Why we should become Bayesians (and often already are without realising it)

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Why we should become Bayesians (and often already are without realising it)

- Frequentist and Bayesian statistics
- Estimation of main effects
  - One exposure/outcome, one level of analysis
  - Many exposures/outcomes, one level of analysis
  - One/many exposures/outcomes, multilevel analysis
- Estimation of bias
  - Selection bias
  - Information bias
  - Confounding

Frequentist approaches

Our “standard” statistical methods are based on frequentist theory which (usually) assume that:

- The data have been sampled from an infinite population
- Generalizability depends on representativeness
- Exposure has been randomized (conditional on the confounders that have been controlled for)
- No information from outside the study is taken into account

These methods were developed for randomized controlled trials (and originally for agricultural experiments) where exposure is randomly assigned, and numbers are large

Frequentist approaches depend on the model chosen; most methods of model selection ignore background information, and make questionable assumptions about interactions, dose-response relationships and lack of (uncontrolled) bias

Frequentist approaches and causal inference

Causal criteria (Bradford-Hill) in epidemiology involve many more considerations including, plausibility, coherence, specificity,

Frequentist approaches attempt to make decisions solely on the basis of the data in the study being analysed

Almost no-one is stupid enough to do this in practice

- We take prior information into account when deciding to do a study
- We take prior information into account when interpreting the findings of a study

Thus, we write the methods and results sections of our papers as frequentists and the introduction and discussion as qualitative Bayesians

Bayesian approaches to randomized trials:

[Pocock SJ. J Roy Statist Soc 1994; 157: 357-416.]

"One might adopt the term 'closet Bayesian' for statisticians and other scientists who adopt strategies in study design and data interpretation which include concepts of prior belief, but who do not explicitly express them in a formal Bayesian framework."

- "Bayesian conceptualization is very useful in study design."
- "It is useful to be a temporary Bayesian when faced with a surprising frequentist result."
- "It is useful that every medical statistics unit should have a resident Bayesian."

"Non-Bayesians need greater help in overcoming computational difficulties, in adapting Bayesian methods to more complex problems... and in learning how to commmunicate Bayesian findings to non-specialists."

Bayesian approaches

Bayesian approaches formally take prior evidence into account.

- Classically, this involves having some belief (the prior distribution) about what the evidence was before we did the study. This belief could be based on:
  - Prior data from similar studies
  - More “subjective” beliefs based on information apart from the data being analysed
- This belief is then updated (the posterior distribution) on the basis of the new study

Some caveats

- I am using the term ‘Bayesian’ fairly loosely to refer to any data analysis which uses prior information
- I am focussing on observational studies, not randomzied trials
- Many of the analyses/methods I will present can be interpreted within a frequentist framework
- I am (mostly) advocating supplementing rather than replacing frequentist with Bayesian methods
- I am not going to present sophisticated Bayesian methods but will mostly use ‘back of the envelope’ calculations
  - “We would welcome suggestions for articles that supply equally easy to implement procedures or SAS or Stata procs. But please spare us methods that can only be implemented through R, WinBUGS, or by spending £100,000 or more on statistical programmers.” (Pearce and Greenland)

Bayesian approaches do not require complex programming

- Our standard methods use approximations which are quite adequate given the other uncertainties with most epidemiologic data
- For example, most of our methods were developed at a time when exact tests were too complex computationally, but we still don't use them now even though we could if we wanted to
- Bayesian methods have become popular at a time when more complex computational methods (e.g. MCMC – Winbugs) are available; but these are not necessary
- We can easily do Bayesian analyses using adaptations of our standard methods

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Effect estimation for one exposure/outcome: dioxin exposure and cancer

- A New Zealand study found an increased risk of (total) cancer in phenoxy herbicide production workers exposed to dioxin: RR=1.24 (95% CI 0.90-1.67)
- A much larger international study had found similar findings
- There is also evidence of the likely aetiological mechanism
- As a result, the International Agency for Research on Cancer has classified dioxin as a Class 1 (sufficient evidence) human carcinogen

Effect estimation for one exposure/outcome: dioxin exposure and cancer

- The “prior data” indicates a RR=1.29 (95% CI 0.94-1.76)
- The new study shows a RR=1.24 (95% CI 0.90-1.67)
- The authors of the study concluded that the New Zealand findings were consistent with those of the larger international study
- The New Zealand study was repeated by different researchers who got the same findings but concluded that there was no statistically significant increase in risk

What if there is no “prior data”, but only “prior knowledge”?

Relation of maternal antibiotic use during pregnancy (X = 1) to sudden infant death syndrome (SIDS, Y = 1), Kraus et al. 1989

Antibiotics might be associated with

- elevated risk (marking effects on the fetus of an infection, or via a direct effect)
- reduced risk (by reducing presence of infectious agents).

Source: Sander Greenland

These are weak speculations, but
suppose strong effects seem unlikely.

A prior for ln(OR) that is normal with mean 0, standard deviation ln(4)/1.96 puts 95% probability on an OR between ¼ and 4

i.e. the prior assumption is that it is “95% likely” that the odds ratio is in the range 0.25-4.00 with the most likely value being 1.00

(i.e. OR=1.00, 95% CI 0.25-4.00)

Source: Sander Greenland

Question:

What is a “data equivalent” for the prior?

That is, what data would give

- 0 as the conventional ln(OR) point estimate
- ln(4)/1.96 as its standard error?

Answers to such questions can be found by thought experiments

Source: Sander Greenland

Augment the observed data with the prior data as a separate stratum:

	$Prior_X=1$			$Prior_X=0$	
	X=1	X=0		X=1	X=0
Y=1	4	4	Y=1	173	602
Y=0	100,000	100,000	Y=0	134	663

RR_{prior} = 1.00

95% PL = 0.25, 4.00

OR = 1.42

95% CL = 1.11, 1.83

Source: Sander Greenland

Now combine the strata using any conventional method…

Approx. posterior median and 95% limits from Woolf, Mantel–Haenszel, and ML:

1.41 (1.10, 1.80) = precision-weighted

In a regression, add the stratum as a set of **two** prior records (X=1,0) with

- an indicator $Prior_X$=1 for the two prior records (X=1,0), 0 for the remaining data
- all other regressors set to their means

