To the Editor: the effect of genetic factors on the response to vitamin D supplementation may be mediated by vitamin D binding protein concentrations

Schoenmakers I[1] and Jones KS[2]

[1]Inez Schoenmakers

Department of Medicine, Faculty of Medicine and Health Sciences, University of East Anglia, Norwich NR4 7TJ, United Kingdom.

e-mail I.Schoenmakers@uea.ac.uk

[2]Kerry S. Jones

MRC Elsie Widdowson Laboratory, Fulbourn Road, Cambridge, CB1 7UR, United Kingdom. Email. kerry.jones@mrc-ewl.cam.ac.uk

DISCLOSURE STATEMENT: The authors have nothing to disclose

To the Editor: the effect of genetic factors on the response to vitamin D supplementation may be mediated by vitamin D binding protein concentrations

We welcome the paper by Yao et al. (1), presenting the vitamin D binding (DBP) genotype distribution and concentrations and their influence on the response to vitamin D supplementation in a large cohort of Chinese adults. There are however several points the reader should consider in the interpretation of these data.

Yao et al. report that supplementation with 2,000IU vitamin D per day failed to correct vitamin D deficiency in 25% of Chinese participants. They used the Endocrine Society (ES) thresholds for vitamin D deficiency for clinical populations (a plasma 25 hydroxy vitamin D (25(OH)D) concentration <50nmol/L) (2). The ES however recommends that for the correction of vitamin D deficiency an 8-week loading schedule of 50,000IU/week followed by a maintenance dose of 1,500-2,000IU/d for adults should be used. However for a study amongst healthy community dwelling adults, without conditions that may increase their vitamin D requirements, the use of population guidelines (e.g. that of the Institute of Medicine (3)) would have been more appropriate.

The authors appear to suggest that there are major racial differences in the increment of 25(OH)D in the response to vitamin D supplementation. However, the selected papers do not represent the balance of available evidence, which shows a lack of influence of race on the dose-response to vitamin D supplementation, albeit this was mostly based on black and white populations (summarised by EFSA (4)). The authors suggest that the low increment in 25(OH)D in Chinese participants may be caused by the predominant vitamin D binding protein (DBP) genotypes in this population and the associated differences in the binding affinity for 25(OH)D. In support of this statement the authors quote the paper by Arnaud,

1993 (5). However, where Arnaud used vitamin D as a tracer and reported DBP genotype-dependent differences in the affinity for 25(OH)D by extrapolation, other studies using $^{[3H]}$25(OH)D showed small, if any differences (6-8). The DBP genotype-dependent differences in baseline 25(OH)D and the increment in its concentration after supplementation reported by Yao, may be predominantly determined by the genotype-dependent differences in DBP concentrations. Through this mechanism, DBP genotype may influence the fraction of 25(OH)D available for cellular uptake and hydroxylation (9). Finally, the authors suggest that the response to vitamin D supplementation was greater for total 25(OH)D than for 25(OH)D_{Bio} by comparing their respective changes, while ignoring differences in their absolute values. A calculation of their proportional change shows that these are similar (+105 and 107% for total and 25(OH)D_{Bio}, respectively), a finding that is to be expected since 25(OH)D_{Bio} is derived from the concentrations of total 25(OH)D and its binding proteins, DBP and albumin. The latter are known not to respond to vitamin D supplementation (10).

Inez Schoenmakers, Ph.D.

Department of Medicine, Faculty of Medicine and Health Sciences, University of East Anglia, Norwich NR4 7TJ, United Kingdom. e-mail I.Schoenmakers@uea.ac.uk

Kerry S. Jones, PhD

MRC Elsie Widdowson Laboratory, Fulbourn Road, Cambridge, CB1 7UR, United Kingdom. Email. kerry.jones@mrc-ewl.cam.ac.uk

The authors report no potential conflict of interest relevant to this letter.

1. **Yao P, Sun L, Lu L, Ding H, Chen X, Tang L, Xu X, Liu G, Hu Y, Ma Y, Wang F, Jin Q, Zheng H, Yin H, Zeng R, Chen Y, Hu FB, Li H, Lin X.** Effects of genetic and non-genetic factors on total and bioavailable 25(OH)D responses to vitamin D supplementation. *J Clin Endocrinol Metab*. 2017;102:100-110.
2. **Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, Murad MH, Weaver CM.** Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2011;96:1911-1930.
3. **IOM** 2011 Dietary reference intakes for calcium and vitamin D. Washington, DC: The National Academies Press
4. **EFSA Panel on Dietetic Products, Nutrition and Allergies.** Dietary reference values for vitamin D. *EFSA Journal*. 2016;14:e04547-n/a.
5. **Arnaud J, Constans J.** Affinity differences for vitamin D metabolites associated with the genetic isoforms of the human serum carrier protein (DBP). *Hum Genet*. 1993;92:183-188.
6. **Bouillon R, van Baelen H, de Moor P.** Comparative study of the affinity of the serum vitamin D-binding protein. *J Steroid Biochem*. 1980;13:1029-1034.
7. **Boutin B, Galbraith RM, Arnaud P.** Comparative affinity of the major genetic variants of human group-specific component (vitamin D-binding protein) for 25-(OH) vitamin D. *J Steroid Biochem*. 1989;32:59-63.
8. **Kawakami M, Imawari M, Goodman DS.** Quantitative studies of the interaction of cholecalciferol ((vitamin D_3) and its metabolites with different genetic variants of the serum binding protein for these sterols. *Biochem J*. 1979;179:413-423.
9. **Jones KS, Assar S, Harnpanich D, Bouillon R, Lambrechts D, Prentice A, Schoenmakers I.** 25(OH)D_2 half-life is shorter than 25(OH)D_3 half-life and is influenced by DBP concentration and genotype. *J Clin Endocrinol Metab*. 2014;99:3373-3381.

10. **Alzaman NS, Dawson-Hughes B, Nelson J, D'Alessio D, Pittas AG.** Vitamin D status of black and white Americans and changes in vitamin D metabolites after varied doses of vitamin D supplementation. *Am J Clin Nutr*. 2016;104:205-214.