


CEBM
www.cebm.net


Evidence-Based Practice
Observational studies and more

Dr Carl Heneghan BM, Bch, MA, MRCP
Clinical Lecturer, University of Oxford
Deputy Director CEBM




UNIVERSITY OF OXFORD

CENTRE FOR EVIDENCE BASED MEDICINE



www.cebm.net

Choosing the right study design




www.cebm.net

An early Clinical Trial

In the late 18th century, King Gustav III of Sweden decided that coffee was poison and ordered a clinical trial.


J Int Med, October 1991;289 -
Reprinted in Ann Intern Med 1992;117:30



www.cebm.net

Study design


- The king condemned a convicted murderer to drink coffee every day.
- Control: another murderer was condemned to drink tea daily.
- Outcome: death.
- Two physicians were appointed to determine the outcome.



www.cebm.net

Results

- The two doctors died first.
- The king was murdered.
- Both convicts enjoyed long life until the tea drinker died at age 83 (no age was given for the coffee drinker).



www.cebm.net

Discussion

One should not rely on such a small sample size. Perhaps the end point was too harsh.

The outcome of the trial had no effect on the decision makers. Coffee was forbidden in Sweden in 1794 and again in 1822.

Conclusions

None possible.

External events and other biases may have confounded the result.

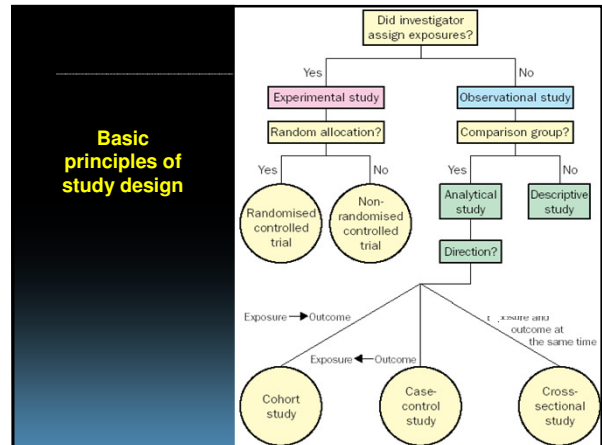
Kings should not mess with clinical trials.

The Lancet published a series of papers in 2002 on conducting clinical research:

Grimes DA, Schulz KF. An overview of clinical research: The lay of the land. *Lancet* 2002;359:57-61.
 Grimes DA, Schulz KF. Descriptive studies: What they can and cannot do. *Lancet* 2002;359:145-9.
 Grimes DA, Schulz KF. Bias and causal associations in observational research. *Lancet* 2002;359:248-52.
 Grimes DA, Schulz KF. Cohort studies: Marching toward outcomes. *Lancet* 2002;359:341-5.
 Schulz KF, Grimes DA. Case-control studies: Research in reverse. *Lancet* 2002;359:431-4.

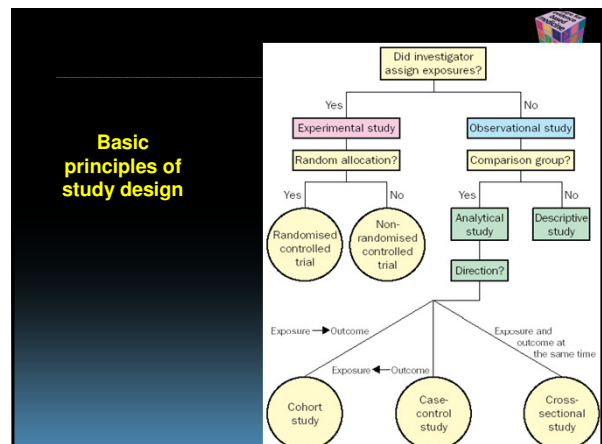
Comparison

<p>Qualitative</p> <ul style="list-style-type: none"> • Understanding • Interview/observation • Discovering frameworks • Textual (words) • Theory generating • Quality of informant more important than sample size • Subjective • Embedded knowledge • Models of analysis: fidelity to text or words of interviewees 	<p>Quantitative</p> <ul style="list-style-type: none"> • Prediction • Survey/questionnaires • Existing frameworks • Numerical • Theory testing (experimental) • Sample size core issue in reliability of data • Objective • Public • Model of analysis: parametric, non-parametric
---	--



