Universitat Autònoma de Barcelona

Estudis de cohorts per validar un model de categorització del risc de fractura per fragilitat en població femenina espanyola en base a l'algoritme FRAX ® de la OMS. Les cohorts FRIDEX i FROCAT

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Cohort studies to validate a model for categorizing the risk for fragility fracture in the Spanish female population based on the WHO FRAX® algorithm. The FRIDEX and FROCAT cohorts.

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Títol

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1. RESUM

Estudis internacionals han demostrat la utilitat de l'eina FRAX de l'Organització Mundial de la Salut (OMS) per a l'estimació del risc absolut de fractura osteoporòtica a 10 anys. S'ha evidenciat que a població femenina espanyola l'eina té una bona capacitat de discriminació per detectar dones que patiran una fractura per fragilitat de les que no, i que millora el model tradicional basat en la densitometria òssia (T-score ≤ -2.5 desviacions estandars). No obstant això, l'algoritme mostra una manca de concordança global entre la probabilitat estimada de fractura i la incidència de fractura observada individual a 10 anys, amb una tendència a infraestimar el risc. Per millorar la capacitat predictiva de fractura osteoporòtica principal s'ha desenvolupat el model FRIDEX, amb 3 categories de risc FRAX (calculat sense T-score de coll femoral) per població femenina espanyola (<5%; ≥5 a <7,5%; ≥7,5%) que inclouen la incidència de fractures reals observades en la cohort, les quals estaven, al seu torn, respectivament dins els nivells tradicionalment considerats com de risc baix (<10%), intermig (10-20%) i alt (> 20%) en altres estudis epidemiològics.

L'objectiu d'aquesta tesi doctoral va ésser validar aquest model FRIDEX de calibració del risc de fractura per fragilitat en població femenina espanyola en base a l'algoritme FRAX en la cohort ampliada FRIDEX i en la població general (cohort FROCAT). En primer lloc els resultats del treball validen les interpretacions de la capacitat discriminativa i predictiva de l'eina FRAX obtingudes en les primeres anàlisi de la cohort FRIDEX i, és important perquè d'aquests casos es va desenvolupar la proposta per categoritzar el risc de fractura en dones espanyoles. En segon lloc, validen externament el model FRIDEX de discriminació del risc de fractura principal a 10 anys en una cohort de dones de base poblacional i diferent de la cohort que ha servit per establir-lo.

2. ABSTRACT

The usefulness of the FRAX tool from the World Health Organization to evaluate the 10-year fracture risk of patients has been shown in many international studies. In the Spanish female population it has been demonstrated that the tool has a a good discriminative ability to detect women who will suffer from a fragility fracture and it is at least equivalent to, if not slightly higher than the bone mineral density (BMD) model (T-score ≤ -2.5 standard deviations). However, it displays weaknesses in the overall concordance between predicted fracture probability and observed fracture incidence, with a tendency to underestimate the risk. To improve the main osteoporotic fracture risk predictive capability, some FRAX thresholds have been developped to identify people with risk of osteoporotic fracture in Spain, based on the stratification from the female FRIDEX cohort into 3 levels of FRAX risk (without femoral neck (FN) T-score) (low risk <5%, intermediate ≥5 to <7.5% and high ≥7.5%) according to the fracture incidence observed in the cohort, which in turn are related with risk ranges traditionally considered to be low (<10%), intermediate (10-20%) and high risk (> 20%) in other epidemiological studies.

The aim of this thesis was to validate the FRIDEX model in the Spanish female population using the FRAX main osteoporotic fracture risk thresholds to 10-year in the updated results of the FRIDEX cohort and in the general population (FROCAT cohort). Firstly, the work validates the discriminatory and predictive ability of the FRAX tool obtained in the preliminary analysis of the FRIDEX cohort, and this is important because from these cases the categorization in the three risk groups was developed. Secondly, it externally validates the FRIDEX model to discriminate fracture risk in women from the general population.

3. INTRODUCCIÓ

L'abordatge de l'osteoporosi ha evolucionat en els darrers anys, des d'un model en el qual la pressa de decisions es basava essencialment en els valors de la densitat mineral òssia (DMO) obtinguts amb la densitometria òssia central tipus DXA (*Dual-energy X-ray Absorptiometry)* fins al progressiu protagonisme de l'avaluació global del risc de fractura en les guies de pràctica clínica (GPC), centrant-se els objectius en la prevenció primària i secundària de les fractures per fragilitat [1].

El risc de tenir una fractura osteoporòtica augmenta amb l'edat i tenint en compte l'augment de l'expectativa de vida en els països desenvolupats, es considera l'osteoporosi un problema de salut pública a tenir en compte en la provisió de serveis sanitaris per la tendència creixent a fracturar-se de la població [2,3]. Les localitzacions comunament relacionades amb la fragilitat són la fractura vertebral, la de coll femoral, la del radi distal i, la d'húmer proximal [4,5]. En molts casos els individus tindran una fractura abans de saber que tenen osteoporosi, esdevindran en ingresos hospitalaris costosos des d'un punt de vista econòmic, sobretot en el cas de les fractures de maluc, i també humà pel risc de tenir una nova fractura i la discapacitat, comorbilitat o mortalitat derivada [6-8].

Sense menystenir el paper de la massa òssia i l'edat avançada en la fisiopatologia de la fractura, hi ha un interés creixent per la cerca activa d'altres factors de risc que en assaijos clínics i metaanàlisi han demostrat tenir una evidència ferma en la predicció del risc de fractura osteoporòtica, com l'antecedent personal o familiar de fractura, el sexe femení, l'índex de massa corporal (IMC), la presa de determinats fàrmacs osteopenitzants, algunes malalties o el risc de caigudes [3,9-12]. També s'han identificat factors relacionats amb l'estil de vida com el tabaquisme o el consum excessiu d'alcohol [13,14]. Paral.lelament hem assistit al desenvolupament

d'eines per estimar el risc de fractures per fragilitat en un temps determinat a través de models matemàtics que inclouen algunes d'aquestes variables, com l'algoritme FRAX® (*Fracture Risk Assessment*) [15], l'escala de risc QFracture [16] o la calculadora Garvan Fracture Risk [17]

3.1. L'algoritme FRAX

FRAX és una calculadora en línia desenvolupada per l'OMS en col.laboració amb la Universitat de Sheffield (Regne Unit) que utilitza factors de risc clínics independents de la massa òssia per a identificar homes i dones ≥ 40 i ≤ 90 anys amb una probabilitat alta de tenir una fractura de maluc i altres fractures osteoporòtiques considerades com a principals (fractura clínica vertebral, avantbraç, maluc i espatlla) en els propers 10 anys, permetent recalcular el risc de fractura si a més a més s'introdueix la DMO femoral (T-score) [18,19]. El model utilitzat per fer el càlcul de risc inclou població d'Europa, Amèrica, Àsia i Australia.

Les variables clíniques considerades per l'algoritme FRAX per calcular el risc absolut de fractura osteoporòtica són l'edat (entre 40 i 90 anys), el sexe, el pes (quilograms), l'alçada (centímetres), la fracturà prèvia per un traumatisme mínim, l'antecedent de fractura de maluc del pare o de la mare, el tabaquisme actiu, el consum d'alcohol (3 o més unitats al dia), la presa de glucocorticoesteroides durant més de 3 mesos (dosi diària de 5 mil.ligrams de prednisolona o del seu equivalent en altres corticosteroides) i el diagnòstic d'artritis reumatoide o d'altres osteoporosis secundàries (inclou la diabetis mellitus tipus 1, l'osteogènesi imperfecta en adults, l'hipertiroïdisme crònic no tractat, l'hipogonadisme o la menopausa precoç (<45 anys), la malnutrició crònica o malabsorció i la malaltia crònica hepàtica).

Conèixer el risc individual de tenir una fractura amb l'eina FRAX és una informació que el clínic pot utilitzar per pronunciar-se a la consulta en una decisió diagnòstica o

terapèutica centrada en el seu pacient. En els anys posteriors a la seva publicació al 2008, els diferents països inclosos en l'aplicació han avaluat com es comporta FRAX en cohorts diferents de les que es van utilitzar en la creació del model. Els treballs s'han centrat en la seva habilitat per discriminar els individus amb alt risc de fractura, la seva capacitat predictiva de fractura, i també en la determinació de llindars cost-efectius per la presa de decisions a la consulta [20-29]. Moltes de les conclusions d'aquests treballs s'han incorporat en les guies de referència per la facilitat d'accés i senzilla utilització de l'eina [30]. A l'ésser dissenyada per calcular el risc en funció de dades de fractura i mortalitat de cada país, no sempre coincideixen les GPC en les indicacions d'actuació, doncs els punts de tall per decidir realitzar una DXA o iniciar un tractament depenen de cada país i els recursos econòmics que destinen en la prevenció de la fractura per fragilitat.

3.2. Estudis a Espanya amb l'eina Frax

Per a la creació de l'eina de càlcul de fractura FRAX per població espanyola es van incloure dades d'incidència de fractura extretes de diferents estudis, majoritàriament estudis retrospectius i alguns prospectius d'àmbit regional, tots ells de finals dels anys vuitanta i principis dels noranta [31]. A Espanya, des del llençament de l'eina FRAX, diferents cohorts han avaluat el seu funcionament (base de dades CETIR i les cohorts ECOSAP i FRIDEX) [32-34], i han evidenciat una bona capacitat discriminativa de l'eina, però amb una tendència a infraestimar el risc de fractura principal osteoporòtica. Així mateix, s'ha publicat amb dades de la cohort FRIDEX un model de càlcul de risc de fractura que proposa uns llindars de risc amb valors de l'eina FRAX (calculat sense DMO) per població femenina (<5%, ≥5 a <7,5% i ≥7,5%). Aquest model està basat en les dades d'incidència real de fractures per fragilitat observades durant 10 anys en la cohort FRIDEX. Aquets punts de tall o llindars son equivalents als llindars (<10%), intermig (10-20%) i alt (> 20%) utilitzats per experts d'altres paisos com Canadà [35] per definir els graus o grups de risc de

fractura a la població. El model, una vegada feta aquesta estratificació en categories de risc, recalcula el FRAX incloent la DMO del coll femoral en el casos de risc no baix per saber quins individus de risc intermig passen a la categoria de risc alt, i quins entre els de risc alt passaven a la categoria de risc intermig o es mantenien en risc alt (≥ 7,5%) (annexe 4) [36]. L'aplicació del model dóna una informació que és d'utilitat al metge per prendre decisions cost-efectives de maneig diagnòstic o terapèutic centrades en el risc de fractura d'un pacient concret a la consulta:

- Prenent en consideració la pacient amb risc baix de fractura [FRAX (sense DMO <5%)], el model proposa promoure hàbits de vida osteosaludables i, en funció de l'edat i la presència d'altres factors de risc de fractura, recalcular el risc de fractura amb FRAX amb la periodicitat que sigui adequada.
- En el cas de que la pacient tingui un risc intermig de fractura [FRAX (sense DMO) ≥ 5 i <7,5%], el model indica que es calculi de nou el risc FRAX amb la T-score de coll femoral. Quan el risc FRAX (calculat amb la DMO) sigui <7,5% el model esmenta igualment fer consell d'estils de vida saludables i, en el cas que sigui ≥ 7,5% considerar a més a més la necessitat de tractament amb fàrmacs antiosteoporòtics.
- Per últim, quan la pacient tingui un risc alt de fractura [FRAX (sense DMO)≥ 7,5%], el model valora l'antecedent de fractures osteoporòtiques. En pacients amb antecedent de fractura de maluc, fractura vertebral o almenys 2 fractures osteoporòtiques en d'altres localitzacions es proposa considerar la instauració de tractament farmacològic. Per contra, sense antecedent de fractures per fragilitat o només 1 fractura que no sigui de maluc o vertebral s'examinaria de nou el risc FRAX amb la T-score de coll femoral com s'ha explicat en l'apartat anterior.

La primera publicació d'aquesta tesi doctoral és l'anomenada "*Rationale of the Spanish FRAX model in decision-making for predicting osteoporotic fractures: An*

update of FRIDEX cohort of Spanish women" a la revista BMC musculoskeletal disorders [37] [Factor d'impacte 2014: 1,717. Quartil i àrea: Q2 (30/72); Orthopedics].

En aquesta publicació s'amplia el nombre de casos de la cohort prospectiva FRIDEX (Factors de RIsc de fractura i DEnsitometria dual de raigs X) amb l'objectiu de confirmar les anàlisis preliminars sobre 816 dones en quan a la capacitat discriminativa i predictiva de l'eina FRAX i la comparació d'aquesta capacitat per discriminar la fractura de FRAX amb la utilització del valor de la DMO de la DXA (T-score ≤ -2,5 DE). Això és important perquè de les dades obtingudes de l'estudi inicial d'aquestes dones seguides durant 10 anys es va proposar el model FRIDEX per categoritzar el risc de fractura en dones espanyoles. Les característiques de la cohort FRIDEX estan descrites en detall en publicacions prèvies [34,38]. Està constituida per dones caucàsiques espanyoles ≥40 i ≤ 90 anys d'edat amb risc de fractura i sense tractament per a la osteoporosis, a les qui el facultatiu responsable sol·licita una DXA per a l'estudi inicial d'osteoporosi o per al seguiment de tractament. Al començament de l'estudi es recull el consentiment per a la realització d'un qüestionari dels principals factors de risc de fractura per fragilitat i contacte telefònic 10 anys després per determinar l'aparició de noves fractures.

La segona publicació d'aquesta tesi doctoral és l'anomenada "*Fracture experience among participants from the FROCAT study: what thresholding is appropriate using the FRAX tool?*" a la revista Maturitas [39] [Factor d'impacte 2014: 2,942. Quartil i àrea: Q1 (14/79); Obstetrice & Gynecology].

Aquesta publicació de la tesi és un estudi realitzat amb la cohort FROCAT que té com a objectiu validar externament el model FRIDEX de discriminació del risc de fractura en 3 nivells (baix, intermig i, alt). La cohort FROCAT està formada per dones majors de 40 anys representatives de població general assignades a metges de

familia de les 4 províncies catalanes estratificades per grups d'edat ajustats al perfil poblacional de Catalunya de l'any 2008.

4. OBJECTIUS

4.1. Objectiu principal

Validar externament el model FRIDEX, que determina els llindars de risc [baix (<5%), intermig (≥ 5 i <7,5%) i alt (≥7,5%)] de fractura principal a 10 anys, en dones de la població general (cohort FROCAT).

4.2. Objectius secundaris

- Avaluar la capacitat discriminativa de tenir una fractura per fragilitat de l'eina FRAX amb un major nombre de casos de la cohort femenina FRIDEX.
- Avaluar la capacitat discriminativa de tenir una fractura per fragilitat del model tradicional basat en la densitometria òssia (T-score ≤ -2,5 DE) amb un major nombre de casos de la cohort femenina FRIDEX.
- Comparar la capacitat discriminativa de tenir una fractura per fragilitat de l'eina FRAX vs el model tradicional basat en la densitometria òssia amb un major nombre de casos de la cohort femenina FRIDEX.
- Avaluar la capacitat predictiva de tenir una fractura per fragilitat de l'eina FRAX amb un major nombre de casos de la cohort femenina FRIDEX.
- Descriure els factors de risc que s'associen a la fractura per fragilitat en la cohort femenina FRIDEX.
- Descriure els factors de risc que s'associen a la fractura per fragilitat en una mostra representativa de la població femenina a Catalunya (la cohort femenina FROCAT).
- Descriure la incidència de fractures per fragilitat en una mostra representativa de la població femenina a Catalunya (la cohort femenina FROCAT).

5. ARTICLES

5.1. Article 1

Azagra R, Zwart M, Encabo G, Aguyé A, Martín-Sánchez JC, Puchol-Ruiz N, Gabriel-Escoda P, Ortiz-Alinque S, Gené E, Iglesias M, Moriña D, Díaz-Herrera MA, Utzet M, Manresa JM. Rationale of the Spanish FRAX model in decision-making for predicting osteoporotic fractures: An update of FRIDEX cohort of Spanish women. BMC musculoskeletal disorders. 2016;17(1). Available from: http://view.ncbi.nlm.nih.gov/pubmed/27317560.

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BMC Musculoskeletal Disorders

RESEARCH ARTICLE Open Access

Rationale of the Spanish FRAX model in decision-making for predicting osteoporotic fractures: an update of FRIDEX cohort of Spanish women

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Abstract

Background: The FRAX® tool estimates the risk of a fragility fracture among the population and many countries have been evaluating its performance among their populations since its creation in 2007.
The purpose of this study is to update the first FRIDEX cohort analysis comparing FRAX with the bone mineral density (BMD) model, and its predictive abilities.

Methods: The discriminatory ability of the FRAX was assessed using the 'area under curve' of the receiver operating characteristic (AUC-ROC). Predictive ability was assessed by comparing estimated risk fractures with incidence fractures after a 10-year follow up period.

