on follow-up Not possible to determine exact number of bleed cases among non-abused in live group but the total in the abused and non-abused groups in live children must be 9
Southall *et al.* (1997)	48	1	Denominator includes cases 36 and 37

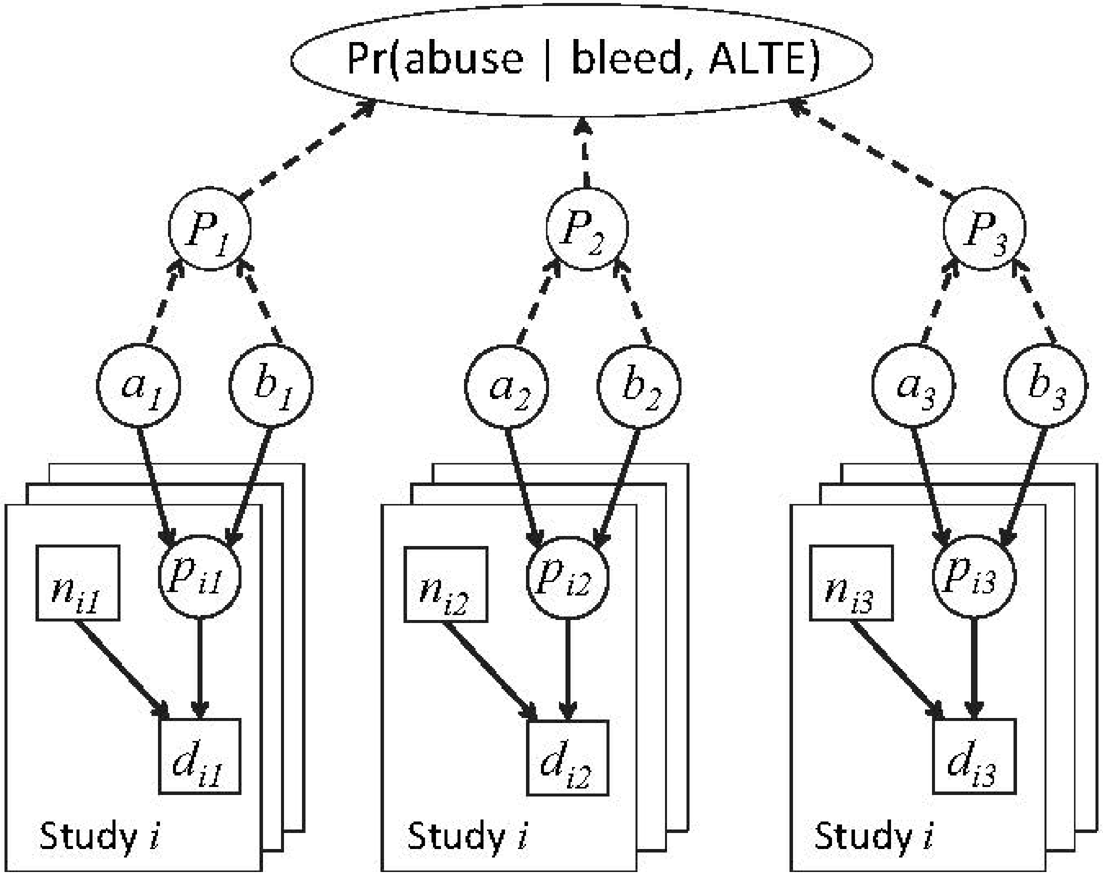


Fig. 2. Graphical representation of the model for calculating Pr(abuse|bleed, ALTE) based on equation (2) (P_1 corresponds to Pr(abuse|ALTE), P_2 corresponds to Pr(bleed|abuse, ALTE) and P_3 corresponds to Pr(bleed|no abuse, ALTE)): □ , data extracted from the literature search; ○ , ⬭ , parameters to be estimated; ▭ , repeated structures; ⟶, stochastic relationships; - - ➤, deterministic relationships

Three Tasks

- **Forecasting [≈ EoC]**: ***If child c is abused, what is the probability c will suffer ALTE & bleed?***

  P(ALTE (c) & bleed(c)] | abuse (c))

- **Backcasting [≈ Bayes]** : ***If child c suffers ALTE & bleed, what is the probability c was abused?***

  P(abuse (c) | ALTE (c) & bleed(c))

- **Attribution [≈ CoE]** : ***If child c suffers ALTE & bleed, what is the probability this was caused by abuse?***

  P(?? | ALTE (c) & bleed(c))

