Author's response to reviews

Title: Assessment of vitamin D and its association with cardiovascular disease risk factors in an adult migrant population: An audit of patient records at a Community Health Centre in Kensington, Melbourne, Australia

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Author's response to reviews: see over
Thank you very much for reviewing our paper. The comments / suggestions provided are taken seriously and appropriate modifications were done to the manuscript. Following are the detailed clarifications to the questions raised.

**Reviewer 1: Robert RS Scragg**

**Main concern**

Q1. Advised to perform log-binomial instead of logistic regression

A1. Log-binomial regression was carried out in SPSS, the directions and the statistical significances of the associations were unchanged.

**Minor essential revisions**

Q1. Inclusion criteria (starting line 177): the authors should state the lower limit of their age range (for adults) so that it is clear to readers where this starts.

A1. Done

Q2. Page 10, migration zones 1,2 and 3: why are the latitudes for Zone 1 not the same for North and South? I have checked reference 30, which is the basis for the categories, but can find nothing in Figure 1 of reference 30 to justify this decision. Can the authors please provide more information to justify the cut-points? Otherwise, they should be the same above and below the equator.

A2. We corrected this by using the same cut-points above and below the equator.

Q3. Framingham risk score (line 204): as this is a measure of cumulative incidence, the authors should state the time period for their scores. I assume this is 10-years, from Table 4, but this should be mentioned in the Methods.

A3. Done

Q4. Page 12, top paragraph: the authors should add-in the time period (? Ten years) for the 15% CHD risk.

A4. Done
Q5. Results from Table 4: the null findings in this are not surprising given the small sample size. The authors should add this (low power and high probability of a type 2 error) as a further limitation in the text under the section on ‘Strengths and Limitations’.

A5. Added

Q6. Table 1:

a. The term ‘odds ratio’ should appear in the title of the table, so that the main results refer to odds ratios associated with have a vitamin D test. Although, please note my comment above about the preference for calculating prevalence ratios.

b. Abbreviations (UOR and AOR) should have full-spelling footnoted in the table.

c. Terms should be consistent: eg. ‘testing’ and ‘measured’ for vitamin D.

A6. All done

Q7. Table 2: same comment as for Table 1 about spelling abbreviations in a footnote. Also ‘UOD’ should be corrected to ‘UOR’.

A7. Done

Q8. Tables 3 and 4: full spelling of abbreviations footnoted.

A8. Done

Q9. Figure 1: abbreviation FRS should be spelt fully in the legend.

A9. Done

Discretionary revisions

Q10. Bottom of page 7: the authors mention recent studies (line 134) and then cite articles published in 2008 and 2007. More recent publications should be used so that the references are more current (eg. existing reference 43 could be mentioned here, as well as recent article on diabetes and blood pressure: Song Y, et al. Blood 25-hydroxy vitamin D levels and incident type 2 diabetes: a meta-analysis of prospective studies. Diabetes Care 2013;36:1422-8; Kunutsor SK, et al. Vitamin D and risk of future hypertension: meta-analysis of 283,537 participants. European Journal of Epidemiology 2013;28:205-21).

A10. Done as suggested
Q11. Lines 234-235: I suggest deleting the last sentence of this paragraph. The authors know nothing about the vitamin D status of their patients pre-migration, as this was not measured by them. They can make a statement about lower latitude pre-migration, but it is not the same as vitamin D status, which could have been low if they worked indoors before leaving their home countries.

A11. Sentence deleted

**Reviewer 2 - Welma Stonehouse**

**Major compulsory revisions:**

**Abstract:**

Q1. Conclusion: The statement: “A focus on ......cardiovascular risk factors may be required to avoid future burden of CHD in this population” is not supported by the evidence presented.

A1. We accept your point and the sentence have been replaced.

Q2. Conclusion: The statement “and greater emphasis should be paid to the pre-migration factors” is very vague, be more specific. The only pre-migration factor that was investigated in this study was latitude and any conclusions and recommendations should be focussed on this factor.

A2. We removed this sentence.

**Background:**

Q3. The background is very long and should be reduced by ~50% to maximum 2 pages.

A3. Every effort has been taken to reduce the background in to 3 pages as we have to present many things (definitions and risk factors of vitamin D deficiency, migration and health risks associated and Framingham risk score). It was hard to shrink it more without sacrificing the background rationale which is appropriate for this paper.

Q4. Why has the FRS been chosen? Has the FRS been validated for use in the Australian population?

A4. FRS is one of the widely used composite indicator globally to assess the cardiovascular risk. It is used in Australia by National Vascular Disease Prevention Alliance to assess the absolute CVD risk and has validated to Australia by Zommer and colleagues.
Q5. Forth hypothesis, “VDD will be associated with CHD events...”. CHD “events” have not been assessed in this study – replace “events” with “a higher FRS”. State how it will vary by migration status.

A5. Done

Methods:

Q6. BMI is an important determinant of vitamin D status and CHD and therefore a confounding factor. Is information regarding BMI available?

A6. BMI was available only in 20% of the sample which was not adequate for the statistical analysis.

Q7. How was VDD defined?

A7. It is defined in the background as serum 25-hydroxyvitamin D (25(OH) D) levels less than 50 nmol/L. Please see page 3, line 66 and page 4, line 76

Q8. Provide details in methods of how hypertension was defined. Were individuals on anti-hypertensive medication defined as hypertensive?

A8. Done. It is stated as “The blood pressure reading of the last visit to the clinic was used to identify the individuals as hypertensive (>140/90 mmHg).” Page 7, line 153

Q9. List the countries that were included in the different zones.

A9. There is a long list of countries and we find it difficult to accommodate it in the manuscript. The list is attached at the end of this document and we are happy to include it as an appendix if publisher permits.