Source: Sander Greenland

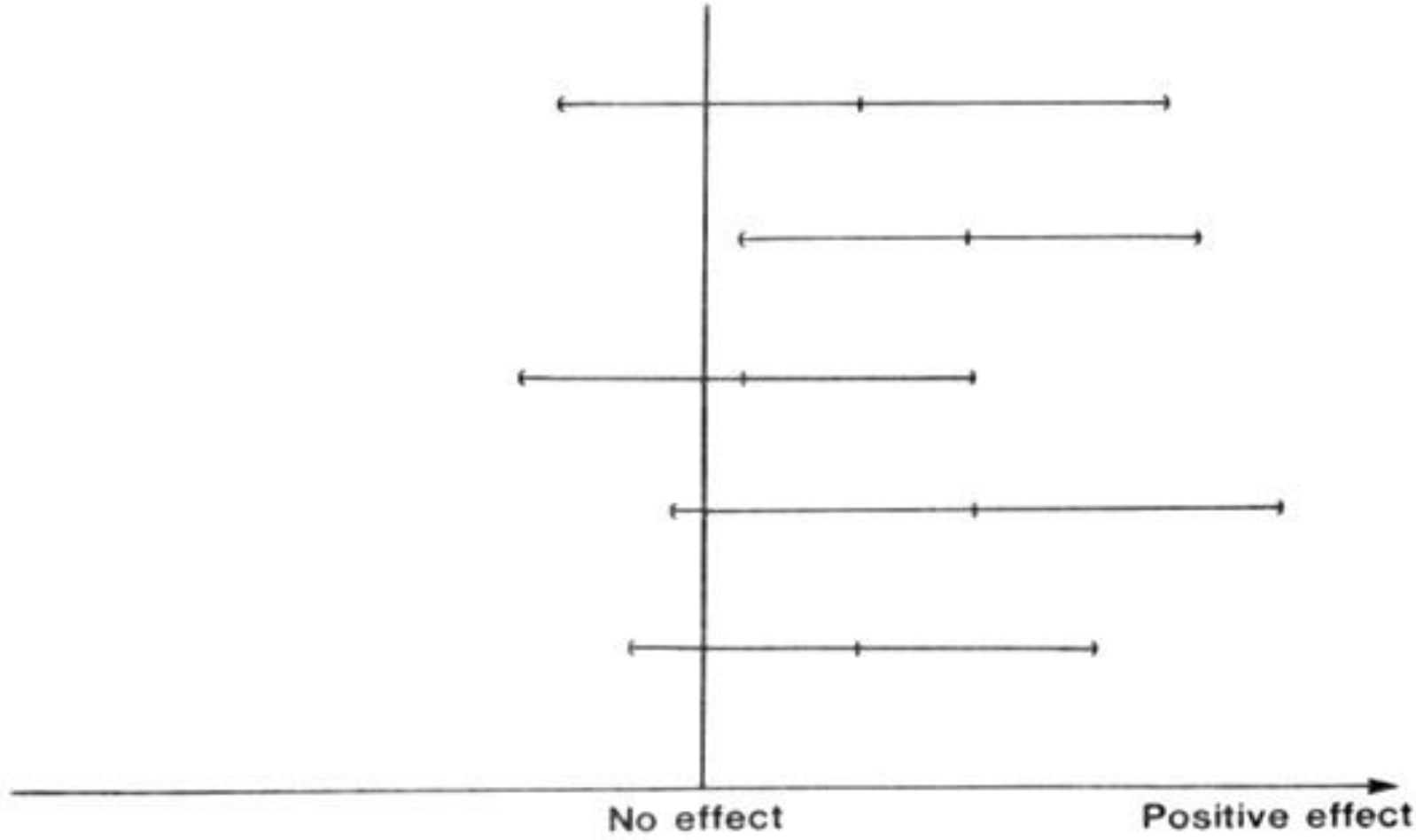
Effect estimation for one exposure/outcome

- One reasonable approach to the analysis of a an exposure-disease association for which there is prior data is to:
  - Summarize the “prior data” as a summary RR and 95% CI (i.e. a meta-analysis)
  - Estimate the RR and 95% CI in the new study
  - Calculate an “updated” summary RR and 95% CI including the new data

Effect estimation for one exposure/outcome

- This is the “classic” Bayesian approach. It is probably also the least useful because:
  - If we don’t have any empirical prior data, then any sensible prior will not include much information and won’t change our estimates very much (and there is always concern about strong “subjective” priors)
  - If we have good empirical prior data, we can just do an updated meta-analysis
  - If we do a series of studies, a series of Bayesian analyses will arrive at the same conclusions as we would have reached with a single meta-analysis conducted at the end of the series

Point estimates and confidence intervals in five hypothetical studies



Effect estimation

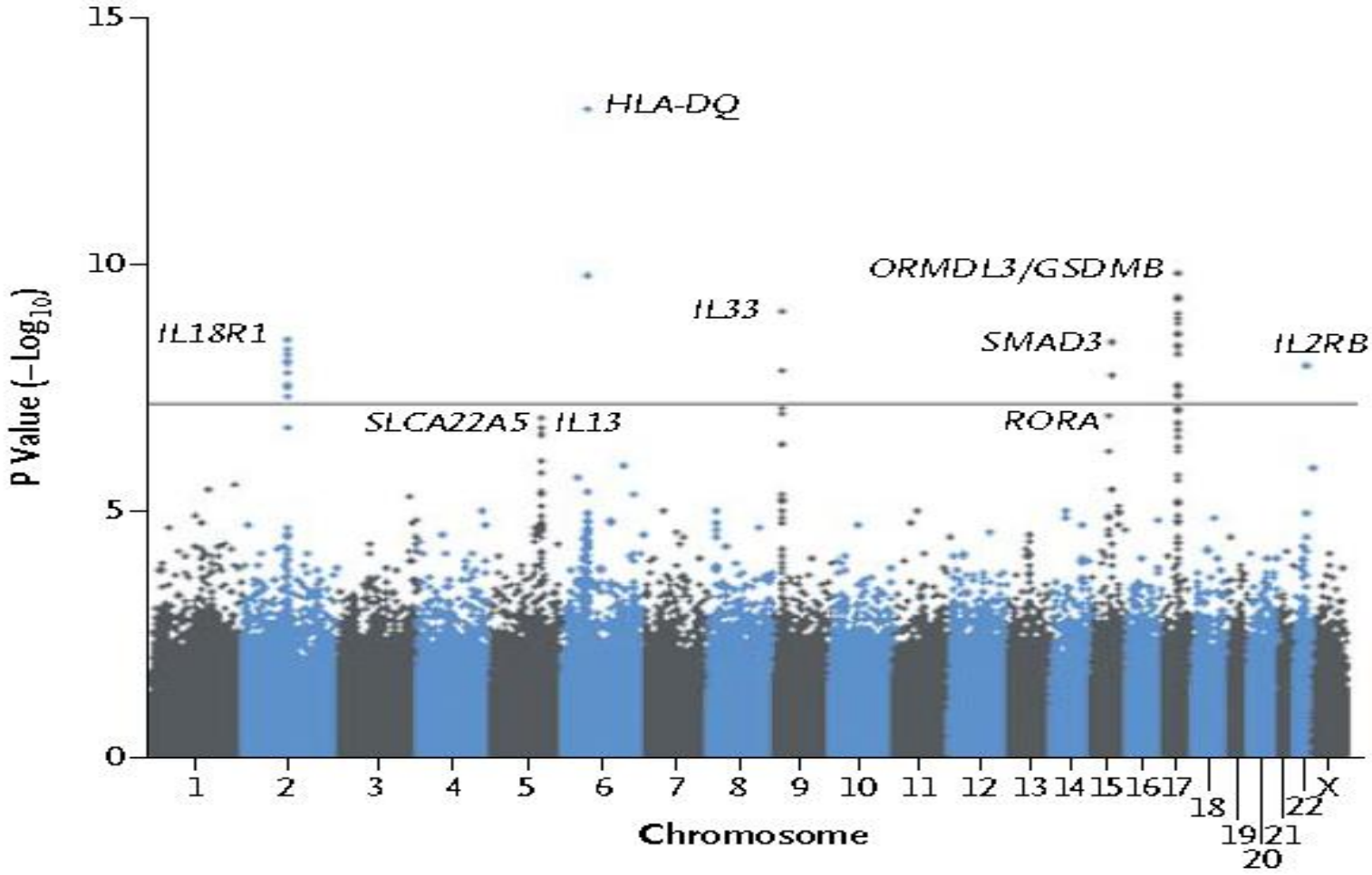
- One exposure/outcome, one level of analysis
- Many exposures/outcomes, one level of analysis
- One/many exposures/outcomes, multilevel analysis

Effect estimation: many exposures/outcomes

- When we do a study involving many different exposures/outcomes, some of them will have strong “a priori” evidence and some will not
- Standard (frequentist) methods for multiple comparisons (e.g. Boferoni corrections) do not take prior knowledge into account, and in any case deal only with the statistical significance, not the magnitude of individual effect estimates
- The strongest associations are likely to be due in part to chance, and to show “regression to the mean” if the study were repeated
- Empirical Bayes (EB) or Semi-Bayes (SB) methods attempt to “correct for” extra variation and to anticipate “regression to the mean”

