BJC

British Journal of Cancer (2015) 112, 1979 | doi:10.1038/bjc.2015.117

Comment on: 'Vitamin D supplements and cancer incidence and mortality: a meta-analysis'

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Sir,

We read with deep interest the article by Keum and Giovannucci (2014) entitled 'Vitamin D supplements and cancer incidence and mortality: a meta-analysis' published in August 2014 in *British Journal of Cancer*, and believe this is a well-conducted meta-analysis of randomised controlled trials (RCTs) which attempted to elucidate the effects of vitamin D supplementation on total cancer incidence and mortality. The findings of study will have a profound influence on future cancer treatment. Nevertheless, we also found some worthwhile issues worth being discussed.

First, two electronic databases (PubMed and Embase) were systematically searched to identify potential RCTs, and the small number of included articles is likely to have negative effect on credibility of the meta-analysis. To make the study more credible, we hope more electronic databases should be thoroughly retrieved by the authors.

Second, in accordance with recommendations in the Cochrane Handbook (Higgins and Green, 2011), the methodological quality of trials should be independently evaluated by two investigators. However, the authors did not describe this in their meta-analysis. In our opinion, the methodological quality of all eligible trials should be evaluated. The items of the methodological quality assessment should include randomisation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, withdrawals and dropouts. Meanwhile, the specific grades or scores for each included article should be provided according to the Cochrane Collaboration guidelines (Higgins *et al*, 2011).

Third, the authors reported that the *Q*-test and I^2 statistic were used to assess heterogeneity across studies. However, the *P* and I^2 values considered significant were not stated in 'statistical analyses' part. From our own perspective, a *P*-value <0.10 is considered significant in *Q*-test (Cochran, 1954) and a I^2 value of at least 50% is taken as indicator of substantial heterogeneity of outcomes in I^2 statistic (Higgins and Thompson, 2002). We wish to know the researchers' viewpoint on this issue.

Fourth, the heterogeneity (I^2) across studies in Figures 2A and B were both equal to 0.0% (Keum and Giovannucci, 2014). This showed no variations between studies, which could not potentially bias the results of this study. Therefore, it was inappropriate that a random effects model was used to calculate the summary relative risk with 95% confidence interval. As far as we know, the Mantel–Haenszel fixed effects model should be used to calculate the data of total cancer incidence and mortality by authors.

Fifth, we suggest that the type of mortality endpoint (the number of days, hospitalisation or intensive care unit) and gender ratio should be listed in Table 1 of main characteristics of the RCTs included (Keum and Giovannucci, 2014), which may provide specific and important guidance for clinical treatment.

Last but not least, the investigators conducted the publication bias assessment using Egger's test and Begg's test, we advise that the visual funnel plots should be provided. The search was limited to English articles, in our opinion, the language bias should be clarified as a limitation of this meta-analysis in 'Discussion' part. The 'Avenell, 2011' in Table 1 and Figure 2 should be replaced by 'Avenell, 2012', which is consistent with the 'Discussion' and 'References' part (Keum and Giovannucci, 2014), please check this point.

All in all, we respect the great contributions of the researchers, they reached an important conclusion that over 2–7 years of duration, the benefit of vitamin D supplementation may be limited to cancer mortality. We agree on the above conclusion of the authors, which has an important value to instruct clinical therapy for cancer. The conclusion will probably not be changed because of our comments. However, we believe that our remarks will further improve the above conclusion and contribute to more accurate elaboration of the results presented by Keum and Giovannucci (2014).

REFERENCES

Cochran WG (1954) The combination of estimates from different experiments. *Biometrics* **10**: 101–129.

Higgins JPT, Green S (eds) (2011) *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0* [updated March 2011]. The Cochrane Collaboration. Available from: www.cochrane-handbook.org.

Higgins J, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savović J, Schulz KF, Weeks L, Sterne JA (2011) The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* **343**: d5928.

Higgins JP, Thompson SG (2002) Quantifying heterogeneity in a meta-analysis. *Stat Med* **21**: 1539–1558.

Keum N, Giovannucci E (2014) Vitamin D supplements and cancer incidence and mortality: a meta-analysis. *Br J Cancer* **111**: 976–980.

