Author's response to reviews

Title: FRAX (TM) tool, the WHO algorithm to predict osteoporotic fractures: an analysis of its discriminative and predictive ability in a Spanish cohort (FRIDEX).

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Author's response to reviews: see over
Dear T. Shipley,

Please find enclosed our manuscript “The discriminative and predictive ability of FRAX tool in a Spanish female cohort (FRIDEX)”. This paper was already submitted at your journal and the actual redaction of it includes all the considerations made by reviewers at their reports.

This study demonstrates –based on the data from a multicentric cohort, the FRIDEX cohort, constituted of women referred by general practitioners and specialists for undergoing central bone densitometry by Dual energy X-ray absorptiometry (DXA) for the initial study of osteoporosis– that FRAX™ without BMD for major and hip fracture demonstrates a good discriminative capacity for Spanish women but its predictive capacity does not adjust well with the current algorithm leading to underdiagnosis for major fracture and hip fractures.

We would appreciate your re-considering it for publication in the BMC Musculoskeletal Disorders as a Research Article. As requested in the Instructions for authors, we state that the manuscript reports an original primary research.

All the authors carefully read the manuscript and fully approve of it. The article is original. We would of course be ready to provide further information about our data and methods you so desire.

Correspondence about the manuscript should be addressed to me.

Thank you very much for your kind attention. We look forward to hearing from you.

Best regards,

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Reviewer (1) ’s report (R1)’
Comments on “FRAX tool, the WHO algorithm to predict osteoporosis fractures: an analysis of its discriminative and predictive ability in a Spanish cohort (FRIDEX)

Major Compulsory Revisions

1• Please provide information on how the following study variables were defined and/or measured: height, weight, body mass index, smoking status, alcohol risk, previous fracture, parental osteoporosis or fractures, glucocorticoids, rheumatoid arthritis, calcium/vitamin D supplements, active bone drugs. For example, it is unclear how alcohol risk is defined (i.e., how many drinks or what amount of alcohol consumption is used to define risk?). If all of the measures were collected by self-report questionnaire, then the authors needs to discuss the potential limitations of this approach. For example, socially desirable responses may result in substantial under-reporting of current smoking status. Appropriate references should be cited for the variable definitions and the questionnaire design.

Updated.

Height, weight, body mass index were obtained during baseline DXA scan. The rest of baseline items were obtained by semi structured questionnaire by interviewer during the same visit. On the other hand, the variables are set according to the instructions of the official website of FRAX (http://www.shef.ac.uk/FRAX/tool.jsp?lang=sp).

The variables which are mentioned in the questionnaire were defined as well according to standard units of measurement for each. Regarding the risk of alcohol consumption, the quantification of consumption in standard drinks (UBEs) allows rapid quantification of consumption and its easy conversion into grams of pure alcohol. The value of the UBE in Spain with a slight North-South gap is set to 10 g of alcohol and is equivalent to a consumption of wine (100ml), sparkling wine (100ml) or beer (200 ml) half and consumption of distilled or combined (25 ml). Weekly risky drinking for women and over 65 years is that is> 17 UBEs and men> 28-UBEs. The phone records of alcohol consumption have
shown good validity and correlation in Mediterranean countries where alcohol consumption is widespread.

Regarding the consumption of snuff, not only made reference to the number of cigarettes smoked per day, but also the time spent as a smoker, which focuses on some characteristics of tobacco use. These two data are included in the concept: number packages / year. To determine this figure performs a simple operation: multiply the number of cigarettes smoked per day by the pool by the number of years been consumed that amount of snuff and the result is divided by 20.

Reference:


2• For what proportion of individuals was a proxy response obtained from a relative or care provider?

Updated.

Only in case of personal circumstances (deafness, slurred speech, etc.) a part of the information was obtained through regular cohabiting relatives of patients in 15 of 770 cases (1.9%).

3• The authors used the telephone questionnaire to obtained information on fragility fractures and then medical records were reviewed to confirm the validity of the fracture self-report. Please discuss the sensitivity and specificity of the fracture self-report when compared to the medical record. The use of self-report could result in under-reporting of fractures, particularly for clinical spine fractures; please discuss this as a potential limitation of the study.

Updated.

Self-reported generally have a significant correlation with those in the medical record. In any case always been found documented as explained. In all cases of fracture the medical records of the patients were reviewed and, when
necessary, we requested a medical report for its validation. All cases of fracture that could not be verified or those arising from a motor vehicle accident or major trauma were excluded from analysis, fractures in the history of the subjects under study.