A Large-Scale, Consortium-Based Genomewide Association Study of Asthma

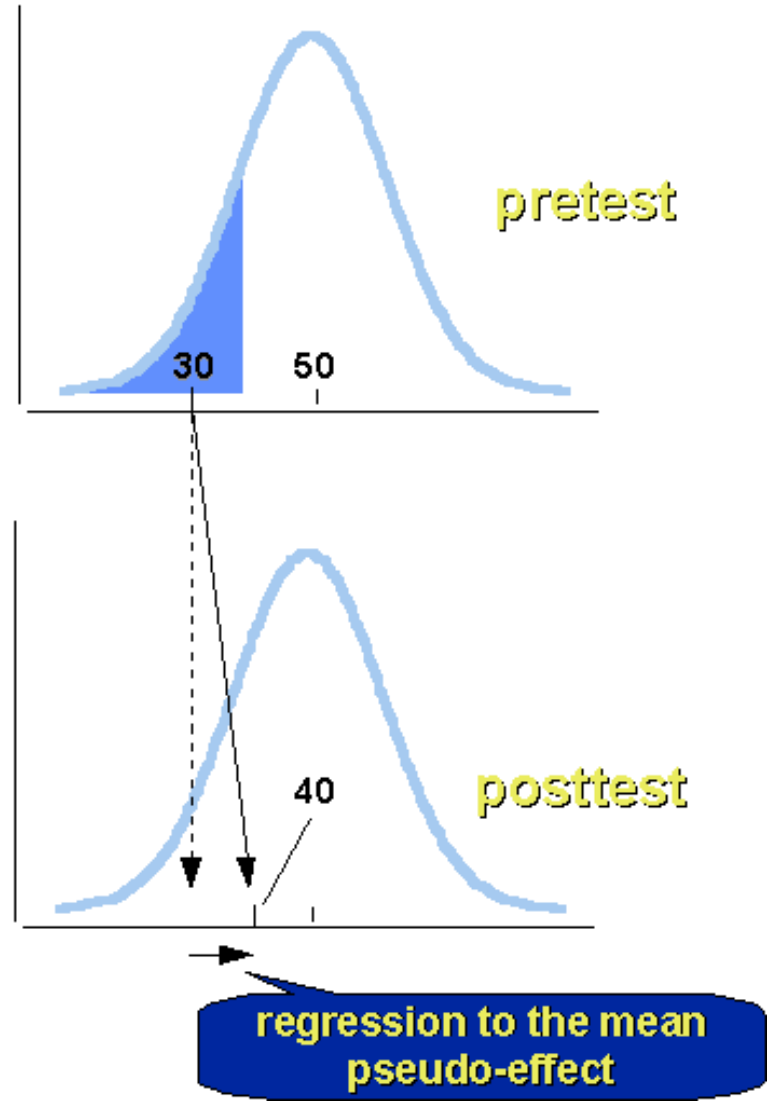
(Moffatt, NEJM 2010)



Moffatt et al. A large-scale consortium-based genomewide association study of asthma. N Engl J Med, 23 September 2010

- Brings together data from 23 studies; largest analysis ever conducted
- 10,365 asthma cases and 16,110 non-asthmatic controls
- 582,892 SNPs evaluated; 15 billion genotypes
- 10 loci identified; largest odds ratio was 1.27
- Estimated that these 10 loci together had a population attributable risk of about 30%

Regression to the mean



High risk occupations for Non-Hodgkin's Lymphoma in New Zealand

A case-control study

Andrea 't Mannetje, Evan Dryson, Chris Walls, Dave McLean, Fiona McKenzie, Milena Maule, Soo Cheng, Chris Cunningham, Hans Kromhout, Paolo Boffetta, Aaron Blair, Neil Pearce

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Example of multiple exposures: New Zealand case-control study of occupation and non-Hodgkin's lymphoma

- Many different job titles and exposures
- Some have strong prior evidence of an association with bladder cancer, but most do not
- In the latter case, we would expect the most "extreme" ORs to be in part due to chance, and to demonstrate "regression to the mean" if the study were repeated

a priori high risk **occupations** and **industries** : **farming**

	cases/ controls (n)	OR	95%CI
OCCUPATION			
611-Market Farmers and Crop Growers	41/44	**1.48**	(0.92-2.37)
6111-Field Crop and Vegetable Growers	12/7	**2.74****	(1.04-7.25)
6112-Fruit Growers	20/20	**1.63**	(0.84-3.16)
6113-Gardeners and Nursery Growers	17/18	**1.27**	(0.63-2.58)
61131-Nursery Grower, Nursery Worker	10/5	**3.16****	(1.03-9.69)
612-Market Oriented Animal Producers	44/81	**0.80**	(0.52-1.21)
6121-Livestock Producers	19/43	**0.65**	(0.36-1.16)
6122-Mixed Livestock Producers	12/19	**1.13**	(0.53-2.40)
6125-Crop and Livestock Producers	14/29	**0.71**	(0.36-1.41)
INDUSTRY			
A011-Horticulture and Fruit Growing	41/32	**2.28****	(1.37-3.79)
A0111-Plant Nurseries	8/3	**4.30****	(1.08-17.2)
A0113-Vegetable Growing	11/8	**2.32***	(0.90-6.00)
A0115-Apple and Pear Growing	9/3	**4.91****	(1.26-19.1)
A0117-Kiwi Fruit Growing	7/6	**1.77**	(0.55-5.63)
A012-Grain, Sheep, Beef Cattle Farming	14/39	**0.56***	(0.29-1.08)
A013-Dairy Cattle Farming	14/36	**0.55***	(0.29-1.07)
A015-Other Livestock Farming	9/2	**9.75****	(2.04-46.5)

*p<0.1
**p<0.05

Semi-Bayes estimates

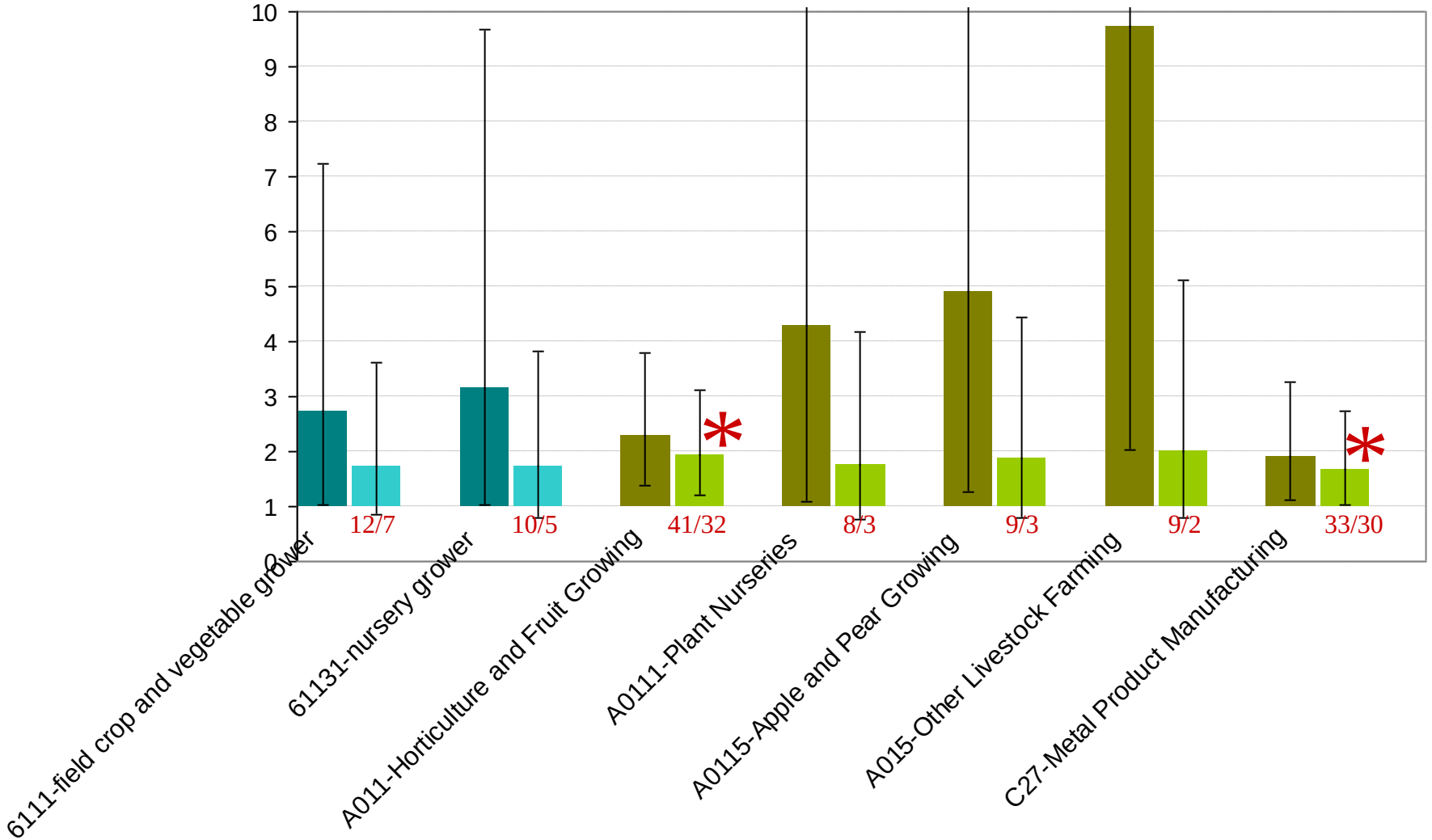
Are these odds ratios elevated due to **chance**?

