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Title

Reply to "Response to 'Hydrochlorothiazide use and risk of nonmelanoma skin cancer: a nationwide case-control study from Denmark' "

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Conflicts of interests

Dr Pottegård has participated in research projects unrelated to the present study and used grants provided by LEO Pharma (manufacturer of bendroflumethiazide) to the institution at which he was employed.

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Letter (word count: 493 Figures: 1)

Dear Editor

We appreciate the comments on our paper entitled: "Hydrochlorothiazide use and risk of nonmelanoma skin cancer: a nationwide case-control study from Denmark" made by Ard van Veelen et al.

In our study¹ we found a strong, dose-dependent, and specific association between the use of hydrochlorothiazide and risk of squamous cell carcinoma. Additionally, we found evidence for a weak association to basal cell carcinoma and in other studies we have seen associations with squamous cell

carcinoma of the lip², and more rare types of skin cancer, i.e. Merkel cell carcinoma and malignant adnexal skin tumours.³ As such, we have shown that use of hydrochlorothiazide is associated to all UV-dependent skin cancers.

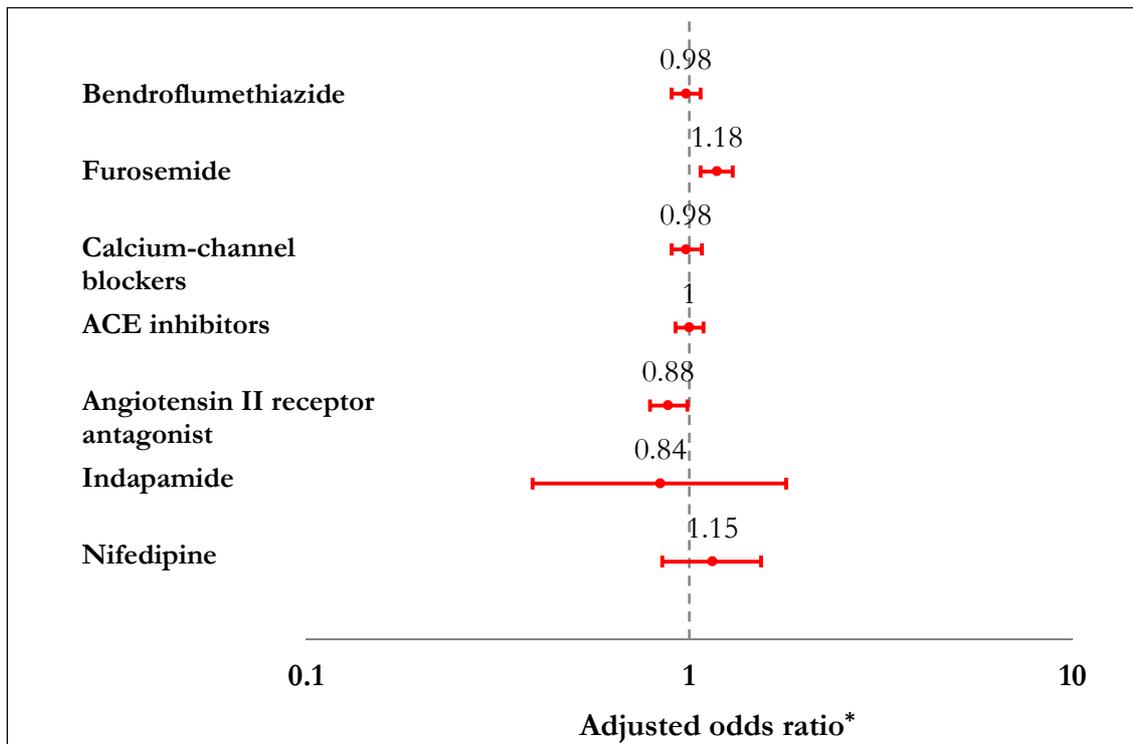
Ard van Veelen et al. highlight the recently published meta-analyses by Gandini et al⁴ and the apparent discrepancy between their conclusion and our findings. This meta-analysis has several important limitations. First, the meta-analysis, as the individual studies it is based on, only consider thiazide and thiazide-like agents as a combined exposure. This is of concern, as we have shown that the association is specific to hydrochlorothiazide (Figure 1).¹⁻³ Secondly, they do not include studies with extensive and detailed dose-response analyses of hydrochlorothiazide. Finally no analyses of cumulative hydrochlorothiazide use were performed, as we did in our study.¹ As such, we do not believe that results from the meta-analyses by Gandini et al⁴ conflict with our conclusions regarding use of hydrochlorothiazide and risk of skin cancer.

Ard van Veelen et al. further express concern over the lack of the control for smoking as a potential confounder in our study. However, we do not agree that the lack of adjustment for smoking would be expected to have any influence on our estimates. First, smoking is a fairly weak risk factor for squamous cell carcinoma. In one meta-analysis, the association between squamous cell carcinoma and smoking was estimated at an odds ratio of 1.52 (95%CI, 1.15-2.01).⁵ As a rule of thumb, an unmeasured confounder can never explain an apparent association that is stronger than its own impact on the outcome. Even under the (highly unlikely) assumption that all users of hydrochlorothiazide are heavy smokers while there are no smokers in the background population, smoking would still only explain a minor part of the observed association. Further, if any confounder, including smoking, constituted a major problem in our comparison between hydrochlorothiazide users and non-users, we would generally expect the same issue to affect our analyses for use of drugs with similar indications as hydrochlorothiazide. As these analyses returned reassuring null-findings (Figure 1), we consider it unlikely that our findings are either wholly or in part explained by unmeasured confounders related to hypertension.

Finally, beyond all the mentioned arguments above, we consider our findings robust, especially because all of the found associations between hydrochlorothiazide use and skin cancer risk have a reasonable biological explanation. The biological mechanism of hydrochlorothiazide use leading to increased risk of skin cancer, can primarily be explained by hydrochlorothiazide's photosensitizing properties.

Figure 1

Association between other drugs and risk of squamous cell carcinoma.



*Error bars indicate 95% confidence intervals.

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