**MAVIDOS Trial analyses: A response to Kovacs**

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In his letter regarding the MAVIDOS1 randomised-trial of antenatal vitamin D supplementation, C. Kovacs asks several questions about our analyses. The first, whether the secondary season\*treatment interaction test was truly pre-hoc seems entirely unnecessary, given that the analysis plan was published in 20122 (and included in the TLDE submission), several years before the trial was unblinded. It is not unusual for the detailed analysis plan not to be documented in EUDRaCT or International Trials Registry, given the very preliminary stage at which these registrations are made; furthermore, as clearly stated in the MAVIDOS TLDE paper1, no interim analyses were performed other than for the TSC/DMC approved safety outcomes of serum calcium concentration at the end of 2 year’s recruitment. We thus utterly refute Kovacs’ implicit assertion that the season\*treatment interaction test was predicated on an undeclared interim analysis.

Kovacs then, as per his recent TLDE editorial3, selectively quotes the season\*treatment interaction on neonatal bone mineral density (BMD). This is inappropriate, since BMD was not the *a priori* primary bone measure, and because bone mineral content (BMC, our primary DXA outcome) is the internationally approved measure in neonates4. The treatment\*season interaction on BMC was significant (p=0.04): amongst winter births, BMC was 5.5g (0.5SD) greater in treatment than placebo group babies (p=0.004). The opposing 2.0g (0.2SD) difference in the autumn subgroup was considerably smaller, and statistically non-significant (p=0.21)1.

Kovacs further comments on the widespread reporting of this secondary outcome. It is notable that the primary outcome, but no secondary outcome, is documented in the TLDE abstract, and both were clearly stated in the press release. Whilst we completely support the accurate reporting of scientific information, the notion that a positive primary outcome represents truth, and that an intriguing, biologically plausible, secondary outcome is automatically false seems misguided, as would be the idea that the MAVIDOS findings might somehow definitively inform public health policy. We are of course fully cognisant of the statistical and biological considerations described by Kovacs; indeed our findings were presented with explicit and appropriate caution. Rather than simply debate the issue *ad nauseam*, we have successfully obtained funding to follow the MAVIDOS children at 6-8 years, in order to demonstrate, or not, persistence of the effect, and are currently undertaking a second trial of vitamin D in pregnancy (SPRING) to provide an opportunity for replication5. We look forward to the ensuing correspondence.

**Author contributions**

NCH, RM, HMI, KMG and CC all contributed to the preparation of the initial draft, and to further development and approval of the final manuscript.

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**Disclosures**

C. Cooper reports personal fees from ABBH, Amgen, Eli Lilly, GSK, Medtronic, Merck, Novartis, Pfizer, Roche, Servier and Takeda, outside the submitted work. N. Harvey reports personal fees, consultancy, lecture fees and honoraria from Alliance for Better Bone Health, AMGEN, MSD, Eli Lilly, Servier, Shire, UCB, Radius, Consilient Healthcare and Internis Pharma, outside the submitted work. R. Moon has nothing to disclose. K. Godfrey reports reimbursement for speaking at Nestle Nutrition Institute conferences, grants from Abbott Nutrition & Nestec, outside the submitted work; in addition, K. Godfrey has a patent Phenotype Prediction pending, a patent Predictive Use of CpG Methylation pending, and a patent Maternal Nutrition Composition pending, not directly related to this work. H. Inskip reports that, whilst not directly receiving funding from other bodies, members of her team have received funding from the following companies from other work: Danone, Nestec, Abbott Nutrition.

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