Their Analysis

- **Authors addressed backcasting:**
  - **Pr(E | R)   (E = abuse, R = ALTE & bleed)**

➢ **Bayesian analysis, using WinBUGS©**
  - **supplies posterior distribution for Pr(E | R)**
  - **given the data, model and assumptions**

Our Analysis

- **Authors addressed backcasting**
- **We address attribution:**
  $$1 \geq \mathrm{PC} \geq \max\{0, 1 - \Pr(R|\overline{E})/\Pr(R|E)\}$$
- **But also take into account uncertainty about exposure *E*:** $\mathrm{PC}^* = \mathrm{PC} \times \Pr(E|R)$

$$\Pr(E|R) \geq \mathrm{PC}^* \geq \max\{0, 1 - \Pr(\overline{E}|R)/\Pr(\overline{E})\}$$

Output

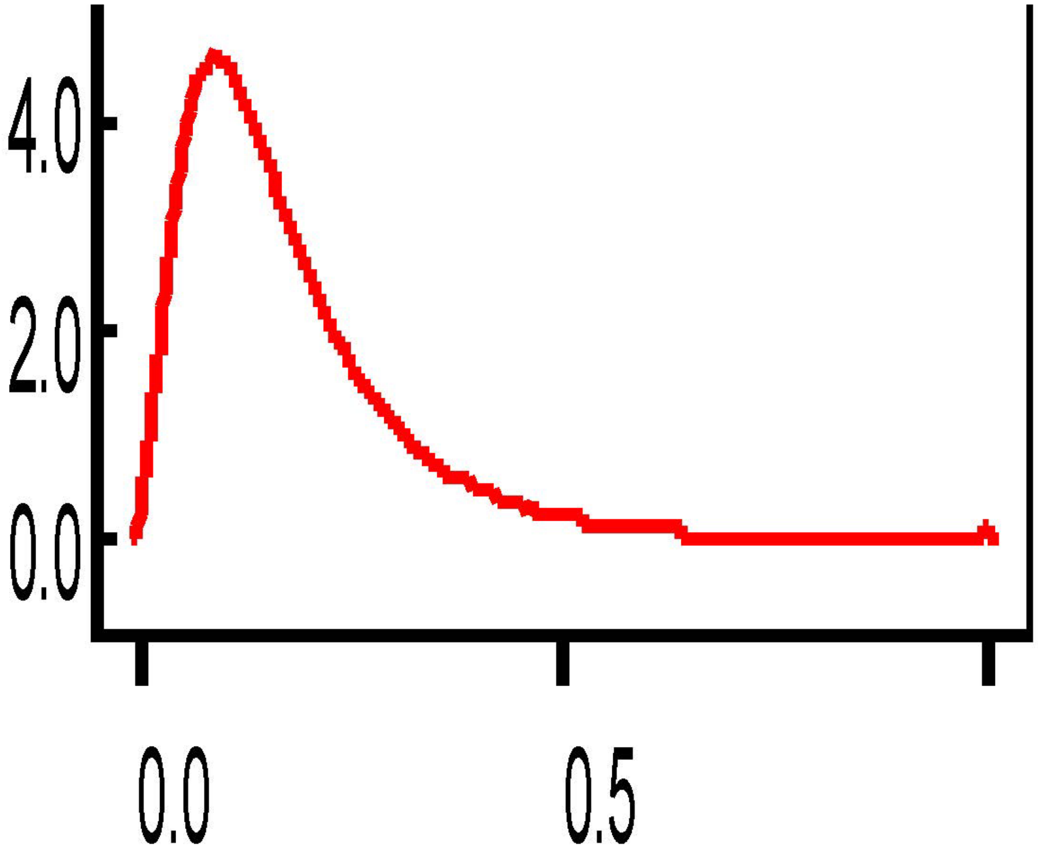
$$\Pr(E|R) \geq \mathrm{PC}^* \geq \max\{0, 1 - \Pr(\overline{E}|R)/\Pr(\overline{E})\}$$