Particularly those odds ratio estimates based on small numbers could be elevated due to chance.

SB adjustment: shrinks the outlying relative risks towards the overall mean (of the relative risks of all occupations/industries).

The larger the individual variance of the relative risks, the stronger is the shrinkage, i.e. the shrinkage is stronger for less reliable estimates based on small numbers.

A priori high risk **occupations** and **industries** – effect of semi-Bayes adjustment

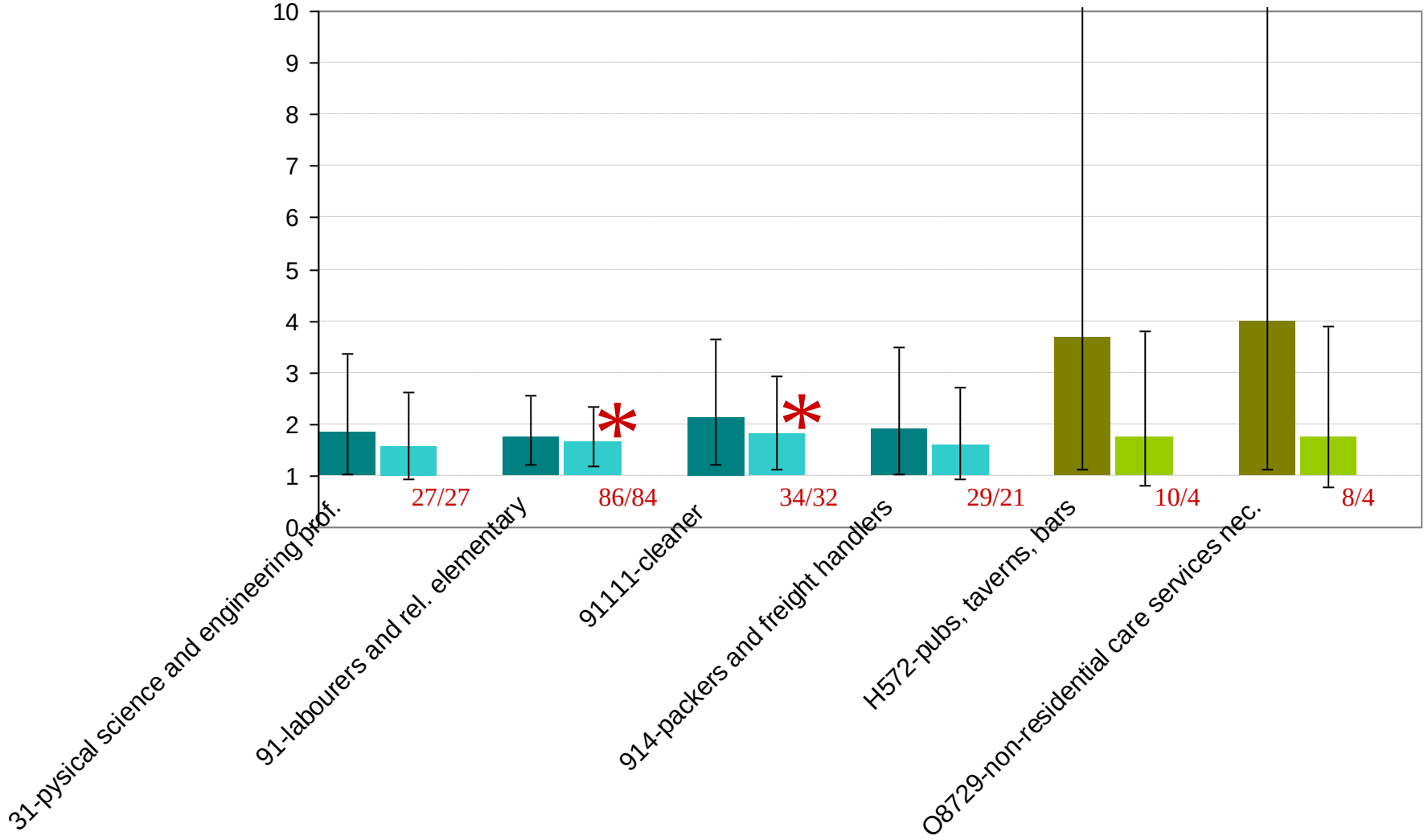


A posteriori high risk **occupations** and **industries**

	cases/ controls (n)	OR	95%CI
OCCUPATION			
31-Physical Science and Engineering Prof.	26/27	**1.85****	(1.03-3.35)
91-Labourers and Rel. Elementary	86/84	**1.76****	(1.22-2.56)
91111-Cleaner	34/32	**2.11****	(1.21-3.65)
914-Packers and Freight Handlers	29/21	**1.89****	(1.02-3.49)
INDUSTRY			
H572-Pubs, Taverns and Bars	10/4	**3.68****	(1.11-12.3)
O8729-Non-Residential Care Services nec	8/4	**3.98****	(1.13-14.1)

**p<0.05

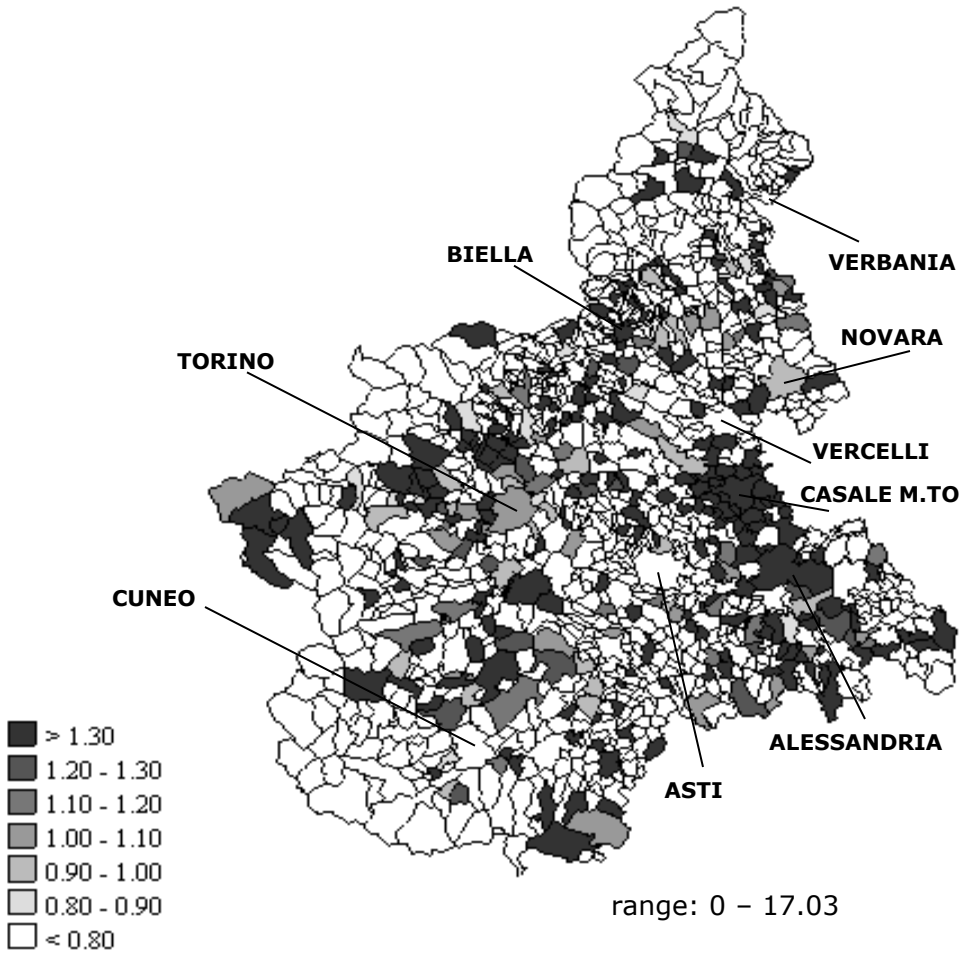
A posteriori high risk **occupations** and **industries** – effect of semi-Bayes adjustment