Quantitative designs

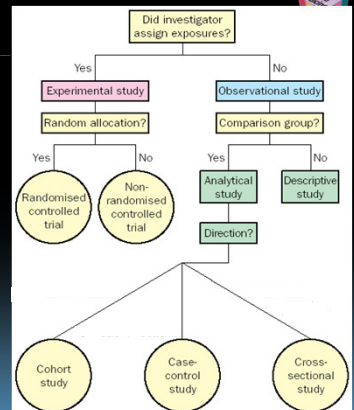
- **Observational:** studies that do not involve any intervention or experiment.
- **Experimental:** studies that entail manipulation of the study factor (exposure) and randomization of subjects to treatment (exposure) groups



Observational Studies

Dominate the literature

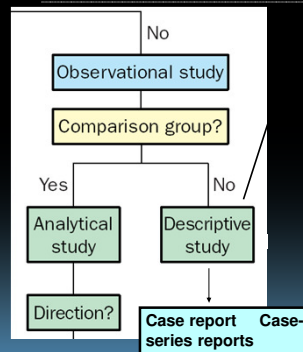
Funai et al.
 Distribution of study designs
 in four major US journals
 Gynecol Obstet Invest 2001;51:8-11



Observational Designs

- **Exploratory:** used when the state of knowledge about the phenomenon is poor: small scale; of limited duration.
- **Descriptive:** used to formulate a certain hypothesis: small / large scale. Examples: case-studies; cross-sectional studies
- **Analytical:** used to test hypotheses: small / large scale. Examples: case-control, cross-sectional, cohort.

Descriptive studies



1. Do not feature a comparison (control) group.
2. Often the first foray into a new area of medicine.
3. Describe the frequency, natural history, and possible determinants of a condition.
4. Hypothesis generation about the cause of the disease.
5. do not allow assessments of causal association.

Descriptive studies

Who, what, why, when, where

1. Who has the disease in question ?
2. What is the condition or disease being studied ?
3. Why did the condition or disease arise ?
4. Where does or does not the disease or condition arise ?

NEWS

Teen fights for life after reaction to twice the drug

7:03am Thursday 10th December 2009

By Dan Heenan

ATEENAGER is intensive care and fighting for her life after taking the severe flu drug Tamflu.

Samantha Millard, of Kirtland Drive, Bicester, has blisters all over her body and severe breathing difficulties after being prescribed the medication.

Last night the 18-year-old was in a critical condition and being treated in the specialist burns unit at Children and Inceptor Hospital after being transferred from Oxford's Churchill Hospital.

Doctors fear she may have the life-threatening Stevens-Johnson syndrome, which causes the skin to peel off.

Case report

Teen: epidermal necrolysis associated with an influenza-B virus and oseltamivir

Dear Editor,

In December 2009, an 18-year-old girl with a past medical history of occasional migraines and a low body mass index (BMI), experienced one week symptoms of influenza, such as fever, cough, sore throat, muscle aches and loss of appetite. Within 24 hours of the onset, she had developed the GP infection. The patient advised she consumed the seasonal Influenza B vaccine but made a seronegative diagnosis of Severe Organ Infection A (SIOI) 2009 infection. She was prescribed oral oseltamivir (Tamiflu) 75mg twice daily for two days.

After 24 hours and three doses of oseltamivir she noticed a rash over her abdomen. Her mother then contacted the GP who advised the patient and noted a widespread maculopapular rash over the trunk and upper limbs, associated tachycardia, pyrexia (temperature 38.4°C), conjunctival injection, mucocutaneous desquamation and purpura. The paediatric and general practitioners of a community child health unit advised the patient to stop oseltamivir. The next day the GP advised the patient bring blisters and ulcers, particularly in the mouth and lips, and advised the patient to the local dermatology team.

On consultation at the department of dermatology, she was admitted and transferred to have an extensive maculopapular rash on her trunk and limbs with blisters being a critical level of epidermal loss in the abdomen. Blistered regional blisters were present on the periphery of the trunk and proximal limbs. There were initially small discrete areas of blistering on the face and lower abdomen (Fig 1). Clinical features were similar to the flu and there was respiratory alkalosis. The skin was extensively desquamated in 48 hours (Fig 2). She was general temperature 38.5°C and tachycardic, but normotensive, normocytic with a normal respiratory examination. Her initial blood tests showed a leucocytosis, elevated creatinine (2-mo patient, mildly deranged liver enzymes and low haemoglobin and normal renal function (Table 1). She had the above flu vaccination. She was admitted to hospital, a skin biopsy and

Case-series: Clinical case series

- **Clinical case-series:** usually a coherent and consecutive set of cases of a disease (or similar problem) which derive from the practice of one or more health care professionals or health care setting,
- A case-series is, effectively, a register of cases.