Results: One thousand three hundred eight women ≥ 40 and ≤ 90 years followed up during a 10-year period. The AUC for major osteoporotic fractures using FRAX without DXA was 0.686 (95 % CI 0.630–0.742) and using FN T-score of DXA 0.714 (95 % CI 0.661–0.767). Using only the traditional parameters of DXA (FN T-score), the AUC was 0.706 (95 % CI 0.652–0.760). The AUC for hip osteoporotic fracture was 0.883 (95 % CI 0.827–0.938), 0.857 (95 % CI 0.773–0.941), and 0.814 (95 % CI 0.712–0.916) respectively. For major osteoporotic fractures, the overall predictive value using the ratio Observed fractures/Expected fractures calculated with FRAX without T-score of DXA was 2.29 and for hip fractures 2.28 and with the inclusion of the T-score 2.01 and 1.83 respectively. However, for hip fracture in women < 65 years was 1.53 and 1.24 respectively.

Conclusions: The FRAX tool has been found to show a good discriminatory capacity for detecting women at high risk of fragility fracture, and is better for hip fracture than major fracture. The test of sensibility shows that it is, at least, not inferior than when using BMD model alone. The predictive capacity of FRAX tool needs some adjustment. This capacity is better for hip fracture prediction and better for women < 65 years. Further studies in Catalonia and other regions of Spain are needed to fine tune the FRAX tool's predictive capability.

Keywords: Osteoporosis, Fracture, FRAX, FRIDEX, Study cohort, Algorithm

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Background

Osteoporosis is of particular public health interest due to its association with subsequent fractures and the well-documented risk of mortality and disability leading to an increase in medical care costs in many regions of the world as a result [1, 2].

Over the last decade the attitude towards osteoporotic fracture risk evaluation has changed because an increase in information about using various clinical risk factors (CRFs) and not only the values of bone mineral density (BMD) [3]. To provide risk assessment, especially for those professionals who are less familiarized with the approach to this health problem, several prediction models have been developed to be used in clinical practice. There are three instruments that have been commonly used in recent times that help to identify people at a high risk of osteoporotic fracture over a period of time: the FRAX® (Fracture Risk Assessment tool) [4], the QFractureScores [5] and the Garvan Fracture Risk Calculator [6, 7].

FRAX instrument was launched by WHO in 2008, and gives the absolute risk of fragility fracture as a percentage during a 10-year period. The risk estimate is carried out by a calculator available online by putting in the value of clinical variables that have shown a strong association with osteoporosis and fracture across different studies and systematic reviews [8–14]. The calculator is able to recalculate the risk with the inclusion of Dual-energy X-ray absorptiometry (DXA) parameters. Epidemiological osteoporotic fracture data in four areas has been used in its construction (clinical spine, distal forearm, hip or proximal humerus), as well as the mortality data available from different continents. Once the tool has been accessed online, it is necessary to select the relevant study population. During the last few years, there have been several studies focused on evaluating how FRAX behaves among different populations other than the one in which the model was developed. Systematic reviews identify studies that assess the FRAX tool ability to discriminate between individuals who are at risk of fracture and those who are not. Also, its predictive ability to identify people at high risk of future fractures, fracture risk thresholds and identifying which risk thresholds are cost-effective when it comes to carrying out a therapeutic intervention. It is still to be determined whether the CRFs are of significance on the outcome of fracture data in different cohorts [15–24].

In Spain, FRAX performance has been assessed during its use in different cohorts since 2008 and it has shown a good discriminative capacity, but a tendency to underestimate major osteoporotic fractures has been observed [25–27]. However, the underestimation was lower in cases of hip osteoporotic fractures. This does not detract from the strengths of the tool for clinical use in decision-making as long as their possible limitations are taken into account.

This study aims to expand the sample before FRIDEX cohort [25] to test the FRAX algorithm against the results of reliability of BMD in its discriminative and predictive ability for predicting absolute risk of fracture in 10 years. This is to provide more evidence for clinicians about how well the tool performs among the Spanish population.

Methods

The FRIDEX cohort features have previously been published [28]. At the beginning of the study, the participants underwent axial bone densitometry DXA after accepting by informed consent to answer a questionnaire on risk factors (QRF) for osteoporotic fracture and further contact. Self-reported incident fractures 10 years later were assessed using a telephone questionnaire (TQ).

Eligibility criteria

Patient inclusion criteria

Randomized sample (simple computerized randomization stratified) was obtained from Caucasian women ≥ 40 and ≤ 90 years of age at the time of inclusion in the FRIDEX cohort, who understood and spoke the Spanish language, and were able to respond to the initial QRF and a 10-year follow up TQ. None of these patients had been treated with antiosteoporotic medication (AOM) prior to the study. Some of these patients, however, may have been treated with AOM during the 10-year study period.

Patient exclusion criteria

Patients who refused informed consent to participate in the study and those without a telephone contact number or did not respond after 3 phone calls made at different times according to the procedure manual. Patients with physical or psychological difficulties that prevented their participation in the study with or whose relatives refused them permission to participate. Subjects with Paget's disease or bone cancer were also excluded.

Data collection

The baseline QRF variables were collected from 2000 to 2010 along with DXA, and they included patient demographic (date of birth, sex) and anthropometric characteristics (weight, height, body mass index (BMI)). During the same visit, clinical risk factors for fracture including QRF were recorded as well: family history of hip fracture (father/mother), medical history of fragility fracture, smoking, alcohol risk intake, history of glucocorticoids intake and medical history of antiosteoporotic medication.

Analysis carried out by using a Lunar GE model *Prodigy Advance* densitometer with 11.4 software and with BMD and T-score determination with NHANES III references. DXA criteria were determined according to the recommendations made by the International Society for Clinical Densitometry (ISCD) in 2007 (http://www.iscd.org/official-positions/). The densitometry diagnostic criteria of osteoporosis used were the 1994 WHO criteria (T-score ≤ −2.5 standard deviation of the average mean value for young women at the femoral neck (FN)) [29].

After a 10-year follow up period (2000–2010) variables regarding new self-reported fragility fractures occurring from the time of inclusion and number of falls over the last year were collected. The major osteoporotic fractures (hip, humerus, forearm and clinical spine) during the follow up period were taken as the endpoint event. In all cases of fracture, medical records were contrasted and those cases of self-reported fractures that were impossible to confirm with medical records were also excluded from analysis.

The estimated absolute risk of sustaining a major osteoporotic fracture or hip fracture during the 10-year period according to the FRAX-Spain tool (both with and without baseline FN T-score) was determined through the official website (version 3.2 accessed on October 2010) and analysed by two blinded investigators.

Statistical analysis

The characteristics of the population were described according to descriptive univariate analysis. We used the Chi-square test to evaluate the association between qualitative variables. The Student's t-test or, if necessary, its nonparametric equivalent, the Mann-Whitney U test, was implemented to evaluate the differences in the distribution of a quantitative variable according to the categories defined by a binary exposure. To assess the differences in the distribution of a quantitative variable according to the categories defined by a categorical variable with more than two categories, ANOVA analysis of variance or its corresponding non parametric test (Kruskal-Wallis) were used.

The discriminating ability of the FRAX tool to identify people at increased risk of fracture after a 10-year period was assessed using the area under the curve (AUC) of receiver operating characteristic (ROC) curves and the Hosmer-Lemeshow goodness-of-fit test.

The calibration was assessed by comparing estimated risk of fracture with observed fracture incidence.

All the statistical tests were undertaken with a confidence interval of 95 % and with the use of the 17th version of the SPSS statistical package.

This work follows the STROBE initiative for cohort studies' guidelines [http://www.strobe-statement.org/index.php?id=strobe-publications WebCite].

Results

Three thousand three hundred ninety-seven cohort patients were 2:1 randomly selected among patients who had completed the 10-year period. A total of 1918 women were contacted at the end of the 10-year period and in 1479 cases was impossible to contact by telephone: 490 (14.4 %) unknown telephone or postal address, 792 failed to respond to 3 calls (23.3 %), and 197 deaths (5.8 %). Out of 86 subjects that refused to participate (4.5 %), 33 were excluded due to cancer (1.8 %) and 491 because they had been receiving AOM at baseline (25.6 %). This left a total of 1308 participants that fulfilled the inclusion criteria and provided informed consent to participate in the study.

Table 1 shows the distribution of the baseline characteristics in the individuals selected and those selected, but did not participate in the study. Overall, no significant differences were observed between these two groups. The only significant differences were found among participants with a 2 year age differences (57.5 vs. 59.3 years), that had had fewer previous fractures (22.6 vs 26.0 %), were taking less glucocorticoids (4.7 vs. 6.5 %) and had less osteoporosis according to baseline DXA scan (32.7 vs 37.3 %).

We examined the frequency of fragility fractures during the 10-year study period: a total of 153 fractures were registered, 133 of which corresponded to any of the four areas of FRAX major osteoporotic fractures: hip, humerus, forearm or clinical spine. 108 women reported a total of 133 major osteoporotic fractures which were contrasted: 26 women with 27 hip fractures, 26 with 33 proximal humerus fractures, 40 with 56 distal radius fractures, and 16 with 20 clinical vertebral fractures (Table 2).

A summary of the main participants' characteristics can be seen in Tables 3 and 4 (with their relative risks [RR]). Every risk factor is shown and categorized as major or hip fracture respectively. Risk factors included in the FRAX tool were also taken into consideration, along with the variable of falls during the previous year. The BMD measurement computed by WHO international reference standard for description of osteoporosis as a T-score ≤ −2.5 standard deviation (SD) and osteopenia as a T-score between −1.0 and −2.5 SD was also taken into account. The CRFs values across both major and hip fractures show significant differences in age, previous fractures and due to the existence of DXA osteoporosis diagnosis. Table 3 shows in the analysis of major osteoporotic fracture significant differences in patients with fractures related to low BMI and in patients without fractures related to normal baseline DXA. Table 4 shows significant differences among patients with rheumatoid arthritis and taking corticoids in the hip osteoporotic fracture group.

Table 1 FRIDEX cohort (Contacted/Non-Contacted)

	Contacted	Non-Contacted	*p*-value	95 % CI
	1918 (56.5 %)	1479 (43.5 %)		
Age (SD)	57.5 (8.1)	59.3 (9.9)	0.001	[1.1–2.4]
BMI Kg/cm^2 (SD)	27.7 (4.6)	27.5 (4.5)	0.506	ns
BMI < 20 Kg/cm^2 (%)	2.4	2.6	0.723	ns
Personal history of fractures (%)	22.6	26.0	0.014	[0.5–6.3]
Parental Hip Fracture (%)	22.7	21.1	0.335	ns
Current Smoking (%)	10.8	10.8	0.802	ns
High alcohol intake (%)	0.7	0.9	0.667	ns
Glucocorticoids (%)	4.7	6.5	0.022	[0.2–3.4]
Rheumatoid arthritis (%)	1.3	1.8	0.158	ns
Ca + vitamin D supplements (%)	22.2	22.2	0.916	ns
Osteoporosis in DXA (%)	32.7	37.3	0.012	[1.4–7.8]

CI confidence interval, *SD* standard deviation, *BMI* body mass index, *ns* non statistical significance, *DXA* dual-energy X-ray absorptiometry

The mean of FRAX risk for major fracture among women with fracture was 6.44 (6.94 SD) without FN T-score and 8.25 (9.19 SD) with FN T-score, and for hip fracture it was 2.38 (5.20 SD) and 3.59 (7.39 SD), respectively. The mean for major fracture among without fracture women was 3.35 (2.81 SD) without FN T-score and 3.73 (3.48 SD) with FN T-score, and for hip fracture it was 0.74 (1.40 SD) and 0.86 (1.94 SD), respectively. All measurements show significant differences ($p < 0.001$) between women with fracture and without fracture.

The AUC ROC analysis was carried out to compare fracture discrimination on the basis of three different scenarios for major and hip fractures: guidance on the basis of BMD testing alone in decision-making (FN T-score), FRAX tool calculated without BMD, and FRAX with FN T-score. For major fracture the best-case scenario was obtained with FRAX tool including FN T-score [AUC = 0.714, 95 % CI 0.661–0.767], followed by FN BMD alone [AUC = 0.706, 95 % CI 0.652–0.760] and FRAX tool without BMD [AUC = 0.686, 95 % CI 0.630–0.742]. For hip fracture the best-case performance analysis was obtained with FRAX without BMD [AUC = 0.883, 95 % CI 0.827–0.938], followed by FRAX including FN T-score [AUC = 0.857, 95 % CI 0.773–0.941] and FN BMD alone [AUC = 0.814, 95 % CI 0.712–0.916]. In all cases, the results showed significant differences ($p < 0.001$) with the reference value [AUC = 0.50].

The adjusted predictive capacity of FRAX analysed using the mean ratio between observed fractures (ObsFx) during the 10-year follow-up period of the cohort and the fracture risk estimates rates (ExpFx) was 2.29, CI 95 % 1.91–2.74) for major osteoporotic fracture and 2.28 [CI 95 % 1.56–3.32] for hip fracture using the FRAX tool without BMD, and on the introduction of the FN T-score was 2.01 [CI 95 % 1.68–2.41] and 1.83 [CI 95 % 1.25–2.67], respectively (Table 5). This ratio remained similar when we categorized the results based on age, except among women younger than 65 years of

Table 2 All fractures at 10 year follow up in two groups of age

	<65 years	≥65 years	Total	*p*-value	95 % CI
	n = 1056 (80.7 %)	*n* = 252 (19.3 %)	*n* = 1308		
Age (SD)	54.1 (5.3)	70.3 (4.4)	57.2 (8.2)	<0.001	[15.6–16.9]
	Women/Fractures	Women/Fractures	Women/Fractures		
All fractures	101/1.29 (9.6 %)	52/74 (20.6 %)	153/208 (11.7 %)	<0.001	[5.7–16.3]
Major fractures[a]	65/78 (6.2 %)	43/55 (17.1 %)	108/133 (8.3 %)	<0.001	[6.0–16.8]
Hip	6/6 (0.6 %)	20/21 (7.9 %)	26/27 (2.0 %)	<0.001	[3.9–10.7]
Vertebral	10/13 (1.0 %)	6/7 (2.8 %)	16/20 (1.4 %)	0.026	[0.3–3.9]
Humerus	21/24 (2.3 %)	5/9 (3.2 %)	26/33 (2.4 %)	0.409	ns
Wrist	28/35 (2.9 %)	12/18 (6.0 %)	40/56 (3.5 %)	0.016	[0.2–6.2]

CI confidence interval, *SD* standard deviation, *ns* non statistical significance
[a]Major osteoporotic fractures (hip, vertebra, humerus, wrist)

Table 3 Baseline fracture risk factors between patients for 'major osteoporotic fracture'

	With Fracture (*n* = 108)	Without Fracture (*n* = 1200)	*p*- value	95 % CI	RR	RR 95 % CI
Age (SD)	61.6 (9.4)	56.8 (8.0)	<0.001	[2.9–6.6]		
Age > 65 years (%)	39.8	17.4	<0.001	[12.9–31.9]	2.77 [a]	[1.9–4.0]
BMI (SD)	27.6 (4.6)	28.0 (4.7)	0.518	ns	-	-
BMI < 20 (%)	5.6	2.3	0.036	[1.1–7.7]	2.27 [b]	[1.1–4.4]
Previous fracture (%)	42.6	19.5	<0.001	[13.5–32.7]	2.72	[1.9–3.9]
Parental hip fracture (%)	15.7	14.1	0.637	ns	1.13	[0.7–1.8]
Smoker (%)	9.3	11.7	0.452	ns	0.79	[0.4–1.4]
Alcohol risk (%)	0.9	0.7	0.541	ns	1.35	[0.2–5.4]
Corticoids (%)	8.3	4.7	0.093	ns	1.74	[0.9–3.2]
Rheumatoid arthritis (%)	2.8	1.0	0.120	ns	2.46	[0.9–5.7]
Falls previous year (%)	34.3	22.3	0.005	[2.7–21.3]	1.71	[1.2–2.5]
Osteoporosis (baseline DXA) (%)	51.9	26.1	<0.001	[16.1–33.6]	6.07 [c]	[2.9–12.9]
Osteopenia (baseline DXA) (%)	41.7	49.9	0.103	ns	2.95 [d]	[1.4–6.4]
Normal (baseline DXA) (%)	6.5	24.0	<0.001	[12.3–22.7]	-	-

CI confidence interval, *RR* relative risk, *SD* standard deviation, *BMI* body mass index, *ns* non statistical significance, *DXA* dual-energy X-ray absorptiometry
[a] < 65 vs ≥ 65 years
[b] < 20 vs ≥ 20
[c] Osteoporosis vs normal
[d] Osteopenia vs normal

age in which case the FRAX without/with BMD result dropped in the hip fracture category to 1.53 [CI 95 % 0.70–3.32] and 1.24 [CI 95 % 0.57–2.68], respectively.

The Hosmer-Lemeshow test was carried out in order to assess the 'goodness of fit' obtained by grouping data according to quintiles of results of fracture (Fig. 1). First of all it shows the observed and predicted values of the sample within major fracture and hip fracture for the results of the FRAX tool without BMD and with the FN BMD T-score. It then shows the same results after multiplication (simulation) by approximately the number of times that the ObsFx is greater than the ExpFx.

