

STATISTICS REVISITED: A REVIEW FOR CONTRIBUTORS AND READERS

Measuring risk: How, when and why?

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(Accepted 15th May 2002)

The Journal of Family Planning and Reproductive Health Care 2002; **28**(3): 159-161

Introduction

Individuals wishing to make informed choices about their health care need, among other things, information about the risks associated with each available option. Risk is the probability that an event will occur. A variety of study designs are used in reproductive health care to assess the risks associated with interventions. This paper describes the different methods, and explains why we need each approach.

Exposures and outcomes

An exposure in a study (also known as an explanatory or independent variable) may be a treatment (e.g. a new drug to treat ovarian cancer) or some other factor (e.g. decision to have an induced abortion, being in poorer socio-economic circumstances, or receipt of an information leaflet or medical advice). Non-exposed individuals do not receive the intervention of interest although they may receive current best treatment, usual care or a placebo. Outcomes (also known as dependent variables) are often death or morbidity (e.g. deep venous thrombosis). The risk associated with an intervention is measured in the different studies by comparing the risk of the outcome of interest among the exposed group with the risk of the outcome in the non-exposed group. Many exposures are associated with an increased risk of disease, in other words are thought to be harmful. Some exposures, however, are associated with a reduced risk of disease; for example, the combined oral contraceptive pill (COCP) is protective for ovarian cancer.

Why we need different study designs

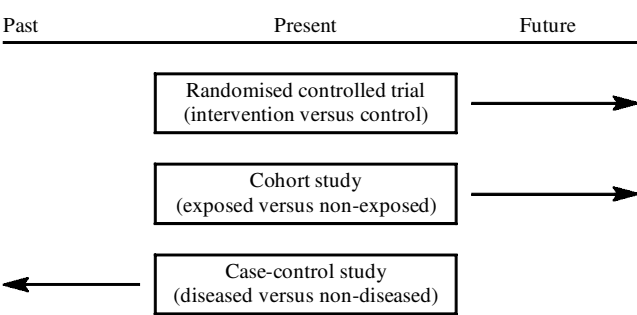
Studies that assess the risks associated with interventions can be classified as either experimental or observational. In experimental studies (e.g. randomised controlled trials), researchers deliberately assign participants to an intervention (exposure) group or to a comparison (control) group. Each group is followed, forward in time, so that the occurrence of the outcome of interest can be ascertained. The random allocation of trial participants into different groups by the researchers, not the study participants or their usual health care providers, tends to ensure that the groups have similar characteristics, and removes the often subtle selection processes that take place when people can choose between treatments.

The general absence of confounding means that experimental studies are regarded as the ‘gold standard’ for

assessing the efficacy of interventions. Most trials, however, are too small to assess with statistical robustness uncommon adverse effects. Moreover, in many clinical situations it would be unethical to randomly assign individuals to a particular intervention. For instance, it would be unethical to randomly assign women to use of the COCP, another method of contraception or a placebo. Yet knowledge about the harmful and beneficial effects of different contraceptives, and other reproductive health care interventions, is very important. These considerations demand a different methodological approach.

In observational studies (e.g. cohort and case-control) researchers observe and record the exposure status of participants rather than actively allocate individuals to particular interventions. This means that observational studies are more prone to bias and confounding than experimental studies, and so require a more careful interpretation of their results. Cohort studies start with two (or more) groups of individuals who are initially free of disease and who have or have not experienced the exposure of interest. The individuals are then followed, forward in time, in order to determine how often the outcome of interest occurs in each group. Case-control studies start with a group of individuals (cases) with the outcome of interest (often disease) and a group of individuals (controls) without the outcome. Each group is then asked about certain exposures in the past. Figure 1 shows schematically the direction of inquiry for the different study designs. Cross-sectional studies are another type of observational study in which the presence and absence of exposures and outcomes are assessed at one point in time. Since there is not a temporal relationship between exposure and outcome, cross-sectional studies are usually uninformative when trying to assess the risks associated with an intervention.

Figure 1 Direction of inquiry of the different study designs used to measure the risks associated with an intervention



Cohort studies are useful when the exposure of interest is rare, and case-control studies useful when the outcome is rare. Both types of study can examine multiple exposures for an outcome. Compared with case-control studies, cohort investigations are less susceptible to confounding or bias (especially selection and recall bias), are more able to examine the multiple effects of an exposure, and are better at looking at time relationships. Cohort studies, however, are often time-consuming, especially if there is a long duration period between exposure and development of the outcome (latent period). Cohort studies therefore can seem expensive. Conversely, case-control studies can often be done more quickly, more cheaply and are more suited to investigating relationships with a long latent period. Case-control studies are also less prone to problems resulting from the loss of participants to follow-up.

Measures of risk

There are three commonly used measures of risk: relative risk (also known as the risk ratio or rate ratio), absolute risk (also termed risk difference or excess risk) and odds ratio.