Case-series: Clinical case series

- Clinical case-series are of value in epidemiology for:
 - Studying predictive symptoms, signs and tests
 - Creating case definitions
 - Clinical education, audit and research
 - Health services research
 - Establishing safety profiles

Case reports and case series from *Lancet* had significant impact on medical literature

Joerg Albrecht¹, Alexander Meves², Michael Bighy²

J. Albrecht et al. / Journal of Clinical Epidemiology 58 (2005) 1227–1232

Case reports

	Number	Percentage
Frequency of being cited by other publications		
0	5	(8%)
1	8	(12%)
2-5	19	(30%)
6-10	9	(14%)
11-20	7	(11%)
21-50	11	(17%)
51-100	4	(6%)
336	1	(2%)
Reports that quote other reports or case series	35	(55%)
Yes	29	(45%)
No	5	(8%)
Case reports that were followed by published trials	11	(17%)
Yes	53	(83%)
No	60	(94%)
Case reports that were followed by trials in the current controlled clinical trials register (11/2002)	4	(6%)
Yes	60	(94%)
No	17	(27%)
Outcome (overall impression)	44	(69%)
Success (final character of disease)	3	(5%)
Failure	35	(55%)
Reference to other case reports (or case series)	29	(45%)
Yes	17	(27%)
No	29	(45%)

Case reports

Case series

	Number	Percentage
Frequency of being cited by other publications		
0	2	(5%)
1	3	(8%)
2-5	10	(26%)
6-10	4	(10%)
11-20	9	(23%)
21-50	6	(15%)
51-100	3	(8%)
Reports that quote other reports or case series	21	(54%)
Yes	18	(46%)
No	12	(31%)
Case reports that were followed by published trials	5	(13%)
Yes	34	(87%)
No	27	(69%)
Case reports that were followed by trials in the current controlled clinical trials register (11/2002)	2	(5%)
Yes	11	(28%)
No	4	(10%)
Number of patients	3	(8%)
4	3	(8%)
5	3	(8%)
6	3	(8%)
7	2	(5%)
8	3	(8%)
9	2	(5%)
10	3	(8%)
Not reported	1	(3%)
Case series that reported mixed response including patients where the treatment had failed	4	(10%)
Yes	4	(10%)
No	4	(10%)
Case series that reported failure of treatment only	31	(79%)
Yes	17	(44%)
No	22	(56%)

Conclusions:

'Case reports and case series can be well received, and have significant influence on subsequent literature and possibly on clinical practice.'

Many were followed by clinical trials.

Often, report rare conditions for which trials may not be feasible.

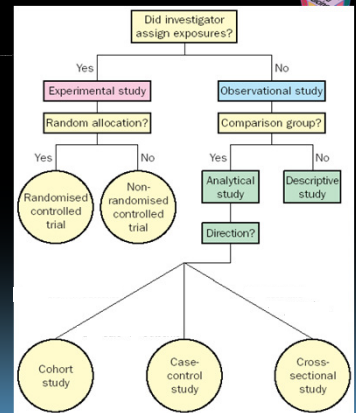
Strong publication bias favouring positive results

Case series: what to look for

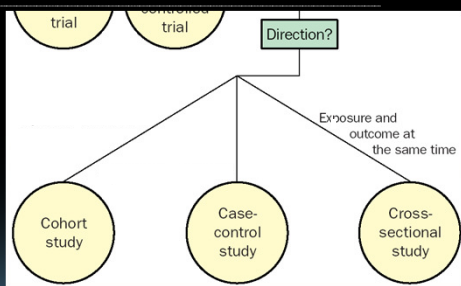
- The diagnosis (case definition) or, for mortality, the cause of death
- The date when the disease or death occurred (**time**)
- The place where the person lived, worked etc (**place**)
- The characteristics of the population (**person**)
- The opportunity to collect additional data from medical records (possibly by electronic data linkage) or the person directly
- The size and characteristics of the **population at risk**

Observational Designs

- **Exploratory:** used when the state of knowledge about the phenomenon is poor: small scale; of limited duration.
- **Descriptive:** used to formulate a certain hypothesis: small / large scale. Examples: case-studies; cross-sectional studies
- **Analytical:** used to test hypotheses: small / large scale. Examples: case-control, cross-sectional, cohort.



