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Does vitamin D supplementation improve bone density in vitamin D-deficient children? Protocol for an individual patient data meta-analysis

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ABSTRACT

Introduction Our previous study-level (aggregate data) meta-analysis suggested that vitamin D supplements may be beneficial for bone density specifically in children with vitamin D deficiency. However, the misclassification of vitamin D status inherent in study-level data means that the results are not definitive and cannot provide an accurate assessment of the size of any effect. Therefore, we propose to undertake an individual patient data (IPD) meta-analysis to determine whether the effect of vitamin D supplementation on bone density in children differs according to baseline vitamin D status, and to specifically estimate the effect of vitamin D in children who are vitamin D deficient.

Methods and analysis This study has been designed to adhere to the Preferred Reporting Items for Systematic Review and Meta-Analyses of IPD statement. We will include randomised placebo-controlled trials of vitamin D supplementation reporting bone density outcomes at least 6 months after the study commenced in children and adolescents (aged <20 years) without coexistent medical conditions or treatments causing osteoporosis. We will update the search of the original review to cover the period 2009–2017, using the same methods as the original review. Fully anonymised data on all randomised patients will be requested. Outcomes will be femoral neck, total hip, lumbar spine and proximal and distal forearm bone mineral density, and total body bone mineral content. A two-stage IPD meta-analysis will be used to examine the effect of baseline serum 25-hydroxyvitamin D (25(OH)D) on treatment effect for each bone density outcome. Restricted maximum likelihood will be used to estimate the random-effects meta-analysis models, with 95% CI for summary effects. Heterogeneity will be assessed by I^2 and potential publication bias (small-study effects) and availability bias by funnel plots, Egger's test and Peter's test.

Ethics and dissemination Ethics approval will not be required as the data are to be used for the primary purpose for which they were collected and all original individual studies had ethics approval. Results of the IPD meta-analysis will be submitted for publication in a peer-reviewed journal.

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Strengths and limitations of this study

► The major strength of this study is that using an individual patient data (IPD) meta-analysis of randomised controlled trials (RCTs) rather than a study-level approach allows more accurate risk of bias assessments, greater consistency across studies in inclusion and exclusion criteria, and—most crucially for this study—accurate identification of subgroups of interest, and examination of effect modifiers at the individual level (rather than the study level, which is prone to ecological bias and low power).

► Pooling across existing studies dramatically improves the power to detect genuine subgroup effects and treatment effect modifiers, which would otherwise require a very large single study.

► Importantly, IPD meta-analysis is more feasible and less costly than new large-scale RCTs and avoids the ethical problem of research waste.

► One limitation is the need to address the potential influences of variability in vitamin D assays on clinical assessment of vitamin D status which will be done by a sensitivity analysis.

► There is also the potential for bias due to lack of availability of IPD, though as we have agreement in place to access data in most major trials, this risk is minimal, and if necessary this can be managed by incorporation of aggregate data into analyses.

INTRODUCTION

Optimising bone mass throughout lifetime is critically important for preventing fractures at all ages. Of note, fractures occur at a similar rate between children and older adults.[1] Moreover, as in adults,[2] low bone mineral density (BMD) in children is also an important risk factor for childhood fracture.[3–6] Therefore, maximising bone mineral accretion in childhood has potential benefits in the prevention of childhood fractures, though prospective studies are needed to further examine this topic.

Improved bone acquisition in childhood is also likely to have benefits in the prevention of osteoporosis and fracture in later life. This

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is because low BMD is a major risk factor of fractures in older people and BMD in later life is a function of peak bone mass (PBM) and the rate of bone loss after PBM is achieved.[7 8] The detrimental influence of having suboptimal bone acquisition in childhood seems to be comparably important as age-related bone loss in increasing the risk of osteoporosis and related fractures.[9] Although the specific age at which PBM is achieved is uncertain with estimates ranging from late adolescence to the late 30's and varying by site measured,[10–13] the greatest bone acquisition occurs during puberty[14] and up to 90% of PBM is achieved in the youth years.[15 16] Therefore, it is critically important to intervene in childhood and adolescence to maximise PBM and so potentially lessen the detrimental impact of bone loss later on.

