

## Statin use does not protect from fractures: the healthy adherer effect is a plausible explanation in observational studies

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Dear Editor,

The conclusions of the recently published meta-analysis by An et al. [1], including 23 observational studies and 10 randomized controlled trials (RCTs), are as follows: “statin treatment may be associated with a decreased risk of overall and hip fractures, an increased BMD at the total hip, at the lumbar spine, and OC.”

We disagree with these conclusions, for the following reasons.

First, observational studies are in any case prone to residual confounding, even when the reported data allow a careful control for many known or suspected confounders. So they may just suggest a hypothesis, needing appropriate RCTs for confirmation.

Unfortunately, the authors seem to overlook a powerful potential confounder, the “healthy-adherer” effect.

Ten years ago, a meta-analysis [2] of RCTs and cohort studies showed that a good adherence not only to drug therapy but also to placebo is associated with positive health outcomes, when compared to a poor adherence to both, placebo included. This supports the “healthy-adherer” effect, i.e., the

adherence to drug therapy may be a surrogate marker for a general healthier behavior.

Famous RCTs showed better outcomes in groups with a good adherence to placebo, e.g., in WHI [3], comparing hormonal replacement therapy versus placebo in postmenopausal women, high-adherers in the placebo arm showed significant favorable outcomes, including fewer hip fractures (HR 0.50; 95% CI 0.33–0.78) and a decrease in mortality (HR 0.64; 0.51–0.80) [3], after adjusting for potential confounders. Moreover, low-adherers to placebo were more likely to show low adherence to statins and osteoporosis medications [3].

Likewise, in the Fracture Intervention Trial (FIT), comparing alendronate versus placebo, in the placebo arm high-adherers showed substantial benefits compared to low-adherers [4].

Second, a compelling indirect evidence of such confounder comes from a prospective cohort study of statin patients using data from British Columbia [5]. In this study, after multivariable-adjustment, high-adherers were less likely than low-adherers to have not only myocardial infarction but also accidents. This effect was greatest for motor-vehicle accidents (HR 0.75; 0.72–0.79) and workplace accidents, but was also significant for burns, falls, fractures, open wounds, poisoning.... Other unexpected protective associations were dental problems, drugs dependency, food-borne bacterial infections, and gout. Conversely, high-adherers used more screening services.

This study strongly supports the hypothesis that high-adherers to statins show healthier behaviors than comparable less-adherent patients.

Therefore, controlling for known/supposed confounders does not guarantee to consider the unknown or less documented ones and it cannot account for psychological factors, such as attitudes toward the prescribed therapy, or the belief in its effectiveness.

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The views expressed are the first author’s own and do not necessary represent the views of his organization.

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Third, RCTs only, and not observational studies, are designed to prove causality. Figure 2 [1] (“cohort studies OR for statins and fracture risk”) includes also the only two RCTs [6, 7], where the pooled RR is 1.004. Figure 3 [1] (BMD at total hip, lumbar spine, and femoral neck) separates the two RCTs [8, 9], and their pooled Std. mean difference are not significant and around zero. Figure 4 [1] also separates the RCTs: their pool shows a borderline significance favoring statins for OC, and non-significant Std. mean difference for BALP and S-CTX.

Thus, statins do not seem to protect from fractures; the observational studies’ results may have simple alternative explanations.

#### Compliance with ethical standards

**Conflicts of interest** None.

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