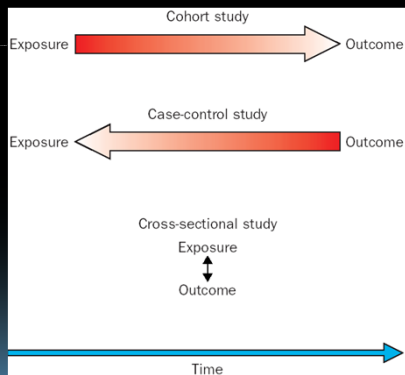
Analytical Studies



Comparison of the Characteristics of

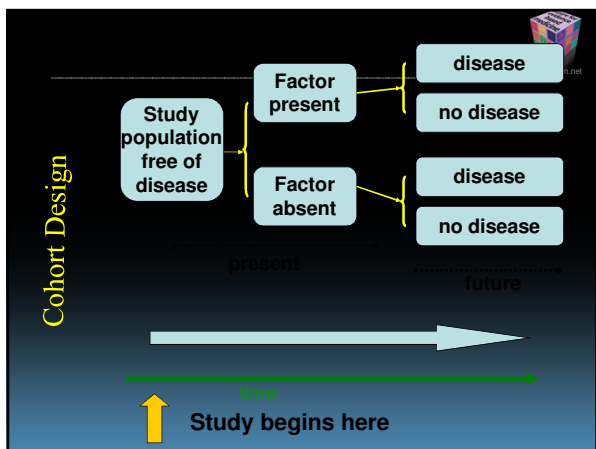
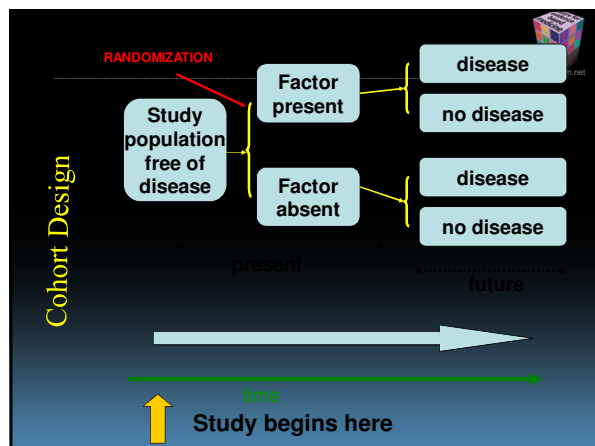
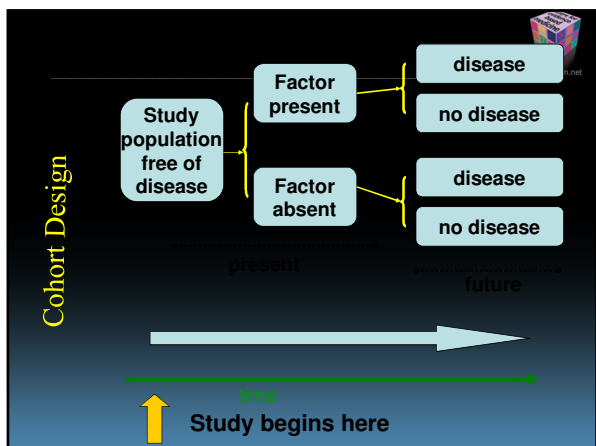
Cohort Study & Case-Control Studies

Usually very expensive	Usually less expensive
Complete source population denominator	Sampling from source population
Can calculate incidence rates or risks and their differences and ratios	Can usually calculate only the ratio of incidence rates or risks
Convenient for studying many diseases	Convenient for studying many exposures



..... several famous large cohort studies continue to provide important information

Ndoff R, Peto R, Boreham J, Sutherland I. Smoking and dementia in male British doctors: prospective study. BMJ 2000;320:1097-1102



Examples: *The Framingham study.*

- Began in 1948 with 5,209 participants
- – 5,123 spouses and children added in 1971
- Selection not based on exposures, but on stable population, wide spectrum of occupations,
- Single hospital, annual updated population list
- Allowed calculation of incidence rates and other descriptive measures for many outcomes