Relative risk and absolute risk

Randomised controlled trials and cohort studies follow individuals forward in time in order to ascertain the rate of new cases of disease (incidence of disease) in exposed and non-exposed groups. Both types of study calculate the relative risk by taking the ratio of the incidence rate of disease among the exposed group over the incidence rate of disease in the non-exposed group (Table 1). Relative risks demonstrate the strength of association between an exposure and an outcome, useful when trying to assess aetiological relationships. They are uninformative, however, when trying to determine the clinical significance of any findings. This is because relative risks obscure the background risk of the outcome of interest in the study population. Strong associations (e.g. 3.0 or 0.3) with an uncommon event will result in the exposure ‘causing’ only a few additional new cases of the outcome, whereas weaker associations (e.g. 1.5 or 0.8) with a common event will result in many more new cases. The clinical importance of an effect can be assessed in randomised trials and cohort studies by determining the absolute risk: the incidence rate of disease in the exposed group minus the incidence rate of disease in the non-exposed group. The reciprocal of the absolute risk is the ‘number needed to treat’, or if an

Table 1 Calculation of relative risk, absolute risk and odds ratio

Outcome (disease)	Exposed	
	Yes	No
Yes	a	b
No	c	d
Total	a + c	b + d

Incidence rate of outcome = $\frac{\text{number of new events in the specified period}}{\text{number of people at risk in the specified period}}$.

Relative risk = $\frac{\text{incidence rate of outcome in the exposed}}{\text{incidence rate of outcome in the non-exposed}} = \frac{a/(a + c)}{b/(b + d)}$.

Absolute risk = incidence rate of outcome in the exposed – incidence rate of outcome in the non-exposed = $a/(a + c) - b/(b + d)$.

Odds: ratio of the occurrence of an event to the non-occurrence of the event.

Odds ratio = $\frac{\text{odds of exposure in cases}}{\text{odds of exposure in non-cases}} = \frac{(a/b)}{(c/d)}$.

adverse event is being studied, the ‘number needed to harm’. These figures show, on average, how many people need to be given an intervention for one person to benefit or be harmed. For more details regarding these terms see Laupacis et al.¹ and Sackett et al.²

Table 2 demonstrates the calculation of the relative and absolute risk using data from the Royal College of General Practitioners’ (RCGP) Oral Contraception Study.³ In this cohort study, women who had ever used COCPs were 1.17 times more likely to have a pill-related serious illness compared to never users. In other words, COCP users had a 17% increased risk of serious illness compared with never users. The absolute risk of serious disease in COCP users was 101.7 per 100 000 woman-years; that is, if 100 000 women used the pill for 1 year there would be about 100 extra cases of pill-related serious disease. The ‘number needed to harm’ was 983 [i.e. $1/(101.7/100\,000)$], indicating that for every woman developing a new case of serious illness during a year’s use, 983 women would not have had such an experience.

Table 2 Calculation of relative and absolute risk of pill-related serious disease in the Royal College of General Practitioners’ (RCGP) Oral Contraception Study^a

	Incidence rate of any pill-related serious illness per 100 000 woman-years	Relative risk (ever/never)	Absolute risk (ever – never)
Ever COCP users	683.9	1.17	101.7 per 100 000 woman-years
Never COCP users	582.2		

^aData taken from Hannaford and Kay.³
COCP, Combined oral contraceptive pill.

In another example, a randomised controlled trial investigated the effect of educational leaflets on knowledge of contraception in women taking the COCP.⁴ Of the 82 women who received a summary leaflet, 45 knew the rules about pill failure compared to 35 women out of the 82 women randomised to receive no leaflets. The relative risk of knowledge about pill failure was 1.29. Therefore, women who received the leaflet were 30% more likely to have knowledge regarding pill failure than women not given this intervention.

When an exposure is not associated with an outcome, the true relative risk equals one and the true absolute risk equals zero. When the relative risk is less than one, the exposure is protective of developing the outcome of interest. For example, the RCGP Oral Contraception Study estimated that the relative risk of ovarian cancer in ever COCP users (exposed) to never users (non-exposed) was 0.6.⁵ In other words, the risk of ovarian cancer among ever users was 40% less than observed in never users.

Odds ratio

Case-control studies cannot calculate the incidence of disease because the population at risk is not defined. Instead, these studies estimate the proportion of exposed individuals among cases and non-cases (controls) who represent the population from which the cases were derived (i.e. they would have been designated as cases if they had developed the disease). The inability to derive incidence rates means that relative risks cannot be calculated from case-control studies. Instead, these studies estimate the odds ratio. Odds is the ratio of the probability of the occurrence of an event to the non-occurrence of the event.

In a case-control study, the odds ratio is the ratio of two odds, i.e. the ratio of the odds of exposure to non-exposure in cases to the odds of exposure to non-exposure in controls (Table 1). The odds ratio equals one when the exposure is not related to outcome. When the outcome is relatively uncommon (e.g. occurs less than 1 in 100) the odds ratio approximates the relative risk. Lack of information about incidence rates also prevents case-control studies from estimating directly the absolute risk associated with an exposure; potentially a serious handicap when trying to understand the clinical significance of a finding.

