**Response to Letter: Genetics and Vitamin D supplementation in pregnancy**

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**Disclosure Summary**

RJM has nothing to disclose. CC reports personal fees, consultancy, lecture fees and honoraria from ABBH, Amgen, Eli Lilly, GSK, Medtronic, Merck, Novartis, Pfizer, Roche, Servier and Takeda, outside the submitted work. NCH reports personal fees, consultancy, lecture fees and honoraria from Alliance for Better Bone Health, AMGEN, MSD, Eli Lilly, Servier, Shire, Consilient Healthcare and Internis Pharma, outside the submitted work.

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We thank Dr Paschou and colleagues for their interest in our recent publication ([1](#_ENREF_1)) and their thoughtfully considered clinical implications of our findings.

We agree that ethnic clustering of genotypes in *DHCR7,* which might have previously conferred an evolutionary advantage to protect against vitamin D toxicity, might now contribute to the paradoxically low 25-hydroxyvitamin D [25(OH)D] levels at latitudes close to the equator.

Antenatal vitamin D supplementation is a proven approach to increasing maternal 25(OH)D status in pregnancy ([2](#_ENREF_2)) and reduces the incidence of symptomatic neonatal hypocalcaemia ([3](#_ENREF_3)). We agree with Paschou et al that, based on our findings, genetic variation is likely to contribute to the poor response to supplementation in some women. However we have also previously demonstrated that lower 25(OH)D status before supplementation, poorer compliance with supplementation and greater weight gain during pregnancy are associated with a lower achieved 25(OH)D after supplementation ([4](#_ENREF_4)). As such, in the absence of genetic screening incorporated into routine clinical practice, these clinical markers should be used to guide counselling regarding antenatal vitamin D supplementation. We have also previously identified a number of characteristics of women who are less likely to take prenatal vitamin D supplementation. These include: being of younger age, less well educated, a smoker, in second or subsequent pregnancy, and having a higher BMI ([5](#_ENREF_5)). Women with these characteristics might therefore benefit from greater support to optimise antenatal health.

Any analysis of the economic and healthcare benefit of undertaking routine 25(OH)D screening in pregnancy will be country dependent; such an approach is not currently employed in the United Kingdom, but supplementation with 400 IU/day vitamin D throughout pregnancy is advised for all women ([6](#_ENREF_6)). The 25(OH)D level which is considered to represent vitamin D repletion remains hotly debated, but, perhaps more importantly, confirmation of a seasonally dependent benefit of antenatal vitamin D supplementation for offspring bone mass demonstrated in the MAVIDOS trial ([2](#_ENREF_2)), and elucidation of effects on other outcomes, is required through further rigorously conducted randomised controlled trials in pregnancy ([7](#_ENREF_7)). Such as approach will be essential to demonstrate clear clinical benefits of supplementation, rather than selecting an optimal 25(OH)D level based on observational studies, which are subject to confounding and reverse causality ([8](#_ENREF_8)).

**References**

**1.** Moon RJ, Harvey NC, Cooper C, D'Angelo S, Curtis EM, Crozier SR, Barton SJ, Robinson SM, Godfrey KM, Graham NJ, Holloway JW, Bishop NJ, Kennedy S, Papageorghiou AT, Schoenmakers I, Fraser R, Gandhi SV, Prentice A, Inskip HM, Javaid MK. Response to antenatal cholecalciferol supplementation is associated with common vitamin D related genetic variants. The Journal of clinical endocrinology and metabolism2017;

**2.** Cooper C, Harvey NC, Bishop NJ, Kennedy S, Papageorghiou AT, Schoenmakers I, Fraser R, Gandhi SV, Carr A, D'Angelo S, Crozier SR, Moon RJ, Arden NK, Dennison EM, Godfrey KM, Inskip HM, Prentice A, Mughal MZ, Eastell R, Reid DM, Javaid MK. Maternal gestational vitamin D supplementation and offspring bone health (MAVIDOS): a multicentre, double-blind, randomised placebo-controlled trial. The lancet Diabetes & endocrinology2016; 4:393-402

**3.** Harvey N, Holroyd C, Ntani G, Javaid M, Cooper P, Moon R, Cole Z, Tinati T, Godfrey K, Dennison E, Bishop N, Baird J, Cooper C. Vitamin D supplementation in pregnancy: a systematic review. Health Technol Assess2014; 18

**4.** Moon RJ, Harvey NC, Cooper C, D'Angelo S, Crozier SR, Inskip HM, Schoenmakers I, Prentice A, Arden NK, Bishop NJ, Carr A, Dennison EM, Eastell R, Fraser R, Gandhi SV, Godfrey KM, Kennedy S, Mughal MZ, Papageorghiou AT, Reid DM, Robinson SM, Javaid MK. Determinants of the Maternal 25-Hydroxyvitamin D Response to Vitamin D Supplementation During Pregnancy. The Journal of clinical endocrinology and metabolism2016; 101:5012-5020

**5.** Moon RJ, Crozier SR, Dennison EM, Davies JH, Robinson SM, Inskip HM, Godfrey KM, Cooper C, Harvey NC. Tracking of 25-hydroxyvitamin D status during pregnancy: the importance of vitamin D supplementation. Am J Clin Nutr2015; 102:1081-1087

**6.** National Institute for Health and Clinical Excellence. Antenatal care (NICE Clinical Guideline 62). [www.guidance.nice.org.uk/cg622008](http://www.guidance.nice.org.uk/cg622008).

**7.** Baird J, Barker M, Harvey NC, Lawrence W, Vogel C, Jarman M, Begum R, Tinati T, Mahon P, Strommer S, Rose T, Inskip H, Cooper C. Southampton PRegnancy Intervention for the Next Generation (SPRING): protocol for a randomised controlled trial. Trials2016; 17:493

**8.** Harvey NC, Cooper C. Vitamin D: some perspective please. BMJ (Clinical research ed)2012; 345:e4695