Effect estimation:
many exposures/outcomes

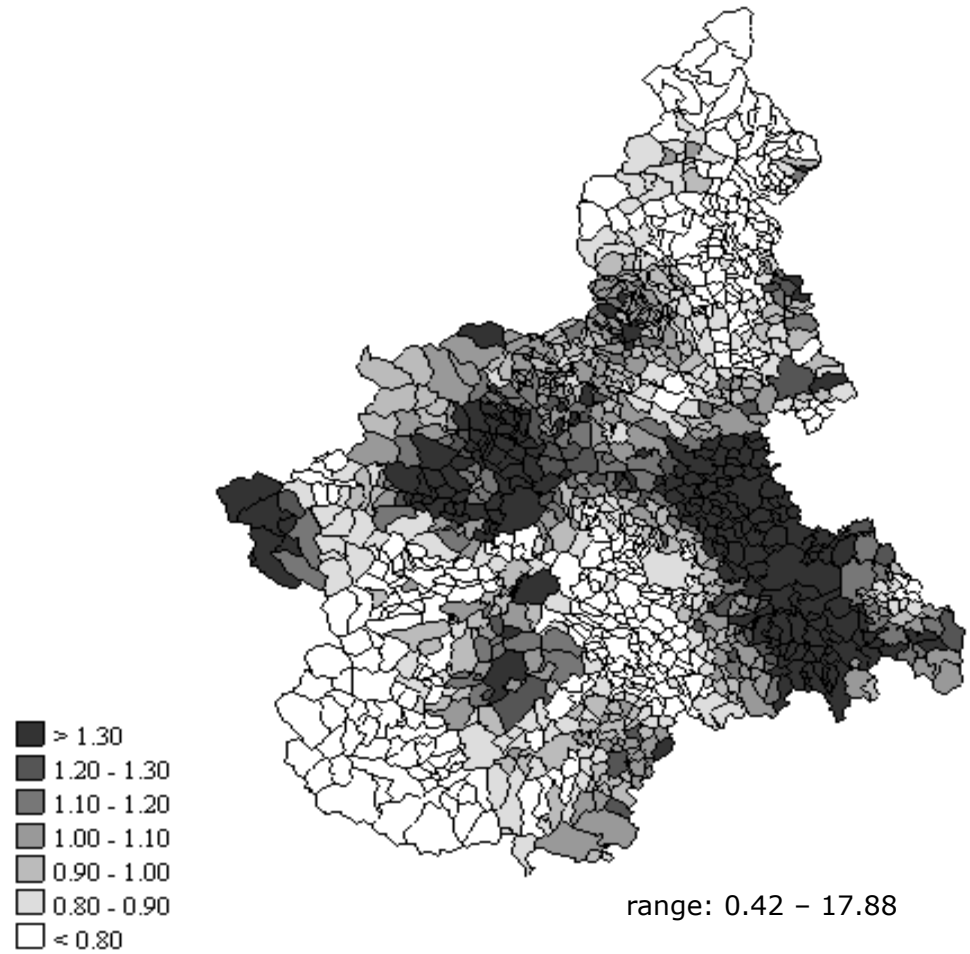
- In some instances, “exposures” may be linked (e.g. adjacent geographical areas, or adjacent years when examining time trends)

Mesothelioma rates in Piedmont, Italy: men [Maule MM, et al]



range: 0 – 17.03

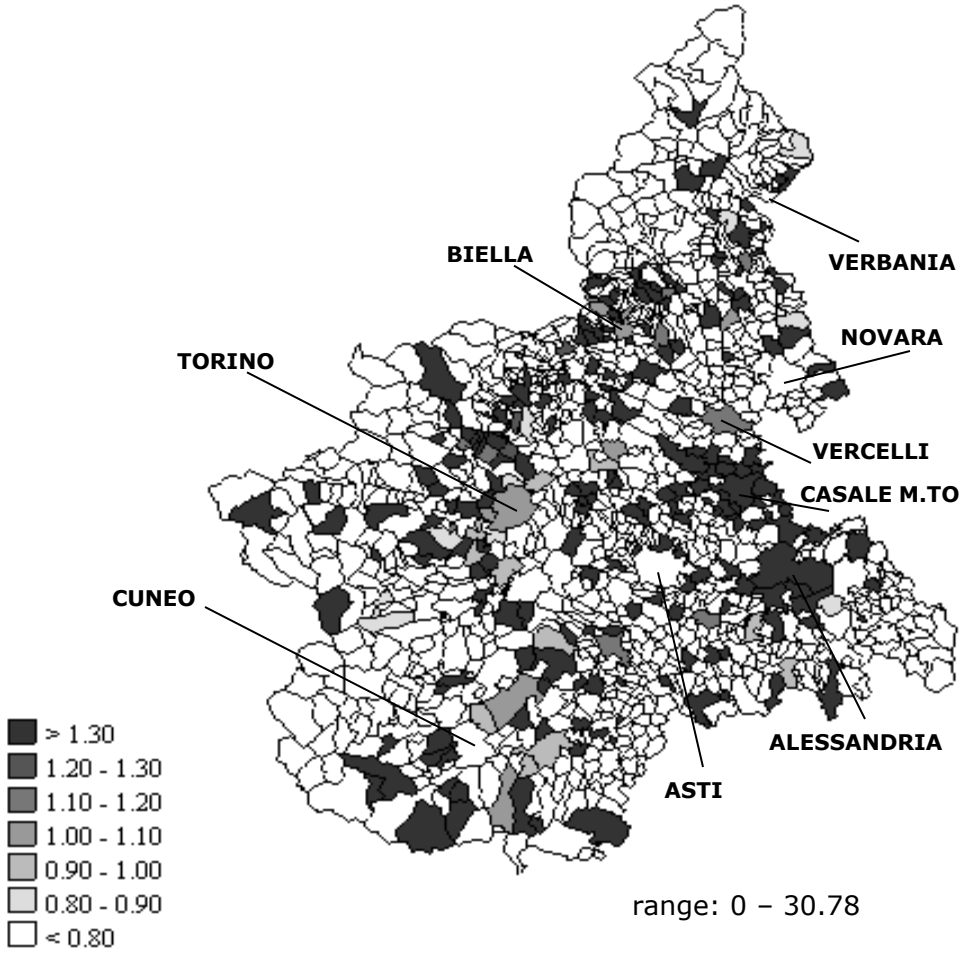
BMR Pleura (men)



