What are the weaknesses of observational studies?

There are also inherent weaknesses with observational studies when they are used to evaluate treatment effects. Potential problems relate to various biases, the quality of the data, and the often exploratory nature of the analysis.

Potential biases
Retrospective studies that rely on participant recollection of events, behaviors, etc. are susceptible to recall bias, since cases may have a biased recollection of drug exposure than controls.

Group comparability, a key element of the randomized clinical trial, is a concern in observational studies. If the use of one treatment or another in patients with a given condition occurred randomly, then comparing users and non-users would be valid. However, users often receive a particular intervention based on the severity of symptoms or the risk of disease complications. Patients with a milder form of disease may take less potent drugs, or may receive no treatment at all. This so-called “indication bias” must be considered in observational studies.

Conversely, drug use can also be a marker of “healthy” users — patients who are less sick. For decades, we were led to believe that hormone replacement therapy (HRT) reduced the risk of coronary events. This information came from observational studies, which showed a lower coronary risk among users compared to non-users of HRT. Although reports indicated that users were healthier, had fewer risk factors and saw their physicians more often, the observation was not accepted until randomized clinical trials provided no evidence that HRT is cardioprotective. This type of selection bias may also account for the observation that users of lipid-lowering statins run a lower risk of developing Alzheimer’s disease (AD) than non-users. AD is less common in subjects with higher education and/or higher socioeconomic status, and this segment of the population is more likely to be prescribed and remain adherent.
to preventive measures, to have health insurance, and/or be able to pay for expensive treatments. Moreover, cognitively impaired subjects may not be prescribed preventive medications. Only well-designed clinical trials can resolve this debate.

\[\text{What are the specific limitations of observational studies?}\]

Although case reports and case series may provide an early warning of drug toxicity, they also can cause “false alarms.” Unexpected or serious adverse events that occur during a particular treatment are not necessarily related to that treatment. However, an analysis of 47 early case reports did conclude that the majority of suspected adverse events were subsequently confirmed.\(^5\) A prudent approach is to wait and see if similar additional cases are reported. It has been suggested that publication of a suspected treatment-induced adverse event should be delayed until at least three cases have occurred.

The principal limitation of cross-sectional studies is their inability to address temporal and causal relationships. If users of a drug have a medical condition, it may not be possible to distinguish whether they were prescribed the drug because of their condition, or whether their condition was drug-induced.

Case-control studies are also susceptible to the same biases. Lack of comparability between the groups being evaluated remains a key concern.