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Prospective Cohort Studies

Prospective cohort studies (PCS) observe one or more groups of subjects longitudinally over time to determine the incidence of a specific outcome after different exposures to a particular factor (for instance drugs, interventions or risk factors). Thereby, nature and strength of a potential relationship between exposure and outcome can be assessed: For example, how many subjects with asymptomatic peripheral arterial disease will develop intermittent claudication and what risk factors are associated? Or does anticoagulant therapy affect the incidence of endoleaks after endovascular aortic repair?

Several important aspects need to be considered when assessing observational studies: First, PCS are being used to investigate causes of diseases, particularly if the more rigorous methodology of randomized controlled trial (RCT) is unethical or not feasible. Representing the next best available scientific method, PCSs are usually designed to test hypotheses about prognosis or etiology. *However,* PCS are susceptible to confounding! Therefore, they are intrinsically inappropriate to prove efficacy of treatment interventions or validity of diagnostic tests. In observational studies, exposures are never randomly assigned increasing the risk that, in reality, unmeasured variables other than the exposure (i.e. "confounders") explain the outcome difference and not the investigated exposure. In this context, confounding means "confusion of effects". In above example, unrecognized smoking or diabetic status could confound for instance the suspected effects of carrying matches or obesity on developing intermittent claudication. Similarly, reverse causation may theoretically occur without notice - for instance if patients at higher risk of the disease receive a specific treatment earlier. In PCS, outcomes occur normally after enrolment suggesting the "direction" of a potentially causal relationship. Nonetheless, investigators always need to scrutinize the temporal sequence between exposure and outcome. In addition, they must control for suspected confounders using appropriate statistical methods. Stratification (sub-grouping) and multivariate regression models are the two most commonly used statistical techniques; both have their own assumptions, advantages and limitations, but none of them can eliminate bias related to unmeasured or unknown confounders. Generally, PCS are apt in generating hypotheses and suggesting causality but can never prove it.

Second, a major objective of PCS is to establish incidence rates for specific outcomes or diseases. The proportions of subjects developing the outcome are then compared between the exposure groups to provide a "risk ratio" (i.e., relative risk, RR) indicating strength and direction of the association between exposure and outcome. A RR of 1.0 reflects absence of any association since exposed subjects are neither more nor less likely to develop the outcome than unexposed subjects. A RR greater than 1.0 implies a positive correlation between exposure and the risk of developing the disease, whereas a RR of less than 1.0 implies a protective effect of the exposure regarding the disease. *However,* losing subjects during follow-up is a main concern in longitudinal research leading to missing (and probably selective) information. Differential loss of information may introduce "length-time" bias and mislead risk calculations in PCS: if subjects drop out from the study for reasons that are related to their exposure or outcome (e.g. sicker patients leave the study before they die), then study findings are likely biased. The loss of only a few cases developing the outcome can seriously affect the numerator and hence distort the result of incidence analyses. The rarer the outcome the more significant is this effect.[1] Therefore, loss to follow-up should be anticipated and sample sizes increased accordingly. For example, if it is likely that 20% of participants will be lost, the power calculated sample should be increased by a factor of 1/(1−0.20), or by 25 percent.[2] Nonetheless, adapted sample sizes cannot fully compensate for missing follow-up data. Investigators need to give every effort to collect complete follow-up information and should declare the aggregate proportion of missed follow-up.

Third, the main advantage of PCS over retrospective cohort and case−control studies is that baseline exposure status is correctly assessed, not only recalled. This reduces the risk of selection bias, because it is much less likely in a PCS that an outcome would influence the individual classification of an exposure or affect study inclusion post hoc. For example, presence of an endoleak unlikely affects classification of anticoagulant therapy if the latter was determined upfront. This, *in contrast,* means that PCS data analysis must await sufficient follow-up time after a study started. Therefore PCS may be very expensive and time consuming and are not suitable for rare diseases or diseases with a long latency.

Fourth, all of the above can only be achieved if selection and size of the target population and choice and timing of the variables to be measured are determined in advance. Therefore, PCS rely on carefully designed case record forms (CRF, either on paper or electronic). *However,* even in carefully designed PCS, external validity may be insufficient, if the study population is not representative of the patients of interest (selection bias).[3] Furthermore, failure to collect CRF data in real time (leading to "retrospective recording") is another reason for concern, particularly, if multicentre or large samples are involved. To reduce this risk, CRF should be clear and unambiguous, easy to complete and in a format that suits all users and simplifies data analysis.

And finally, PCS should be reported according to the STROBE guidelines. Reading these guidelines before starting a study will improve the study design and increase the probability of successful study completion.

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