Table 4 Baseline fracture risk factors between patients for 'hip osteoporotic fracture'

	With fracture (*n* = 26)	Without fracture (*n* = 1282)	*p*- value	95 % CI	RR	RR 95 % CI
Age (SD)	69.7 (6.8)	56.9 (8.0)	<0.001	[9.7–15.9]	-	-
Age > 65 (%)	76.9	18.1	<0.001	[42.5–75.1]	13.97 [a]	[5.8–33.5]
BMI (SD)	27.2 (3.5)	27.9 (4.8)	0.310	ns		
BMI < 20 (%)	3.8	2.5	0.664	ns	1.55 [b]	[0.3–8.2]
Previous fracture (%)	53.8	20.7	<0.001	[13.8–52.4]	4.28	[2.0–9.0]
Parental hip fracture (%)	19.2	14.1	0.460	ns	1.44	[0.6–3.6]
Smoker (%)	0	11.7	0.063	ns	-	-
Alcohol risk (%)	0	0.7	0.834	ns	-	-
Corticoids (%)	15.4	4.8	0.036	[3.3–24.5]	3.48	[1.3–9.2]
Rheumatoid arthritis (%)	7.7	1.0	0.034	[3.6–17.0]	7.18	[1.9–22.3]
Falls previous year (%)	38.5	23.0	0.065	ns	2.06	[1.0–4.4]
Osteoporosis (baseline DXA) (%)	65.4	27.5	<0.001	[19.4–56.3]	6.80 [c]	[1.8–26.3]
Osteopenia (baseline DXA) (%)	26.9	49.7	0.021	[5.5–40.1]	1.60 [d]	[0.4–6.8]
Normal (baseline DXA) (%)	7.7	22.9	0.067	ns	-	-

CI confidence interval, *RR* relative risk, *SD* standard deviation, *BMI* body mass index, *ns* non statistical significance, *DXA* dual-energy X-ray absorptiometry
[a] < 65 vs ≥ 65 years
[b] < 20 vs ≥ 20
[c] Osteoporosis vs normal
[d] Osteopenia vs normal

Table 5 Ratio Observed fractures/Expected fractures by FRAX tool by age

	Major fractures[a]				Hip fractures			
All (1308 women)	Obs Fx	Exp Fx	Ratio Obs/Exp	CI 95 %	Obs Fx	Exp Fx	Ratio Obs/Exp	CI 95 %
FRAX tool without BMD	108	47.1	2.29	[1.9–2.4]	26	11.41	2.28	[1.6–3.3]
FRAX tool with T-score FN	108	53.6	2.01	[1.7–2.4]	26	14.20	1.83	[1.3–2.7]
<65 years (1056 women)	Obs Fx	Exp Fx	Ratio Obs/Exp	CI 95 %	Obs Fx	Exp Fx	Ratio Obs/Exp	CI 95 %
FRAX tool without BMD	65	27.2	2.39	[1.9–3.0]	6	3.91	1.53	[0.7–3.3]
FRAX tool with T-score FN	65	30.6	2.12	[1.7–2.7]	6	4.84	1.24	[0.6–2.7]
≥65 years (252 women)	Obs Fx	Exp Fx	Ratio Obs/Exp	CI 95 %	Obs Fx	Exp Fx	Ratio Obs/Exp	CI 95 %
FRAX tool without BMD	43	19.9	2.16	[1.6–2.8]	20	7.50	2.67	[1.7–4.0]
FRAX tool with T-score FN	43	23.0	1.87	[1.4–2.4]	20	9.36	2.14	[1.3–3.2]

ObsFx observed fractures, *ExpFx* expected fractures, *CI* confident interval, *BMD* bone mineral density, *FN* femoral neck
[a]Major fractures (hip, vertebra, humerus, wrist)

Discussion

The FRAX tool has been analysed in this study to measure its discriminative capacity as a model for the prediction of osteoporotic fracture compared with the BMD model, as well as its predictive capacity and the 'goodness of fit' among the Spanish female population. A previous calibration test as an evaluation of the reliability assessment of FRIDEX cohort results was carried out using a lower number of women [25]. This analysis suggests that the results are consistent with the abovementioned population. This study also provides information on the frequency of risk factors of osteoporotic fractures.

Risk factors of osteoporotic fracture

Age is a variable related to the incidence of fracture and in our cohort the overall reported rates of fractures is higher in the group over 65 years old ($p < 0.001$). When focusing individually on hip, clinical spine, forearm and humerus fractures, the proportion of fractures increases with age. However, these differences were not statistically significant in the case of humerus fractures in our sample. In addition to age, prior fragility fracture, low BMI, rheumatoid arthritis or glucocorticoids intake are clinical factors related to the pathogenesis of osteoporotic fracture, and indeed, the results of our study have shown statistical significance in major fracture and hip fracture. These results align well with other studies undertaken in our population, which have identified the same relevant factors for fragility fracture except for BMI [30]. We also have found previously published data that investigate relationship between BMI and fracture in Spanish postmenopausal women, but focusing in high BMI. In this context, some reported a relation between vertebral fracture and high BMI [31] and, conversely, other studies found no relation in this site, only for proximal humerus fractures [32]. So further studies will be needed to clarify these variations.

We also note that in evaluating Spanish FRAX tool estimates without T-score, the risk of main fracture and hip fracture obtained is significantly higher among women with fractures than those without fractures. The contribution of BMD in the osteoporotic fracture risk is reflected in the results of our sample as well, showing a lower average of BMD and increased FRAX estimates with FN T-score between women with fracture compared to women without fracture ($p < 0.05$) (Tables 3 and 4).

Assessing FRAX-Spain discrimination performance

The ROC analysis used to assess the discriminatory capacity of the FRAX osteoporotic fracture estimates, shows a more accurate AUC of FRAX in major fractures with a FN T-score [0.714, 95 % CI 0.661–0.767] and for hip fracture with FRAX without BMD [0.883, 95 % CI 0.827–0.938)]. These findings match those already reported in the previous FRIDEX sample and are similar to those found in other research conducted in Spain [25, 27].

The aforementioned finding bear out the current trend for assessing fracture risk using clinical risk factors rather than only using the DXA results.

Regarding the older population with a higher susceptibility to fractures, especially in the case of hip fractures, these results are particularly relevant as they enhance clinical decision-making in practices that have a more limited access to DXA. It is worth noting that results in other nearby countries have shown a similar ability using FRAX with FN T-score to identify women at a high risk of major fracture compared to when the FN BMD is solely used [15, 19].

Assessing FRAX-Spain predictive performance

The adjusted predictive capacity of the FRAX tool analysed using the ObsFx/ExpFx ratio shows no correlation

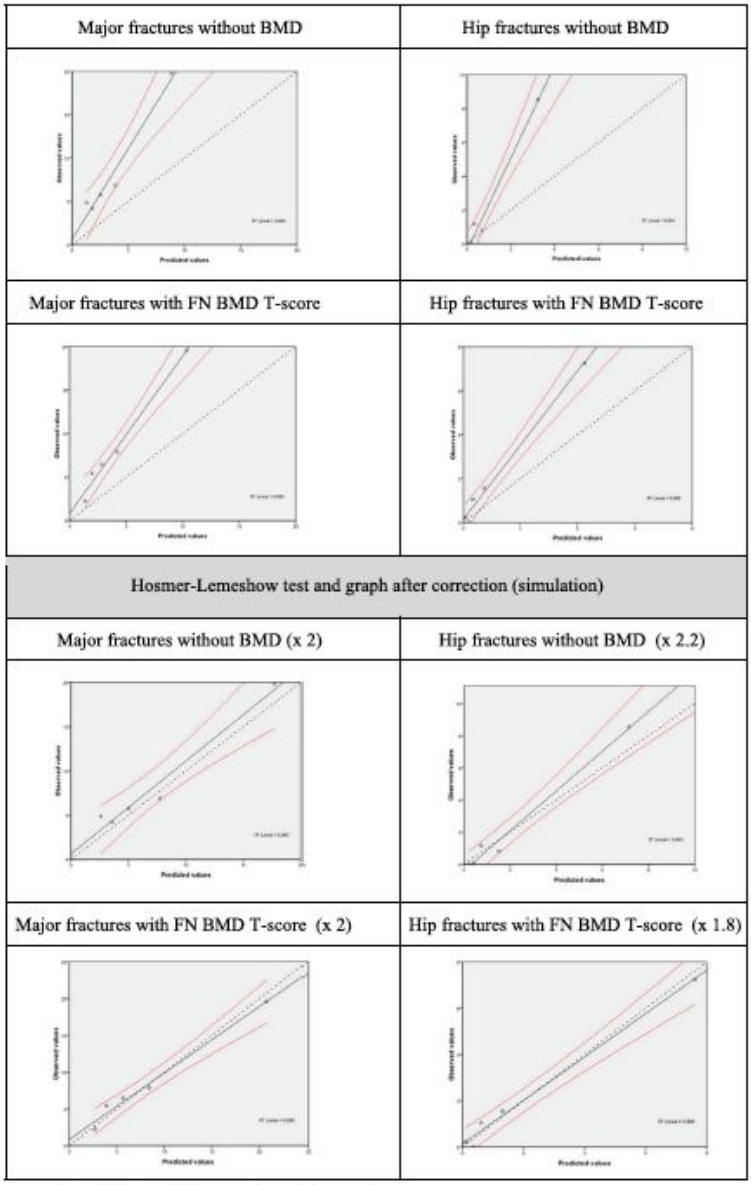

Fig. 1 Hosmer-Lemeshow test with the original results of the FRAX tool

between observed and expected fracture rates among Spanish population. All the women in the sample cohort when analysed together showed a higher frequency of fragility fracture (close 2 times more) than would be expected with FRAX tool either if it is calculated with the FN T-score or without BMD (Table 5). This difference is lower for hip fracture with FRAX with FN T-score of DXA (ObsFx/ExpFx ratio all cohort 1.83) and clearly better in women < 65 years old (Table 5). It could be explained by the mean age of the women in the study, with 80 % of the cohort being under the age of 65. Osteoporotic fracture that tends to occur in early menopause

affects the lumbar spine more than the hip, as hip BMD decreases exponentially with advancing age [33–35]. As observed in our study, when the ratio of observed to expected hip fracture is calculated for those aged 65 or older with FRAX with FN T-score, the probability of hip fracture increases two fold again.

The Hosmer-Lemeshow test was carried out to assess the goodness of fit between observed fractures and the expected fractures according to FRAX. A satisfactory goodness of fit was obtained by multiplying the results by the ObsFx/ExpFx ratio taking into account the CI 95 % (Fig. 1).

The Spanish FRAX model has been evaluated in other cohorts. The ECOSAP cohort published similar hip fracture risk prediction, but they did not collect clinical vertebral fractures, therefore the interpretation of the results for prediction of major osteoporotic fractures is difficult [26]. In contrast, the methodology for collecting incident fractures considered by FRAX in the CETIR database was complete (clinical spine, hip, distal forearm and proximal humerus) and self-reported with further validation too [27]. In the results observed, the ObsFx/ExpFx ratio for major fractures was 2.4 (CI 95 %: 2.1–2.7) and 0.8 (CI 95 %: 0.6–1.1) for hip fractures. Therefore, the major fracture results are in accordance with our findings indicating that the FRAX model underestimates fracture risk in Spanish women [25]. The possible explanation for this underdiagnosed has already been justified because for Spain, the data included in FRAX are from studies conducted in the 90s [25–27], validated in areas of a low incidence of hip fracture and more up-to-date fracture incidence and mortality data is required for fracture predictions [18, 36–38]. Therefore, some authors have suggested that these methodological factors may affect the interpretation of calibration, and should be taken into account before making an assessment of the tool [39–41]. The ratio for hip fracture in this case is closer to 1, the desired value. One possible explanation of this lack of accuracy may be due to the fact that, although the initial formation of the two cohorts followed very similar schemes, the other female Spanish cohorts were younger [25, 27]. The differences among the three Spanish cohorts' findings can also be justified by the fact that the ECOSAP and CETIR cohorts were comprised of a low proportion of women over 70 years, a shorter average follow-up period, a low proportion of hip fractures and a different method of follow up was used [26, 27]. Therefore, this could account for the differences in the hip fracture ratio. The predicted probabilities of fragility fracture using the Spanish FRAX tool have also been analysed in FRODOS and ESOSVAL cohorts but the observed incidence of osteoporotic fracture was not recorded. Therefore, their data cannot be used to assess the predictive ability of the tool [42, 43].

The study has some strengths and limitations. The strengths of our study include among the 3397 potentially eligible subjects contacted for the study, there were no significant differences in most of the basic characteristics between participants and non-participants. The differences found in mean age, prior fracture, corticosteroids use and osteoporosis BMD result were very small, thus we assume that the sample was representative from the population from which it was taken. To determine incident osteoporotic fractures some countries, in the first place, review hospital hip fracture discharge statistics assuming that all proximal femoral fractures result in hospitalization. In the case of the remaining major fractures (humerus, clinical spine, forearm) others studies used incidence fracture data taken from a cohort in Malmö, working on the premise that the ratios would be similar [44–48]. In the present study, all fractures recorded via the use of a telephone questionnaire were contrasted with existing medical record data and only included in the final analysis if the fractures were also found both in the medical records and via the telephone questionnaire. There are also limitations. Working on the assumption that the women included in the FRIDEX cohort could have a higher risk of osteoporotic fractures than the general population due to the fact that it is a population that had previously been selected to undergo a DXA scan for different reasons. Currently, there is evidence that the women included in the FRIDEX cohort have not a higher incidence of fragility fracture than the general population, although they have more risk factors for fragility fracture [7, 25, 49]. In the present analysis, deceased patients were excluded and this should be taken into consideration. Despite the fact the number of deceased patients only made up 5.8 % of the cohort, it could lead to a misinterpretation of observed fractures [50]. Finally, our data has been confined to women and we still do not know if a similar result would be obtained in men, further studies would be necessary to ascertain this.

Conclusions

In summary, based on the study's finding, the FRAX tool has been found to show a good discriminatory capacity for detecting women at high risk of fragility fracture. In the case of hip fractures, this discriminatory capacity of the FRAX tool without BMD was found to be higher than when using BMD alone. Possibly, further studies in Catalonia and other regions of Spain would be required to fine tune the FRAX tool's predictive capability.

Abbreviations

AOM, antiosteoporotic medication; AUC, area under curve; BMD, bone mineral density; BMI, body Mass Index; CI, confidence Interval; CRFs, clinical risk factors; DXA, dual-energy X-ray absorptiometry; ExpFx, expected fractures; FN, femoral neck; ISCD, International Society for Clinical Densitometry; ObsFx,

observed fractures; QRF, questionnaire on risk factors; ROC, receiver operating characteristic; RR, relative risk; SD, standard deviation; TQ, telephone questionnaire.

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Availability of data and materials
There is a willingness to share primary data related to the research on request, presented in additional file in machine-readable format.

Authors' contributions
Study conduct: RA, GE. Data collection: RA, MZ, GE, AA, NP, PG, SO, MI, MAD. Data analysis: RA, JCM, DM, MU, JM. Data interpretation: RA, JCM, DM, MU, JM. Drafting manuscript: RA, MZ, JCM, DM. Revising manuscript content: RA, MZ. Approving final version of manuscript: RA, MZ, GE, AA, JCM, NP, PG, SO, EG, MI, DM, MAD, MU, JM. RA takes responsibility for the integrity of the data analysis.

Competing interests
The authors declare that they have no competing interests.

Consent for publication
Not applicable.

Ethics approval and consent to participate
This work has been approved by the ethical committee of the Clinical Research Ethics Committee of the Vall d'Hebron University Hospital (Barcelona, Spain). All subjects were informed and had given the consent to participate.

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5.2. Article 2

Azagra R, Zwart M, Aguyé A, Martín JC, Casado E, Díaz-Herrera MA, Moriña D, Cooper C, Díez-Pérez A, Dennison EM; on behalf of FROCAT Study Group. Fracture experience among participants from the FROCAT study: what thresholding is appropriate using the FRAX tool? Maturitas. 2016;83:65-71. Available from: http://dx.doi.org/10.1016/j.maturitas.2015.10.002.

6. DISCUSSIÓ

El conjunt dels 2 articles que s'exposen a continuació configuren una unitat temàtica en la present tesi per compendi de publicacions, amb l'objectiu final de validar un model de categorització del risc de fractura per fragilitat en població femenina espanyola basat en l'algoritme FRAX de l'OMS publicat al 2008 [15]. Es tracta de 2 estudis en diferents cohorts de dones espanyoles amb seguiment a 10 anys.

6.1. Article 1

L'article 1 "*Rationale of the Spanish FRAX model in decision-making for predicting osteoporotic fractures: An update of FRIDEX cohort of Spanish women*" és una ampliació de la cohort FRIDEX [34,37,38], constituida per 1308 dones caucàsiques entre 40 i 90 anys en el moment de començar l'estudi, que havien estat derivades a fer una DXA a la Unitat de Densitometria Òssia de l'Hospital Universitari Vall d'Hebron pel seu metge de familia o altres especialistes tant extrahospitalaris com del propi hospital, seguint la pràctica mèdica habitual que suposa sol.licitar una DXA davant la presència d'algun factor de risc de fractura. El periode d'estudi va ser el comprès entre els anys 2000 i 2010. Es va dur a terme una selecció aleatoria estratificada per edat de dones que no prenien cap medicació per l'osteoporosi en el moment d'ingressar en la cohort. Es va obtenir el consentiment de les participants prèvia informació sobre la seva participació en l'estudi, consistent en respondre a un qüestionari inicial sobre factors de risc de fractura osteoporòtica i atendre a una trucada telefònica que recollia l'aparició de nous factors de risc de fractura i incidència de noves fractures a conseqüència d'un traumatisme mínim al final del periode de seguiment de 10 anys.