– ***a random* interval containing PC***

- **How to interpret?**
- **How to display?**
- ***Help sought!***

Upper bound on PC*

$$\mathrm{PC}^* \leq \Pr(E|R)$$



Mean	Standard deviation
0.18	0.15

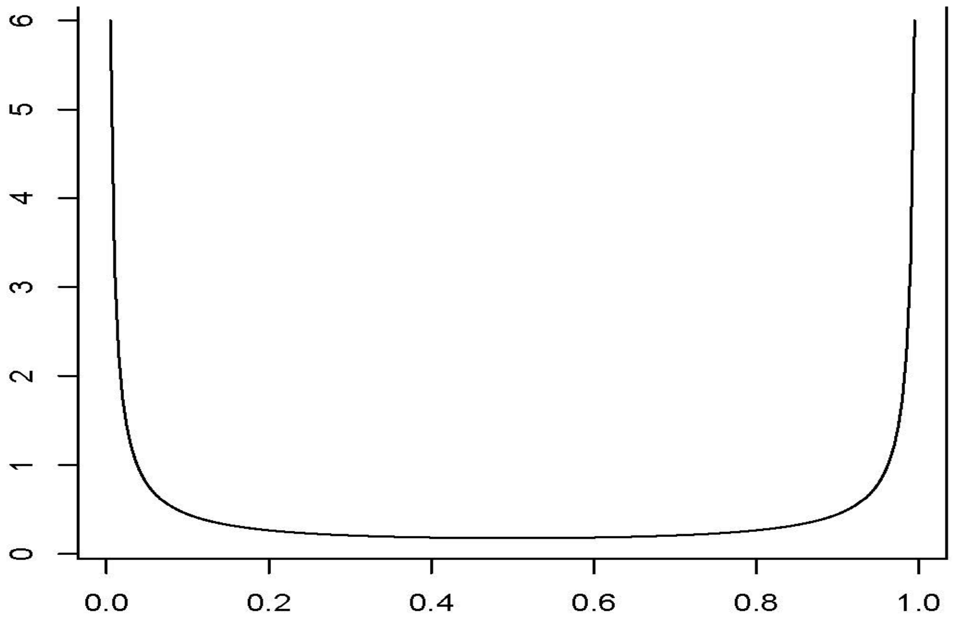
Lower bound on PC*

$$\mathrm{PC}^* \geq \max\{0, 1 - \Pr(\overline{E}|R)/\Pr(\overline{E})\}$$

For lower bound we also need prior probability of abuse, Pr(E) = Pr(abuse)

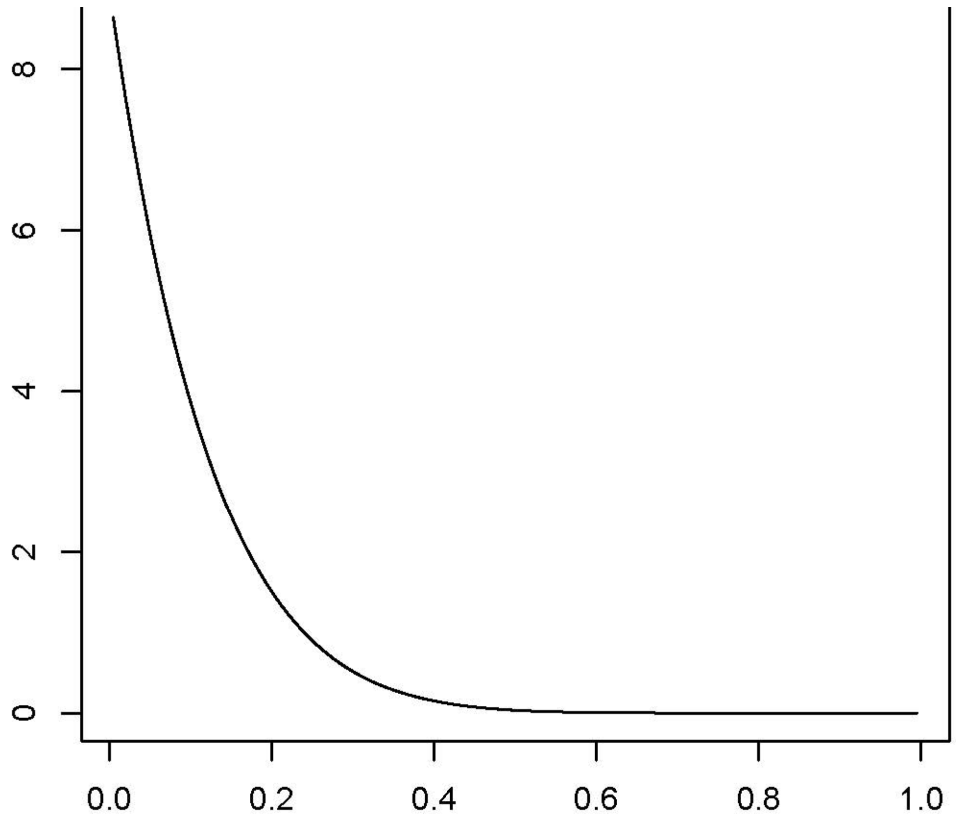
- ***no relevant data***
- ***use vague(ish) prior***
- ***conduct sensitivity analysis***

