Acta Neuropsychiatrica

# STATISTICALLY SPEAKING

## Risks risky and not so risky

Research studies often report results which in some way quantify the *risk* of an outcome. In psychiatry such outcomes include the development of a psychiatric disorder following exposure to a risk factor (the focus of epidemiological studies); the experience of a relapse in the period immediately after a patient's recovery (the focus of long-term outcome or maintenance therapy studies); and a serious event such as violent behaviour or a suicide attempt. Risks of such outcomes are presented in a number of forms, and a recurring difficulty is how to present the numerical value in a way that is most helpful to clinicians, patients and policy makers.

Making sense of such risks means evaluating both the *statistical significance* of the risk and the dimension of the risk – often called the *clinical significance* of the risk. This can then be used as the basis for a meaningful clinical discussion with patients in helping them understand what risk means.

The statistical significance of an estimated risk is dependent upon the size of the sample and the size of the risk (or risks) of the disorder under question; if these are low, large sample sizes are required for reliable conclusions (and it should be kept in mind that large can be very large, running into the thousands). Far more useful than statistical significance is the closely related concept of the confidence interval (CI) for the estimate. A CI – say a 95% CI – defines a range of values around the estimate for which the common interpretation is that we can be 95% confident that the true value is in that range. A wide range can encompass both 'acceptable' and 'unacceptable' levels of risk – and thus complicates decision making.

While there are a number of risks used in epidemiology, two kinds are most commonly reported in psychiatry:

1 *Absolute Risk* (AR; also *crude risk* or simply *risk*) is the probability of an event over some period of time. Examples would be a relapse in the 24 months following recovery from an episode of bipolar depression, or dying in the 10 years after treatment for cancer. In epidemiological studies, this refers to the base rate of a disorder, for example, the rate of foetal abnormality is approximately 2%. Exposure to an antidepressant during pregnancy carries a risk of congenital abnormality of 3% – note how this increased risk can be expressed as either an increase of 50%, or an increase of 1% point, both of which are correct, but with differing impressions of seriousness.
2 *Relative Risk* (RR) is the ratio of the risks in two groups differing on some factor. If the lifetime risk of a major depressive episode is 24% for females and 15% for males then the RR = 24/15 = 1.6. Not infrequently, statistical methods or study design make reporting an RR-like measure – the *odds ratio* (OR) – either more convenient or unavoidable. An OR = 2.5 tells us that the odds in one group are 2.5 times the odds in the other. Although an RR of *r* means that something is '*r* times more likely' in the usual sense of that phrase, the OR does not quite mean that (since it refers to odds not probabilities) and care needs to be taken especially when the OR is large, but the underlying probabilities are not much different.

Size is not everything and the characteristics of the population where the risk is estimated, or the characteristics of the individuals to whom it is applied, are of critical importance. Age, gender, racial type [a major confounder in genome-wide association studies (GWASs)] and genotype are all instances of features that modify risk. A classic example of a characteristic having a profound effect on a risk is that of sickle cell disease that affords protection against developing malaria. A clinician who is interested in a particular population can, if the data are provided within the study, conduct a sensitivity analysis. In this, the risks for a particular group are calculated and compared to the rate for the whole population.

All risks are to some extent an 'average' across heterogeneity and never capture each patient's uniqueness – to what extent that matters is often unknown and to what extent clinicians should use clinical experience to modify tabulated risks when applying them to an individual is a controversial topic.

One area within psychiatry that has been contentious is the risk of developing schizophrenia following exposure to cannabis. Andreasson et al. (1) conducted a longitudinal study on a cohort of Swedish conscripts. Exposure (and frequency of use) to cannabis was assessed at the time of conscription. The National Case Register was used to identify those that developed schizophrenia.

There were 197 cases of schizophrenia among the 41 280 recruits (90.6% of the total sample) that reported no exposure to cannabis; a rate of 0.48%. The risk of schizophrenia was higher among those that reported using cannabis at least once (49 cases from 4290 subjects – a rate of 1.14%). The rate of schizophrenia was higher among those with the highest



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Table 1. Results from the work reported in the study of Andreasson et al. (1)

| Cannabis consumption | *N* | % | Cases of schizophrenia | RR | 95% CI |
|---|---|---|---|---|---|
| 0 | 41 280 | 90.6 | 197 | 1 | — |
| 1–10 | 2836 | 6.2 | 18 | 1.3 | 0.8–2.2 |
| 11–50 | 702 | 1.5 | 10 | 3.0 | 1.6–5.5 |
| >50 | 752 | 1.7 | 21 | 6.0 | 4.0–8.9 |
| Total | 45 579 | 100 | 246 | | |

consumption of cannabis, with a rate of 2.8%, a sixfold increased risk (Table 1).

While this study demonstrated an increased risk of developing schizophrenia following exposure to cannabis, it does not specify the population to which this risk applies (women were not included in this study; does the same risk apply to them as well?).

The Dunedin prospective birth-cohort study (2) measured cannabis exposure and its association with the development of schizophreniform psychosis by the age of 26. What they did in this study was to examine the risk according to genetic variations on the catechol-o-methyltransferase (COMT) gene (a gene involved in the metabolism of dopamine release into synapses). The rate of schizophreniform psychosis (2.6% overall) was higher among those that used cannabis, but this was most pronounced for those that carried the Val/Val variant of the COMT gene; it was also higher among those that were heterozygous (Val/Met), but there was no significant increase for those with the Met/Met polymorphism.