Q10. Provide more details of how the FRS is calculated. Indicate that the 10 year CHD risk score was calculated.

A10. The method of calculation of FRS is quite lengthy and it is given in detail in reference 16.

Discussion

Q11. It cannot be assumed that all populations categorised in Zones 1 and 2 were vitamin D sufficient before migration, e.g. several Middle-Eastern populations have been shown to have high prevalence of VDD due to factors such as sun-avoidance behaviour, clothing (covering up) and air
pollution. Thus, some migrants may be VDD before migration. Please discuss this and include the names of the countries within the different zones.

A11. We agree with you and added a sentence to the limitations on this. “Our results need to be interpreted cautiously as some countries located in a sufficient vitamin D zone have reported high VDD levels ranging from 30-50% [39] because in which people wear full-cover clothing…”

Q12. The study design have several limitations for testing the hypotheses related to CHD risk which needs to be taken into account and discussed:

- The sample size for this investigation was very small. What is the statistical power to test this relationship?

- The results have limited generalizability since people attending medical centres may be different from the general population.

- The length of stay or level of acculturation is also a very important factor to take into account, but information on this was unfortunately not available which limits conclusions. The authors have mentioned this in their limitations.

A12.

O Sample 1 (n=2187) and 2 (n=1190) are fairly large and the statistical power is adequate to answer our first and second hypothesis. Sample 3 is small due to the filtering process. We included this point to the discussion as well as to the limitations.

O We accepts this fact and included as a limitation.

O We understands the value of length of stay in Australia, but it was not available in the data set.

Q13. What does the “mandatory health checks” involve? If testing is limited to TB and HIV it may not be true to say that this is a reason for their lower CHD risk.

A13. The intention of the VISA medical process is as follows. Quoted from following web, https://www.immi.gov.au/allforms/health-requirements/overview-health-req.htm

“To meet the health requirement you must be free from a disease or condition that is:

- considered to be a threat to public health or a danger to the Australian community
- likely to result in significant health care and community service costs to the Australian community
- likely to require health care and community services that would limit the access of Australian citizens and permanent residents to those services as they are already in short supply. We
refer to this as 'prejudice to access'. For more information, see significant costs and services in short supply.

However, the most common diseases to result in a failure to meet the health requirement for a permanent visa include:

- intellectual impairment
- HIV infection
- renal disease or failure
- cancer
- Alzheimer's/dementia.’

Even though cardiovascular diseases are not listed directly under the conditions that result failure in visa process and it depends on the severity of the individual case. More importantly cardiovascular diseases, renal disease and some cancers share the common risk factors. Because of all these factors we assumed a significant filtering occurred at the level of immigration department.

Q14. Migrant populations may be different in other ways from non-migrant populations, e.g. they may be younger, more educated. How did the migrant population differ from the non-migrant population with regard to demographic factors, e.g. age, BMI?

A14. A significant difference was not observed between the mean ages of migrants (42 years) compared to the non-migrants (43 years). But the females were more among migrants (60% in migrants and 51% in non-migrants). Other factors like level of education and occupation was not available. We were not interested in including a table with baseline differences as we were dealing with 3 different samples. Ideally it would have been better to present 3 tables with baseline characteristics of each different sample.

Conclusion:

Q15. The sentence “This audit demonstrated the fact that pre-migration zone is an important information in relation to future risk of CHD”. Be more specific, why is this important, say which zone plus the countries in this zone and how it is associated with risk of CHD.

A15. Agreed and corrected.

Discretionary Revisions:

Q1. As part of the testing patterns in the Centre, it would be interesting to know what action is taken when VDD is diagnosed and for what proportion of VDD individuals vitamin D supplements were prescribed.

A1. It would be really interesting to explore the prescribing pattern of the centre for VDD. However after considering the complexity of such an exercise we decided to explore it later.
Q2. Statistics are given for the proportion of resident Australians born overseas. Are there any statistics available for the proportions of these VDD at risk migrant populations in Australia?

A2. The statistics are added to page 4 line 92

**Minor essential revisions:**

Q1. Abstract: Indicate in methods how future risk of coronary heart disease (CHD) was estimated: e.g. by calculating the Framingham risk score to estimate the 10 year CHD risk score.

A1. Done

Q2. Abstract, conclusion, 2nd sentence: indicate the direction of the association between pre-migration latitude and future CHD risk.

A2. Done

Q3. Methods, last paragraph of methods, “Univariate and multivariate......between VDD, CHD outcomes”. Replace “outcomes” with “risk factors and future CHD risk score/FRS”. CHD outcomes were not assessed in this study.

A3. Done

Q4. Results, second paragraph, sentence “....were almost 1.5 times more likely to become VDD than those...” It is not appropriate to use the word “become” since the vitamin D status pre-migration is not known. Table 1: Define “UOR” below table. Rather say “more likely to be VDD...”

A4. Done

Q5. Results: 3rd paragraph, heading “Association of vitamin D with CHD risk factors and FRS”. Replace “vitamin D” with “zone of origin”. Table 3: Add units of measure to hypertension and cholesterol criteria. Indicate at bottom of table what the FRS of <15 is based on.

A5. Done

Q6. Table 3: at bottom of table “vitamin D”- is this serum 25(OH)D?

A6. Yes and it is added.
Q7. Table 4: Provide the total number of subjects in each zone and for non-migrants.

A7. Included

Q8. Table 4: Define UOR below table.

A8. Done

Q9. Discussion, 3rd line, “pre-migration risk factors”- only latitude was assessed. Replace “risk factors” with “latitude”.

A9. Done

Q10. Discussion: Provide a reference for statement regarding Current Australian recommendations for testing VDD

A10. Added

Countries in each zone

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<th>Zone 1</th>
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<th>Zone 3</th>
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