The long-term benefits of improving PBM in childhood are likely to be very substantial. Using simulated data, Hernandez *et al* examined the relative importance of improving PBM and slowing age-related bone loss in the development of osteoporosis.[17] It was predicted that the onset of osteoporosis would be delayed by 13 years for a 10% increase in PBM, but only 2 years for a 10% decrease in the rate of age-related bone loss before menopause. A 10% increase in PBM is estimated to be equivalent to 1 SD higher BMD at the lumbar spine (LS) from the age of 60. As 1 SD decrease in LS, BMD has been associated with a 60% increase in the risk of hip fracture,[18] a 10% increase of PBM could translate to approximately a 40% reduction in the relative risk of hip fracture.

Vitamin D supplementation of children who are vitamin D deficient (serum hydroxyvitamin D (25(OH)D) <50 nmol/L) appears to be one of the most promising options to explore for improving PBM. Childhood vitamin D deficiency is considered a significant public health issue around the world.[19] For example, in a nationally representative sample of US children, the prevalence of deficiency was 18% and around 69% children had a level of 25(OH)D <75 nmol/L.[20] Besides rickets, vitamin D deficiency has other potential adverse effects on bone health in children by reducing bone mineralisation. Observational data support the premise that vitamin D deficiency impacts on bone acquisition in older children and adolescents.[19 21 22] For example, in a cohort of 178 Finnish boys and girls aged 14–16 years, serum 25(OH)D levels at baseline were significantly correlated with the change in LS BMD (r=0.35) and FN BMD (r=0.32) over 3 years. In girls who experienced menarche less than 2 years after the study began, there was 4% greater accumulation in LS BMD in girls who had 25(OH)D ≥37.5 nmol/L than those who had 25(OH)D <20 nmol/L (16.7% vs 12.7%).[21]

Our meta-analysis of six randomised controlled trials (RCTs) of vitamin D supplementation in children for improving BMD further supports this.[23 24] When the baseline serum 25(OH)D levels from those RCTs were not considered in the pooled analysis, the effects of vitamin D supplementation on total body (TB) bone mineral content (BMC) or hip or forearm BMD were not statistically significant and effect sizes were small (standardised mean difference (SMD) ≤0.10), with a slightly larger, but still not statistically significant effect at the LS (SMD +0.15, P=0.07). However, when pooled analysis was restricted to those studies that had a mean baseline serum 25(OH)D level of less than 35 nmol/L, we found a larger and statistically significant effect of vitamin D supplementation on TB BMC (SMD 0.21, 95% CI 0.01 to 0.41) and LS BMD (SMD 0.31, 95% CI 0.00 to 0.61, P=0.05). Importantly, the magnitude of the summary effects from studies with low mean baseline serum vitamin D levels for these bone outcomes were at least 0.2 SMD higher than those from studies with higher mean baseline 25(OH)D levels (≥35 nmol/L). This analysis is likely to have underestimated the effect of vitamin D in deficient children, as even the studies in which the study sample's mean baseline 25(OH)D was less than 35 nmol/L, around one out of five participants would be expected to have sufficient vitamin D (serum 25(OH)D ≥50 nmol/L), that is, there is substantial misclassification of vitamin D status of individual study participants. The RCTs published after this review found similar results with this meta-analysis, supporting the potential for vitamin D supplementation to be beneficial in vitamin D deficient but not replete children.[25–27] However, definitive data are needed to underpin health policy and clinical practice for vitamin D supplement use in children, and vitamin D testing in children and potentially the choice of cut-off for vitamin D sufficiency for bone health in children.

