Author's response to reviews

Title: A retrospective cohort study on the influence of UV index and race/ethnicity on risk of stress and lower limb fractures

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Author's response to reviews: see over
Dear Sir,

The authors thank the reviewers for their thoughtful comments. We have modified the manuscript to address the questions raised and feel the manuscript is improved from the effort. The changes in the manuscript are underlined and colored red. We provide our feedback to the reviewers comments and/or questions in a point by point manner in the text below.

Reviewer #1

There is no proof that the hypothesis, potential UV B exposure indeed is associated by better vitamin D status, nor in the data analysis nor in published literature. Indeed it is far from obvious from other studies in the US that region and potential UV B exposure is tightly or even poorly correlated with 25OHD levels. This aspect should be much better discussed as the authors assume that this association is accepted and proven.

We agree, which is why we pointed out both in the introduction and in the discussion that UV availability is only one of several factors that determine Vitamin D status. The (apparent) lack of strong relationship was actually a driving force for the analysis.

The evidence for a role on vitamin D and or calcium on stress fracture risk is best assessed by RCT and this aspect is lacking in the introduction or discussion. Moreover previous studies in the US and in Israeli soldiers evaluated multiple risk factors and showed at least 5-10 predisposing factors to be involved. So I am surprised that the authors did not from the start plan such multiple factor analysis. Moreover a case control 25OHD measurement would have been very helpful especially as probably a serum bio bank is available for a large number of these recruits.

The results of randomized controlled trials with regards to vitamin D and/or calcium is presented in the introduction.

The data were actually analyzed by utilizing both univariate and multivariate analysis. In neither case was low solar load at home of record predictive of heightened risk of either stress fracture or lower limb fracture. We decided to only present the simple odds ratio data to make the manuscript easier to present and understand.

While the military maintains a biobank, it is only available for medical research when there is a compelling reason to justify access. It is unlikely that permission would be granted for the experimental question posed in this epidemiological study without evidence that geolocation is a strong predictor of vitamin D status or for fracture risk. Given the enormous cost to perform ~600,000 vitamin D analyses, it made more sense to address the question using an epidemiological approach.
If there would be a threshold for vitamin D status, (and thus with UVB exposure) followed by a plateau effect on stress factor risk, then the whole analysis would not be able to detect such effect.

True, but the question we are addressing is whether geolocation is by itself a risk factor for vitamin D deficiency and/or it’s medical consequences.

It would be very informative to compare the risk of fractures of this population with that of the general population of that age/gender/race.

The authors are not aware of a robust civilian dataset of same age individuals. That is what makes the military data unique and valuable. The incidence rates we report are within the range observed in previous studies examining injury incidence of trainees (e.g., Brudvig et al., Mil Med 1983, 148: 666-667; Pester and Smith, Orthop Rev 1992, 21: 297-303; Jones et al., Am J Sports Med 1993, 21: 705-710)

Abstract should clearly mention that the Ms deals with US military personnel

done

In the discussion the authors should use either 25OHD levels or vitamin D status but not vitamin D levels as this was not measured.

done

Reviewer #2:

Major Compulsory Revisions

The authors followed up on a recommendation published by Craney et al. in Am J Clin Nutr in a review of evidence on the effect of vitamin D deficiency on health. They graded soldiers’ Home Of Record state, with each of 144 cells given an annual average UV index level. They then compared this with data on bone injuries as reported in the SADR, SIDR & HCSR/TED databases. Having done power analysis (#=20%), the failure to find a relationship between UV index level & fractures should rule out this connection, with a likelihood of 80%.

First, I must commend the authors on their idea of using these data to this end. But I do have some concerns about the methods that should be addressed: 1) Codes for pathological fractures were included, as were codes for frank fractures. Readers would benefit from a break down into these 3 categories, before and after dedicated stress fracture codes were implemented. This would also support or cast doubt on the assumption in lines 140-2.
A figure has been added to the manuscript that provides the year by year frequency of ICD-9 codes for pathological and stress fractures (figure 1a) and the year by year frequency of stress-type, lower limb and frank fractures (figure 1b). Fig. 1 shows that use of the ICD-9 codes for pathological fractures declined shortly after the ICD-9 codes designated specifically for stress fractures were introduced. By 2007 there were very few cases with the pathological fracture codes. This supported the concept that clinicians were using the pathological fracture codes for stress fractures prior to having a specific ICD-9 code for this injury.

Vitamin D levels show considerable seasonal fluctuation. While this is probably true in southern states, in northern states where daylight is almost twice as long in the summer than in the winter, calculating annual averages seems incorrect. Monthly data being available, it seems only natural to break the data down by month or season of induction.

