Author’s response to reviews

Title: Vitamin D levels in schoolchildren: A cross-sectional study in Kuwait

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Author’s response to reviews:

Dear Editor,

Thank you for your personal comments, and the comments of the reviewers. Kindly note that each and every one of the comments has been addressed below (in blue).

With regards to the Editor comments, amendments have been made as follows:

This manuscript requires some substantial modification. The two reviewers have outlined a number of improvements to the paper, which I ask the authors to address.

Have been fully addressed.

The Author should have highlighted the role of vitamin D in humans beyond musculoskeletal disorders.

I have originally wrote:

“It is well understood that adequate vitamin D status is important for optimal bone health, and that low levels of vitamin D is associated with elevated levels of parathyroid hormone and accordingly inadequate bone mineralization [13]. More recently, vitamin D deficiency has been linked to a wide range of ailments and diseases [20]. Adults with low levels of vitamin D have
been shown to possess a higher risk for heart disease, diabetes, cancers, high blood pressure and immune-related diseases [14, 15]. Children with diabetes, metabolic syndrome, asthma, dermatitis, and anemia have also been found to possess lower levels of vitamin D compared to controls [16–19].”

Upon your comment, I have included a new paragraph with regards to the role of vitamin D in non-skeletal disorders following the above paragraph:

“There is evidence to support a beneficial role of vitamin D in a number of non-skeletal tissues and systems. For example there is some data on the role of vitamin D in cardiovascular diseases. Experimental animal and cell culture studies have demonstrated a variety of effects by which the vitamin D receptor activation exerts cardiovascular protective actions [14].

There is also evidence to show that vitamin D has a role in increasing the effect of the innate immune processes while restraining the adaptive immune system, leading to improved outcomes in autoimmune disease. In addition, vitamin D has been found to have an antimicrobial effect in certain bacterial infections such in those with frequent respiratory tract infections and dental caries [14]. Studies have found an inverse correlation between inflammatory markers such as TNF-α and C-reactive protein and between 25(OH)D levels, which suggests that inflammation is a common factor between most non-skeletal health disorders and low 25(OH)D levels [15].”

The Author must point out what are the international agenda on Vitamin D deficiency and how international organizations are engaging countries to overpower this issue of public health significance.

I have extensively added:

“International health organizations such as the Institute of Medicine, IOM, have set specific guidelines and recommendations to overcome the widespread vitamin D deficiency. They have raised awareness of its importance in promoting and maintaining overall health. They have set guidelines to encourage raising serum levels of vitamin D via safe exposure to sun rays and by consuming more vitamin D rich foods and beverages [20]. The US Department of Agriculture’s Nutrient Database lists foods and their vitamin D levels on their website for general use. On the
other hand, food companies have been encouraged to fortify more foods for consumers based on scientific evidence that consumption of fortified milk for 24 months significantly increased 25(OH)D levels and reduced bone loss in the lumbar spine and hip [21]. Supplementation is recommended when attempts to obtain enough dietary vitamin D or sun exposure fail. The IOM recommends that infants up to one-year old require 400 IU, and children 1-18 years old should receive 600 IU [22].

In addition, various organizations and institutions have raised the cutoff for normal serum vitamin D levels that was once as low as 25 nmol/L to levels that are suggested to promote overall health. Despite the fact that the new cutoff varies between institutions, there is a general consensus that optimal levels of 25(OH)D should be above 50 nmol/L [20]. This cutoff is based on evidence that lower levels have been associated with various disease outcomes, suggesting that higher levels may be protective [14].

There is also a general agreement that screening high risk individuals for vitamin D deficiency is required. Individuals at risk include but are not limited to chronically ill and hospitalized patients and those with osteoporosis, renal or liver diseases, pregnant and lactating women, infants and the elderly [23]. Children at high risk require no less than 1000 IU of dietary vitamin D [22].”

The authors should have stressed on the current government policies and priorities if any to modulate the issue.

I have added:

“Thus far, these international guidelines have been adapted in various populations, including the Arabian Gulf region. However, just recently, the Prince Mutaib Chair for Biomarkers of Osteoporosis PMCO in King Saud University, Riyadh, KSA, in cooperation with the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis, have formulated unified guidelines for the prevention, diagnosis and treatment of vitamin D deficiency in the Saudi population [24]. The guidelines take into account the ethnic, geographical and cultural factors that exist in the region, which are also major determinants of vitamin D status. The PMCO, therefore, recommends vitamin D supplementation for all of those whose serum vitamin
D levels fall below 50 nmol/L (the deficiency cutoff), while frail, osteoporotic and older patients should target a level of 75 nmol/L.

With regard to children, supplementation is recommended for children of all ages, especially females as follows: infants up to 6-months old should receive 400 IU/day, infants 6-12-months old should receive 400-600 IU/day, children over one-year old should receive 600-1000 IU, and obese children should receive 1200-2000 IU/day [24]. Supplementation of 1000-2000 IU/day is also recommended during pregnancy. Similarly, the UAE has set some guidelines to overcome the widespread vitamin D deficiency in the region, through which supplementation is recommended for everyone [25].”

The study design should be included in the title.

Done.

There have been several grammar and writing mistakes throughout the text. The authors are suggested to consult some senior faculty to refine the manuscript for language issues.

The manuscript has been reviewed by a language editor.

With regards to the comments from Saeed Akhtar (Reviewer 1), amendments have been made as follows:

Please overwrite this text when additional grammar and writing mistakes throughout the text. I have pointed out up to line No 108 however this needs to be fixed. The authors are suggested to consult some senior faculty to refine the manuscript for language issues.