Our previous aggregate data meta-analyses are potentially subject to ecological bias and study-level confounding. We used subgroup analysis to examine the difference in meta-analysis results for those studies with low (<35 nmol/L) versus high mean baseline vitamin D (<35 nmol/L). However, it is well known that differences at the study level do not necessarily reflect genuine differences at the individual level.[28 29] For example, the different treatment effects in these two subgroups may be due to other study-level differences, rather than the mean baseline vitamin D level. Further, those studies with a mean below 35 nmol/L contain an estimated 20% of participants with a baseline value above this value, and this misclassification being ignored in the analysis. Further research requires the use of individual-level information to examine differences in participants' responses to vitamin D supplementation. Therefore, the aims of this individual patient data (IPD) meta-analysis are to determine whether the effect of vitamin D supplementation on bone density in children differs according to baseline vitamin D status, and specifically estimate the effect of vitamin D in children who are vitamin D deficient.

METHODS AND ANALYSIS
This is the protocol for an IPD meta-analysis of RCTs of vitamin D supplementation for improving bone density outcomes in children to determine whether the effect of vitamin D supplementation on bone density in children differs according to baseline vitamin D status,

and specifically estimate the effect of vitamin D in children who are vitamin D deficient. The protocol has been designed and written to adhere to the Preferred Reporting Items for Systematic Review and Meta-Analyses of IPD (PRISMA-IPD) Statement[30] and in accordance with that we have registered the protocol in the International Prospective Register of Systematic reviews prior to commencing the review. Any important protocol amendments will be recorded in PROSPERO and also noted in the methods of the final review.

The processes for identification of studies, selection of studies for inclusion and extraction of data on study characteristics and aggregate study data will be identical to that of our published Cochrane review of vitamin D supplements for improving BMD in children.[23 24] We will therefore include all the RCTs included in that review (to search date 9 August 2009). We will perform a search update for additional potential studies for inclusion, using the same search strategies as previously to cover the period from 2009 to the current date. The details of these methods, together with the additional methods for the IPD meta-analysis are presented below.

Inclusion criteria

► Types of studies: RCTs of vitamin D supplementation compared with placebo, with a treatment period of at least 3 months[31] will be included.
► Types of participants: Trials in children (aged <10 years) and adolescents (aged 10–19 years) without coexistent medical conditions or treatments causing osteoporosis will be included.
► Types of interventions: Trials of vitamin D supplementation regardless of type or dose of vitamin D supplement or method of administration, compared with placebo will be included.
► Types of outcome measures: While fractures in later life would be the ideal outcome measure, for intervention studies in children, this would require following large numbers of participants for decades. Such studies have not been performed to our knowledge, so in this review BMD will be used as a surrogate outcome, as is commonly seen in intervention studies in children.

Studies reporting areal or volumetric BMD or BMC, measured a minimum of 6 months after the study commenced, will be included. Measurement sites will include femoral neck, total hip, TB, LS and proximal and distal forearm. Primary outcome measures will be areal or volumetric BMD at the total hip, LS, distal forearm and TB BMC, where possible taken as per cent change from baseline. Other bone density sites will be considered secondary outcomes. Measurement methods can include dual X-ray absorptiometry, single-photon or dual-photon absorptiometry and peripheral quantitative CT. Studies must also have a measure of variance for outcome measures to be included in the meta-analysis of aggregate data. We considered including studies which used quantitative ultrasound (QUS) measures but no studies prior to 9 August 2009 and none that we are aware of subsequent to this date have used this outcome. Given that QUS measures bone characteristics different to actual BMD, and the majority of studies report bone density, we have not included this outcome in the IPD meta-analysis.

Exclusion criteria

We will exclude non-randomised or uncontrolled trials, observational studies, and animal studies and those that performed exclusively in neonates (aged <1 month) or only reported QUS outcomes.

