Iron and vitamin D deficiency in children living in Western-Europe
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Reply to JP van Wouwe and CI Lanting

Akkermans MD, Eussen SR, van der Horst-Graat JM, van Elburg RM, van Goudoever JB, Brus F.
LETTER TO THE EDITOR

Dear Editor,

We appreciate the interest of Van Wouwe and Lanting in our recent published article entitled ‘A micronutrient-fortified young-child formula improves the iron and vitamin D status of healthy young European children: a randomized, double-blind controlled trial’. In this study, we showed that the use of young-child formula (YCF – study product) during 20 weeks by predominantly Caucasian children aged 1-3 years from Germany, the Netherlands and the United Kingdom resulted in stable levels of serum ferritin and increased levels of serum 25-hydroxyvitamin D (25(OH)D) while these levels decreased in children consuming non-fortified cow’s milk (CM – study product). In their letter, Van Wouwe and Lanting raised an important question whether a daily supplement of vitamin D (recommended for young children in all three participating countries) would be equally effective in improving vitamin D status in these children.

At baseline, only 30.5% of the children in our study sample used a vitamin D supplement. In these vitamin D supplement users, the baseline prevalence of vitamin D deficiency (VDD) (defined as 25(OH)D <50 nmol/l) was 7.4% compared to a prevalence of 30.8% in the non-vitamin D supplement users (p<0.001). After 20 weeks of YCF use, the VDD prevalence was 7.4% and 15.5% for vitamin D supplement users and non-users, respectively (p=0.286). It seems that our intervention with YCF did not influence the prevalence of VDD in our vitamin D supplement users while we observe a 50% decrease in VDD prevalence in our non-vitamin D supplements users. To investigate the effect of YCF use on VDD prevalence in vitamin D supplement users and non-users more closely, we performed additional logistic regression analyses including the covariates ‘vitamin D supplement use’ (yes/no), ‘treatment arm’ (YCF/CM) and the interaction of both covariates (‘vitamin D supplement use * treatment arm’). In this way, we analyzed the effect of YCF on VDD prevalence in four subgroups (CM + vitamin D supplements, YCF + vitamin D supplements, CM without vitamin D supplements and YCF without vitamin D supplements) as suggested by Van Wouwe and Lanting. The results of these analyses show a trend towards an interaction effect (p=0.067) suggesting a different effect of YCF on VDD prevalence in vitamin D supplement users versus non-users. This is also illustrated by the different probability of VDD after the intervention between vitamin D supplement users...
and non-users as shown in Table 1. We postulate two potential explanations for this observation. Firstly, the likelihood of a successful intervention is presumably higher for children with lower 25(OH)D levels at baseline, as predominantly observed in our non-users of vitamin D supplements, than in children with higher and/or adequate 25(OH)D levels at baseline due to the use of vitamin D supplements. Secondly, if children already have an adequate vitamin D status at baseline (which applies to 92.6% of our children using vitamin D supplements), an increase in their 25(OH)D levels, although probably small considering the tight regulation of vitamin D homeostasis, will not result in a lower prevalence of VDD and therefore not lead to a significant lower probability of VDD after the intervention (Table 1).

The YCF studied contained 1.7 µg/100ml of vitamin D. About 40% of the children consumed 300-500 ml/day and about 20% consumed >500ml/day, i.e. a daily vitamin D intake of approximately 5.1 to >8.5 µg. These intakes are lower than the recommended vitamin D supplementation dosages in most Western-European countries. Therefore, we would like to advocate for YCF to be a part of a toddlers’ healthy diet containing other products contributing to an adequate vitamin D intake rather than ‘calling’ YCF the solution for VDD in young European children. Furthermore, and as Van Wouwe and Lanting already mentioned, implementing a nutritional intervention in attempt to improve the (quality of the) current nutritional intake of toddlers is a challenge and should therefore not be based on one strategy only. Firstly, there should be a more strict focus on vitamin D supplementation policies because this helps to prevent VDD.2,3 Furthermore, fortification of commonly used food products such as YCF improves compliance, in contrast to the low compliance to vitamin D supplements as frequently reported in young European children.2,4-6 Moreover, fortified YCF will also improve the intake of iron and other important micronutrients for young growing and developing children.

Van Wouwe and Lanting also comment on the higher than prior estimated dropout rate of 25% in our study and therefore question the use of YCF for young European children. Although we did not observe a difference in percentages of dropouts between YCF and CM users, we agree with the authors that the non-fresh milk (milk in powder form that had to be diluted with water) could have been a reason for children to refuse the milk. It should be noted that a relatively high proportion of children (~40%) in the study were already consuming regular and ‘fresh’ cow’s milk at the study enrollment. This may have impeded the switch from cow’s milk to one of our study products. A less challenging and probably
more convenient time to introduce YCF would have been at the age of 1 year because of the similar tasting follow-on formula that children receive until the age of 1 year if not breastfed. If still breastfed at 1 year of age, this should be stimulated to be continued.

In conclusion, we support the national European guidelines for a healthy diet for toddlers, including the use of a vitamin D supplement, although one should realize that achieving a healthy diet for toddlers and compliance to use of vitamin D supplements remains a huge challenge. Fortified products such as micronutrient-fortified YCF may play an important role in ensuring adequate intake of iron and vitamin D in toddlers as shown in our study.

Table 1 Vitamin D deficiency1 before and after the intervention in vitamin D supplement users and non-users separately

<table>
<thead>
<tr>
<th></th>
<th>CM</th>
<th>YCF</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vitamin D supplement users</strong></td>
<td></td>
<td></td>
<td>0.608 (0.057-4.053)²</td>
</tr>
<tr>
<td>Vitamin D deficiency, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>4 (8%)</td>
<td>3 (7%)</td>
<td></td>
</tr>
<tr>
<td>20 wk</td>
<td>4 (11%)</td>
<td>2 (7%)</td>
<td></td>
</tr>
<tr>
<td><strong>Non-users of vitamin D supplements</strong></td>
<td></td>
<td></td>
<td>0.145 (0.054-0.386)³*</td>
</tr>
<tr>
<td>Vitamin D deficiency, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>30 (29%)</td>
<td>36 (33%)</td>
<td></td>
</tr>
<tr>
<td>20 wk</td>
<td>33 (45%)</td>
<td>13 (16%)</td>
<td></td>
</tr>
</tbody>
</table>

1Vitamin D deficiency was defined as serum 25-hydroxyvitamin D <50 nmol/l. 2Logistic regression analysis using Firth’s penalized likelihood while adjusting for sex and country (stratification factors), age, vitamin D status at baseline and sun exposure. 3Logistic regression analysis while adjusting for sex and country (stratification factors), age, vitamin D status at baseline, the vitamin D intake from food and sun exposure. OR column (right) shows the odds of having vitamin D deficiency in YCF users compared with CM users. *p <0.001. Abbreviations: CI, confidence interval; CM, cow’s milk; OR, odds ratio; YCF, young-child formula.
REFERENCE LIST