The manuscript has been revised by an English language editor.
Line 51: "intolerable high temperatures" is not an appropriate expression. May be replace high temperature.

Done.

Line 54-66: Country wise data alongside levels of vitamin D in children of various ages may be presented in tabulated form by adding more countries of the region.

Kindly note that my aim was to represent some of the data from neighboring countries in order to hypothesize that vitamin D deficiency is common and that carrying out a study to assess vitamin D levels in young children is worthwhile. I did not intend to represent a full review of the studies in the region.

Line 71: "More recently, vitamin D deficiency has been linked to a wide range of ailments and diseases." Not supported by a reference.

Reference added.

Line 78: Data pertaining to the magnitude of prevalence of Vitamin D have been depicted in introduction section while little has been said on risk factors associated with low levels of vitamin D.

Vitamin D risk factors have been mentioned in the discussion section under the subtitle "Vitamin D and common risk factors in children". I have also added a new paragraph in the introduction: "Some of the well-known risk factors of vitamin D deficiency are female gender, certain age groups such as neonates, preschool children, and the elderly, obesity, veiling, dark skin, African and Asian ethnicities, winter season, and low socio-economic status [15]."
Line 83; "The study was granted the approval of the Joint...." Joint Committee for the Protection---- granted the approval for carrying out this study:

Line 82-91: Please condense these approval in para.

Line 98: were recalled : replace with were contacted

Line 100: presented " were presented

Line 100-103: Please rewrite making it more scientific expression

104-105: Interviewer - administered questionnaires and body measurements were performed by 3 trained dieticians and took about 20-30 minutes to complete" please say " Three trained dieticians completed Interviewer - administered questionnaires and body measurements in 20-30 minutes.

These comments have been amended and the manuscript has been fully revised by an English language editor.

Line 105; presented - accompanied by their mothers for clarity in answering questions.
Done.

Line 106; were applied - ???? clarify
Different questionnaires were used to collect data on lifestyle, sun exposure, and physical activity. A detailed explanation of these questionnaires was included below the sentence as follows:

“Skin color/type was evaluated based on the Fitzpatrick classification of skin phototype [21], which classifies the skin according to its susceptibility to sunburn and tanning into 6 types. Skin color/types were regrouped into light (2, 3), medium (4), and dark (5, 6). Skin type 1 was not found among the children. Sun exposure was evaluated by asking the parents to provide a rough estimate of the average daily time their child spent under the sun in the past month. The parent responded by choosing up to 5 minutes, up to 15 minutes, or 30 minutes/or more. Physical activity was evaluated by asking the parent to provide a rough estimate of their child’s level of physical activity by engaging in active playing, running, jumping, climbing, playing football or basketball, or other activities. The parent responded by choosing daily, weekly, or rarely.”

Line 108 ; Height, weight, head and wrist circumference were measured- a very short sentence . join it with the next sentence - not a scientific way of write up ng your comments to the authors.

The manuscript has been revised by an English language editor.

With regards to Ramzi Shawahna (Reviewer 2), amendments have been made for each comment as follows:

1. The number of participants need to be included in the results sections of both the abstract as well as the main manuscript.

Done. The number of samples has been removed from the methods and added in the results of the abstract and the manuscript.

2. How did you ensure consistency between the three trained dietitians who administered the questionnaire? Please provide more details.
There was a very good level of consistency with the three dieticians given that the questions were read to the subjects exactly as written (in Arabic), they were trained by the same researcher at the same time, and daily follow up took place during recruitment by the researcher to ensure quality data recording.

3. Please provide more details like the manufacturer, model, number, ..etc of the instruments and kits used for quantification of vitamin D, PTH and calcium.

The paragraph regarding this information has been rewritten as follows:

“Blood was withdrawn by a nurse/lab technician and was sent to, London, UK for measurement of serum vitamin D, 25(OH)D, parathyroid hormone (PTH), serum adjusted calcium (adj Ca). Elecsys Vitamin D total assay using an immunoassay analyzer (Roche diagnostics, USA) was used to quantify 25(OH)D, with inter- and intra-assay CV% of 3.43% and 5.44%, respectively. Intact PTH was measured with an electrochemiluminescence immunoassay using an immunoassay analyzer (Roche, USA) with inter- and intra-assay CV% of 1.6% and 3.9%, respectively, and adjusted calcium was measured with Calcium Gen.2 using Cobas c analyzer (Roche diagnostics, USA) with inter- and intra-assay CV% of 0.7% and 0.9%, respectively.”

4. Please add the sample size used in this study as a limitation.

The sample size has been added in the limitations. I agree that a better assessment would have been possible with a larger sample size.

5. The study design "cross-sections" is a limitation itself.

A cross-sectional type study is very common in research. Although it has its limitations, its advantages outweigh its limitations in descriptive studies. Because it is convenient, inexpensive and relatively time effective, it is perhaps the preferred type of study when it comes to assessing prevalence and associations in a given population. I would not consider it a limitation on its own.
Some minor comments:

Acronyms like (GCC, adj Ca, ...etc) need to be defined once they appear in the text, even in the abstract.

Done. Please note that I have changed the GCC to Arabian Gulf region/countries.

2. In some places sentences and phrases need to be revised for clarify, grammar and some need to be divided into two sentences. Examples Page 3 Lines 59-58 and Page 3 Lines 56.

3. Page 3 Lines 60-66, the whole paragraph needs revision for grammar and clarity.

4. Page 4 Line 77, please revised the grammar.

5. Page 4 Line 86, please revised the grammar.

6. Page 5 Line 105 please revised "dieticians".

The manuscript has been revised by an English language editor.

I am looking forward to receiving your feedback.

With Regards

Khulood Alyahya