Search methods for identification of studies

To update our search, we will use the same methods in an electronic search as the original review, applied from 2009 to the current date. The search strategies will include a search of the Cochrane Central Register of Controlled Trials (CENTRAL current issue), MEDLINE (2009 to present), EMBASE (2009 to present), CINAHL (2009 to present), AMED (2009 to present) and ISI Web of Science (2009 to present). There will be no language restrictions. The search strategy used for MEDLINE is outlined in online supplementary appendix 1 of our published review[24] with the strategy being adapted as appropriate for other databases. We will examine the reference lists and ISI citations of all included studies. We will also hand search conference abstract issues of key journals (*Osteoporosis International*, *Journal of Bone and Mineral Research*, *Asia Pacific Journal of Clinical Nutrition*, *Journal of the American Dietetic Association*, *Proceedings of the Nutrition Society*, *Journal of Nutrition*) for 2 years prior to the date of the electronic search to identify recent trials that are not yet published in full, and search trial registries (WHO and US National Institutes of Health online registries) for ongoing trials. We will also ask all authors of this protocol (who are content experts as well as chief investigators on major vitamin D RCTS in children) to check the list of included studies for omission of potentially relevant studies missed by the search.

Study selection and data collection for additional studies to those in original review

Methods of study selection and data collection for aggregate data (ie, study-level data) are the same as used in the original review.[23 24] Two researchers will independently assess all potentially relevant articles against the inclusion/exclusion criteria. Two researchers will also extract aggregate data independently using an existing template. We will extract details regarding the study population, treatment periods, baseline demographic data, type and dose of vitamin D given and bone density outcomes at baseline and all other time points measured. We will also, where possible, extract data on baseline sex, age, pubertal stage, baseline serum vitamin D, method of vitamin D assay used and details of laboratory accreditation/quality assurance for the assay, physical activity, height, weight, body mass index (BMI), dietary calcium intake and calcium supplement use, vitamin D intake, levels of sun

Table 1 Estimated numbers of individual participants (from studies already agreeing to provide data) with data for each bone density outcome, by treatment group and baseline vitamin D status

Baseline 25(OH)D	LS BMD		Hip BMD		TB BMC		Forearm BMD	
	Vitamin D*	Control	Vitamin D	Control	Vitamin D	Control	Vitamin D	Control
<50 nmol/L	456	254	318	185	489	323	240	143
≥50 nmol/L	144	73	121	61	85	41	239	143

*Vitamin D=participants receiving active intervention that is, vitamin D supplementation; control=participants receiving placebo.
BMC, bone mineral content; BMD, bone mineral density; LS, lumbar spine; TB, total body.

exposure and ethnicity, as well as compliance. We will also collect data on adverse effects where available.

Two researchers will assess each trial for risk of bias independently, addressing randomisation, allocation concealment, blinding of those providing treatment and of study participants, completeness of outcome assessment, selective reporting and other potential sources of bias as per the Cochrane handbook.[32] When necessary, we will contact authors of primary studies to obtain additional information. Differences between reviewers will be decided by consensus where possible, with referral to a third reviewer if consensus is not possible. If a study provides their IPD (see below), we will use it to help inform the risk of bias assessment (eg, in relation to baseline balance, missing data).[33]

Collection of IPD for all included studies

Key authors of each currently identified major trial (the authors of this protocol) have agreed to supply IPD (seven studies), and author TW has additional unpublished bone density pilot data in 50 deficient children. From means and SDs of serum 25(OH)D in these studies, we have estimated the number of individual participants with data for each bone density site, by vitamin D status (<50 nmol/L being deficient) for both intervention (vitamin D) and control groups (table 1). As this shows, the numbers are substantial. These are minimum numbers as we anticipate additional studies will be identified providing more data. We are aware of two such potential studies in 123 children with serum 25(OH)D <50 nmol/L (100<35 nmol/L).[26 27] These are substantially higher than in any individual RCT (50% more than largest RCT comparison).

Fully anonymised data on all randomised patients will be requested. The outcome data requested will be femoral neck, total hip, LS and proximal and distal forearm BMD, and TB BMC measured at baseline and at any other time point during the study (including postsupplementation). Participant characteristics requested will be baseline age, sex, ethnicity, serum 25(OH)D, dietary calcium intake, pubertal stage and physical activity level as well as change in 25(OH)D over the trial period and compliance. Data will be accepted in any suitable electronic format, but an example format detailing the recommended coding will be created and offered to all collaborators. Checks on the data will be made to ensure data are correctly coded, that missing data are correctly identified, that extreme values are genuine and to ensure that the data are consistent with published results. Data from all trials will be incorporated into a single database with fields that are consistent (as far as possible) across trials.