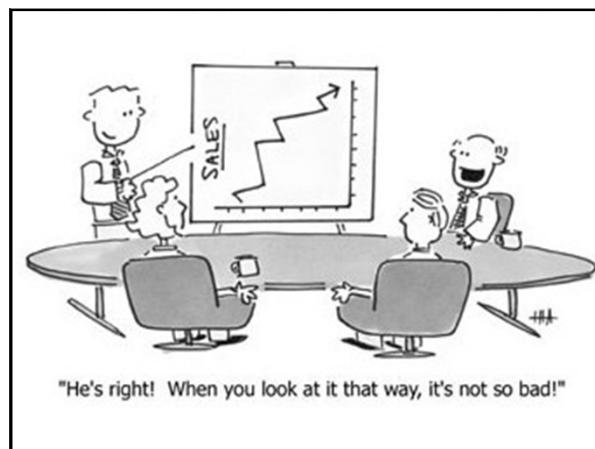
Source: Dawber et al: An approach to longitudinal studies in a community. *The Framingham study.* Ann NY Acad Sci. 1963; 147: 609

CEBM
www.cebm.net

Crunching the numbers

Dr Carl Heneghan BM, Bch MA, MRCP
Clinical Lecturer, University of Oxford
Deputy Director CEBM


CENTRE FOR EVIDENCE BASED MEDICINE



Catching my eye today is this roll of toilet paper called, "Hemo Roll".


It's a product of Slovakia, made by a company named "Tento".

The paper is infused with herbal compounds that are claimed to help prevent hemorrhoid inflammation with continued use. According to the product's website...




RCT: Well conducted → no bias

- 5 patients with haemorrhoids received Hemo-Roll
- 5 people received placebo
- 4 out of 5 with Oximax got better
- 2 out of 5 with placebo got better



Participants are not convinced...
"It could have happened by chance!"

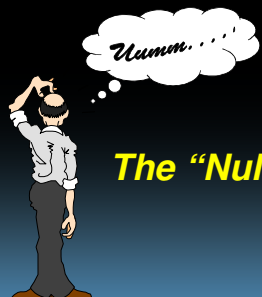
- So how many would you want before you believe the results?
- 10 in each arm?
- 20?
- 100?



It could have happened by chance and nothing was really going on

Umm...

The "Null Hypothesis"

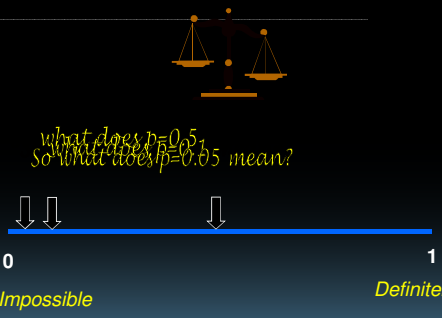


The p-value

- What does a p-value of 5 tell us?

It could have happened by chance

what does $p=0.05$ mean?
So what does $p=0.05$ mean?


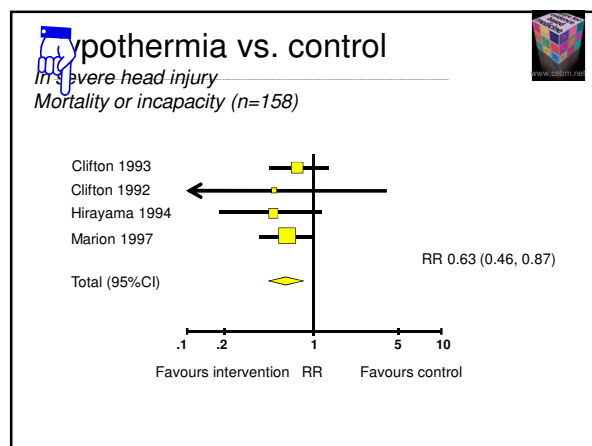
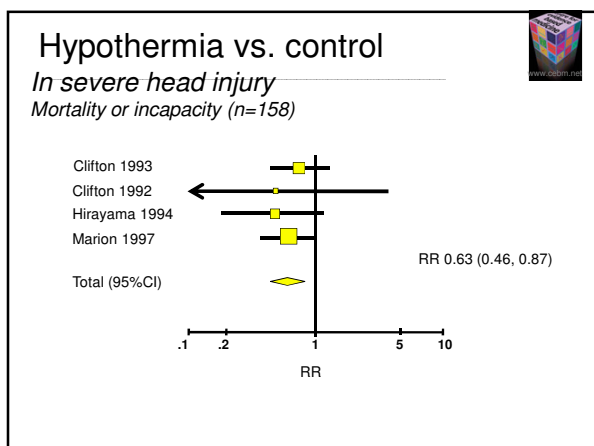