Examination of the risk in subpopulations can be done by stratifying the sample and examining the risk within each subsample (males vs. females; Caucasians vs. Asians, etc.) or through the use of multivariate approaches in which the contribution to risk of a range of variables can be calculated. The COMT study presented a series of regression models each of which in principle allowed different risks to be calculated based on a combination of risk factors. For more than simple estimates of risk, such models are highly dependent on large sample sizes in order to produce reliable weightings of the different risk factors and even a study such as this could only examine a small number of combinations of risk factors.

The clinical significance of an identified risk will depend upon the importance and impact of the health problem being studied, e.g. schizophrenia. Second, it will depend on the change to the AR. An RR might be high (say a 10-fold increased risk of developing Ebstein's anomaly following uterine exposure to lithium), but when the AR is low (1:10 000) the change to the AR will be from 1:10 000 to 10:10 000 or 1:1000 – still a low risk. Note that from a public health perspective, if a large part of the population is exposed to a risk factor, then even very small changes in risk can be important; even a tiny fraction of a large number can translate into an 'overwhelming' number of cases.

A crucial aspect of this is how to communicate this risk to patients, who would have little understanding of what the risk means. For many patients a 50% increased risk or a RR of '2' would suggest to them that this represents a 50% chance of an adverse outcome. This is not an uncommon error, especially when reported in the media concerning contentious issues. Patients (and carers) need to be able to understand what the risk means and using simple diagrams or charts can aid in explaining to them, or translating the risk into something meaningful.

Graphical representation, using number affected per 100 (or more if necessary) with and without exposure to the risk factors is one way to help patients get an understanding of what the risk means. In Fig. 1, we show how this can be demonstrated for the risk of congenital abnormality following uterine exposure to a selective serotonin reuptake inhibitor (SSRI). The first author has found this quite useful in practice.

An alternative way is to express the risk in terms that everyone can understand such as the Numbers Needed to Harm. For example, Nutt (3, p. 4) explained the risk of developing schizophrenia following cannabis exposure as:

'. . .our research estimates that, to prevent one episode of schizophrenia, we would need to stop about 5000 men aged 20–25 years from ever using the drug'.

A recent complex study of the benefits of mammographic screening in Norway (4) showed that the number of deaths per 10 000 person-years in the screened group was reduced by 28% over historical controls, while in the non-screened group it was reduced by 18%, for a differential benefit of 10% points. But what does this mean? An accompanying editorial (5) applied these findings to US rates and in Fig. 2 we use a modified form of Fig. 1 to show what it means for 2500 fifty-year-old women screened over 10 years. The difference is hard to see since it

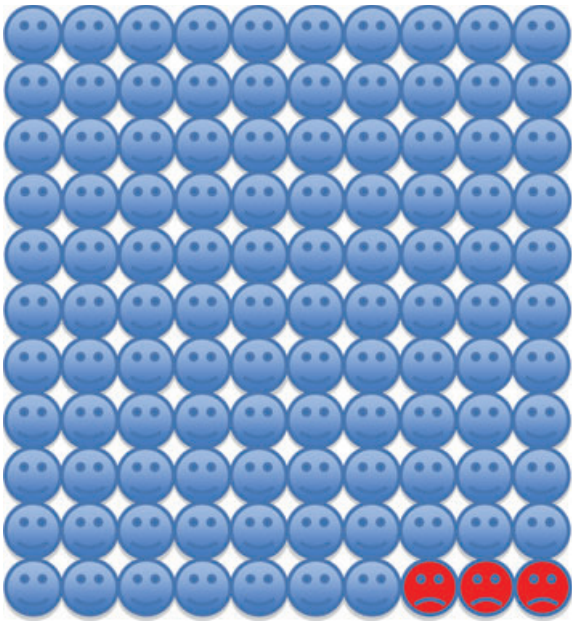

*Fig. 1.* Illustration used by first author to show the risk of congenital abnormality following uterine exposure to an SSRI.



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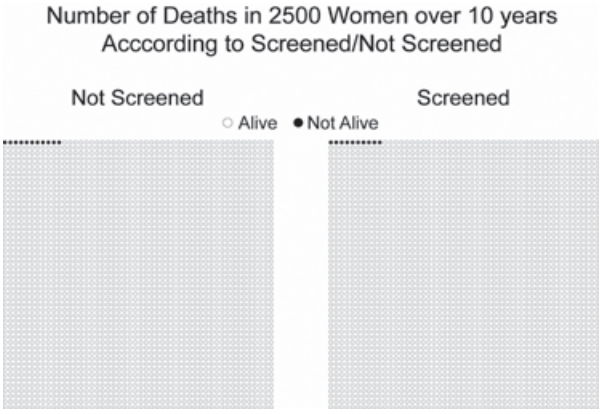


*Fig. 2.* Illustration to show benefits of screening as reported in the study by Welch (5).

corresponds to 10 deaths versus 11 deaths. It is important to note that what is shown is the difference *when applied to a small rate of death*, namely 4.4 per 1000 women. There is a sense in which the difference is neither large nor small of itself – its effects are made large or small by the underlying risk.

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