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LETTER

# Fracture risk reduction with use of dipeptidyl peptidase-4 inhibitors: response to Driessen et al.

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Dear Editor,

We would like to thank Dr. Driessen and colleagues [1] for their interest in our article [2] and welcome the opportunity to respond. Dr. Driessen and colleagues raised a potential weakness in the statistical methodology used in our study. They are concerned that the reported association between DPP-4 use and the reduction of the fracture risk may be affected by an immortal time bias. We agree that an immortal time bias may lead to results in favor of the studied drug.

The index date was defined based on the first DPP4-I (for the DPP4-I users) or the first metformin (for the metformin-only users) prescription. As correctly assumed by Dr. Driessen, it is possible that some DPP-4 patients survived event free until the time of the first DPP4-I prescription, which caused the immortal time bias.

However, we used multivariate time-dependent Cox regression models, with a time-dependent exposure definition, by means of which each patient day was classified into one of two categories (DPP-4i exposition: yes/no). DPP-4i exposure time (days) was calculated based on prescribed daily dosages and package sizes. Time-dependent hazard ratios (HRs) and 95% CIs were estimated using the Cox regression models. We hope that this resolves the immortal time bias problem.

As patients treated with DPP-4 may have longer diabetes duration, we also performed 1:1 matching not only by diabetes duration but also by age, sex, index year, BMI, and physician. However, our results should be treated with caution, as some important information is lacking. For example, data related to socioeconomic status and lifestyle-related risk factors (e.g., smoking, alcohol consumption, and physical activity) were not available. These factors can be different in DPP-4 users and non-users and have a big impact on fracture risk.

**Compliance with ethical standards**

**Conflict of interest** No disclosures.

## References

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2. Dombrowski S, Kostev K, Jacob L (2017) Use of dipeptidyl peptidase-4 inhibitors and risk of bone fracture in patients with type 2 diabetes in Germany: a retrospective analysis of real-world data. Osteoporos Int. doi:10.1007/s00198-017-4051-y

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