Number in treatment arm	5
Responders in treatment arm	4
Proportion responding in treatment arm	0.8
Number in control arm	5
Responders in control arm	2
Proportion responding in control arm	0.4
p-value	0.29

Number in treatment arm	5	10
Responders in treatment arm	4	8
Proportion responding in treatment arm	0.8	0.8
Number in control arm	5	10
Responders in control arm	2	4
Proportion responding in control arm	0.4	0.4
p-value	0.29	0.09

Number in treatment arm	5	10	15	20	100
Responders in treatment arm	4	8	12	16	80
Proportion responding in treatment arm			0.8	0.8	0.8
Number in control arm			15	20	100
Responders in control arm			6	8	40
Proportion responding in control arm			0.4	0.4	0.4
p-value	0.29	0.09	0.03	0.01	<0.0001

• Before I show the homeopathic dose of confidence intervals, let's explore your views...




Natural frequency approach

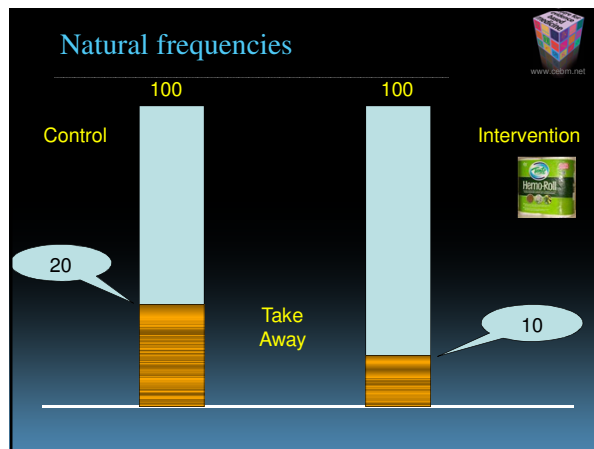
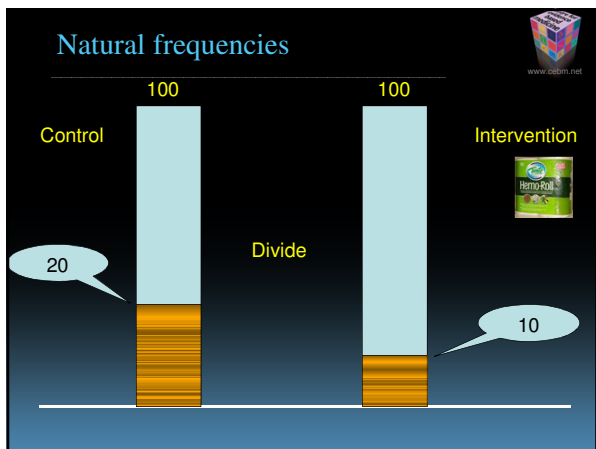
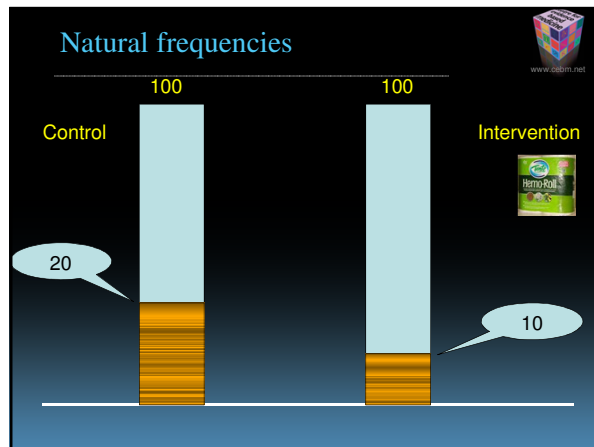
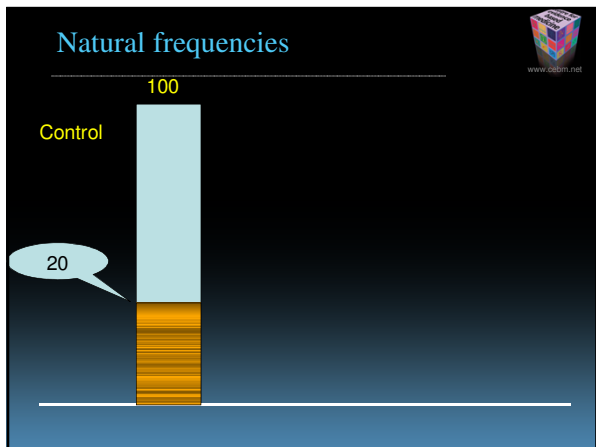