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Published online 31 March 2015

BJC

British Journal of Cancer (2015) 112, 1979–1980 | doi:10.1038/bjc.2015.118

Response to Comment on: 'Vitamin D supplements and cancer incidence and mortality: a meta-analysis'

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Sir,

A letter by Jiang *et al* (2015) raised important issues for conducting meta-analyses. Although Jiang *et al* acknowledge that these issues are unlikely to alter our findings, these points are worth discussing as they do illustrate gaps between meta-analysis in principle and meta-analysis in practice.

It is important to clarify that the choice of fixed *vs* random effects model should not be guided by I^2 value, but rather by *a priori* scientific belief about the nature of the exposure–disease relationship under study. Because a fixed-effect model requires a strong assumption that variation in effect estimates across studies is solely due to the play of chance, the random-effects model based on the DerSimonian–Laird estimator is generally considered as the standard weighting scheme in the current practice of meta-analysis. Conceivably, the effect of vitamin D supplements on cancer endpoints may vary depending on various factors including study population, dose and duration of intervention, baseline vitamin D status, etc., which varied across the studies included, so the choice of the random effects model is justified. In fact, Jian *et al* stated the importance of accounting for methodological qualities of RCTs and of providing information on gender ratio of population (which was provided in Table 1 as % males (Keum and Giovannucci, 2014)), all of which are potential contributors to heterogeneity across the trials. Furthermore, as I^2 value was 0%, both the DerSimonian–Laird random effects model and the inverse-variance fixed effect model lead to the same summary estimates. Even if a fixed-effect model should be used, our data are not rare enough for Mantel–Haenszel fixed effect to be preferred over the inverse-variance fixed-effect model among other options.

When publishing a meta-analysis under limits on word count and on the number of tables and figures, priority should be given to highlight key findings rather than to state the obvious. Most of the points Jiang *et al* argue we 'should' have stated relate to this priority issue. First, restriction to English only articles and small number of trials included are self-evident limitations of

our meta-analysis. Limited word count could be better used to discuss more fundamental limitations (e.g., our findings based on trials on short-term duration of vitamin D supplementation are silent about a potential long-term benefit vitamin D supplementation). Second, as meta-analysis is only as valid as studies included, it is undeniably important to appraise study quality. Yet, given only four trials available, which precludes a meaningful subgroup analysis by score, calculating an arbitrary score based on 'randomisation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, withdrawals and dropouts' does little to enhance the credibility of the findings. Furthermore, while the criteria suggested by Jian *et al* are important methodological aspects to consider, more fundamental factors that affect the validity of findings concern underlying vitamin D status of the population, increment of 25(OH)D or attained vitamin D status due to intervention, and duration of treatment. These points cannot be meaningfully graded because, for instance, we do not know the appropriate level of 25(OH)D. Thus, we opted for qualitative appraisal of study quality through discussion section.

Third, heterogeneity is an important issue in meta-analyses. Thus, statements such as 'I^2-values of 25%, 50% and 75% are used to classify low, moderate and high heterogeneity, respectively' or 'Test of heterogeneity is low-powered, and thus, a *P*-value of less than 0.1 rather than 0.05 was used to determine statistical significance of heterogeneity' are helpful information for potential readers. Yet, given our results that I^2-value is 0 and *P*-value for heterogeneity is far from 0.1, those cut-off points are rather irrelevant here. Likewise, publication bias deserves a critical evaluation in meta-analysis. While funnel plot is a possibility, it is limited to subjective evaluation of publication bias. Results from Eggers' test and Begg's test we provided are statistical analogues of funnel plot and allow for an objective evaluation of publication bias albeit low powered when the number of included studies is small.

Meta-analysis is a process of putting together scattered pieces of puzzles available to infer about the complete picture. While suggested standard guidelines for conducting meta-analysis should not be ignored, it is at researchers' discretion to identify and highlight important aspects of the findings from the incomplete status of knowledge. Thus, rather than mechanically following so-called the standard protocols, researchers may be able to conduct a more meaningful meta-analysis by factoring in the underlying biology behind the research question at hand.

REFERENCES

Jiang De-Qi, Li Ming-Xing, Chen Qing-Zhuang, Wang Yong (2015) Comment on 'Vitamin D supplements and cancer incidence and mortality: a meta-analysis. *Br J Cancer* **112**: 1979.

Keum N, Giovannucci E (2014) Vitamin D supplements and cancer incidence and mortality: a meta-analysis. *Br J Cancer* **111**: 976–980.

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Published online 31 March 2015