The reviewer raises a good point. We used the annualized value to stratify the data into 3 regions. This seems like a logical approach as it captures the regions that have low UV light during winter months and the regions where it is very high or sustained over the course of the year. Whether we stratify to obtain 3 groupings using UV index or by annualized direct normalized irradiation, the regional breakout is quite similar – moreover, the relative risk outcomes are similar.

To study if the outcomes are affected by the inclusion of summer months when solar intensity would be sufficiently high throughout the USA to stimulate vitamin D synthesis, we ran a separate analysis including only trainees who entered basic training during the fall, winter and spring months. The outcomes of this analysis have been added to the results section.

Studies based on diagnosis databases like this one, are limited by the coding system employed. While this might be effective for frank fractures, this is not necessarily accurate for stress fractures, where some time might elapse between the first encounter and the final diagnosis. To be clearer, a soldier complaining of tibial pain might be sent for an X-ray or a bone scan for a suspect tibial stress fracture. In the majority of cases, the diagnosis is negative. But the clinician at the first encounter would probably have to code "stress fracture". This source of noise needs to be discussed, in light of what is customary in the relevant military clinics.

The following was added to the discussion section to address this aspect of the study design: “The analysis also relied on ICD-9 codes to tabulate injuries rather than examination of actual medical records. As such, it is possible that the incidence of injuries are somewhat over- and/or under-reported.” That said, the stress fracture incidence we report falls within the range of medically diagnosed stress fractures reported by others (see refs above).
So, in all, the study is trying to correlate a crude measure of sunlight exposure to a crude measure of stress fractures, which is supposed to be mediated by vitamin D. Obviously, the authors failed to find the expected relationship. Is the data able to support a lack of relationship (with 80% certainty)? In my opinion, the problems I have mentioned prevent that conclusion. I therefore think that with further analysis, this data is worthy of publishing, but these limitations must be stated, together with the fact that, as the data is presented currently, there is no clear “take home” message.

A closing sentence was added at the end of the conclusion paragraph to provide a clear “take home” message.

Minor Essential Revisions:

Specific comments:

Background: UV index is usually used in connection with the risk of UVA radiation. Vitamin D synthesis is by UVB. My brief review of Pubmed failed to find a good source connecting UV index and vitamin D levels. This should be discussed. Also see Fioletov VE, McArthur LJ, Mathews TW, Marrett L. On the relationship between erythemal and vitamin D action spectrum weighted ultraviolet radiation. J Photochem Photobiol B. 2009 Apr 2;95(1):9-16. Epub 2008 Dec 24.

The reviewer raises a good point with regards to a limitation of relying on the UV index. We have inserted reference to the work of Fioletov et al. in the discussion and address the possible impact of using a more selective index (for potential to stimulate vitamin D synthesis) to stratify our data into 3 discrete solar load groups.

In our view, using either UV index or the vitamin D action spectrum weighted UV as the index of solar load are magnitudes better for stratification than latitude, which has been the basis of most of the literature addressing relationships between geolocation and risk of vitamin D deficiency or vitamin D-related health outcomes. As we mention in the discussion, the annualized maps produced by these methods are strikingly similar. As such, it is likely that the trainees would largely have been stratified into same low, moderate and high groups regardless of what UV load indices we used to bin them.
The introduction does not make a clear case for the necessity of the study. Did the authors think that a positive finding might justify screening for HOR, and if in certain areas measure vitamin D or supplement it?

The following sentence was added to the introduction, “The product of this work will provide evidence for or against the idea that living at latitudes or regions where there is limited or restricted ability to synthesize vitamin D from solar exposure, significantly increases the relative risk of bone related injury.”

It is not clear from the paragraph on statistics what models were tested in the logistic regression in order to see if UVI had any effect after correcting for the well known risk factors for stress fractures (age, gender, race, height, weight).

We have attempted to clarify that the univariate logistic regression was performed to derive the odds ratios. Univariate logistic regression was used to assess the relationship between HOR UV index and race/ethnicity for stress fractures and lower extremity fractures. Then, HOR UV index was stratified by race/ethnicity and logistic regression was used to assess the relationship of HOR UV index levels for each separate race/ethnicity. Multiple regression analysis does not change the outcomes described in the manuscript.

The beginning of the discussion repeats the results too overtly.

The opening paragraph states the primary outcome(s) of the study. No changes were made.

I think the authors should make a recommendation on further research or explain why they do not. It might be to test the relationship between HOR and vitamin D levels in a cohort of recruits (this would seem as justifiable as the present study).

Done.