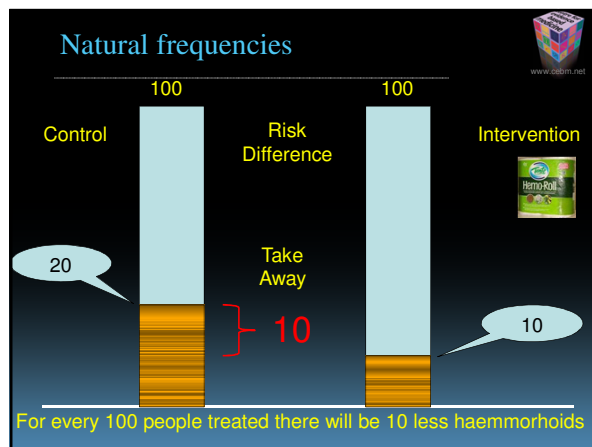
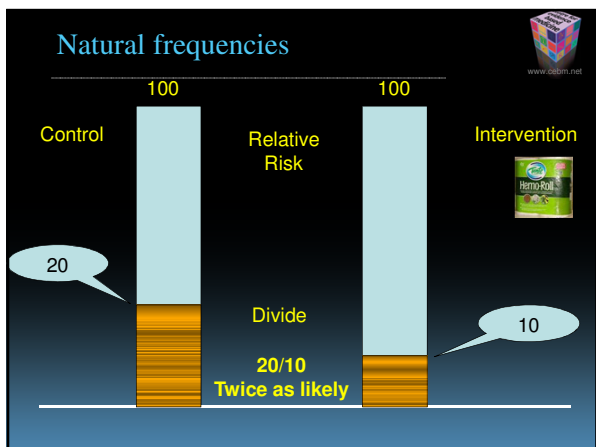
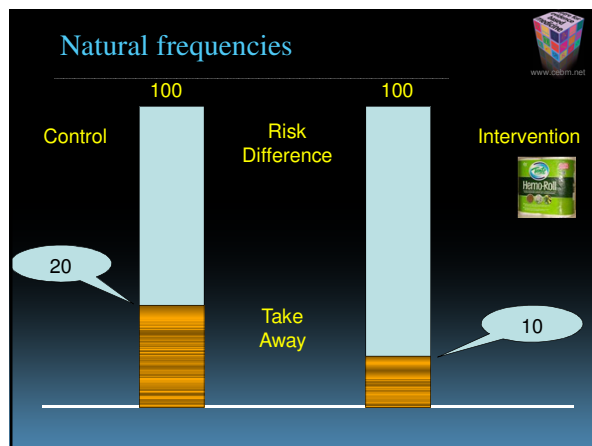
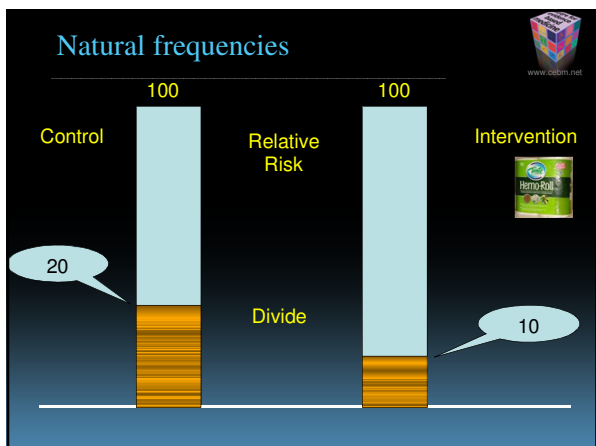
CENTRE FOR EVIDENCE BASED MEDICINE

