Workshop 10 — Appraising a study on risk factors or aetiology

Clinicians are not infrequently involved in giving advice on risk factors for various diseases, especially those that are more serious or chronic. Prudent avoidance of exposures to such risk factors is generally believed to help reduce the risk of developing such serious or chronic diseases by individuals, and as a means of reducing disease burdens in the community. Less frequently, clinicians may be involved in attributing causations for certain diseases in patients in the course of medico-legal scenarios. For practitioners in public health, accessing information on risk factors and aetiologies of different diseases is even more important, in order that appropriate prevention strategies can be designed.

In general, a study on risk factors or aetiology examines causal relationships, which in theory should be best achieved through the conduct of a randomised controlled trial (RCT). However, as putative outcomes are often harmful or have adverse health consequences, an RCT to address such questions cannot be regarded as ethically appropriate if conducted specifically to document such harmful outcomes. Hence, most information on risk factors or aetiology comes from observational studies, in particular those using the analytic designs of cohort study or case-referent study. Some information on harmful effects of drugs and other medical interventions as side-effects may be documented through RCT, and this was discussed earlier in Clinical Epidemiology Workshop 8.[1]

In this Workshop, we focus on observational analytic studies and discuss the four major questions to be answered when appraising a study on risk factors or aetiology.

(1) How much higher is the risk of the adverse outcome associated with the exposure? Is there a dose/exposure-response (biological gradient) relationship?

These were two of the nine criteria that Austin Bradford Hill proposed for examining whether an observed association could be regarded as evidence for causation, and were amongst the only three criteria that could be ascertained in an individual study (the other one being temporality).[2] The risk of having an adverse outcome from exposure to a certain risk factor relative to no exposure is the relative risk (RR), which is the ratio between two absolute risks or incidence rates. The higher the RR, the more likely is the association causal and of clinical or public health importance. Intuitively, if increasing levels of exposure are accompanied by increasing risks of a certain outcome, a causal relationship would be more likely.

Furthermore, observed dose/exposure-response relationships are less likely explained by confounding.

True RRs can only be ascertained in cohort studies in which the incidence rates (over a defined period of time) among different groups can be calculated directly. In a case-referent study, the RR for a certain exposure is estimated by calculating the odds ratio (OR) [ratio of odds (not probability) of exposure among the cases to that among the referents]. This only reflects the true RR well in rare diseases. When time to event or survival analysis is conducted in a cohort study, the RR is expressed as the hazard ratio, eg in Cox's proportional hazards regression.

(2) Are the results about the risk factors basically valid?

All three sources of bias (selection bias, information bias, confounding) should be examined. The relative importance and frequencies of different types of biases vary and depend on the basic study design and were discussed in detail in earlier workshops.[3-5] The specific questions to be answered for ascertaining the validity of study results in a study of risk factors are structured under the three major sources of bias[6] (Box).

(3) Are the results reasonably reliable or precise?

The precision of the effect of the risk/protective factor on an adverse health outcome (eg 95% confidence interval) should be reported to enable judgements about the clinical or public health importance of the result, by examining both the upper and lower bounds of the estimated effect.

(4) Can the results be applied in another setting, especially that of relevance to me?

After we have satisfied ourselves that the results are basically valid and reasonably reliable, and that they have clinical or public health importance, we then consider whether we can apply the results in different settings.

Were the backgrounds of study subjects similar to my own setting? A positive answer would support external validity and applicability. On the other hand, one must not forget the best available evidence approach in the practice of evidence-based medicine.[6] Whether the results lead directly to selecting or avoiding the exposure in question depends on its clinical or public health importance, as well as on cost-benefit analyses.

Attributing causation in individuals and groups involves an understanding of the attributable fraction (AF) or attributable risk percent, that is, the proportion of exposed persons with the adverse health outcome who would have developed that outcome as a result of the exposure. This is different from the proportion of exposed persons actually developing the outcome within a defined period—the incidence rate [I_e]. This is because persons without the exposure can also develop the adverse outcome, the part that can be attributed to the exposure would be the difference in the incidence rates between the exposed group [I_e] and the unexposed group [I_0] expressed as a fraction of the total incidence rate among the exposed group—$(I_e – I_0)/I_e$ (after adequate adjustment for confounding). When both the numerator and denominator are divided by I_0, the AF can be expressed alternatively as $(RR – 1)/RR$ or estimated using $(OR – 1)/OR$ in case-referent studies where no true incidence rates can be calculated. If the AF is >50%, it can be said that on the balance of probability, the adverse outcome in an exposed group (or individual) is more likely (>50%) than not attributable to the exposure. This, in turn, is reflected by a reported RR of >2, so long as it has been adequately adjusted for confounding and evaluated for validity.

A detailed discussion on the application of results in formulating public health interventions and policies is beyond the scope of this Workshop. However, it is important to note that the proportion of persons in the population that is exposed needs to be considered in addition to the magnitude of the effect (RR), and such information may or may not be available from results of individual studies. The proportion of a certain disease in the population attributable to a specific exposure is called the population attributable fraction (PAF) or population attributable risk percent and is the difference in the incidence rates between the population [I_p] (consisting of both exposed and unexposed persons) and the unexposed group [I_0] (in the situation if no exposure occurs in the entire population) expressed as a fraction of the total incidence rate in the population—$(I_p – I_0)/I_p$ (after adequate adjustment for confounding). In the simplest situation where exposure status can be dichotomised, the proportion of persons [P_e] exposed would affect the overall incidence rate in the population [$I_p = I_e \cdot P_e + I_0(1 – P_e)$].

BOX. Validity of study results

Validity — selection bias
- Were the sources of study subjects in the different groups (case and referents; or exposed and unexposed cohorts) described, as well as the inclusion and exclusion criteria, and were representative samples selected?
- Were the response or participation rates for the sampled subjects in the different groups reported and reasonably high? Were the reasons for non-participation reported?
- Was follow-up complete or loss to follow-up reported (in a *cohort study*)?

Validity — measurement/information bias (including misclassification)
- Were outcomes, exposures and/or confounding factors measured using the same approaches and tools in all groups?
  - Were objective and unbiased outcome criteria used, especially in cohort studies?
  - Were objective and unbiased assessments of exposures used, especially in case-referent and historical cohort studies?
- Were the assessors for outcomes in *cohort studies* blinded to the exposure statuses of the study subjects?
- Were the assessors for exposures in *case-referent studies* blinded to the case or referent statuses of the study subjects?
- Was the temporal relationship correct, especially in case-referent studies and historical cohort studies?
- Was lag-time or latency period being allowed for?
- Was follow-up sufficiently long for *cohort studies* for observing the relevant health outcomes?

Validity — confounding
- Was an appropriate comparison/referent group with similar background chosen?
- Were all known important factors (risk and protective) affecting the outcome(s) being taken into consideration when examining the effects of a specific risk factor? Moreover, were they adjusted for as necessary in the analysis?
- Were there reasonable numbers of events (10-20 events per risk/protective factor) so that statistical adjustments could be effective?

By substituting this expression for I_p and dividing both the numerator and denominator by I_0, the PAF can be expressed as $P_e(RR – 1)/[1 + P_e(RR – 1)]$. The RR can be estimated by the OR in a case-referent study of a rare disease. Moreover, if the referent group is a good representative sample of the population where the cases are derived from, then the prevalence or proportion of referents having the exposure can be used as the P_e in calculating the PAF. In general, the greater the PAF, the more important is the specific risk factor in contributing to the disease burden in the population and priority should be given to it when it comes to designing prevention strategies.

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