Statistical analyses

We plan to analyse bone density outcomes at 12 months as all studies in our systematic review provided bone density measures at this time point. Only two studies were of longer duration,[34 35] namely 2 years, but if sufficient studies of this or a longer duration are identified, we will consider additional meta-analyses of longer-term data, for example, using a multivariate meta-analysis of multiple outcomes (multiple time points[36]).

A two-stage IPD meta-analysis framework will be used to examine the effect of baseline serum 25(OH)D on treatment effect for each bone density outcome, that is, hip, LS and forearm BMD and TB BMC. In the first stage, each trial providing IPD will be analysed separately to provide interaction estimates between baseline serum 25(OH)D and treatment effect. This will be done using a separate linear regression analysis for each bone density outcome, where the final (12-month) bone density at a given site will be regressed against baseline bone density, baseline serum 25(OH)D, the treatment effect and the interaction term. For trials that contained multiple centres or for a cluster-design, the first stage of the analysis will handle the clustering appropriately. The estimates of effect from each study's IPD analysis will be compared with published aggregate data for each study.

In the second stage, the interaction estimates will be synthesised using a random-effects meta-analysis to produce a summary interaction estimate. This two-stage approach naturally ensures that clustering of participants within trials is accounted for, and that ecological bias is avoided in the summary interaction estimate. Where some baseline values are missing for some participants in a trial, multiple imputation will be applied in each trial separately, and the first stage repeated for each imputed dataset, with Rubin's Rules used to combine the results to produce final estimates for each trial to take forward to stage two.

Restricted maximum likelihood will be used to estimate the random-effects meta-analysis models, with 95% CI for summary effects derived using the Hartung-Knapp approach to appropriately account for uncertainty in the estimated variance terms.[37 38] Baseline 25(OH)D will be primarily analysed as a continuous variable. When

analysed as a continuous variable, baseline score will be entered as a linear term primarily, but sensitivity analysis will examine if non-linear trends are more plausible, using fractional polynomials. Although power is drastically reduced when dichotomising, baseline 25(OH)D will also be examined as a binary variable in secondary analysis (in keeping with published studies), with a cut-off of 50 nmol/L used a priori to define low and high levels, as this is the most widely accepted definition of vitamin D deficiency,[39] but we will also undertake a secondary analysis with a lower cut-off of 35 nmol/L in view of this being a potential cut-off identified in the original aggregate data meta-analysis. This is feasible as we have estimated that the numbers of participants with levels <35 nmol/L range from 226 for hip BMD to 480 for TB BMC.

Note that if there are repeated follow-up scores (eg, at 6 months and 12 months), the first stage will be adapted to include a repeated measures model where all follow-up times are jointly analysed, and the correlation among repeated measures from the same participants accounted for.[40] This approach can naturally handle missing follow-up scores for some participants, under a missing at random assumption. A multivariate meta-analysis will then be considered in the second stage of our meta-analyses, to jointly synthesis the multiple interaction estimates at the time points from each study, accounting for their correlation.[36] If different studies use different BMD measures, that is, volumetric versus areal BMD, then the first stage will produce results as SMDs for synthesis in the second stage.

Overall treatment effects and treatment effects for each vitamin D subgroup will be produced in such a two-stage approach. Other possible predictors of treatment response (age (continuous), sex, pubertal status (eg, prepubertal vs postpubertal), BMI, body composition, compliance and method of vitamin D assay) will also be investigated in secondary analyses. A sensitivity analysis will also be performed to determine any difference in effects according to whether the vitamin D assay used was or was not standardised according to vitamin D standardisation program methods. All summary and study-specific results will be presented in tables and via forest plots, with heterogeneity assessed by I^2, estimates of between-study variance and 95% prediction intervals. The entire process will be reported according to the PRISMA-IPD guidelines.[30]

Where possible, to reduce the potential for availability bias, aggregate data from studies not providing their IPD will be incorporated in the meta-analysis using novel methods.[41] For example, if interactions can be obtained directly from study authors or publications of the non-IPD studies, these will be incorporated in the second stage of our meta-analyses. The potential for publication bias (small-study effects) and availability bias will be examined using contour-enhanced funnel plots and suitable tests such as Egger's test and Peter's test.[42] If necessary, sensitivity analysis excluding studies at high risk of bias will be undertaken.