Trial of Hemo-Roll 2



Control group	Intervention group
200 people	200 people
40 people have haemorrhoids	20 people have haemorrhoids
20%	10%





Summary

It could have happened by chance and nothing was really going on

Relative risk - divide

Risk difference – take away

Natural frequencies how many in a 100

Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial

*The DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators**

Summary
Background Rosiglitazone is a thiazolidinedione that reduces insulin resistance and might preserve insulin secretion. The aim of this study was to assess prospectively the drug's ability to prevent type 2 diabetes in individuals at high risk of developing the condition.
Methods 5269 adults aged 30 years or more with impaired fasting glucose or impaired glucose tolerance, or both, and no previous cardiovascular disease were recruited from 191 sites in 21 countries and randomly assigned to receive rosiglitazone (8 mg daily; n=2365) or placebo (2634) and followed for a median of 3 years. The primary outcome was a composite of incident diabetes or death. Analyses were done by intention to treat. This trial is registered at ClinicalTrials.gov, number NCT00095654.
Findings At the end of study, 59 individuals had dropped out from the rosiglitazone group and 46 from the placebo group. 306 (11.6%) individuals given rosiglitazone and 686 (26.0%) given placebo developed the composite primary outcome (hazard ratio 0.40, 95% CI 0.35–0.46; p<0.0001); 1330 (50.5%) individuals in the rosiglitazone group and 798 (30.3%) in the placebo group became normoglycaemic (1.71, 1.57–1.87; p<0.0001). Cardiovascular event rates were much the same in both groups, although 14 (0.5%) participants in the rosiglitazone group and two (0.1%) in the placebo group developed heart failure (p=0.01).
Interpretation Rosiglitazone at 8 mg daily for 3 years substantially reduces incident type 2 diabetes and increases the likelihood of regression to normoglycaemia in adults with impaired fasting glucose or impaired glucose tolerance, or both.

The screenshot shows a web browser window with the following details:

- Address bar: <http://www.bmj.com/content/333/7572/764.full.pdf.html>
- Page title: **Prevention of diabetes**
- Article title: **Prevention of diabetes**
- Subtitle: *Drug trials show promising results, but have limitations*
- Text:

D iabetes affects one in 20 adults worldwide and 333 million cases are projected worldwide by 2025. Treatment can prevent some of the microvascular and macrovascular complications, but diagnosis is often delayed until complications present, so attention has focused on prevention and early screening. Two strategies currently exist for reducing the onset of diabetes—lifestyle interventions and drugs. The Diabetes Prevention Program Research Group study found that lifestyle interventions delivered over 2.8 years reduced the incidence of diabetes by 58%. A similar reduction in risk was found in a Finnish study of 522 people at risk. The problem is that these interventions are labour intensive—one study needed 16 one to one sessions delivered by case managers to achieve target weight reduction and exercise levels. Although lifestyle interventions produce successful results in research settings, they are difficult to replicate even in well funded health care systems. Considerable interest has focused on the prevention of diabetes with drugs. For instance, the Diabetes Prevention Program Research Group study found a 51% reduction in the incidence of diabetes with metformin at 2.8 years. Previously rosiglitazone was shown to be effective in controlling blood sugar levels

confidence interval 0.35 to 0.96, P<0.0001). Rosiglitazone did not reduce the risk of diabetes. These results are promising, but they should be interpreted with caution. The mean fasting plasma concentration of glucose in both groups at baseline was 5.8 mmol/L whereas the two hour impaired glucose tolerance test had a value of 8.7 mmol/L. The study population was therefore composed predominantly of people with impaired glucose tolerance rather than those with abnormal fasting glucose. Fasting glucose concentrations rather than impaired glucose tolerance are usually used to screen for diabetes in the United Kingdom. Secondly, the rationale for using a composite end point of death and diabetes is unclear. Several considerations should be taken into account when using a composite end point. These include whether the component outcomes carry similar weight of importance to patients; and whether the component outcomes are likely to have similar relative risk reductions. This is not the case for death rates, which were similar in both groups and therefore should be analysed separately. Furthermore, despite the population being at low risk of heart failure (10 year risk 0.33%) a significant increase (0.4%) in heart failure was seen in the rosiglitazone group compared with placebo (7/65, 1/60 to 3/69, number needed to harm

