When Confounding by Indication is Compounded by Recall Bias; Comment on the Article by Onat et al.: Letter to the Editor

Endikasyona Göre Etki Karışımına Hatırlama Yanlılığı Eklenince; Onat ve Arkadaşlarının Çalışması Üzerine

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In a previous issue of the journal, Onat et al. reported an observational study on the risk of incident coronary artery disease from a randomly selected population-based cohort followed for approximately 8 years and concluded that the use of statins in individuals with no prevalent cardiovascular disease at baseline was associated with an increased risk of incident coronary heart disease in comparison with non-use.[1] In addition to highly significant differences in unadjusted comparisons, the increased risk also persisted after multivariable adjustment for conventional cardiovascular risk factors in a Cox regression model (HR: 2.42, 95% CI 1.80; 3.25). Such a sensational conclusion deserves a discussion as to how statin treatment that has long been known to be beneficial for primary prevention of coronary heart disease in multiple randomized controlled trials may spuriously appear harmful in an observational setting.[2]

Treatment allocation is by definition non-random in an observational study. That is, the decision to treat is based on the perceived need for that very treatment. However not all components of the "perceived" need for a treatment are represented as observable variables. Such unobserved variables that determine the need for a treatment, statins in this case, may result in a substantial baseline risk difference between users and non-users of statins, therefore during follow up not only one may fail to reproduce the benefits of statins with the same magnitude as that in the randomized controlled trials but also may observe that "statin users" are at increased risk of coronary heart disease, which is the likely case for the apparently harmful effects of statins in the study by Onat et al. Such confounding due to a baseline excess risk of outcome that leads to being allocated to a treatment is referred to as confounding by indication.[3]

Confounding by indication is a type of bias that arises in observational studies of drug effects due to differences in baseline risk that may be unmeasured and it is difficult, and oftentimes impossible to eradicate even

with sophisticated statistical tools such as propensity score or instrumental variable methods, let alone multivariable adjustments.[4]

Another issue to be mentioned is retrospective ascertainment of statin exposure, which given the facts that questionnaires usually underestimate medication exposure and that cohort members who suffer a study outcome event are more likely to recall related exposures (recall bias) probably compounds the bias due to confounding by indication 3 in this study. Observational study is an invaluable tool providing essential real-life information about the effects of medication exposures however it is also essential that researchers seeking to characterize medication effects by observational studies be aware of the fundamental methodologic principles and beware of the well-known fundamental pitfalls like those that probably ailed this study. It is worrying to see however that in an observational study of such size and impact these fundamentals were not adequately addressed and discussed.

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