

## Re: Errors in the NOF meta-analysis of calcium and vitamin D supplements

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Dear Editor,

The manuscript entitled “Calcium plus vitamin D supplementation and risk of fractures: an updated meta-analysis from the National Osteoporosis Foundation [1]” sought to update a former AHRQ evidence report [2]. The study was commissioned by the NOF to inform the organization, since a significant controversy exists regarding the effectiveness of supplemental calcium and vitamin D to prevent fractures. We chose to use the per protocol analyses data across studies to be consistent with the two former AHRQ evidence reports [2, 3] and to assess the actual effect of supplementation among individuals who were adherent throughout the duration of various

studies included in the meta-analysis. It is challenging for a public-health organization to formulate accurate guidance solely from intention to treat analyses, where half of the population in some cases either dropped out or were not adherent by the end of the study. In both former AHRQ evidence reports [2, 3], adherence to the interventions were considered as part of the risk of bias assessment and analysis as adherence was important to estimate the actual doses received by the study participants for the purpose of deriving dietary reference intake (DRI) values; we chose for the same reason to continue this type of analysis. Though others may disagree with the decision to use per protocol analysis, alteration of the number of fractures among the studies present in Table 1 of Weaver et al. (2016) [1] and/or substitution with intention to treat analyses data does not influence the pooled relative risk or outcomes of the NOF meta-analysis. It is standard protocol for bodies such as the AHRQ to exclude studies in a non-English language; it is unclear from the English abstract if the study [4] mentioned by Bolland and colleagues in their letter was designed to assess fracture outcomes. It also is unclear if the participants in the latter Chapuy et al. (1994) one-page narrative manuscript [5] were still randomized to the original study protocol (a large number of individuals are no longer present in the study). Since both studies by Chapuy and others show similar beneficial effects of supplemental calcium and vitamin D, it is unlikely that substitution of the Chapuy et al. (1992) [6] data with the Chapuy et al. (1994) [5] data will affect the pooled relative risk and/or outcomes of the NOF meta-analysis.

The NOF utilized (and continues to apply) rigorous basic elements of process when accepting commercial support. This process is modeled based on recommendations from the 2009 US Institute of Medicine (IOM) report on *Conflict of Interest in Medical Research, Education, and Practice* [7], as well as the processes of the US Preventive Services Task Force [8] and

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ACCME Standards for Commercial Support [9]. Furthermore, it is the internal process of the NOF that all contracted universities or consulting groups and expert volunteers serving as authors on any particular manuscript be blinded of the funding source until the manuscript is submitted for publication. The NOF is willing to share all documented communications with funding organizations for any of its activities. Data from the NOF meta-analysis [1] are publically available.

#### Compliance with ethical standards

**Conflicts of interest** Authors have declared all conflicts of interest in the original manuscript (DOI: [10.1007/s00198-015-3386-5](https://doi.org/10.1007/s00198-015-3386-5)).

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