La variable principal d'avaluació en l'estudi era l'aparició de noves fractures per baix impacte relatades per les participants des del moment d'inclusió en l'estudi a l'any

2000. En aquest sentit els investigadors van comprovar en tots els casos de fractures incidents que tinguessin un registre confirmatori en el historial clínic hospitalari o d'Atenció Primària i no fossin produides per un traumatisme d'alt impacte. Les localitzacions d'interés de les fractures recollides eren les clàssicament considerades com a osteoporòtiques (excloses les de la cara, cap i dits). El document de recollida de dades permetia identificar la refractura en una mateixa localització. Es van contrastar totes les fractures explicades per les pacients amb els registres mèdics corresponents accesibles des de la història clínica informatitzada, i es van excloure de l'estudi els casos en que no es van poder confirmar. A fi de l'anàlisi de dades es van combinar les fractures seguint el criteri de fractures principals de l'eina FRAX *[major osteoporotic fracture]* que agrupa les que tenen lloc a nivell de columna vertebral, maluc, canell i espatlla. La rigurositat en la recollida de les fractures osteoporòtiques incloses en el treball és una de les fortaleses de l'estudi, i és d'especial rellevància per les fractures en altres localitzacions diferents de la de maluc. Per determinar la incidència de fractures de maluc alguns països fan una revisió de les altes hospitalàries a on consta el codi de fractura de maluc amb la presumpció que totes les fractures en aquesta localització són ateses als seus serveis d'urgències o resulten en hospitalització [40-43]. En el casos que no es disposen de registres propis sobre dades de fractura (vèrtebra, canell i espatlla) fan una extrapolació de les incidències calculades a Suècia, assumint que els valors seran similars als observats en aquest país [44-45]. En el nostre estudi el registre de noves fractures es va fer a través d'un qüestionari telefònic estructurat amb inclusió només de les que s'havien comprovat en registres mèdics, evitant la duplicació de registres quan s'utilitzen bases de dades nacionals (per exemple per reingressos de la mateixa persona) o la inclusió de totes les fractures de maluc sense diferenciar de manera apropiada les secundàries a fragilitat de les d'un fort impacte. En qualsevol cas, el fet que les noves fractures siguin referides pels pacients o siguin extretes de registres oficials condiciona que s'estiguin infraestimant la presència de fractures vertebrals morfomètriques i aquelles fractures

vertebrals desconegudes tant pel pacient com pel metge. Una altra possible limitació de les dades aportades amb aquest estudi és la manera de detectar les fractures que les pacients no recorden.

6.1.1. Els factors de risc de fractura osteoporòtica

Entre els factors clínics de fractura osteoporótica es van analitzar el que s'utilitzen en el càlcul de risc de fractura amb l'eina FRAX i també les caigudes en l'any anterior. L'edat és una de les variables que es relacionen de manera més robusta amb la fractura osteoporòtica, i en la nostra cohort de manera global la incidència de fractures era més gran en el grup de més de 65 anys ($p<0,001$). També la proporció de fractures de maluc, columna vertebral, avantbraç i húmer analitzades de manera individual augmentava amb l'edat. No obstant això, aquestes diferències no van ésser significatives en el cas de les fractures d'húmer. A més de l'edat, l'osteoporosi densitomètrica, l'artritis reumatoide, l'antecedent personal de fractura, un IMC<20 kg/m^2 o la ingesta de glucocorticoides van mostrar significació estadística per fractures principals i/o maluc. Ara bé, només els 3 primers ho van ser en els resultats preliminars publicats de la cohort FRIDEX [34]. Aquests resultats s'alineen bé amb d'altres estudis duts a terme a la nostre població a excepció del baix IMC [46]. També hem trobat dades publicades que investiguen la relació entre l'IMC i la fractura en dones postmenopàusiques espanyoles, però centrant-se en l'IMC alt. En aquest context, alguns treballs van comunicar una relació entre les fractures vertebrals i un alt IMC [47] i, per contra, altres estudis no van trobar relació en aquesta localització però sí per fractures d'húmer proximal [48]. Al capdavall podem concloure que calen més estudis per aclarir aquestes variacions.

També es va observar que el resultat de risc de fractura FRAX (sense DMO) a 10 anys puntuava signicativament més alt tan en fractures principals com de maluc respecte a les no fracturades. La contribució de la DMO en el risc de fractures per fragilitat ja s'ha comentat i es reflecteix novament en els valors calculats de FRAX

amb la T-score de coll femoral, que són pitjors quan la DMO és més baixa ($p<0,05$) [9].

6.1.2. La capacitat discriminativa de l'eina FRAX

Per avaluar la validesa de l'eina FRAX, un dels aspectes que es va tenir en compte va ser la capacitat discriminativa de FRAX entesa com la probabilitat/capacitat que té el model d'identificar els individus amb risc molt alt de fractura i els que tenen un risc molt baix de fractura per fragilitat. Encara que pot estar discutida pels alguns experts estadístics, la corva ROC (*Receiver-Operating Characteristic*), mitjançant l'anàlisi de l'àrea sota la corva ROC, comunament anomenada AUC (*Area Under the Curve*) és probablement l'eina més utilitzada internacionalment en els estudis del camp de les fractures per fragilitat. Quan aquest índex dona un valor d'1 indica que la capacitat per predir fractures és perfecte i quan és de 0,5 que la probabilitat no es diferencia de la produida per l'atzar. En la cohort FRIDEX, l'anàlisi ROC mostra una AUC per fractura principal més precisa per FRAX calculat amb la T-score de coll femoral [0,714 (interval de confiança 95% (IC 95%) 0,661-0,767)] i per fractura de maluc amb FRAX calculat sense la DMO [0,883 (IC 95% CI 0,827-0,938)]. Aquestes troballes confirmen les dades publicades en els resultats inicials de la cohort FRIDEX [34] i recolzen la idoneïtat de la tendència actual d'avaluar el risc de fractura osteoporòtica utilitzant factors de risc clínics i no només l'ús dels resultats de la DXA, essent d'especial interés en la població de més edat, això és amb més risc de fractura de maluc, i que tenen limitat l'accés a les proves densitomètriques. Tradicionalment, la disminució de la DMO mesurada mitjançant la DXA ha estat un dels factors mesurables més determinants per predir la fractura per fragilitat. No obstant aquest fet, la prova de la DXA (T-score $\leq$ -2,5 DE) presenta baixa sensibilitat i moderada especificitat per predir la fractura per la qual cosa no la fa aconsellable com a prova de cribratge poblacional [49]. Al comparar els resultats globals de la cohort FRIDEX es mostra una bona capacitat discriminativa de la fractura osteoporòtica de l'eina FRAX respecte del model basat en la DXA, en aquest darrer

anàlisi ampliat de la cohort amb uns valors per fractura principal de la l'AUC ROC de la DMO mesurada a coll femoral de 0,706 (IC 95% 0,652-0,760) (p<0,001) i per fractura de maluc de 0,814 (IC 95% 0,712-0,916) (p<0,001). Val la pena assenyalar que els resultats en països propers al nostre han demostrat una capacitat discriminativa similar utilitzant FRAX calculat amb la T-score a coll femoral en comparació a quan es fa servir únicament la DMO a nivell de coll femoral [20,24].

6.1.3. La capacitat predictiva de l'eina FRAX

Un altre dels aspectes que es va utilitzar per valorar la validesa de l'eina FRAX va ésser la seva calibració comparant la relació entre l'estimació del risc de fractura a 10 anys amb FRAX per a població espanyola i la incidència de fractura observada en els 10 anys de seguiment de la cohort FRIDEX. La capacitat predictiva ajustada [Observada/Estimada (Obs/Exp)] va ser per fractura osteoporòtica principal de 2,29 (IC 95% 1,9-2,4) i per fractura de maluc de 2,28 (IC 95% 1,6-3,3) fent el càlcul de FRAX sense introduir el valor de la DMO femoral, i una vegada introduida la T-score femoral va ser de 2,01 (IC 95% 1,7-2,4) i de 1,83 (IC 95% 1,3-2,7) respectivament. Aquesta relació es va mantenir similar a l'avaluar els resultats en funció de l'edat, excepte per a les dones menors de 65 anys d'edat, en les quals FRAX sense/amb la DMO femoral va disminuir per fractura de maluc a 1,53 [IC 95% 0,7-3,3] i a 1,24 [IC 95% 0,6-2,7] respectivament. Aquest resultat s'explica per l'edat mitjana de les dones de la cohort, en la que el 80% de les dones són menors de 65 anys, i és conegut que l'incidència de la fractura de fémur augmenta amb l'envelliment de la població (85,4% del total de fractures de fémur tenen lloc en majors de 75 anys) [50].

La prova de Hosmer-Lemeshow es va dur a terme per avaluar la bondat d'ajust entre les fractures observades i les fractures estimades amb l'eina FRAX. Es considera que l'ajust és bo quan la comparació de les freqüències observades amb les estimades s'associa al valor 1 de la variable binomial. La gràfica de la bondat

d'ajust dels resultats es mostren abans i després de fer la simulació de multiplicar per la ratio Obs/Exp obtinguda amb les dades de la cohort.

Convé fer ressaltar que el model FRAX s'ha avaluat en altres cohorts espanyoles. La cohort ECOSAP va publicar dades similars de predicció de risc de fractura de maluc, però no van recollir dades de fractures vertebrals i només es va fer seguiment durant un periode de 3 anys amb extrapolacions als 10 anys, per tant la interpretació dels seus resultats referent al risc de fractura principal amb l'eina FRAX cal prendre-la amb prudència [33]. Tanmateix, la metodologia per a la recollida de fractures que es va utilitzar a la base de dades CETIR va ser completa (fractura clínica vertebral, maluc, avantbraç distal i húmer proximal), però no tenen posterior validació en els registres mèdics electrònics i, per tant, no aporten contrast de la informació de fractures que subministren les pacients que acudeixen a fer-se la DXA [32]. En els resultats publicats la relació de fractures principals Obs/Exp va ser de 2,4 (IC 95% 2,1-2,7) i per a les fractures de maluc de 0,8 (IC 95% 0,6-1,1). Per tant, els resultats per la fractura principal coincideixen amb els nostres suggerint que el model FRAX de forma global, sense altres ajustos, subestima el risc de fractura en dones espanyoles [34]. La possible explicació d'aquest infradiagnòstic per a l'eina FRAX a Espanya s'ha justificat perquè les dades de fractura incloses en l'algoritme matemàtic del model FRAX provenen d'estudis realitzats en els anys noranta [32-34], alguns d'àrees amb baixa incidència de fractura de maluc, i en conseqüència, s'haurien de tenir en compte dades d'incidència de fractura actualizats que reflexessin la variabilitat de la incidència de fractura en els darrers anys [3,23,50,51]. La relació de fractures de maluc Obs/Exp en aquest treball s'acosta a l'1. Una possible explicació d'aquesta divergència de resultats és que malgrat la formació similar inicial de la cohort FRIDEX i la de la base de dades CETIR, en aquesta darrera la mostra de dones era més jove [32,34]. Les diferències trobades en la predicció de fractura de maluc entre les 3 cohorts principals espanyoles també poden ésser explicades pel fet que les cohorts ECOSAP i CETIR

estaven composades per una baixa proporció de dones majors de 70 anys, hi havia una baixa proporció de fractures de maluc, la mitjana del període de seguiment va ser més curta i, es va utilitzar un mètode de seguiment diferent [32,33]. En darrer terme, la predicció de fractura utilitzant l'eina FRAX també s'ha analitzat a les cohorts FRODOS i ESOSVAL, però sense recollir la incidència de noves fractures, consegüentment, les seves dades no es poden utilitzar per a avaluar la capacitat predictiva de l'algoritme [52,53].

6.2. Article 2

L'article 2 *"Fracture experience among participants from the FROCAT study: what thresholding is appropriate using the FRAX tool?"* és una cohort retrospectiva de 1090 dones ≥ 40 i ≤ 90 anys en l'any 2001-2002, això és, 10 anys abans del moment d'inclusió en l'estudi, entre els anys 2011-2012 [39]. Les participants són dones seleccionades de manera aleatòria dels contingents de metges de familia dels Centres d'Atenció Primària de l'Institut Català de la Salut, seguint una estratificació per edat i província d'acord amb el cens a l'any 2008. Una vegada recollit el consentiment informat de participació en l'estudi, per una banda es va calcular el risc FRAX de fractura osteoporòtica amb dades de les variables de risc corresponents a l'any 2001-2002, i per l'altra, es va interrogar sobre la incidència de noves fractures osteoporòtiques entre els anys 2001-2002 i 2011-2012. Tots els casos de fractures informades pels pacients es van verificar amb les històries clíniques i es van excloure aquells casos que no es van poder comprovar.

La incidència acumulada de fractura principal osteoporòtica (estandaritzada per 100.000 dones/any) va ésser significativament més gran en el grup de més de 65 anys d'edat, sobretot a maluc i columna vertebral ($p<0,001$). O sigui, semblen coincidir amb les anàlisi duts a terme en altres cohorts espanyoles [36]. La incidència de fractures vertebrals simptomàtiques va ser superior que en la cohort FRIDEX [36], però quasi 5 vegades més baixa que la que es revisa en una altra

cohort espanyola que va utilitzar radiografies de columna vertebral toraco-lumbar per identificar-les [54]. En quan a les fractures humerals mostren incidències similars a altres estudis realitzats [55].

6.2.1. Els factors de risc de fractura osteoporòtica

A continuació s'exposa la contribució en el risc de fractura osteoporòtica de les diferents variables clíniques a la cohort FROCAT, talment com hem fet amb la cohort FRIDEX ampliada. En aquesta cohort de dones de la població general, l'edat avançada, la fractura prèvia i el tabaquisme són factors que mostren una associació significativa amb la fractura osteoporòtica, de la mateixa manera que apareixen indefectiblement representats en altres treballs fets en població espanyola [32-34]. En l'anàlisi de la incidència acumulada de fractura osteoporòtica es van trobar diferències significatives en el global de fractures principals i de manera individual a columna vertebral i maluc en el grup de més de 65 anys d'edat.

El següent factor de risc a considerar és el valor de la DMO. A diferència de l'estudi d'ampliació fet amb la cohort FRIDEX [37], en la cohort FROCAT no es disposava de la DXA per a tots els casos, només va estar disponible en 234 (21,5%), però val la pena dir que la DMO va ser significativament normal en població no fracturada.

Dels restants factors inclosos en l'eina FRAX, pocs han mostrat una associació consistent en la mostra. Una explicació podria ser la baixa prevalença en el cas de les variables baix pes, ingesta d'alcohol, osteoporosi secundària o presa de glucocorticoides. En canvi, l'antecedent familiar de fractura de maluc estava ben representat i malgrat ha demostrat ésser un factor de risc de fractura independent en metanàlisis i altres estudis [10], ni en aquest estudi ni en la cohort FRIDEX va tenir significació estadística [34,37]. Això es podria explicar per l'edat mitja de les cohorts inferior a 65 anys, i és raonable concloure que com més gran sigui la població més probable serà que un dels seus pares hagi patit una fractura de maluc.

La variable nombre de caigudes en l'any anterior no es comptabilitza en l'algoritme FRAX. Malgrat això aquest factor ha demostrat ser un predictor de risc de fractura per fragilitat independent de la massa òssia i, en aquest estudi, com en d'altres realitzats en població espanyola, mostra diferències significatives en dones amb fractures incidents [34,36,54]. Per tant, hi ha una creixent evidència que es podria incloure com a predictor a les escales de risc de fractura per fragilitat.