A potential limitation of self-reported fractures is in vertebral fractures. In our study the total self-reported fractures were 16% higher than they were registered and so were excluded from the final analysis. It can be an advantage for risk predictions proposed by FRAX™.

4• Table 1 compares the baseline characteristics of the study non-participants with the study participants before several exclusions were made. It is more appropriate to include participants after these exclusions; Table 1 should be revised accordingly.

Updated.

5• On page 13, the authors note that “The lower part of the figure [Figure 4] represents the same results after multiplication (simulation) by the number of times that the ObsFx is greater than the ExpFx (table 6).” The authors should describe the simulation methodology in the analysis plan.

Updated.
The proportion of fractures expected is calculated by the sum of an individual probability of fracture from all women included/100.

6• On page 18, the authors note that FRAX tool is based on DXA values of the femoral neck and that prediction may change with the use of the lumbar spine T-score. One relevant reference for discussion is found in Osteoporos Int; 2011; 22:839–847; Spine–hip discordance and fracture risk assessment: a physician-friendly FRAX enhancement by W. D. Leslie et al.

Updated.
Although it has described that a correction can adapt the lumbar spine BMD and improve the prediction for major and vertebral fractures of FRAX (Leslie WD, 2011), in our study by incorporating the lumbar spine BMD did not improve the discriminative ability of FRAX measured by AUC with femoral neck BMD neither for major or vertebral fracture (data not showed).

7• The authors have not described how the relative risk values in Tables 3 and 4 were computed. This information should be included in the analysis plan.

Updated.

The RR was calculated by quotient between prevalence of each risk factor in fractured women and in non-fractured.

**Minor Essential Revisions**

8• Figure 1: the centre set of numbers in the flow chart should be accompanied by descriptive labels; the figures for male and female at the bottom of the page should be replaced with written labels.

Updated.

9• Figures 2 and 3: the numbers reported above the ROC curves (i.e., at the top of the page) should be accompanied by descriptive labels: AUC ROC; 95% confidence interval; pvalue. However, Table 5 repeats most of the information already reported in Figures 2 and 3. Therefore, the authors should carefully consider the value of including these figures.

Update.

We removed the values are not described in the figure and keep the table 5

10• Figures 4 and 5: the word “linear” is mis-spelled in the two right-hand panels; the text within the graphs is in a font that is too small to be easily read and therefore the font size should be increased.
Updated.

11. Figures 4 and 5: please provide figure notes that explain what is represented by the dashed line and the solid lines.

Updated.

12. Table 1: the sample size values should be accompanied by the labels “n =”.

Updated.

13. Table 2: The headings for columns 2 and 3 should be revised: “Women with fracture (n = 65)” and “women without fracture (n = 705)”. The second and third columns in Tables 2 and 3 are the same. The two tables can therefore be combined in order to reduce the total number of tables that accompany the manuscript.

Updated.

14. Abbreviations are not used consistently throughout the manuscript. For example, on page 9, the abbreviation TQ is defined, but then this abbreviation is not used in place of “telephone questionnaire” on page 10 in the first paragraph (5th line).

Updated.

**Discretionary Revisions**

None

**Reviewer (2)**

Major issues
1. The authors should discuss the inherent problems with ROC analyses in the present setting.

Page: 18; Paragraph: 2. ROC analysis for sensitivity and specificity could not be valid indicators, because the gold standard FRAX is not perfect. We are however not testing the FRAX predictive sensitivity and specificity, but a concrete application of it in a defined population.

2. How were data on mortality collected? It seem that no fracture data were available in those patients who died during follow-up?

Page: 9; Paragraph: 4. Dead patients were not studied because of the impossibility of obtaining the study variables and to answer the questionnaire.

3. Fracture data was captured in retrospect. This introduces the possibility of recall-bias. This issue should be discussed.

Page: 19; Paragraph: 2. Another limitation of the study is the recall-bias introduced by the fracture data retrospective capture.

4. A total of 18% of the participants received vitamin-D and calcium supplementation. How did this affect the fracture risk and evaluation of FRAX? The potential confounding should be discussed.

There’s no significant difference between Calcium/Vit D supplement intake between participants and no participants. These statistical results make us assume that Calcium/Vit D supplements do not affect the fracture risk. Moreover Calcium/Vit D supplement intake is not considered in FRAX™ tool.

