Reply to "Statins probably do not cause cataracts"

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To the Editor

Dr Spence alerts the readers of the journal of the possibility that the association between statin use and increased risk of cataract reported in our recently published paper [1] is flawed by the presence of indication bias. It is well known that indication bias is often a threat to the validity in observational studies [2] if the indication for the medication under study is associated with the outcome of interest [3], and we agree that randomized clinical trials are the gold standards for the patients enrolled in the trial.

It should be argued that, although clinical trials are not affected by indication bias and the randomization guarantees the control of all potential confounders, they suffer from inherent limitations, as they are not designed specifically to detect adverse events, so their number, the duration of follow-up, or the criteria for adverse events recording can hinder risk detection [4]. In our opinion, it is important to critically consider the evidence arising from different types of study, taking into account the specific limitations. A typical example is the incidence of muscle side effects with statins, which seldom occur in RCTs but are much more prevalent in the free living population [5, 6].

Since indication bias affects mainly the results obtained by studies comparing users of a certain drug with non-users, in our study we controlled for this bias using a case control study nested into a cohort of new-users of statins. Therefore, all enrolled patients have been prescribed with statin, then all likely suffering from hypercholesterolemia. We observed that subjects with treatment coverage (adherence) of at least 50% of the observation period have about a 20% increased risk compared to subjects with a coverage of <25% (and dyslipidemic), suggesting a dose/exposition effect [1]. In our case, a possible indication bias could be conceivable if the increased risk was due to a greater severity of hypercholesterolemia, assuming that the greater severity is associated with a greater adherence. This assumption, however, lacks confirmation [7], also considering that asymptomatic disease deprives the patient a motivational boost. Moreover, a rule-out analysis [8] was carried out to assess if the adjustment for severity of hypercholesterolemia (unmeasured confounder) could fully explain the observed association between high adherence to statin treatment and cataract. We considered different prevalence of the unmeasured confounder in the population (from 20% to 80% by 20%), an exposure prevalence of 25% and an observed association measure between high adherence to statin treatment and cataract of 1.196. The results showed that cataract risk among patients with high cholesterol levels should be at least 2.5 fold higher than patients with low cholesterol levels to allow severe hypercholesterolemia to be fully responsible for the association observed in our analysis for all scenarios. Since this value seems to be unrealistic, it is unlikely that high adherence to statin treatment is not associated to cataract onset. A literature survey does not unequivocally indicate the role of high levels of cholesterol as a risk factor for cataracts. Furthermore, in patients with very high cholesterol levels, such as in patients with familial hypercholesterolemia, however, there is no evidence for increase prevalence of cataract [9]. On the other hand, in some studies, the presence of cataract was found to be associated with high levels of cholesterol and oxidative stress [10]. Cholesterol representing about 40% of the total lipids of human lens fibers [11], so factors modifying its level and/or repartition may alter optical lens properties. In his review Cenedella [12] describes how inherited defects in enzymes of cholesterol metabolism and use of drugs which inhibit lens cholesterol biosynthesis may be associated with cataracts in animals and men.

Finally, the aim of the article is not to warn against the use of statins [13] but simply alert the scientific community that under circumstances differing from those of RCTs statin treatment could result in an increased risk of developing cataracts. Whether concomitant drug treatments and other circumstances can explain and confirm these findings remains to be addressed.

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