6.2.2. L'anàlisi de sensibilitat de la calibració del model FRIDEX

Posteriorment al càlcul de FRAX (sense DMO) es va fer una estratificació del risc obtingut tenint en compte les 3 categories de risc proposades en estudis prèviament publicats de la cohort FRIDEX (risc baix per FRAX< 5%, intermig per FRAX entre ≥ 5 i <7,5%, i alt per FRAX ≥ 7,5%), les quals incloïen la incidència de fractures observades en la nostra cohort seguint rangs tradicionalment considerats com de risc baix (<10%), intermig (10-20%) i alt (> 20%) en altres estudis epidemiològics com els de la *Canadian Association of Radiologists and Osteoporosis Canada* (CAROC) canadenca o els de validació de les taules de risc cardiovascular Framingham-REGICOR [56,57]. L'objectiu del present treball va ser fer un anàlisi de sensibilitat de l'estratificació FRIDEX de risc de fractura per fragilitat amb l'eina FRAX (sense DMO) aplicada en dones espanyoles provinents de població general i, per tant, fer la seva validació externa. En la cohort FROCAT no es van incloure els individus amb tractament a l'inici del periode d'estudi (2001-2011), pero sí es va fer l'anàlisi de sensibilitat per tots 2 escenaris, sense/amb tractament iniciat durant el periode d'estudi. En analitzar la cohort una vegada excloses les dones que havien rebut fàrmacs antiosteoporòtics durant el periode d'estudi (884) i utilizant els llindars FRIDEX proposats, entre les 621 dones (70,2%) amb baix risc de fractura, una mitja de 5,2% [IC 95% 3,4-7,6] va patir una fractura per fragilitat, entre les 99 (11,2%) amb risc intermig, el 12,1% [IC 95% 6,4- 20,2], i entre les 164 (18,6%) d'alt risc, el

15,9% [IC 95% 10,6-24,2]. Així doncs, l'anàlisi de sensibilitat de l'estratificació del risc del model FRIDEX amb l'eina FRAX per a Espanya en població general no va mostrar diferències significatives amb els resultats prèviament publicats [36]. Altrament, amb la inclusió de les 206 dones que prenien o havien pres tractament amb medicaments antiosteoporotics (MAO) una vegada iniciat el periode d'estudi, l'anàlisi de sensibilitat no va mostrar tampoc diferències: entre les 739 dones (67,8%) amb baix risc de fractura, una mitja de 6,8% [IC 95% 5,0-8,8] va patir una fractura per fragilitat, entre les 130 (11,9%) amb risc intermig, el 18,5% [IC 95% 12,2-26,2], i entre les 221 (20,3%) d'alt risc, el 24% [IC 95% 18,5-30,2]. Val la pena dir que inicialment l'eina FRAX no estava dissenyada per ésser utilitzada per a identificar el risc de fractura en pacients que rebien tractaments per l'osteoporosi ni per avaluar l'eficàcia del tractament. Aquest fet podria considerar-se com una limitació, ja que difereix del disseny inicial de l'algoritme, però recentment han aparegut estudis de seguiment de grans cohorts en les que s'evidencia que els resultats de predicció del risc de fractura a 10 anys no difereixen gaire quan s'inclou a la gent que inicia un tractament amb MAO [55,58], i això no obstant, la prescripció de MAO en dones amb risc de fractura osteoporòtica és baixa en el nostre país [59].

Hi ha limitacions i fortaleses al nostre estudi. La principal limitació de l'estudi és que la cohort FROCAT prové de població general, i per aquest motiu només vam tenir 234 DXA recollides i l'anàlisi de sensibilitat es va fer pels llindars de risc obtinguts amb FRAX sense la DXA, doncs no podíem recalcular el risc intermig tal i com recomana el següent nivell del model FRIDEX. Així les coses, el treball valida el model FRIDEX per FRAX sense DMO i, especialment, els llindars que identifiquen les pacients amb baix (<5%) i alt risc (≥ 7,5%) de fractura osteoporòtica a 10 anys en població femenina espanyola.

S'ha dut a terme un estudi de cohorts retrospectiu sobre fractures que s'han produït en els últims 10 anys abans de l'entrevista i, l'aparició de biaixos de memòria

implícita en aquest tipus de disseny pot afectar la fiabilitat dels resultats a causa, per una part, de la dificultat en la recol·lecció de dades i, per l'altra, de la qualitat de la informació recollida. No obstant això i, a l'igual que hem comentat abans en el primer article, la rigurositat com es va recollir aquesta variable minimitza aquest fet. Novament es van dur a terme dos controls. En primer lloc, en tots els casos de fractures relatades pels pacients es van revisar les seves històries clíniques o proves d'imatge mèdica, i quan les fractures no es van poder verificar els subjectes van ser exclosos de l'anàlisi. Aquesta comprovació entre els conjunts de dades primàries i secundàries és possible en la nostra institució i permet la revisió de la informació mèdica del metge de capçalera i de l'hospital en tots dos sentits. Segon, la recerca activa d'esdeveniments de fractura es van realitzar en les històries clíniques informatitzades dels metges de familia per tal de recuperar les fractures no referides pels participants. Tenint en compte que les fractures principals incloses en l'algoritme FRAX (maluc, vertebral, canell i húmer) són simptomàtiques i possiblement condicionen una visita dels pacients fracturats amb el seu metge d'atenció primària, ja sigui en la fase aguda, abans d'ésser referit a l'hospital per a una radiografia per confirmar la presència de fractura o, si han anat a l'hospital en primer lloc, després de l'alta per a monitoritzar les prescripcions o serveis d'atenció domiciliària, els autors consideren que almenys les fractures més greus serien enregistrades pels metges d'atenció primària. Per tant, és un conjunt fiable de dades tenint en compte que quan la informació prové exclusivament dels pacients pot haver confusió en recordar una lesió que podria considerar-se important, però que no va esdevenir en fractura. Per contra, possibles errors de registre es poden detectar quan s'entrevista als pacients. Comptat i debatut la fiabilitat de la recol·lecció de dades per determinar les fractures osteoporòtiques incidents ja s'ha validat a Espanya [60], el sistema de recollida de fractures referides pel pacient és el més comunament utilitzat [33-34,36] i només en uns pocs casos es duu a terme mitjançant proves radiològiques, com serien aquells en que interessa descartar fractura vertebral per identificar de manera apropiada fractures assimptomàtiques

[54]. Una altre limitació de l'estudi va ésser excloure en el moment de l'entrevista (2011-2012) a les persones que havien mort, fet que podria disminuir la incidència de fractures observades. La relació entre fractura osteoporòtica i la mortalitat està ben documentada, i també ho és la presència de certes comorbiditats que no s'inclouen en el càlcul de l'algoritme FRAX (malaltia de Parkinson, esclerosi múltiple, malaltia pulmonar obstructiva crònica, osteoartritis i malalties del cor) i la fractura per fragilitat, encara que en alguns casos això és controvertit perquè els tractaments utilitzats en algunes d'aquestes malalties també s'han associat amb el risc de fractura osteoporòtica [61]. En el nostre estudi era important incloure informació sobre les noves fractures i donada la dificultat per obtenir detalls de fractures incidents en població difunta vam decidir excloure'ls. Per tant es tracta d'un biaix de selecció ja que la incidència de fractures podria ésser major. En última instància, pel fet que la cohort sigui de població resident a Catalunya, podria no ésser suficientment representativa d'altres Comunitats Autònomes espanyoles i, com es tracta d'una cohort femenina, faltaria donar resultats en població masculina.

7. CONCLUSIONS

Els resultats de les anàlisis en les cohorts FRIDEX de població seleccionada per DXA i les anàlisis de sensibilitat dels resultats en la cohort FROCAT de població general ens permeten fer la validació interna i externa del model FRIDEX, que determina els llindars de risc de fractura principal a 10 anys en població femenina espanyola [baix (<5%), intermig (≥ 5 i <7,5%) i alt (≥7,5%)], a fi de decidir instaurar, mantenir o millorar estils de vida o aconsellar un tractament farmacològic amb MAO per prevenir fractures.

La capacitat discriminativa de les dones amb alt risc de fractura per fragilitat de l'eina FRAX en l'ampliació de les anàlisis de la cohort FRIDEX és bona en comparació al model tradicional basat en la densitometria òssia. Per a fractura principal els millors resultats de la AUC van ser per FRAX calculat amb la DMO femoral [AUC=0,714, IC 95%: 0,661-0,767], seguit de la DMO a coll femoral [AUC=0,706, IC 95%: 0,652-0,760] i FRAX sense la DMO [AUC=0,686, IC 95%: 0,630-0,742]. Per a fractura de maluc van ser per FRAX sense la DMO [AUC=0,883, IC 95%: 0,827-0,938], FRAX amb la DMO [AUC=0,857, IC 95%: 0,773-0,941] i la DMO femoral [AUC=0,814, IC 95%: 0,712-0,916].

La capacitat predictiva de tenir una fractura per fragilitat de l'eina FRAX amb un major nombre de casos de la cohort femenina FRIDEX és consistent amb els resultats preliminars de la cohort, amb una ratio Obs/Exp de FRAX sense la DMO per a fractura principal de 2,29 (IC 95%: 1,91-2,74) i per a fractura de maluc 2,28 (IC 95%: 1,56-3,32], i de FRAX amb la DMO de 2,01 (IC 95%: 1,68-2,41] i 1,83 [IC 95%: 1,25-2,67] respectivament.

Els factors de risc de fractura per fragilitat en la cohort femenina FRIDEX que van mostrar significació estadística per a fractures principals i/o maluc van ser l'edat, l'osteoporosi densitomètrica, l'artritis reumatoide, l'antecedent personal de fractura, un IMC<20 kg/m² o la presa de glucocorticoides.

Els factors de risc de fractura per fragilitat en la cohort FROCAT de població general que van mostrar significació estadística per a fractures van ser l'edat avançada, l'antecedent de fractura i les caigudes en l'any previ. Per contra, el tabaquisme i un resultat de la DXA >-1 DE es van relacionar amb l'absència de risc fractura.

En les taxes d'incidència de fractures per fragilitat en la cohort FROCAT, representativa de la població femenina a Catalunya, s'han trobat diferències significatives entre les dones majors i menors de 65 anys en el conjunt de fractures, fractures principals, fèmur proximal i vertebral clínica. No s'han trobat diferències significatives en les fractures d'húmer proximal i canell. Les taxes estandarditzades per 100.000 dones/any en <65 anys han estat de 1348 (13,3%), 699 (7%), 42 (0,4%), 56 (0,6%), 140 (1,4%) i 468 (4,6%) respectivament. Les taxes estandarditzades per 100.000 dones/any en ≥ 65 anys han estat de 2480 (24,8%), 2053 (20,5%), 560 (5,6%), 640 (6,4%), 293 (2,9%) i 560 (5,6%) respectivament.

8. SUMMARY

The results based on the analysis of the FRIDEX cohort, selected to undergo a DXA scan, and the sensitivity analysis performed in the FROCAT cohort from general population, allow us to internal and externally validate the use of FRIDEX model in the Spanish female population, which determines 3 levels of risk of osteoporotic fracture with FRAX without DXA [low risk (<5%), intermediate (≥ 5 and <7.5%) and high (≥7.5%)] in order to consider, maintain or improve a healthy lifestyle or to advise pharmacological treatment with anti osteoporotic medication.

The discriminatory ability of the FRAX tool for detecting women at high risk of fragility fracture in this updated analysis of the FRIDEX cohort is good when compared to the BMD model alone in decision-making (FN T-score). For major fracture the best-case scenario was obtained with FRAX tool including FN T-score [AUC=0.714, 95% Confidence Interval (CI) 0.661-0.767], followed by FN BMD alone [AUC=0.706, 95% CI 0.652-0.760] and FRAX tool without BMD [AUC=0.686, 95% CI 0.630-0.742]. For hip fracture the best-case performance analysis was obtained with FRAX without BMD [AUC=0.883, 95% CI 0.827-0.938], followed by FRAX including FN T-score [AUC=0.857, 95% CI 0.773-0.941] and FN BMD alone [AUC=0.814, 95% CI 0.712-0.916].

The predictive capacity of fragility fracture using the FRAX tool in this expanded sample from FRIDEX cohort using the ratio Observed fractures/Expected fractures was 2.29 [CI 95% 1.91-2.74] for major osteoporotic fracture and 2.28 [CI 95% 1.56-3.32] for hip fracture using the FRAX tool without BMD, and on the introduction of the FN T-score was 2.01 [CI 95% 1.68-2.41] and 1.83 [CI 95% 1.25-2.67], respectively.

The risk factors of fragility fractures from the updated FRIDEX cohort that showed statistical significance across major and/or hip fractures were age, DXA osteoporosis diagnosis, rheumatoid arthritis, previous fractures, low body mass index (<20 kg/m^2) and the use of glucocorticoids.

The risk factors of fragility fractures from the FROCAT cohort that showed statistical significance in fractures were age, prior fracture and ≥2 falls in previous year. Conversely, smoking and normal results of DXA were associated with nonfractured individuals.

The incidence of suffering fragility fractures among women from the general population in Catalonia (FROCAT cohort) was significant for women over 65 years old when analysing together all fractures, major fractures, and specially for hip and spinal fractures. No significant differences were found in the proximal humerus fractures and wrist. The standardised rates by 100.000 women/year <65 years old were 1348 (13.3%), 699 (7%), 42 (0.4%), 56 (0.6%), 140 (1.4 %) and 468 (4.6%), respectively. The standardised rates by 100.000 women/year ≥65 years old were 2480 (24.8%), 2053 (20.5%), 560 (5.6%), 640 (6.4%), 293 (2.9%) and 560 (5.6%), respectively.

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10. ANNEXES

10.1. Annexe 1: Descripció de la cohort FRIDEX (protocol d'estudi)

Azagra R, Roca G, Encabo G, Prieto D, Aguyé A, Zwart M, et al. Prediction of absolute risk of fragility fracture at 10 years in Spanish population: validation of the WHO FRAX® tool in Spain. BMC Musculoskeletal Disorders. 2011;12:30.

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STUDY PROTOCOL Open Access

Prediction of absolute risk of fragility fracture at 10 years in a Spanish population: validation of the WHO FRAX ™ tool in Spain

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Abstract

Background: Age-related bone loss is asymptomatic, and the morbidity of osteoporosis is secondary to the fractures that occur. Common sites of fracture include the spine, hip, forearm and proximal humerus. Fractures at the hip incur the greatest morbidity and mortality and give rise to the highest direct costs for health services. Their incidence increases exponentially with age.
Independently changes in population demography, the age - and sex- specific incidence of osteoporotic fractures appears to be increasing in developing and developed countries. This could mean more than double the expected burden of osteoporotic fractures in the next 50 years.

Methods/Design: To assess the predictive power of the WHO FRAX™ tool to identify the subjects with the highest absolute risk of fragility fracture at 10 years in a Spanish population, a predictive validation study of the tool will be carried out. For this purpose, the participants recruited by 1999 will be assessed. These were referred to scan-DXA Department from primary healthcare centres, non hospital and hospital consultations. Study population: Patients attended in the national health services integrated into a FRIDEX cohort with at least one Dual-energy X-ray absorptiometry (DXA) measurement and one extensive questionnaire related to fracture risk factors. Measurements: At baseline bone mineral density measurement using DXA, clinical fracture risk factors questionnaire, dietary calcium intake assessment, history of previous fractures, and related drugs. Follow up by telephone interview to know fragility fractures in the 10 years with verification in electronic medical records and also to know the number of falls in the last year. The absolute risk of fracture will be estimated using the FRAX™ tool from the official web site.

Discussion: Since more than 10 years ago numerous publications have recognised the importance of other risk factors for new osteoporotic fractures in addition to low BMD. The extension of a method for calculating the risk (probability) of fractures using the FRAX™ tool is foreseeable in Spain and this would justify a study such as this to allow the necessary adjustments in calibration of the parameters included in the logarithmic formula constituted by FRAX™.

Background

Epidemiology of osteoporotic fractures

Osteoporosis is an asymptomatic disease until it is complicated by a bone fracture occurring without trauma or after a minimum trauma. It is the most common bone disease in humans and represents an important health care problem in developed countries. The high incidence of osteoporosis worldwide and its main complication, osteoporotic fractures, also known as fragility fractures, have been recognised for more than 20 years [1]. One of the first meta-analyses on fracture risk published in 1996 demonstrated the association between bone mineral density (BMD) and the risk for osteoporotic fracture [2].

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The probability of a woman with menopause presenting an osteoporotic fracture during the remainder of her life (the most frequent are; vertebral, forearm, humerus or hip) surpasses even the risk of having breast cancer, with this probability being approximately 40% higher in developed countries and very close to the risk of coronary disease in the same countries [3].

According to the recent guidelines by the American College of Physicians for the screening of osteoporosis in males, this disease is considered to be underdiagnosed and under-treated, perhaps due to the relatively lower frequency. A 60-year-old white man has a 25% risk of having an osteoporotic fracture during his lifetime, with even more severe consequences than in women [4]. Indeed, the post-hip fracture mortality at one year in men is double that in women [4]. The influence of fragility fractures on the quality of life of both men and women has also been widely reported [5].

According to data estimated in subjects over the age of 50 years in Europe in the year 2000, 620,000 new hip fractures, 575,000 shoulder fractures, 250,000 proximal humerus fractures and 620,000 symptomatic vertebral fractures were reported, representing almost 35% of the fractures described in the world [6]. The direct costs of osteoporotic fracture in Europe are of around a total of 36 billion Euros per year [7].

The greatest clinical relevance of osteoporosis is constituted by osteoporotic fractures, and these are implicated in the increase in morbimortality and loss of quality of life attributable to this disease. Thus, attention must be focused on the identification of patients with a high risk of fragility fracture [8], than on the identification of those with osteoporosis, diagnosed exclusively by densitometry.

Although BMD (measured by densitometry) is an important component of fracture risk, several other risk factors have also been demonstrated to greatly contribute to the risk of fracture and should be taken into account when performing a global evaluation of risk [8].

Clinical determinants of osteoporotic fracture

In the last years different studies have been carried out with the aim of identifying the clinical risk factors which may be used in the search for therapeutic strategies, with or without the use of densitometry [9].

The last version of the European guidelines for the diagnosis and treatment of osteoporosis in postmenopausal women published in 2008 [10] proposes the strategy of evaluation together the results of densitometry and clinical risk factors of fracture to decide which diagnostic and therapeutic interventions to implement.