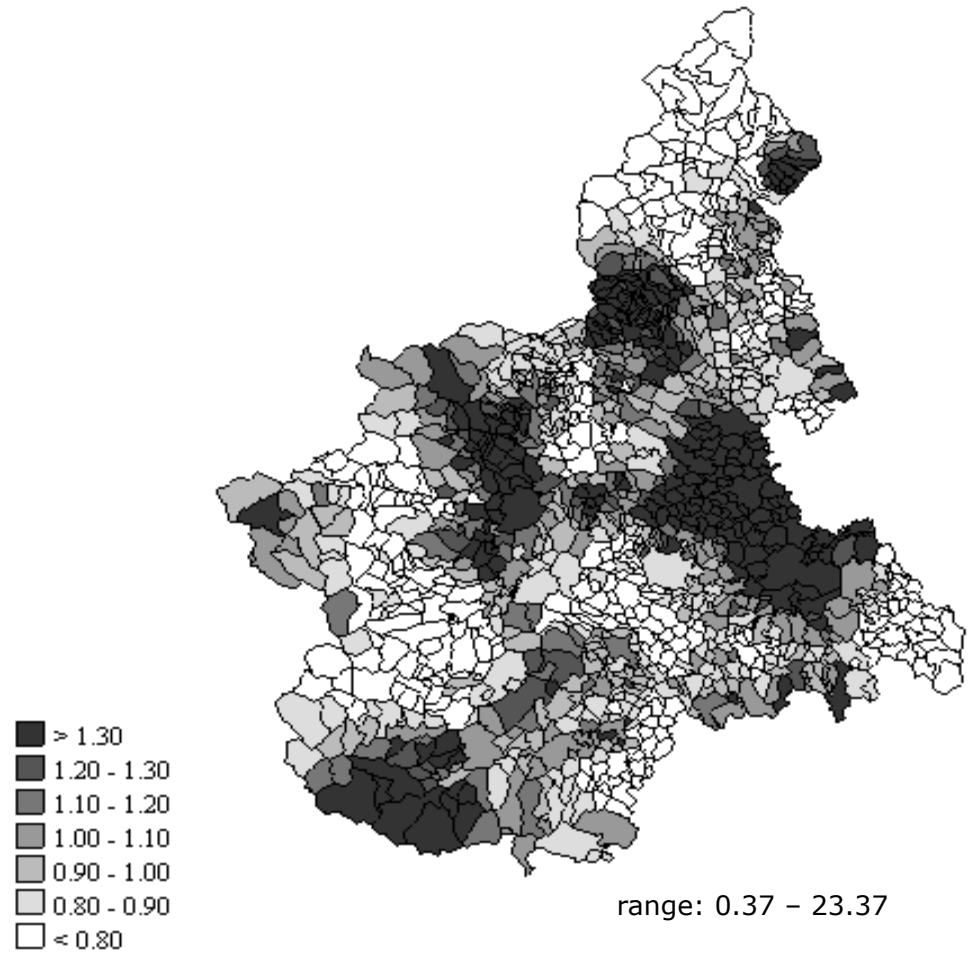
range: 0.42 – 17.88

Mesothelioma rates in Piedmont, Italy: women [Maule MM, et al]

BMR Pleura (women)



range: 0 – 30.78



range: 0.37 – 23.37

Effect estimation

- One exposure/outcome, one level of analysis
- Many exposures/outcomes, one level of analysis
- One/many exposures/outcomes, multilevel analysis

Hierarchical Regression for multiple comparisons:
Application to a case-control study of occupational risks for lung cancer

Marine Corbin, Roel Vermeulen, Hans Kromhout, Susan Peters, Lorenzo Simonato, Lorenzo Richiardi, Franco Merletti, Neil Pearce, Milena Maule

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Existing methods for adjustment for multiple comparisons

- Traditional Bonferroni adjustment:

$\Rightarrow$ Criticized because

  - It treats all the associations equally
  - It only affects the p-values

- Semi-Bayes adjustment towards the global mean
  - Specification of an *a priori* true standard deviation of the log ORs
  - Shrinkage of the log ORs towards the global mean

Hierarchical Regression

- Inclusion of prior knowledge about carcinogenic exposures in a 2nd-stage model: Occupations with similar exposures to known carcinogens entail similar risks of disease

- Shrinkage of the log ORs towards each other when they have similar carcinogenic exposures

The first-stage models

- Estimation of the ORs of lung cancer through logistic regression for the 129 occupations represented by 3-digit ISCO codes and held by at least 10 subjects

- Adjustment for age, centre and cigarette smoking status

$$\text{logit}\left[\Pr\left(Y=1\middle|\text{occ}_i, w\right)\right]=\alpha_i+\text{occ}_i\beta_i+\mathbf{w}\gamma_i$$

The 2nd-stage model (1)

- DOM-JEM: Job Exposure Matrix that classifies occupations in three categories of exposure (0=none, 1=low, 2=high) to several lung carcinogens

- Selection of 3 lung carcinogens (Agents classified by the IARC Monographs as *group-1 = carcinogenic to humans*): asbestos, chromium and silica to be included in the 2nd-stage model

The 2nd-stage model (2)

$$\beta = \mathbf{Z}\pi + \mathbf{U}$$

Occupation	Elements of matrix Z					
	Asb1	**Asb2**	**Ch1**	**Ch2**	**Si1**	**Si2**
Nursery workers and gardeners	0	0	0	0	1	0
Farm machin. operators	0	0	0	0	0	1
Loggers	0	0	0	0	0	0
Fishermen	0	0	0	0	0	0
Production supervisors	0	0	0	0	0	0
Miners & quarrymen	1	0	0	0	0	1

The 2nd-stage model (3)

$$\boxed{\boldsymbol{\beta} = \mathbf{Z}\boldsymbol{\pi} + \mathbf{U}}$$

$\mathbf{U}$ is a vector of the error terms representing the residual effect of being employed in each occupation after accounting for the exposure to asbestos, chromium and silica

$$\mathbf{U} \sim \mathrm{N}\left(\mathbf{0}, \tau^2 \mathbf{T}\right)$$

$\tau^2\mathbf{T}$ is specified a priori

$\Rightarrow$ τ controls the global strength of the shrinkage and is set successively to 0.76, 0.59, 0.41, 0.23

$\Rightarrow$ $\mathbf{T}$ is a Diagonal matrix where t_{ii} is inversely related to the sum of the categories of exposure of the occupation to asbestos, chromium and silica

Computation of the Hierarchical Regression estimates

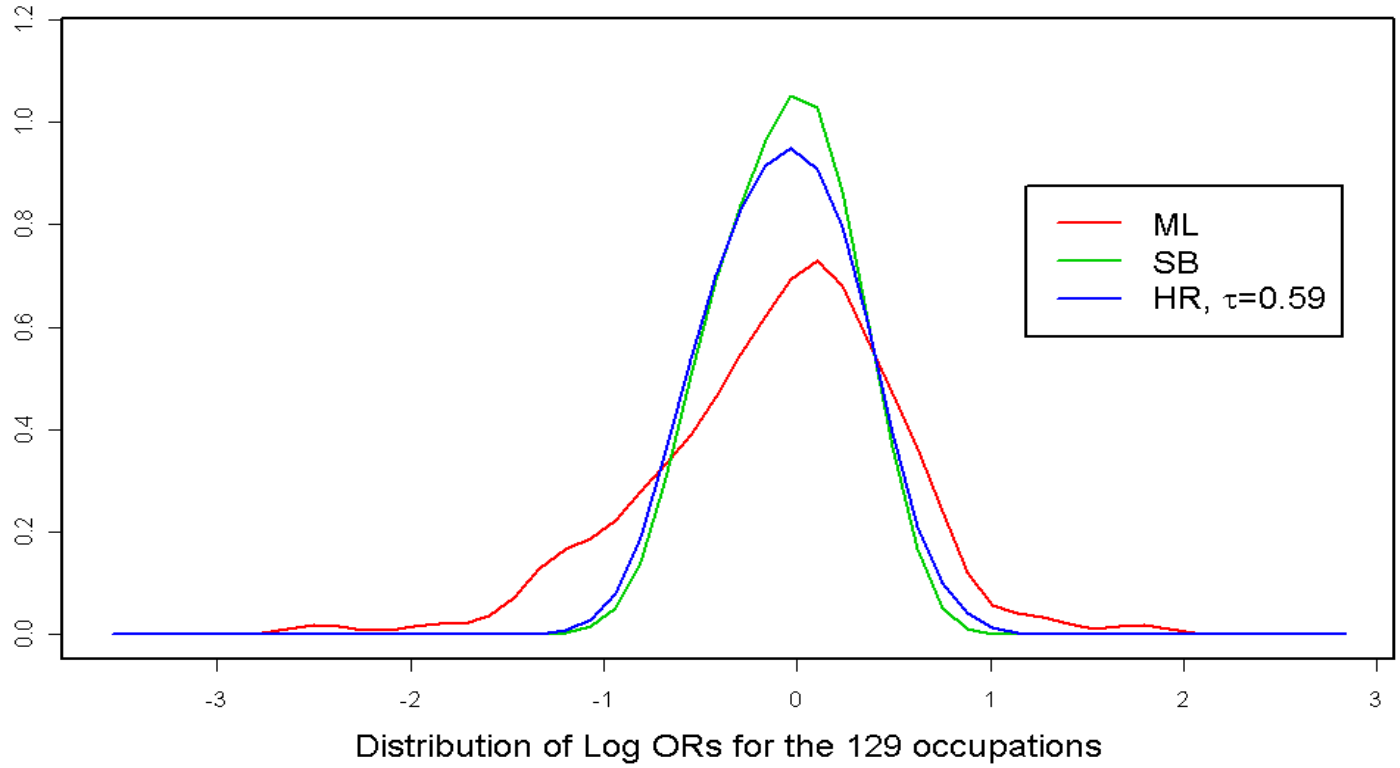
- Estimation of the 2nd-stage coefficients $\tilde{\pi}$ through weighted least squares
- Computation of the prior means $\mathbf{Z}\tilde{\pi}$ for the occupations coefficients
- Computation of the posterior Hierarchical Regression estimates