The Grading of Recommendations Assessment, Development and Evaluation system will be used to rate the quality of the body of evidence for each outcome as per the Cochrane Handbook for Systematic reviews of Interventions.[43]

RESULTS

The entire IPD meta-analysis process, including results will be reported according to the PRISMA-IPD guidelines.[30]

DISCUSSION

Definitive data on the effectiveness of vitamin D supplements for improving bone density in deficient children are needed to inform health policy and clinical practice for vitamin D supplement use and vitamin D testing in children and to provide better evidence to support the minimum threshold for vitamin D sufficiency to optimise bone health in children. In the absence of definitive data confirming effectiveness and accurately estimating the magnitude of any effect, it is not possible to model health economic benefits of approaches to assessing and optimising vitamin D status in children. In a highly cost-effective way, this IPD meta-analysis will provide a definitive answer to the question of whether supplementing vitamin D-deficient children provides worthwhile benefits for bone density.

This is critical information as there is an urgent need to develop approaches to improve PBM in childhood. Based on current evidence, vitamin D supplementation of children who are vitamin D deficient is one of the most promising options and has potential to have a major impact on the risk of fracture in later life. The accumulation of even small annual improvements in acquisition of bone mass are likely to be important—a 10% increase in PBM could in theory result in around a halving of the relative risk of hip fracture in older adult life. Given the impacts of osteoporotic fracture on the health system, community and individuals, and that fractures and their associated disease burden are increasing, putting in place effective and efficient strategies for long-term prevention is critically important.

An IPD meta-analysis involves obtaining, cleaning, harmonising and then synthesising raw data from existing studies.[29 33] In contrast to our previous aggregate data meta-analyses, using individual-level information allows more accurate risk of bias assessments, more consistency across studies in inclusion and exclusion criteria, and—most crucially for this study—accurate identification of subgroups of interest, and examination of effect modifiers at the individual level (rather than the study level, which is prone to ecological bias and low power[28 44]). Pooling across existing studies, also dramatically improves the power to detect genuine subgroup effects and treatment effect modifiers, which would otherwise require a very large single study.[45]

IPD meta-analysis is more feasible and less costly than new large-scale RCTs and avoids the ethical problem of research waste.[46] It will eliminate the need for further costly and complex RCTs in this area. Such RCTs would be likely to be challenging from a feasibility perspective. Our pilot work identified major feasibility challenges for recruitment, namely low response rates and difficulty reaching and identifying children who are vitamin D deficient. For example, when recruiting through high schools the response rate was only 14.4% from a mail-out to 1070 parents/children with a prevalence of vitamin D deficiency of only 22%[47] possibly due to healthy responder bias. Even if feasible, a large-scale RCT of vitamin D supplementation with bone density outcomes targeting this population would be very expensive. Roughly 440 children would be required to have power to detect potentially clinically important differences of around 1.5% per annum in LS and femoral neck BMD. We estimate that such a study in Australia would cost a minimum of $A750 000 taking into account the unusually high costs of staffing needed to overcome recruitment challenges, as well as the costs of screening serum 25(OH)D levels (estimate five tests to identify one eligible child). By comparison, we estimate the cost of implementing this IPD meta-analysis will be close to a quarter of this.

In summary, given the impacts of osteoporotic fracture on the health system, community and individuals, putting in place effective and efficient strategies for long-term prevention is critically important. This IPD meta-analysis will provide the most robust evidence to date to delineate the role of vitamin D in optimising bone development in children and underpin appropriate evidence-based clinical and public health actions in this area.

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