The FRAX ™ tool, a useful tool for clinical practice

In 2008, the WHO published a new promising tool for the evaluation of absolute risk of fragility fracture: the FRAX™ tool [11], WHO fracture risk assessment tool. This is a scale including 11 of the clinical risk factors which have demonstrated a strong association with the incidence of fracture in previous studies according to the WHO experts. Factor number 12 in this scale also includes a single value of Dual-energy X-ray absorptiometry (DXA) central bone densitometry: the T-score of the femoral neck. An introducing these data of a patient provided in the form of the FRAX™ website, an individualised calculation of the percentage of prediction of absolute risk of: (a) major osteoporotic fracture (clinical vertebral, hip, forearm or humeral fracture) and (b) hip fracture in the following 10 years may be made [11].

To develop the logarithmic formula of FRAX™, were included parameters from different European cohorts from the EVOS study focused on vertebral fractures [12]. As representatives of the Spanish population were included people from Oviedo and other three Spanish cities. However, they had very low rates of response: in some cases were less than 8%, with a total number of subjects potentially insufficient to be representative of Spanish population [13].

On the other hand, it should be pointed out that as recommended in the description of the FRAX™ tool, this scale should be developed and validated in each country. Cost-effectiveness studies are also recommended with the data from each country to obtain an approximation of the cost which each country is willing to accept as reasonable for the prevention of fragility fractures.

It is therefore reasonable for the first step before the generalised use of the FRAX™ scale in the medical offices of our country to carry out the validation of this scale in a larger cohort made up of the patients usually attended at the different health care levels in which diagnostic; treatment and follow up interventions for osteoporosis are undertaken. On the other hand, recent evidence [14-17] also recommend the evaluation of other risk factors related to low mass and risk of fragility fracture and not considered in the FRAX™ tool when assessing fracture risk such as the presence of chronic obstructive pulmonary disease (COPD), the use of some drugs such as aromatase inhibitors (increasingly more frequent in women treated for breast cancer), daily calcium intake and usual physical activity which are related to bone mass and risk of fragility fracture.

Falls and fragility fractures

Fragility fractures are defined as those which occur after non major impact produced by a fall from a height of less than that of the patient with no added inertia to that of the displacement of its foot when walking.

Since more than 20 years ago studies have demonstrated the importance of falls on the incidence of new

fractures in predisposed subjects, with a strong association between the number of falls and fracture. This association is even more important in patients over the age of 75 years than the classical association described between osteoporosis and fracture [16]. Different variables related to the greater risk of falls have also been reported such as factors of the individuals themselves (muscular strength of the lower extremities, equilibrium or postural competence, difficulties in vision, cognitive deterioration), purely environmental factors (home lighting, rugs, pets...) and iatrogenic factors (different groups of drugs, drug combinations) [18-21].

Despite these evidence on the potential influence of falls on the occurrence of fragility fractures, they have not been included as risk factors in the FRAX™ tool for the determination of absolute fracture risk at 10 years, probably due to the publication of studies with contradictory long term results which impede consistent establishment of their association.

The importance of being able to determine the association between the number of falls and the appearance of fragility fracture may be established by the possibility of their prevention, thereby reducing the risk of falling. Different studies have presented good results with different training techniques and a recent Cochrane review [22] provides measures of the potential benefit of interventions such as programmes of multidisciplinary detection and intervention (RR 0.73;CI 95%: 0.63-0.85), muscular strengthening and balance retraining (RR 0.80; CI 95%: 0.66-0.98), evaluation and modification of risks at home (RR 0.66; CI 95%; 0.54-0.81), withdrawal of psychotropic drugs (RR 0.34; CI 95%: 0.16-0.74) and a 15-week intervention of Tai Chi group exercises (RR 0.51; CI 95%: 0.36-0.73) among others.

The latest guidelines published in our country recommend intervention related to the risk of fall in subjects with osteoporosis according to a maximum grade of evidence (SEIOMM Guidelines 2008, AATRM Guidelines) [23,24].

The high incidence of falls in the elderly (30% of subjects over the age of 65 years living at home fall every year) [22], as well as the associated morbidity and the tests available demonstrate the relevance of a study such as this to establish their association and determine the need for their inclusion as important and preventable risk factors in tools such as FRAX™ to assess the absolute risk of osteoporotic fractures.

FRAX™ is a tool which is evolving and in the future may become a commonly used tool in medical centres in our country, especially in Primary Care (PC) in which the greatest number of subjects with osteoporosis is attended and where programmes of prevention of osteoporotic factors may be carried out. This is another argument reinforcing the need for urgent validation of this scale in our country, and it is the main objective of this study.

Objectives

Main objective

To determine the predictive validity of the WHO FRAX™ risk scale to identify subjects with the greatest absolute risk of fragility fracture in the next 10 years in a Spanish population in a clinical cohort designed to promote the study of different risk factors of presenting osteoporotic fractures.

Secondary objective

To analyse the association between clinical and environmental risk factors (number of falls, exposure to drugs, dietary calcium intake) and the occurrence of osteoporotic fracture in a susceptible Spanish population.

Methods/Design

Study of predictive evaluation of a tool to assess the risk of osteoporotic fracture through the follow up of a cohort initiated in 1999.

Study population and enrolment procedures

This multicentre study is carried out by family practitioners and other specialists who refer patients to the same reference centre for undertaking BMD. The criteria for referral follow the recommendations of the WHO of not performing a population screening but to select cases among those of greatest risk of having osteoporosis and subsequent osteoporotic fractures or the follow up and control of patients already receiving treatment.

The FRIDEX cohort (Factors of fracture risk and central bone densitometry). This cohort is constituted of men and 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 or treatment follow up, who accept to answer an extensive questionnaire on risk factors (RF) for osteoporotic fracture (family history of osteoporosis and hip fracture, clinical risk factors and lifestyle habits related to diet and toxic substances) [see Table 1]. This cohort was initiated in 1999 at the Bone Densitometry Unit of the Department of Nuclear Medicine of the University Hospital Vall d'Hebrón in Barcelona and at the end of 2009 had included 25,783 persons of both genders who had undergone a total of 41,849 DXA and questionnaires on RFs.

Since the beginning of the study verbal informed consent to participate in the cohort was obtained from all the patients and an extensive questionnaire on clinical risk factors was carried out. The data collected is stored in a specific database (DB) for this cohort.

Table 1 Total FRIDEX (2000-2010 years) cohort description

		Total	Men	Women
Cases		25,783	2,349	23,434
		N (SD)	N (SD)	N (SD)
Age		61.2 (10.2)	65.0 (10.8)	60.8 (10.1)
Weight		68.1 (12.2)	75.3 (13.3)	67.4 (11.9)
Height		155.6 (7.4)	165.7 (7.2)	154.6 (7.4)
		N (%)	N (%)	N (%)
Parental Osteoporosis or Fracture	Yes	4,220 (16.4%)	153 (6.5%)	4,067 (17.4%)
	No	21,524 (83.6%)	2,192 (93.5%)	19,332 (82.6%)
Parental Hip Fracture	Yes	166 (6.3%)	10 (2.6%)	156 (6.9%)
	No	2,462 (93.7%)	372 (97.4%)	2,090 (93.1%)
Previous Fractures	Yes	6,865 (26.6%)	837 (35.6%)	6,028 (25.7%)
	No	18,918 (73.4%)	1,512 (64.4%)	17,406 (74.3%)
Current Prescriptions	Yes	13,928 (54.0%)	1,048 (44.6%)	12,880 (55.0%)
	No	11,855 (46.0%)	1,301 (55.4%)	10,554 (45.0%)

Informed consent to participate is requested in the reference centre and a questionnaire on risk factors (QRF) for osteoporotic fractures is given during the visit and anthropometric parameters are determined. Ten years after the first QRF and DXA the patients are asked to answer a phone survey (See additional file 1) to know the evolution of the study variables and outcomes (fragility fractures).

Study population

Urban setting. Primary care (PC), extrahospitalary (E) and hospital specialties (H).

Integrants of the FRIDEX cohort. Randomised sample (simple computerised randomisation stratified by sex) of men and women from 40 to 90 years of age in the FRIDEX cohort for 10 years since the baseline DXA and QRF. At the end of 2009 this sub-cohort included 5,813 persons recruited from January 1 to December 31, 2000.

Eligibility Criteria

A total of 3,684 subjects were randomised, 9.3% being males to maintain the original proportion of the global study cohort.

Inclusion criteria

The study subjects were Caucasians, ≥ 40 and ≤ 90 years of age at the time of inclusion in the FRIDEX cohort, understood and spoke the Spanish language, were able to respond to the initial and/or follow up telephone questionnaire (TQ) and accepted to participate in the study providing the corresponding informed consent. Physically or psychically handicapped patients were included if the relatives or care providers accepted to answer the TQ.

Exclusion criteria

Subjects < 40 or > 90 years of age at the time of the first DXA and QRF were excluded since FRAX™ does not allow the calculation of the adjusted risk outside this age range. Patients with physical or psychic limitations impeding their participation and whose relatives did not accept to respond to the TQ were excluded as were those with Paget's disease, cancer with bone involvement or disease which may simulate osteoporosis (i.e. myeloma). Patients of ethnic groups other than Caucasian were not included since other studies have demonstrated different risk characteristics. Patients not providing consent to respond to the TQ and those without a telephone to contact or did not respond after 3 calls made at different times according to the procedure manual were also excluded from the study.

Sample Size (figure 1):

For the main objective (predictive validation of FRAX™ it has been calculated that a sample of 1,070 individuals are needed in a bilateral contrast to guarantee that the sample estimates the percentage of incidence of new fractures with a precision of 3%. If an annual loss rate of 1% during the 10 years of follow up of the study is considered, a sample of 1,177 subjects is required. In the pilot study carried out in April 2009 in a randomised sample of 149 cases with three telephone calls / person, 47 persons could not be contacted (31.5%). One hundred two (68.5%) were contacted, of which 3 (4.9%) living patients and the relatives of 2 dead patients refused to participate. Cases receiving anti-osteoporotic drugs and/or those with cancer (35 people) and 6 males were excluded. Information was obtained on data at 10 years in 97 of the 149 cases. A total of 3,664 individuals should therefore be contacted, thus our population of 5,813 subjects potentially eligible guarantees the necessary sample size.

Finally, in the pilot study of 149 patients and after fulfilling the exclusion criteria we obtained a sample of 56 (37.6%) of the 149 cases. With more conservative calculations, a maximum of 3,056 subjects should be contacted plus 20% for safety. Thus 3,664 persons should be contacted, therefore our originally recruited population of 5,813 subjects greater than 40 years of age included in the cohort until the end of 2000 sufficiently guarantees the necessary sample size. Consequently, 3,664 subjects were randomly selected from the 5,813 patients included in the cohort during the year 2000.

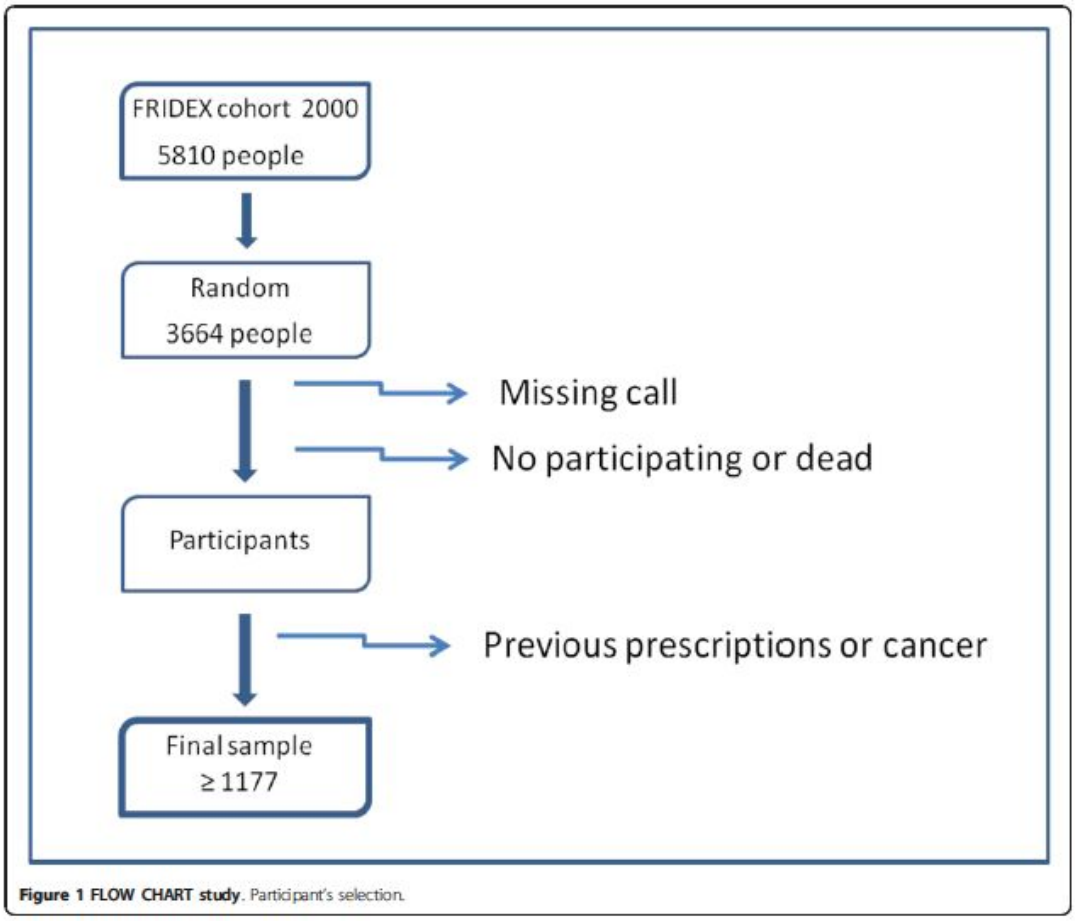

Figure 1 FLOW CHART study. Participant's selection.

A sample will be obtained by months in the year 2000. Ordering will be performed using randomised numbers for each month and the calls will be made in this order until the required number is achieved. The approximate calculation is of 317 cases / month with a range from 190 to 395 cases in the different months of 2000, and the calls will be made until the figure calculated per month is met.

Overview of outcome measurements

Data collection

The baseline variables of both BMD and QRF were collected at the time of inclusion (2000). The follow up variables (fractures and incidental falls) will be collected by telephone questionnaire (TQ) during 2010 and the beginning of 2011 to complete the 10 years of follow up. The TQ will collect data regarding the fractures occurring from the time of inclusion until the date of the TQ as well as other information on known factors of fracture risk.

Baseline variables

These include variables related to the patient: Demographic (date of birth, sex), anthropometric (weight, height, body mass index).

BMD measurement will be determined by central DXA according to the 2004 and 2007 recommendations of the International Society for Clinical Densitometry ISCD (available at: http://www.iscd.org/Visitors/positions/OfficialPositionsText.cfm) for the interpretation of the results using a Lunar GE model "Prodigy Advance" densitometer with 11.4 software and with BMD and T-score determination with NHANES III references. The densitometry diagnostic criteria used are the 1994 WHO criteria which classify the results into 3 groups according to the levels of BMD values of the femoral

neck: normal (T-score > -1), osteopenia (T-score between -2.5 and -1) and osteoporosis (T-score ≤ -2.5).

Additional file 1 shows the clinical factors of fracture risk analysed with the structured questionnaire (QRF), dietary intake of calcium and drugs use.

The estimated absolute risk of fracture at 10 years according to the FRAX™ tool is determined through the official web site (available at: http://www.shef.ac.uk/FRAX). The calculations of probability of fracture with or without the T-score will be analysed in parallel by two blinded investigators (patients anonymised and assigned an alphanumeric code). On the appearance of any difference a third and fourth blinded investigator will analyse the results and will recalculate the case.

Follow up variables

These variables include the appearance of incidental fracture in the last 10 years (dependent variable): the telephone questionnaire will be carried out with a telephone call made after 10 years of follow up. All the fractures will be confirmed through medical records and/or consultations to the health care centres after receiving authorisation from the participants. In all cases the follow up at 10 years will be completed in these subjects. In cases of death, the data related to the cause of death and the appearance of fractures will be requested from the relatives and by record checking.

The number of falls during the last year will be determined with the TQ. Review of the literature has shown different ways to analyse the falls occurring in the study subjects. The most frequently used method is considered in this study which asks about the number of falls during the year prior to the interview and whether a fracture was produced in any of the falls. Other variables to be collected during this period are: the appearance of important diseases, the taking of osteopenic drugs and the use of walking aids. Additional file 2 shows the telephone questionnaire.

Analysis plan

The characteristics of the population will be described according to univariate descriptive analysis. Simple comparisons of the baseline characteristics will be made among the participants and non participants of the cohort. The Chi-square test will be used to evaluate the association between qualitative variables. The Student's t-test or, if necessary, its non parametric equivalent, the Mann-Whitney U test, will be implemented to evaluate the differences in the distribution of a quantitative variable according to the categories defined by a binary exposure. To assess the differences in the distribution of a quantitative variable according to the categories defined by a categorical variable with more than 2 categories, ANOVA analysis of variance or its corresponding non parametric test (Kruskal-Wallis) will be used.