5. A total of 29% of the potential participants were excluded due to treatment with specific anti-osteoporotic medication. Presumably, these were the patients with the highest risk of fracture. How did exclusion of such a large proportion of participants affect the evaluation of FRAX? The potential confounding should be discussed.
Participants in treatment with active bone drugs, leaving apart if this has been prescribed because a clinical judgement of increased risk of fracture or not, have an impaired bone metabolism so they are not clinical appropriate candidates to apply FRAX™ tool.

6. It is strongly suggested to expand the analysis to include the performance of e.g. age and sex. Previous studies have suggested that age performs virtually as well as FRAX. The present dataset could be of interest to validate this finding. Such analyses could alter the conclusion significantly.

We value your comment. The aim of this study is to validate it for the Spanish population FRAX. The appearance suggested by the reviewer may be a good target for future studies in this cohort but with a higher number of participants.

7. The potential selection bias that could result in the cohort having a higher risk of fracture and a higher prevalence of risk factors than the general population is addressed by the authors in the discussion, however, the sentence “However, there is no evidence that patients pre-selected strategically may have a greater risk than the general population” is inappropriate – the burden of proof is on the authors.

We have corrected this sentence. Page: 17; Paragraph: 4: that could mean that patients pre-selected strategically may have a greater risk than general population.

8. A conclusion should be stated at the end of the discussion (as in the abstract).

Page: 18; Paragraph: 4. Definitely, FRAX™ without BMD for major and hip fracture demonstrates a good discriminative capacity with the AUC ROC for Spanish women but its predictive capacity does not adjust well with the current algorithm leading to underdiagnosis for major fracture and hip fractures.
9. Adherence to guidelines such as STROBE is strongly advised to improve published papers in general. The present paper could easily be adapted to such standard. Comments are welcome.

We consider important the reviewer's comments on STROBE guidelines for epidemiological studies, but several studies basic on cohort published recently in this and other important do not provide these guidelines as references: 7, 11, 28, 30, 31 and 32.

Minor issues

10. Subheadings in the introductions should be removed.

Updated.

11. It is suggested that a note is made on the fact, that the FRAX algorithm is neither published nor freely available for independent researchers.

Updated at page 6, 3rd paragraph.

12. In the abstract (page 3), the number and age distribution of participants, duration of follow-up should be stated. Similarly, it should be stated in the abstract how fractures were ascertained.

The study subjects were 770 women from 40 to 90 years of age in the FRIDEX cohort for 10 years. The fractures were determined by telephone questionnaire and subsequent testing in medical records.

13. On page 5, the sentence "For many years the clinical, social and economic importance of osteoporotic fractures has been known to favour the incidence of new fractures and lead to disability [2]" is confusing. As is stands, the sentence implies that social and economic factors may be important risk factors for fracture. The quoted paper, however, deals with the consequences of fractures. The sentence should be rephrased or supported by other data.
Updated. It is well known that osteoporotic fractures involve a higher incidence of new fractures and lead to disability [2].


Updated.

15. On page 6, the statement “This has been demonstrated in different international studies” should be supported by reference to such studies.

Updated.

We removed the following part of the text: “This has been demonstrated in different international studies”.

16. On page 7, the sentence “The objective of this study is to evaluate..” should read “The objective of this study was to evaluate..”.

Updated.

17. On page 8, the sentence “The protocol, procedures and main characteristics of the study has recently been published..” should read “The protocol, procedures and main characteristics of the study have recently been published..”

Updated.

18. On page 12, the sentence “except that the participants are a mean of one year younger” should read “except that the participants were one year younger on average”. The sentence “table 2 described the main characteristics” should read “table 2 describes the main characteristics”.

Updated.
19. It should be stated clearly in the methods section, that the Spanish edition of FRAX that was applied.

The FRAX™ tool was determined through the official website (version 3.2 accessed on October 2010).

20. Abbreviations should be used consistently once defined. On page 12 “That is, of Bone Mineral Density by DXA” should read “That is, of BMD by DXA”. Similar adjustments should be made throughout.

Updated.

21. On page 14, the sentence “… that they were one year older and were taking a larger percentage of glucocorticoids..” should read “… that they were one year older and more patients were on glucocorticoids..”

Updated.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:** No competing interests