$$\tilde{\beta}_{\mathrm{HR}} = \mathbf{B}\mathbf{Z}\tilde{\pi} + (\mathbf{I} - \mathbf{B})\hat{\beta}$$

$\mathbf{B}$ { increases when the variance of $\hat{\beta}$ increases
decreases when $\tau^2\mathbf{T}$ increases

Results (1)

	ML	SB	HR			
			τ=0.76	τ=0.59	τ=0.41	τ=0.23
Mean of the log ORs distribution	-0.12	-0.07	-0.08	-0.07	-0.06	-0.04
Standard Deviation of the log ORs distribution	0.63	0.31	0.41	0.35	0.28	0.20
Mean of the Standard Deviations of the log ORs	0.45	0.32	0.37	0.34	0.28	0.20



Results (3)

Occupation	ML	SB	HR			Carcinogenic exposure		
			τ=0.76	τ=0.59	τ=0.23			
	OR [95% CI]	OR [95% CI]	OR [95% CI]	OR [95% CI]	OR [95% CI]	Asb	Ch	Si
Tailors and dress makers	2.1 [0.9-5.0]	1.5 [0.8-3.0]	1.6 [0.8-3.5]	1.5 [0.7-3.0]	1.0 [0.7-1.6]	0	0	0
Metal melters and reheaters	2.1 [0.7-5.7]	1.4 [0.7-3.0]	1.8 [0.9-3.9]	1.8 [0.9-3.5]	1.7 [1.1-2.6]	1	2	0
Miners and quarrymen	1.2 [0.6-2.4]	1.1 [0.6-2.0]	1.2 [0.6-2.4]	1.3 [0.7-2.4]	1.3 [0.7-2.5]	1	0	2
Painters, construction	1.8 [1.1-3.1]	1.6 [1.0-2.6]	1.7 [1.0-2.7]	1.6 [1.0-2.5]	1.2 [0.9-1.7]	1	0	0

Conclusions

- Hierarchical Regression uses more specific priors than Semi-Bayes adjustment towards the global mean and performs then a more appropriate shrinkage if the information included in the 2nd-stage model is reliable

- The choice of τ^2 depends on
  - The number and the reliability of the variables included in the 2nd-stage model.
  - The strength of their association with the outcome and the exposures of interest
  - The specification of the first-stage model

- Hierarchical regression is a valuable method to adjust for multiple comparisons in occupational studies when a reliable JEM is available

Heirarchical regression: Equivalents and special cases

[Greenland S. Int J Epidemiol 2000; 29: 158-67]

- Multilevel modelling
- Bayesian regression
- Empirical Bayes (EB) regression
- Bayes Empirical Bayes (BEB) regression
- Stein regression
- Penalized likelihood regression
- Best Linear Unbiased Prediction (BLUP)
- Mixed-model regression
- Ridge regression
- Random-coefficient regression
- Variance-components analysis

Source: Sander Greenland

Heirarchical regression: Equivalents and special cases

[Greenland S. Int J Epidemiol 2000; 29: 158-67]

- Hierarchical regression unifies frequentist and Bayesian methods of analysis
- It also effectively takes account of “clustering” – a one-level model produces confidence intervals that are too wide
- Conventional least squares and maximum likelihood are also special cases with just one level of analysis
- EB “adjustments” are a special case where the second-stage “prior” means are estimated from the data
- We can also add ‘second level’ information, e.g. on which occupations involve exposure to particular chemicals, or which chemicals have common properties

Source: Sander Greenland

Why we should become Bayesians (and often already are without realising it)

- Basics of frequentist and Bayesian statistics
- Estimation of main effects
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Approaches to bias modeling:
uncontrolled confounding

- We have no information on a potential confounder (e.g. smoking)
- If we can make assumptions about the associations between the potential confounder and the main exposure and between the potential confounder and the disease we can make “adjusted” estimates controlling for the potential confounder
- By varying these assumptions we can do a “sensitivity analysis” of the likely bias due to uncontrolled confounding

Cause-specific Mortality in a New Zealand cohort study of meat workers

Cause of death (ICD-9)	Obs	Exp	SMR	95% CI
All Causes	227	203.6	**1.12**	0.98 - 1.27
All Cancer (140-208)	69	61.4	**1.12**	0.88 - 1.42
Larynx (161)	1	0.4	**2.63**	0.07 – 14.62
Lung (162)	23	12.9	**1.79***	1.13 – 2.68
Haematologic (200-208)	6	6.3	**0.96**	0.35 – 2.09
NHL (200, 202)	4	2.8	**1.45**	0.49 – 3.45
Leukaemia (204 – 208)	2	2.3	**0.86**	0.17 – 2.75

Systematic Error (bias): lung cancer in meat industry workers

- No information on smoking or ethnicity
- There was a small increase in mortality (SMR=1.31) but not incidence (SIR=0.90) for other smoking-related cancers
- Census information suggests that smoking rates in food and beverage workers are only slightly higher than in other workers, and that this could only account for a RR of 1.20
- Lung cancer mortality in Māori males is 1.4 times than in non-Māori males, and that in Māori females is 2.8 times that in non-Māori females; assuming that 40% of the cohort is Māori (compared with 15% of the general population) this would produce a RR of 1.09

Approaches to bias modeling

[Steenland K, Greenland S. Am J Epidemiol 2004; 160: 384-92]

- Ordinary sensitivity analysis does not take account (easily) of uncertainties about the relationship between the confounder and disease, or random error in the “sampling” of the study population
- It also does not (easily) take account of multiple sources of bias
- It does not easily allow for control of (other) confounders
- It can sometimes be improved upon through the use of Monte Carlo Sensitivity Analysis or Bayesian methods

Approaches to bias modeling: misclassification

- Misclassification is a problem of missing data – we have data on a ‘measured’ variable, but not data on the ‘true’ variable
  - If there is a validation substudy, we can use multiple imputation
  - ‘Standard’ sensitivity analysis
  - Probabilistic/Monte Carlo sensitivity analysis
  - Bayesian sensitivity analysis using data augmentation

Approaches to bias modeling:
misclassification of the main exposure

- We have no information on the true exposure (e.g. asbestos levels in the lung)
- We have imperfect information on a surrogate for the main exposure (e.g. cumulative asbestos exposure from a job-exposure-matrix)
- If we can make assumptions about the association between the true exposure and the surrogate measure (e.g. it's sensitivity and specificity) then we can "impute" the missing values for the true exposure
- By varying these assumptions (about sensitivity and specificity) we can do a "sensitivity analysis" of the likely bias due to misclassification

Adjustment for misclassification of the smoking status in the association between smoking and lung cancer: *Multiple imputations and probabilistic sensitivity analysis*

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The lung cancer case-control study

- Incident lung cancer cases notified 2007-2008 to the NZ Cancer Registry (aged 20-75)
  - Population controls selected from the Electoral Roll