Prior 1: **Pr(abuse) ~ β(0.1, 0.1)**



Mean	Standard deviation
0.5	0.46

Prior 2: Pr(abuse) ~ $\beta(1, 9)$



Mean	Standard deviation
0.1	0.09

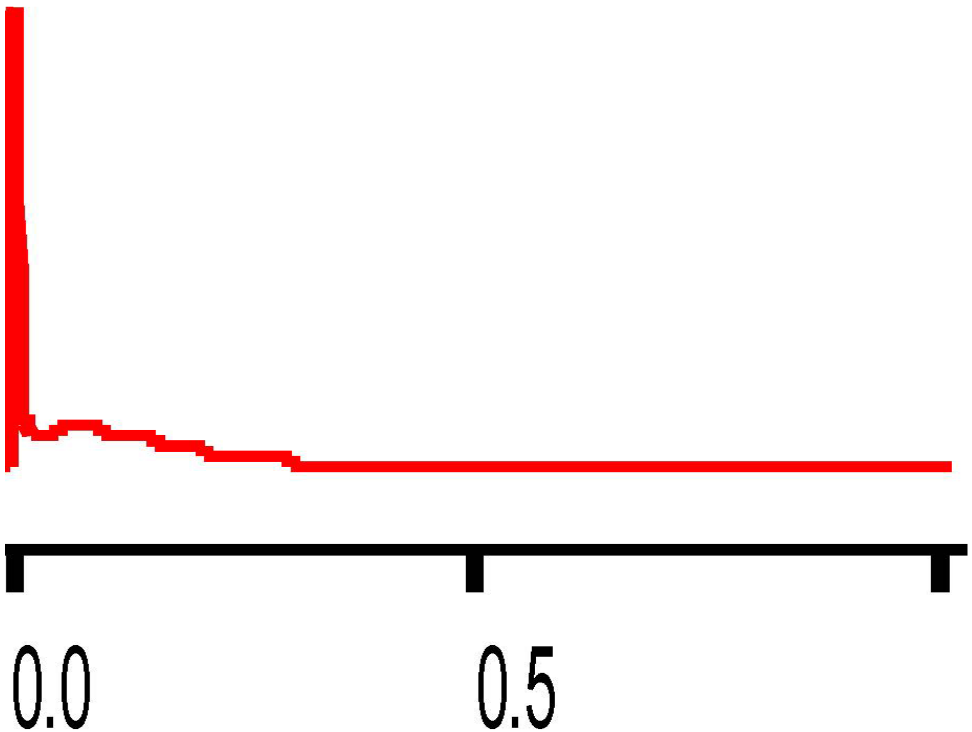
Lower bound on PC*

Prior 1: Pr(abuse) ~ $\beta(0.1, 0.1)$		
0 with probability:	**0.58**	
Else:	Mean	Standard deviation
	0.18	0.15

Prior 2: Pr(abuse) ~ $\beta(1, 9)$		
0 with probability:	**0.29**	
Else:	Mean	Standard deviation
	0.16	0.16

Length of interval for PC*

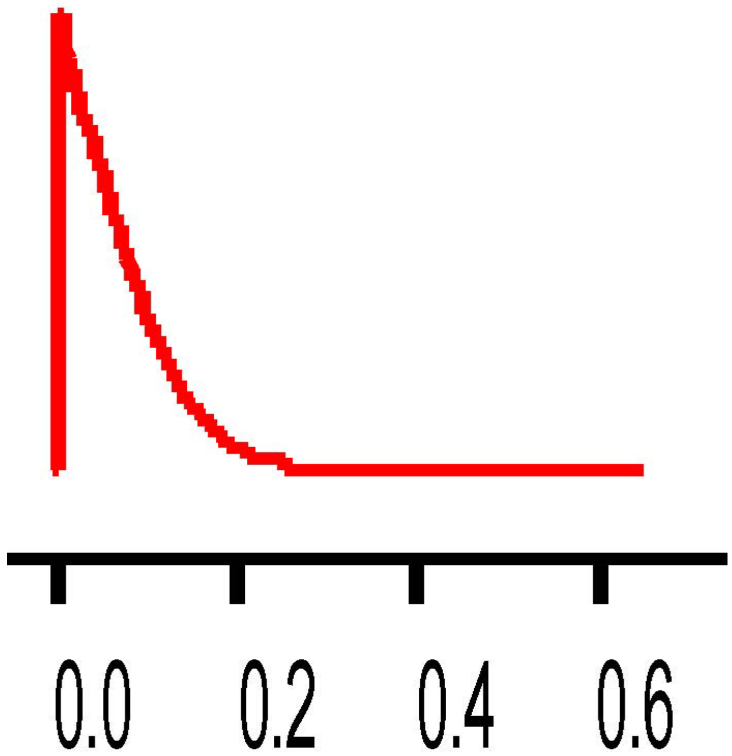
1. **Prior:** **Pr(abuse) ~ β(0.1, 0.1)**