Table 3 gives an example of a case-control study and the resulting odds ratio. In the example, women who had a myocardial infarction (MI) were more likely to smoke than controls. The odds ratio can be interpreted as indicating that, in this study, smokers were more than three times more likely to have an MI than non-smokers.

Table 3 Case-control study of 103 cases of myocardial infarction (MI) and 309 controls^a

Outcome variable	Exposure variable (smoking status at recruitment)		Total
	Smoker	Non-smoker	
MI cases	67	36	103
Controls	104	205	309

^aData taken from Owen-Smith et al.⁶
Odds ratio = (67/36)/(104/205) = 3.67.

Confidence intervals

Whatever the measure of risk calculated it is important to also present a surrounding confidence interval (CI), especially for the main comparison of interest. Epidemiological studies can only estimate the true size of any effects.⁷ The 95% CI shows the range of values in which the true value will lie on 95% of occasions. If the 95% CI surrounding a relative risk or odds ratio excludes one, there is 95% ‘certainty’ that the exposure is adversely or beneficially associated with the outcome of interest. By convention, such results are deemed to be statistically significant. When considering absolute risks, if the 95% CI excludes zero there is 95% ‘certainty’ that the exposure is associated with the outcome. Most statistical packages will calculate these CIs.

Examining the 95% CIs in Table 4, the following conclusions can be reached:

- For the cohort study, the true relative risk of any pill-related serious illness among ever COCP users lay, with 95% confidence, between 1.09 and 1.25. In other words, it might have been as small as a 9% greater risk of serious disease than in never users or as large as a 25%

increase. The range excluded one, therefore the risk of serious disease associated with ever use of the COCP was statistically significant. The true absolute risk of ever COCP usage for any serious illness lay, with 95% confidence, between 60 and 143 per 100 000 woman-years. This range excluded zero, therefore the conclusion was the same as above.

- For the randomised controlled trial, the true effect (relative risk) of the educational leaflet on knowledge about contraception lay, with 95% confidence, between 0.94 and 1.77. This range included one, therefore the observed 29% increased risk of improved knowledge among leaflet recipients was not statistically significant. The difference in the proportion of patients in each group with knowledge of the rules of pill failure was 12%, with a 95% CI of –3% to 27%. This range included zero, indicating that the absolute difference of 12% was not statistically significant.
- In the case-control study, the true odds ratio of smoking versus non-smoking among women with MI lay, with 95% confidence, between 2.30 and 5.86. This range excluded one, therefore the risk for MI associated with smoking was statistically significant.

Conclusions

- Different study designs produce different measures of risk. Relative and absolute risks can only be calculated for randomised trials or cohort studies, where the incidence of disease can be determined.
- In randomised trials and cohort studies, both the relative and absolute risk should be presented so that health care professionals, and their clients, can decide for themselves the impact of any exposure.
- Measures of risk should always be presented with their surrounding CI so that judgements about the clinical importance of the findings can be made.

Statements on funding and competing interests

Funding. None declared.
Competing interests. None declared.

References

1 Laupacis A, Sackett DL, Robert RS. An assessment of clinically useful measures of the consequences of treatment. *N Engl J Med* 1988; **318**: 1728–1733.
2 Sackett DL, Richardson WS, Rosenberg W, et al. *Evidence-based medicine. How to practise and teach EBM*. London: Churchill-Livingstone, 1997; 208.
3 Hannaford PC, Kay CR. The risk of serious illness among oral contraceptive users: evidence from the RCGP’s oral contraceptive study. *Br J Gen Pract* 1998; **48**: 1657–1662.
4 Little P, Griffin S, Kelly J, et al. Effect of educational leaflets and questions on knowledge of contraception in women taking the combined contraceptive pill: randomised controlled trial. *BMJ* 1998; **316**: 1948–1952.
5 Beral V, Hermon C, Kay C, et al. Mortality associated with oral contraceptive use: 25 year follow up of cohort of 46 000 women from the Royal College of General Practitioners’ oral contraception study. *BMJ* 1999; **318**: 96–100.
6 Owen-Smith V, Hannaford PC, Warskyj M, et al. Effects of changes in smoking status on risk estimates for myocardial infarction among women recruited for the Royal College of General Practitioners’ Oral Contraception Study in the UK. *J Epidemiol Community Health* 1998; **52**: 420–424.
7 Mollison J, Simpson JA, Hannaford PC. From samples to population: estimation and hypothesis testing. *J Fam Plann Reprod Health Care* 2002; **28**: 101–104.

Table 4 Relative risk, absolute risk and odds ratio with their respective 95% confidence intervals (CI)

Risk measure	Risk estimate	95% CI
Relative risk of ever OCP usage for any serious illness (data from Table 2)	1.17	1.09, 1.25
Absolute risk of ever OCP usage for any serious illness (data from Table 2)	101.7 per 100 000 woman-years	60, 143 per 100 000 woman-years
Relative risk (RCT example)	1.29	0.94, 1.77
Absolute risk (RCT example)	12%	–3%, +27%
Odds ratio of smoking for MI (data from Table 3)	3.67	2.30, 5.86

MI, Myocardial infarction; COCP, combined oral contraceptive pill; RCT, randomised controlled trial.