For the predictive validation of the FRAX™ tool, the appearance of the first fracture occurring during the follow up period will be taken into account. The validation of the results obtained with the FRAX™ will be performed with the Hosmer-Lemeshow test and the calculation of the ROC curve. This test divides the participants into groups (normally 10) based on their estimated risk of fracture (FRAX™) and confirms that each group presents a number of cases of incidental fractures adjusted to the predicted number. On the other hand, the ROC curve considers the scale of FRAX™ risk as a diagnostic test of the presence of future fractures and as such leads to different calculations of sensitivity and specificity changing the cut off point selected. Finally, both probabilities (sensitivity and the complementary of specificity, or 1- specificity) will be graphically represented the curve. The shape of the curve is a visual indicator of the quality of the diagnostic test.

To know the distribution of the factors associated with fracture according to age and sex, bivariate combinations will be used with the Chi-square test among categorical variables and the Student's test among quantitative and categorical variables. To model the number of fractures occurring in our dataset which is, in fact, a count over time, Poisson regression will be used, which is what is precisely required for this type of variables and was used for the creation of the FRAX™ scale. All the statistical tests will be undertaken with a confidence interval of 95% and with the use of the 17th or latest version available of the SPSS statistical package.

Study limitations, potential limitations and biases

Since the FRIDEX cohort is constituted by subjects requiring a DXA scan (according to their physician), it likely that the recruited population will be at a baseline risk greater than that of the general population. Nonetheless, descriptive analysis of the population of this cohort indicates that the percentage of 32.3% of persons with densitometry osteoporosis is very similar to that reported in the literature for women of 50 years of age. Our results may therefore be extrapolated to a population in which the physician is evaluating the risk of low bone mass or fracture (case finding) which is, furthermore, the population recommended for investigation by the WHO.

The QRF used includes the variables of the FRAX™ scale and is complemented by the follow up telephone questionnaire on fractures, falls and new medications prescribed as well as diseases developed in the last 10 years.

The variable "number of falls" was not collected at the beginning of the FRIDEX cohort. Therefore, it may only be considered as an outcome variable in the subgroup of cases with incidental fractures posterior to the collection of this variable. Nonetheless, according to the opinion of the external assessor and the research team, this variable is highly related to the risk of fracture and thus, should be collected and taken into account in this study.

To minimise the effect of possible losses which may imply bias (given the morbimortality associated with fractures and the possible dropouts over 10 years), notable increases in the sample size have been considered necessary such as the cases to be localised among those with a contact telephone number. We believe that this will minimise the losses to follow up or refusal to participate for several reasons: information will be collected by telephone to avoid the difficulties of post questionnaires, which have low response rates in our setting; in addition the participants in the FRIDEX cohort had already accepted to participate in the QRF and almost all of the persons contacted in the pilot study accepted to answer follow-up survey.

There may be a bias in the collection of the information on incidental fractures which is collected based on the patient self-report. Nevertheless, in this study all the new fractures detected will be contrasted with the corresponding medical reports or by consultation with the physicians. Thus silent vertebral fractures will be scarcely detected but the symptomatic vertebral fractures, which are those included in the prediction of the FRAX™, will be collected. In addition, this is the usual method used in large epidemiological studies. The possible limitations inherent to data collection by telephone will be minimised with interviewer training among personnel with health care background through the improvement detected in the pilot study and by the incorporation of potential improvements thereafter.

The study has been approved by the ethical committee of the Clinical Research Ethics Committee of the Vall d'Hebron University Hospital (Barcelona, Spain). Additional file 3 shows the timing of the project.

Discussion

Since more than 10 years ago numerous reports have recognised the importance of other risk factors for new osteoporotic fractures in addition to low BMD. This new evidence has modified the conception of the utility of BMD as the gold standard or as an added element for decision making in the management of osteoporosis in primary health care settings.

The FRAX™ tool was published by the WHO in 2008 and was created to establish a calculation of the probability of absolute risk of osteoporotic fracture at 10 years. This was initially based on the analysis of thousands of person included in several cohorts in Europe [12,13]. Since its publication this tool has also been used to know the risk of fracture in other population cohorts in Europe, the United States of America, Canada, and Japan [25-30]. Likewise, since its publication this tool has undergone new adjustments and calibrations for different populations [30]. On the other hand, some studies have also recently been published, in which the cases of fracture estimated or expected by the FRAX™ tool were significantly lower than the cases of incidental fractures actually observed in the 10 years of follow up [31].

In the case of the Spanish population included in the FRAX™ tool, there are some doubts as to their representativeness because of the scarce response of original study and scarce global number of patients included [12,13], which could represent problems of external validity and should be contrasted with new studies of large cohorts over long periods of follow up to allow the establishment of epidemiological relationships adjusted to each population.

The extension of a method for calculating the risk (probability) of fractures using the FRAX™ tool is foreseeable in Spain similar to what is occurring in other countries and this would justify a study such as this to allow the necessary adjustments in calibration of the parameters included in the logarithmic formula constituted by FRAX™.

From the point of view of validation and economic analysis of the FRAX™ tool, the National Osteoporosis Guideline Group (NOGG) has recently published a calculation with FRAX™ which takes cost-effectiveness to avoid a new fracture in a population in the United Kingdom into account [15]. This is one of the first countries to publish studies on the economic cost which means the willingness to pay and cost-effectiveness to avoid a new fracture in its population. These calculations have been based on the calculation of fracture risk using the FRAX™ tool and determined clinical risk factors.

It can be expected that other counties will establish the same parameters with economic evaluation derived from the application of the FRAX™ tool. A study of the diagnostic validation of the FRAX™ tool is necessary as the first step to establish the criteria of cost-effectiveness and the number of cases to treat to avoid the appearance of new osteoporotic fractures.

Studies in large cohorts over long periods of follow up have allowed epidemiological associations to be established, and although numerous studies have demonstrated the independent association of clinical and environmental risk factors with low BMD, some associations with fractures in populations in different geographical zones are pending thus, the need for extensive epidemiological studies in the Spanish population.

One of the few studies published with the FRAX™ tool in Spain did not provide new knowledge on the idealness

of the cohorts represented [32], thereby justifying a study such as the present which will allow the necessary calibrations and adjustments of the parameters included in the logarithmic formula constituted by the FRAX™. At the same time, the scientific community requires a relatively easy and agile system to determine when a DXA should be requested and/or when treatment for osteoporosis should be initiated based on reliable predictive models similar to those already implemented in the daily routine for the prevention of cardiovascular events.

The WHO has recommended that prospective studies should be performed with this methodology in our population. This is therefore a great opportunity to validate and contribute to the determination of its true utility among the collective of physicians, especially in Primary Care, and in the population by focusing on interventions in the cases of greatest risk of fracture.

Ethics

The study has been approved by the ethical committee of the Clinical Research Ethics Committee of the Vall d'Hebron University Hospital (Barcelona, Spain).

Telephone calls will be made to all the cases of the randomised sample of the cohort. According to the protocol accepted by the reference Clinical Research Ethics Committee [PR registration number (AG) 68/2009], verbal consent will be requested at the onset of the study to continue with the telephone interview, the posterior follow up calls and to compare the fractures in the medical records.

The investigators guarantee and will be responsible for data confidentiality. The clinical data will be introduced into a computerised database in which the patients are identified by an anonymised code. A parallel database will be created containing the data of patient affiliation and the corresponding relational code. Only the Principal Investigator and the study data manage will have access to this database.

Additional material

Additional files 1: Questionnaire on risk factors (QRF). Shows the clinical factors of fracture risk analysed with the structured questionnaire (QRF), dietary intake of calcium and drugs use.

Additional file 2: Telephone Questionnaire (TQ). Shows the follow-up survey of factors that can influence the number and type of fractures, falls, drugs, and others.

Additional file 3: Timing of the Project. Shows the work plan, broken down by task and timetable

List of abbreviations

AATRM: Agència Avaluació Tecnologia i Recerca Mèdiques (Catalan Agency for Health Technology Assessment and Research); BMD: Bone Mineral Density; COPD: Chronic Obstructive Pulmonary Disease; DB: Database; DXA: Dual-energy X-ray Absorptiometry; E: Extrahospitalary specialties; FRAX™: Fracture Risk Assessment tool; FRIDEX: Factors of Fracture Risk and Bone Densitometry DXA cohort; H: Hospital specialities; ISCD: International Society for Clinical Densitometry; NAHNES: National Health and Nutrition Examination Survey; NOGG: National Osteoporosis Guideline Group; PC: Primary Care; QRF: Questionnaire of Risk Factors; RF: Risk Factor; RR: Relative Risk; SEIOMM: Sociedad Española Investigacion Osea y Metabolismo Mineral (Spanish Society for Bone and Mineral Research); TQ: Telephone Questionnaire: follow up; WHO: World Heath Organisation.

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Authors' contributions

RA is the principal investigator, project design and direction, preparation and review of the manuscript. GR coordination field work, preparation and review of the manuscript. GE coordination and management of the cohort, review of the manuscript. AA coordination and analysis of the FRAX™ values, review of the manuscript. MI, NP, MZ, SG, PS, SS, VS, FLE, SO and YF field work, calculation of the FRAX™ values and review of the manuscript. DP statistical analysis and management of the database, review of the manuscript. EG, EC, PT and ADP scientific support and methodological expert, review of the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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10.2. Annexe 2: Primers resultats de la cohorte FRIDEX sobre la capacitat discriminativa i predictiva

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FRAX® tool, the WHO algorithm to predict osteoporotic fractures: the first analysis of its discriminative and predictive ability in the Spanish FRIDEX cohort

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Abstract

Background: The WHO has recently published the FRAX® tool to determine the absolute risk of osteoporotic fracture at 10 years. This tool has not yet been validated in Spain.

Methods/design: A prospective observational study was undertaken in women in the FRIDEX cohort (Barcelona) not receiving bone active drugs at baseline. Baseline measurements: known risk factors including those of FRAX® and a DXA. Follow up data on self-reported incident major fractures (hip, spine, humerus and wrist) and verified against patient records. The calculation of absolute risk of major fracture and hip fracture was by FRAX® website. This work follows the guidelines of the STROBE initiative for cohort studies. The discriminative capacity of FRAX® was analyzed by the Area Under Curve (AUC), Receiver Operating Characteristics (ROC) and the Hosmer-Lemeshow goodness-of-fit test. The predictive capacity was determined using the ratio of observed fractures/expected fractures by FRAX® (ObsFx/ExpFx).

Results: The study subjects were 770 women from 40 to 90 years of age in the FRIDEX cohort. The mean age was 56.8 ± 8 years. The fractures were determined by structured telephone questionnaire and subsequent testing in medical records at 10 years. Sixty-five (8.4%) women presented major fractures (17 hip fractures). Women with fractures were older, had more previous fractures, more cases of rheumatoid arthritis and also more osteoporosis on the baseline DXA. The AUC ROC of FRAX® for major fracture without bone mineral density (BMD) was 0.693 (CI 95%; 0.622-0.763), with T-score of femoral neck (FN) 0.716 (CI 95%; 0.646-0.786), being 0.888 (CI 95%; 0.824-0.952) and 0.849 (CI 95%; 0.737-0.962), respectively for hip fracture. In the model with BMD alone was 0.661 (CI 95%; 0.583-0.739) and 0.779 (CI 95%; 0.631-0.929). In the model with age alone was 0.668 (CI 95%; 0.603-0.733) and 0.882 (CI 95%; 0.832-0.936). In both cases there are not significant differences against FRAX® model. The overall predictive value for major fracture by ObsFx/ExpFx ratio was 2.4 and 2.8 for hip fracture without BMD. With BMD was 2.2 and 2.3 respectively. Sensitivity of the four was always less than 50%. The Hosmer-Lemeshow test showed a good correlation only after calibration with ObsFx/ExpFx ratio.

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Conclusions: The current version of FRAX® for Spanish women without BMD analzsed by the AUC ROC demonstrate a poor discriminative capacity to predict major fractures but a good discriminative capacity for hip fractures. Its predictive capadty does not adjust well because leading to underdiagnosis for both predictions major and hip fractures. Simple models based only on age or BMD alone similarly predicted that more complex FRAX® models.

Background

The major manifestation or clinical consequence of osteoporosis is the appearance of osteoporotic fracture or fragility fracture [1]. It is well known that osteoporotic fractures involve a higher incidence of new fractures and lead to disability [2]. Hip fractures and those of the vertebrae with clinical manifestations are especially important since they carry an increase in mortality [3,4]. There is currently wide consensus regarding the need to develop strategies for the prevention of fractures and in the last years it has been recommended that the decision and the threshold of intervention be based on clinical assessment of risk of fragility fracture [5-8] and not only on the values of BMD and the relative risk as in the meta-analysis by Marshall D et al. [9].

Multiple epidemiological studies have described different clinical risk factors of osteoporotic fracture (CRFs) and which are been associated with an increased risk of developing osteoporosis and/or fragility fractures. Nonetheless, not all have determined a strong association, and the presence of these CRFs has not been uniform in the different studies and systematic reviews [10-14].

Most of the most powerful CRFs are concordant in different populations and, in general, similar for different fractures. Fractures related to falls have additional risk factors such as the number of falls, scarce physical activity and others such as the use of a walking stick, the need for help to get up from a chair, etc.). The CRFs associated with lifestyle such as smoking, alcohol intake or caffeine, low calcium consumption and scarce physical exercise have shown greater variability and lesser uniformity among the different studies [6,7]. Finally, the influence of some risk factors on the risk of fragility fracture has been demonstrated in different meta-analyses and systematic reviews [15-20]. As previously commented, since more than 15 years ago there has been evidence that BMD below the standard values is one of the important risk factors for fragility fracture [21,22]. More recently, however, other CRFs with as great or greater specific weight in the determination of risk of fragility fracture have been reported [11-13,22].

It is well known that there is an important variation in the relative risk of hip fracture in both men and women at an international level. The WHO itself has performed numerous investigations on this difference. In one of the latest studies this difference was defined as a standardised rate at 10 years, being, in the most extreme cases, 15-fold greater between countries such as Norway and Chile [23].

The studies performed by the Bone and Mineral Research Program, in Garvan Institute of Medical Research show that the combination of BMD and non-invasive clinical risk factors in a nomogram could be useful for identifying high-risk individuals for intervention to reduce the risk of hip fracture [24]. With the objective to make a purpose of when were the better moment and the patient who better benefits of new drugs available for the prevention of osteoporotic, World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, UK developed the FRAX tool. Both are useful tools to estimate absolute risk of fracture for clinical practice but both have limitations: They discriminative ability was only moderate in older women (mean 74 years old) which may limit their clinical utility [25].

Both Garvan and FRAX are widely available tools: http://www.garvan.org.au/bone-fracture-risk/ and http://www.shef.ac.uk/FRAX/ but both models still need to be validated in different populations before they can be generalized to other populations and further studies will be needed to validate their contribution in selecting patients who will achieve fracture risk reduction with anti-osteoporosis therapy. With the current available algorithms, a possible clinical application may be to use FRAX as the primary model and to consider using Garvan in patients with recurrent fractures and falls [25].

Since the technical reports of 1994 [26] and their review in 2001 few changes have been made with respect to the WHO recommendations on the management of osteoporosis. In 2007, the WHO published a new tool for the evaluation of absolute risk of fragility fracture: the FRAX tool [27-30]. This tool was developed by WHO to evaluate fragility fracture risk for a 10 year period in patients for many countries [31-33].

The extension of a method for calculating the risk (probability) of fractures using the FRAX tool is foreseeable in Spain similar to what is occurring in other countries since its publication [34,35]. But before its clinical use its necessary to validate the calculator in a local cohort [29,30].

Objectives

The objective of this study was to evaluate the discriminative and predictive capacity of the FRAX tool to determine osteoporotic or fragility fracture in Spain at 10 years.

This study describes the discriminatory capacity using the AUC-ROC *of the* FRAX tool to determine which Spanish women will have an osteoporotic fracture over the 10 years following the determination of the risk. On the other hand, the global predictive capacity of the FRAX tool has been calculated to detect the osteoporotic fractures on comparing the fractures observed over the 10 years with those expected by the FRAX tool.

Methods

Methods/design

The protocol, procedures and main characteristics of the study have recently been published [35].

Briefly, the FRIDEX cohort (**F**racture **RI**sk factors and bone **DE**nsitometry type central dual **X**-ray) is constituted of men and 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 or treatment follow up, who accept to answer an extensive questionnaire on risk factors (QRF) for osteoporotic fracture (family history of osteoporosis and hip fracture, clinical risk factors and lifestyle habits related to diet and toxic substances) [35]. This cohort was started in 1999 at the Bone Densitometry Unit of the Department of Nuclear Medicine of the University Hospital Vall d'Hebrón, Barcelona, Spain.

During the baseline visit at the reference centre informed consent to participate was requested and a QRF for osteoporotic fractures is given during the visit and anthropometric parameters are determined. Ten years after the first QRF and DXA the patients were asked to answer a phone survey to know the evolution of the study variables and outcomes such as new personal or parental fractures, new disease or prescriptions.

Study population and enrolment procedures

This multicentre study was carried out by family practitioners and other specialists who refer patients to the same reference centre for undertaking BMD. The criteria for referral followed the recommendations of the WHO of not performing a population screening but to select cases among those at greatest risk of having osteoporosis and subsequent osteoporotic fractures or the follow up and control of patients already receiving specific treatment.