Mean	Standard deviation
0.11	0.13

Length of interval for PC*

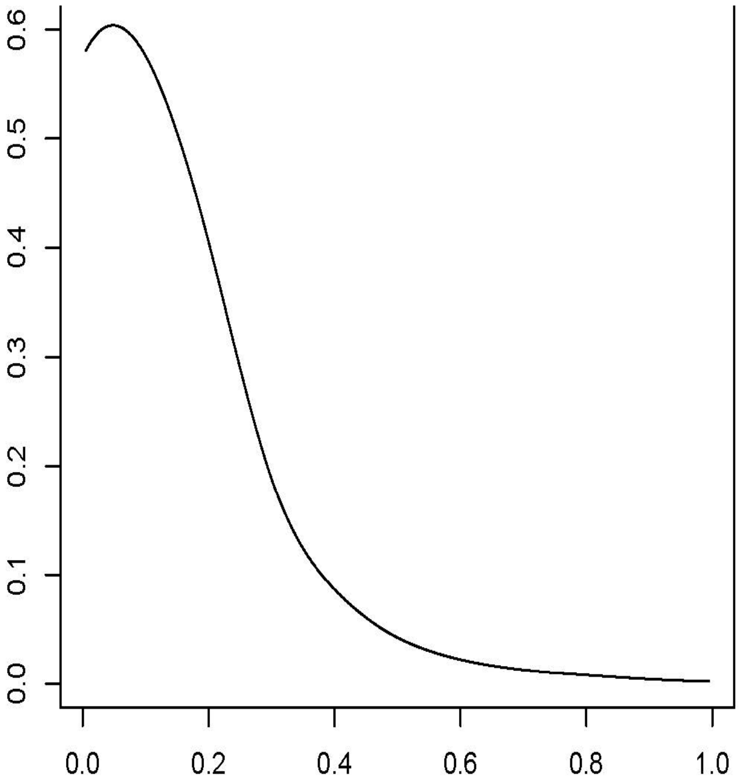
2. Prior: Pr(abuse) ~ $\beta(1, 9)$



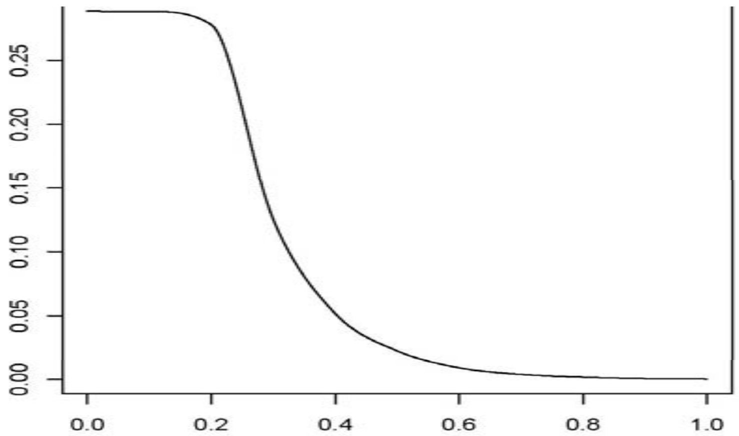
Mean	Standard deviation
0.07	0.06

Probability of inclusion

Pr(abuse) ~ $\beta(0.1, 0.1)$



Pr(abuse) ~ $\beta(1, 9)$



Moral of Story

- **Causes of Effects and Effects of Causes are not the same!**
- **Science, experimentation and statistics help us assess Effects of Causes**
  - **well studied and understood**
- **Assessing Causes of Effects requires different forms of statistical analysis and interpretation**
  - **not well studied or understood**
  - **HELP!!**

Thank you!