Reviewer's report

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

**Version:** 4  **Date:** 20 February 2012

**Reviewer:** Kim Brixen

**Reviewer's report:**

The paper reports a prospective, observational study with 10 years follow-up comprising a random sample of 770 women aged 40-90 referred for DXA. Baseline data were acquired with DXA and by a questionnaire. Follow-up data on incident fractures were collected by telephone interviews validated against case records. A total of 82 fractures in 65 women were recorded including 18 hip fractures in 17 women. The main conclusion is that FRAX discriminates well, however, the Spanish edition needs to be adjusted to be accurate.

**Aim.** The aim of the study is clearly stated and this represents a valid research question based on previously published studies in the literature. Given the current interest in FRAX and need for independent validation of FRAX, the issue of high interest.

**Design.** The study design (prospective, observational) is the best to address the hypothesis.

**Participants.** Details on the inclusion of participants are not completely clear and the particular cohort was not ideal to address the question at hand. The total FRIDEX-cohort comprised 34,636 persons of both genders. However, the interesting figure would be the number of FRIDEX-participants potentially available with 10 years of follow-up.

**Follow-up and outcome.** The follow-up period (10 years) was adequate. However, the acquisition of data regarding fractures was less than perfect since this was based on telephone interviews and no data could be retrieved in 36% of the cases and total of 5% of the initial cohort died during follow-up. Fractures were, however, verified against patient records.

**Confounders and bias.** Fracture data were captured in retrospect. Potentially, this introduces a recall-bias. Participants were selected at random between patients referred for DXA on the basis of risk factors. This introduces a bias – the cohort a priori has a higher risk of fracture and the prevalence of risk factors in the cohort must be higher (and possible skewed) as compared with the general population. This is to some extend discussed by the authors.

**Statistical analyses.** ROC analysis was used to evaluate sensitivity and specificity of FRAX. This approach is problematic although many studies have done the same.

FRAX predicts a risk between 0 and 1. A particular patient may thus have a risk
of e.g. 0.3 for suffering a fracture during the next 10 years.

ROC, however, depends on dichotomies and it could only be used correctly if FRAX predicted that an individual patient to have the risk of 0 or 1 for fracture. In other words, for an individual patient the predicted risk may be of any value between 0 and 1 while the observed risk fracture in the same patient is either exactly 0 or exactly 1 after 10 years. So was the predicted risk of 0.3 wrong if the patient did not fracture?

Performance of FRAX may be evaluated in groups of patients as done by the authors in the section on the Hosmer-Lemeshow approach.

Obvious questions are not addressed; is the predictive power of FRAX superior to that of age and sex alone (see below)?

Discussion. The discussion is kept to the point; however, a few issues are neglected (see below).

Conclusion. Apparently, no conclusion is stated at the end of the discussion, albeit a conclusion – drawn within the boundaries of the presented data - is made in the abstract.

Ethics. Ethical standards were observed.

Style. The paper is well written in a short a concise and straightforward style. The authors, however, do not explicitly follow the guidelines for reporting observational studies (e.g. STOBE).

Major issues
1. The authors should discuss the inherent problems with ROC analyses in the present setting.
2. How were data on mortality collected? It seem that no fracture data were available in those patients who died during follow-up?
3. Fracture data was captured in retrospect. This introduces the possibility of recall-bias. This issue should be discussed.
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.
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.
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.
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.

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

Minor issues
10. Subheadings in the introductions should be removed.
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.
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.
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.
15. On page 6, the statement “This has been demonstrated in different international studies” should be supported by reference to such 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..”.
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..”
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”.
19. It should be stated clearly in the methods section, that the Spanish edition of FRAX that was applied.
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.
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..”
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