	Cases		Controls	
	N	%	N	%
Total	457	100.0%	792	100.0%
Gender				
Men	227	49.7%	431	54.4%
Women	230	50.3%	361	45.6%
Age at interview				
20-50 years	43	9.4%	81	10.2%
51-60 years	118	25.8%	184	23.2%
61-70 years	284	62.1%	424	53.5%
>=71 years	12	2.6%	103	13.0%
Smoking				
Never	49	10.7%	370	46.7%
Ever	406	88.9%	408	51.5%
missing	*2*	*0.4%*	*14*	*1.8%*
Ethnicity				
Maori	79	17.3%	22	2.8%
Non-Maori	378	82.7%	770	97.2%
NZSEI				
Class 1 (75-90) highest	7	1.5%	33	4.2%
Class 2 (60-75)	52	11.4%	94	11.9%
Class 3 (50-60)	67	14.7%	119	15.0%
Class 4 (40-50)	114	24.9%	164	20.7%
Class 5 (30-40)	116	25.4%	208	26.3%
Class 6 (10-30) lowest	101	22.1%	174	22.0%

OR_{crude}=7.51 (5.41-10.43)
$OR_{adjusted}$=7.74 (5.49-10.91)

We will use the lung cancer data set and assume that the measured smoking data is misclassified, and then estimate what the "true" odds ratio for smoking would have been if there had not been misclassification, first using standard sensitivity analysis, and then probabilistic sensitivity analysis

Standard sensitivity analysis - Method

1. Determination of an *a priori* value for the bias parameters (sensitivity={0.6, 0.7, 0.8, 0.9, 1} and specificity ={0.6, 0.7, 0.8, 0.9, 1})
2. Calculation of the corrected frequencies according to the following formulas

	Observed		Corrected data	
	Ever smokers	Never smokers	Ever smokers	Never smokers
Cases	a	b	A	B
Controls	c	d	C	D
Total	a+c	b+d	A+B	C+D

With $A=[a-N_{Cases}(1-SP)]/[SE-(1-SP)]$

$C=[c-N_{Controls}(1-SP)]/[SE-(1-SP)]$

$B=N_{Cases}-A$

$D=N_{Controls}-C$

3. Estimation of the corrected odds ratio of the association between smoking and lung cancer using the corrected frequencies

Standard sensitivity analysis - Results

Sensitivity	Specificity	OR
0.6	1	NA
0.7	1	NA
0.8	1	NA
0.9	1	83.08
1	**1**	**7.51**

Sensitivity	Specificity	OR
1	0.6	17.47
1	0.7	11.66
1	0.8	9.42
1	0.9	8.24
1	**1**	**7.51**

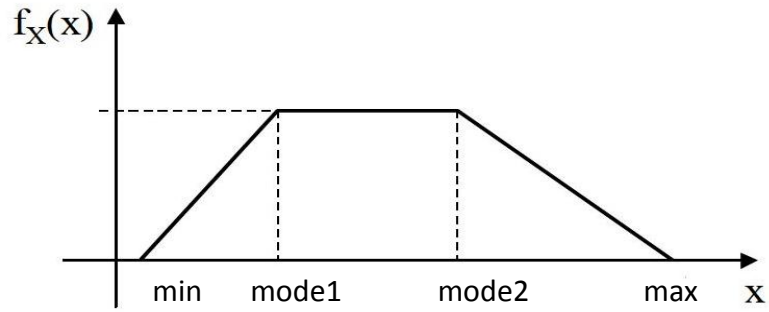
Sensitivity	Specificity	OR
0.6	0.6	NA
0.7	0.7	NA
0.8	0.8	NA
0.9	0.9	91.15
1	**1**	**7.51**

Probabilistic sensitivity analysis

- Probabilistic sensitivity analysis and multiple imputation are useful methods to correct for misclassification
- Both methods have the advantage, compared with “standard” sensitivity analysis, that they enable adjustment for covariates
- A validation substudy must be available to use multiple imputation to correct for misclassification
- Probabilistic sensitivity analysis can be regarded as Semi-Bayesian and it is easier to compute than fully Bayesian sensitivity analysis

Standard sensitivity analysis

1) Determination of an *a priori* distribution for the sensitivity and the specificity: Trapezoidal distribution (min=0.60, mode1=0.85, mode2=0.98, max=1)



Standard sensitivity analysis - Correction for the crude association

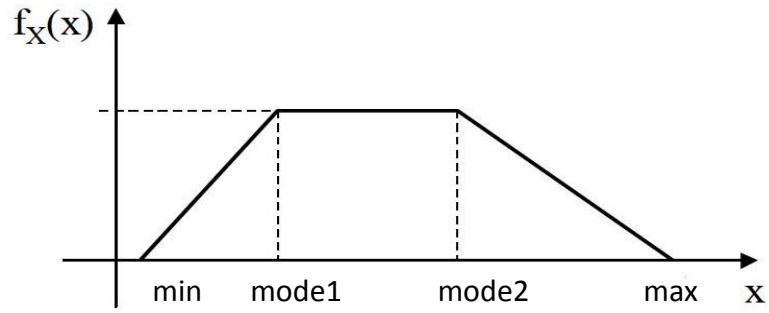
Use of an Excel spreadsheet related to Lash TL., Fox MP., Fink AK. *Applying quantitative bias analysis to epidemiologic data.*

https://sites.google.com/site/biasanalysis/

OR simulation results (N=500)	
Analysis	Median (2.5th-97.5th percentile)
Conventional	7.51 (5.41-10.43)
Corrected for misclassification	17.83 (8.9-288.51)

Probabilistic sensitivity analysis - Method

1) Determination of an *a priori* distribution for the sensitivity and the specificity: Trapezoidal distribution (min=0.60, mode1=0.85, mode2=0.98, max=1)



2) Random draw of 500 combinations for the sensitivity and specificity from these distributions

3) Estimation of the corrected association for each combination of sensitivity and specificity to obtain a distribution of the corrected estimates

Probabilistic sensitivity analysis: Correction for misclassification

Use of a SAS macro program related to Fox MP., Lash TL., Greenland S. *A method to automate probabilistic sensitivity analyses of misclassified binary variables*

1) For each simulation, after calculating the corrected frequencies, the macro program calculates the positive predictive value and the negative predictive value.
2) These values are applied to each individual to simulate the corrected smoking status.
3) The association between smoking and lung cancer can then be estimated through a logistic regression model, adjusting for all the covariates.

Probabilistic sensitivity analysis: Correction for misclassification

OR simulation results (N=500)	
Analysis	Median (2.5th-97.5th percentile)
Conventional	7.80 (5.53-10.85)
Corrected for misclassification	19.78 (9.50-214.78)

Frequentists and Bayesians (some stereotypes)

Frequentist	Bayesian
Significance testing (p-values, CIs)	Effect estimation (confidence intervals/distributions)
Methods/results focus on random error and (measured) confounding	Methods/results focus on systematic error (bias) in addition to random error
Systematic error considered in discussion	Systematic error also considered in methods/results
Prior knowledge only considered in introduction/discussion	Prior knowledge formally incorporated into analysis
Generalisability/representativeness	Causal inference

Problems with p-values

Rothman KJ. A show of confidence. N Engl J Med 1978; 299: 1362-1363.

Gardner MJ, Altman DG. Confidence intervals rather than p-values: estimation rather than hypothesis testing. Br Med J 1986; 292: 746-750.

Pearce N, Jackson RT. Statistical testing and estimation in medical research. NZ Med J 1988; 101: 569-570.

‘Medical professionals and regulators act on the basis of evidence of causation that is not statistically significant’ [US Supreme Court, 2011]

The elephant in the room

Random error is not the main concern in epidemiological studies

Systematic error (bias) is: selection bias, misclassification, confounding

We need to spend as much time/effort quantitatively assessing systematic error as we spend assessing random error

Why we should all be Bayesians

- We write the methods and results sections of our papers as frequentists and the introduction and discussion as qualitative Bayesians
- The Bayesian approach moves the consideration of prior evidence from the introduction and discussion sections to the methods and results sections
- Prior evidence can be used both in effect estimation and in assessment of systematic error (bias)
- Subjective personal judgements (which are inherent in both frequentist and Bayesian methods) are made more explicit and the effects of changes in these assumptions can be assessed

Why we should become Bayesians (and often already are without realising it)

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