Participants reside mostly in urban areas and were referred for DXA scan by family doctors, ambulatory specialists and hospital specialists.

Randomised sample (simple computerised randomisation stratified by sex) was obtained of women from 40 to 90 years of age in the FRIDEX cohort for 10 years since the baseline DXA and QRF.

Eligibility criteria

Patient inclusion criteria

The study subjects were Caucasian women, ≥ 40 and ≤ 90 years of age at the time of inclusion in the FRIDEX cohort [35], understood and spoke the Spanish language, were able to respond to the initial questionnaire done at the surgery and a ten-year follow up structured telephone questionnaire (TQ). All accepted to participate in the study providing the corresponding verbal consent. Physically or psychically handicapped patients were included if the relatives or care providers accepted to answer the TQ.

Patient exclusion criteria

Subjects < 40 or > 90 years of age at the time of the first DXA and QRF were excluded since the FRAX tool does not allow the calculation of the adjusted risk outside this age range. Patients with physical or psychological limitations impeding their participation and whose relatives did not accept to respond to the TQ were excluded as were those with Paget's disease, cancer with bone involvement or disease which may simulate osteoporosis (i.e. myeloma). Patients from ethnic groups other than Caucasian were not included since other studies have demonstrated different risk characteristics. Patients not providing consent to the TQ and those without a telephone to contact or did not respond after 3 calls made at different times according to the procedure manual were also excluded from the study. Dead patients were not studied because of the impossibility of obtain all the study variables or to answer the questionnaire by relatives.

Data collection

The sample ordering was performed using randomised numbers for each month and the calls were made in this order. The baseline variables of QRF and BMD were collected from January to July 2000. The follow up variables were collected at the same month during 2010 by TQ to complete the 10 years of follow up. The TQ was collected regarding the fragility fractures occurring from the time of inclusion until the date of the TQ as well as other information on known factors of fracture risk and falls. 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. Dead patients were not studied because of the impossibility of obtain all the study variables and to answer the questionnaire by relatives.

Baseline variables

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 (100 ml) 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. 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%). BMD measurement was determined by central DXA according to the 2007 recommendations of the International Society for Clinical Densitometry (ISCD) (available at: www.iscd.org/Visitors/positions/OfficialPositionsText.cfm) for the interpretation of the results using a Lunar GE model *Prodigy Advance* densitometer with 11.4 software and with BMD and T-score determination with NHANES III references. The densitometry diagnostic criteria used were the 1994 WHO criteria which classify the results into 3 groups according to the levels of BMD values of the femoral neck: normal (T-score >−1), osteopenia (T-score between −2.4 and −1 inclusive) and osteoporosis (T-score ≤ −2.5).

The estimated absolute risk of fracture during the 10-year period according to the FRAX tool was determined through the official website (version 3.2 accessed on October 2010). The calculations of the probability of fracture with or without the T-score of femoral neck and lumbar spine (L1-L4) were analysed in parallel by two blind investigators (patient entities were kept anonymous and were assigned an alphanumeric code). Two other blinded investigators reviewed the results and recalculated the data on the appearance of any difference.

Analysis plan

The hip fractures during the follow up period were taken as the endpoint event. At first, all fractures were collected by TQ (structured interview), but were only included in the analysis if these fractures were verified against patients records. The characteristics of the population were described according to descriptive univariate analysis. We used the Chi-square test to evaluate the association between qualitative variables. The Student's t-test or, if necessary, its non parametric equivalent, the Mann–Whitney U test, was implemented to evaluate the differences in the distribution of a quantitative variable according to the categories defined by a binary exposure. To assess the differences in the distribution of a quantitative variable according to the categories defined by a categorical variable with more than two categories, ANOVA analysis of variance or its corresponding non parametric test (Kruskal-Wallis) were used. The relative risk (RR) was calculated by quotient between prevalence of each risk factor in fractured women and in non-fractured.

To know the discriminating ability of the FRAX tool we used AUC-ROC and the Hosmer-Lemeshow goodness-of-fit test. The overall predictive capacity ratio was calculated by comparison of observed fractures (ObsFx) in the cohort and period and the expected fractures (ExpFx) by the FRAX tool [sum of individual probability of fracture from all women included/100].

The proportion of fractures expected is calculated by the sum of an individual probability of fracture from all women included/100. Model calibration is done by multiplying the FRAX result by the ratio ObsFx/ExpFx.

All the statistical tests were undertaken with a confidence interval of 95% and with the use of the 17th version of the SPSS statistical package.

This work follows the guidelines of the STROBE initiative for epidemiological studies [http://www.strobe-statement.org/index.php?id=strobe-publications].

Ethics

Procedures for human subject protection and the original protocol [35] were approved by the Clinical Research Ethics Committee of the Vall d'Hebron University Hospital, Barcelona, Spain and by the Ethical Committee of the Institut Universitari d'Investigació en Atenció Primària (IDIAP) Jordi Gol. Barcelona. Spain. Informed consent was obtained before beginning the interviews of all the patients.

Results

Among the person completing 10 years since their inclusion in the cohort, 1,308 could be contacted for this study (Figure 1). About 69 (5.3%) patients died (43.4%). Thirty nine have been detected by searching the telephone number and detect the death. In the other 30

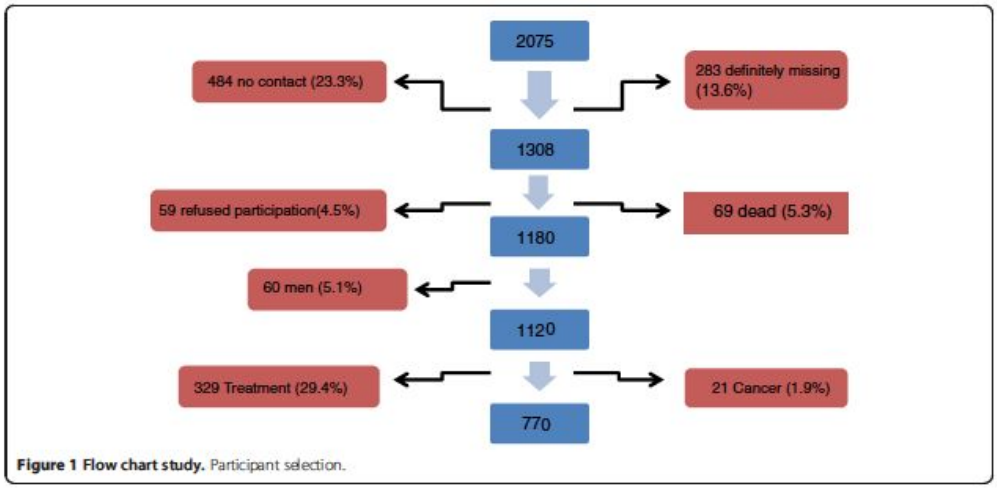


Figure 1 Flow chart study. Participant selection.

cases were detected through contact with family and reported only 2 cases of fracture between baseline and the date of death. A total of 770 women fulfilled the inclusion criteria and provided informed consent to participate.

During the 10 years of study 65 women presented a total of 82 major osteoporotic fractures which could be contrasted: 17 women with 18 hip fractures, 10 with 18 proximal humeral fractures, 25 with 30 forearm fractures, and 14 with 16 vertebral fractures. All the fractures were caused by low intensity impact according to the classical definition of fragility fracture [26].

Table 1 shows the baseline characteristics of the participants and those selected but did not participate in the study. No significant differences were observed between these two groups except that the participants ware one year younger on average (56.8 vs. 57.8 years) and the participants were taking glucocorticoids (3.7 vs. 5.9%).

Table 2 describes the main characteristics of the 770 participating women as well as the results of the variables or risk factors included in the FRAX tool and the results of the baseline DXA expressed as the result stratified according to the WHO classification. It also includes the variable of *falls in the previous year* which was assessed at the end of the study. The CRFs showing significant differences between women with fractures and those without fractures are: age, previous fractures, having rheumatoid arthritis and having a diagnosis of osteoporosis on DXA. The relative risks (RR) of the different CRFs are shown separately for major fracture and hip fracture in Tables 2 and 3.

The values of the different AUC-ROC for major and hip fracture calculated in the cohort of Spanish women are shown in Table 4. That is, of BMD by DXA with the T-score of the femoral neck (FN) and with the T-score of spine L1-L4 and the FRAX tool in three ways: without BMD, with the FN T-score and with spine L1-L4 T-score. The best result was for FRAX tool for hip fracture without the T-score (0.888). In all cases the results presented significant differences with the reference (0.50) except for BMD with spine L1-L4 T-score (p=0.067). Figures 2 and 3 are graphs of the AUC-ROC of the FRAX tool for major fracture and hip fracture. A determination of the AUC-ROC

Table 1 Risk factors among participants/non participants in the current study of FRIDEX cohort

	Participants (n= 1180)	Non Participants (n= 895)	p-value
Age years, mean (SD)	56.8 (8.0)	57.8 (8.5)	<0.001
Weight in Kg., mean (SD)	66.6 (11.5)	65.9 (11.1)	ns
Height in cm., mean (SD)	155.2 (5.9)	155.6 (6.0)	ns
BMI in Kg/cm2 , mean SD)	27.7 (4.7)	27.9 (4.2)	ns
Smoker, n (%)	132 (11.2%)	103 (11.5%)	ns
Alcohol Risk, n (%)	6 (0.5%)	5 (0.5%)	ns
Previous Fracture, n (%)	269 (22.8%)	245 (27.4%)	ns
Parental osteoporosis or fractures, n (%)	185 (15.7%)	138 (15.4%)	ns
Glucocorticoids, n (%)	44 (3.7%)	53 (5.9%)	0.024
Rheumatoid Arthritis, n (%)	12 (1.0%)	11 (1.2%)	ns
Calcium/Vit. D Supplements, n (%)	221 (18.7%)	187 (20.9%)	ns
Active Bone Drugs (antiosteoporotic drugs), n (%)	329 (27.9%)	277 (30.9%)	ns

Table 2 Baseline risk factors and falls in previous year for major fracture

	65 Women with fracture	705 Women without fracture	P- value	CI 95%	RR	CI 95% RR
Age (SD)	61.2 (9.7)	56.4 (7.7)	<0.001	2.4-7.3	2.62 (*)	(1.63 – 4.21)
Weight (SD)	67.4 (11.5)	66.6 (11.4)	0.559	ns	-	-
Height (SD)	155.3 (6.1)	155.1 (5.8)	0.805	ns	-	-
BMI (SD)	28.0 (4.4)	27.7 (4.7)	0.653	ns	1.19 (**)	(0.31 – 4.53)
Previous Fracture (%)	43.1	18.6	<0.001	12.1-36.9	2.91	(1.84 – 4.60)
Parental Hip Fracture (%)	15.4	15.6	0.963	ns	0.98	(0.52 – 1.88)
Smoker (%)	9.2	11.3	0.604	ns	0.81	(0.36 – 1.82)
Alcohol Risk (%)	1.5	1	0.508	ns	1.49	(0.23 – 9.45)
Glucocorticoids (%)	7.7	2.8	0.052	ns	1.15	(0.94 – 1.40)
Rheumatoid Arthritis (%)	4.6	0.7	0.024	1.2-9.0	4.61	(1.83 – 11.63)
Falls in previous year (%)	32.3	22.3	0.066	ns	1.59	(0.97 – 2.60)
Osteoporosis (baseline DXA) (%)	50.8	25.8	<0.001	12.4-37.6	4.96 (ǂ)	(1.98 – 12.43)
Osteopenia (baseline DXA) (%)	41.5	50.9	0.147	ns	2.36 (Φ)	(0.93 – 6.03)
Normal (baseline DXA) (%)	7.7	23.3	0.004	8.4-22.8	-	-

RR: Relative Risk.
(*) < 65 vs. ≥ 65 years.
(**) < 20 vs. ≥ 20.
(ǂ) Osteoporosis vs. normal.
(Φ) Osteopenia vs. normal.

specifically for vertebral fracture was performed, being 0.752 (CI 95%; 0.643-0.861) for the FRAX tool without BMD, 0.815 (CI 95%; 0.725-0.905) with the FN T-score and 0.710 (CI 95%; 0.575-0.844) with L1-L4 T-score, without significant differences among them (p=0.157) (graph not shown). We compare AUC of the ROC curve of FRAX tool for major and hip fracture with a simple model including only age. The AUC in a model that includes only age was 0.668 for major fracture and 0.882 for hip fracture with no significant differences with the results of FRAX tool (p=0.565 and p=0.976 respectively).

Around 27 major fractures and 6 hip fractures were expected with the FRAX tool without BMD, while around 30 major fractures and 7 hip fractures were expected with the inclusion of the T-score of the femoral neck in the FRAX tool (Table 5).

Table 3 Baseline risk factors and falls previous year for hip fracture

	17 Women with fracture	753 Women without fracture	P- value	CI 95%	RR	CI 95% RR
Age (SD)	69.4 (7.1)	56.5 (7.8)	<0.001	9.2-16.7	11.49 (*)	(4.12 – 32.08)
Weight (SD)	64.8 (8.1)	66.7 (11.5)	0.498	ns	-	-
Height (SD)	153.1 (7.3)	155.2 (5.8)	0.139	ns	-	-
BMI (SD)	27.7 (3.0)	27.7 (4.7)	0.945	ns	1.02 (**)	(0.06 – 16.43)
Previous Fracture (%)	47.1	20.1	0.012	3.1- 50.9	3.42	(1.34 – 8.71)
Parental Hip Fracture (%)	17.6	15.5	0.738	ns	1.16	(0.34 – 3.98)
Smoker (%)	0.0	11.4	0.242	ns	0.225	(0.01 – 3.71)
Alcohol Risk (%)	0.0	1.1	1.000	ns	2.42	(0.16 – 37.26)
Glucocorticoids (%)	11.8	3.1	0.102	ns	3.97	(0.96 – 16.45)
Rheumatoid Arthritis (%)	11.8	0.8	0.012	4.3-26.3	12.7	(3.46 - 46.63)
Falls in previous year (%)	35.3	22.8	0.246	ns	1.81	(0.68 – 4.84)
Osteoporosis (baseline DXA) (%)	58.8	27.2	0.004	8.0-55.2	7.86 (ǂ)	(1.02 – 60.80)
Osteopenia (baseline DXA) (%)	35.3	50.5	0.215	ns	2.63 (Φ)	(0.32 – 21.65)
Normal (baseline DXA) (%)	5.9	22.3	0.106	ns	-	-

RR: Relative Risk, ns: no statistical significance.
(*) < 65 vs. ≥ 65 years.
(**) < 20 vs. ≥ 20.
(ǂ) Osteoporosis vs. normal.
(Φ) Osteopenia vs. normal.

Table 4 Area Under Curve (AUC) of Receiver Operating Characteristics (ROC)

		AUC ROC	CI 95%	p - value
AUC ROC 10-year prediction of MAJOR FRACTURE	BMD with FN T-score	0.661	(0.583-0.739)	p<0.001
	BMD with L1-L4 T-score	0.638	(0.565-0.711)	p<0.001
	FRAX® tool without BMD	0.693	(0.622-0.763)	p<0.001
	FRAX® tool with FN T-score	0.716	(0.646-0.786)	p<0.001
	FRAX® tool with spine L1-L4 T-score	0.712	(0.644-0.780)	p<0.001
AUC ROC 10-year prediction of HIP FRACTURE	BMD with FN T-score	0.779	(0.631-0.929)	p<0.001
	BMD with L1-L4 T-score	0.630	(0.487-0.773)	(ns)
	FRAX® tool without BMD	0.888	(0.824-0.952)	p<0.001
	FRAX® tool with FN T-score	0.849	(0.737-0.962)	p<0.001
	FRAX® tool with spine L1-L4 T-score	0.767	(0.658-0.876)	p<0.001

AUC ROC: Area Under Curve of Receiver Operating Characteristics; BMD: Bone Mineral Density; FN: Femoral Neck; L1-L4: Lumbar Spine; CI: Confidence Interval; ns: Not significant.

The ObsFx/ExpFx ratio was 2.4 (CI 95%; 1.9 - 3.1) for major fracture and 2.8 (CI 95%; 1.7 - 4.6) for hip fracture (Table 5) with the FRAX tool without BMD and 2.2 (CI 95%; 1.7 - 2.8) and 2.3 (CI 95%; 1.4 - 3.8), respectively with femoral neck T-score. Expressed in percentages, the FRAX tool without BMD predicts 41.1% of the cases of women with major fracture in 10 years and 46% on adding the algorithm of the T-score of the femoral neck, with these values being 35.5% and 42.8% for hip fractures, respectively.

With respect to the analysis of the sample of the FRIDEX cohort we performed a goodness-of-fit test which stratifies the results in quintiles of risk associated with quintiles of results of fracture.

Figure 4 shows the Hosmer-Lemeshow test for major fracture, with the cases of the sample distributed into quintiles and the line of regression for the results of the FRAX tool without BMD and with the FN T-score. The lower part of the figure represents the same results after calibration (simulation) by the number of times that the ObsFx is greater than the ExpFx (Table 5). Figure 5 shows the results for hip fracture in the same way.

Discussion

According to the comparative analysis of the baseline characteristics between the participants and the non participants for any reason we found that the non participants did not differ from the participants except in that

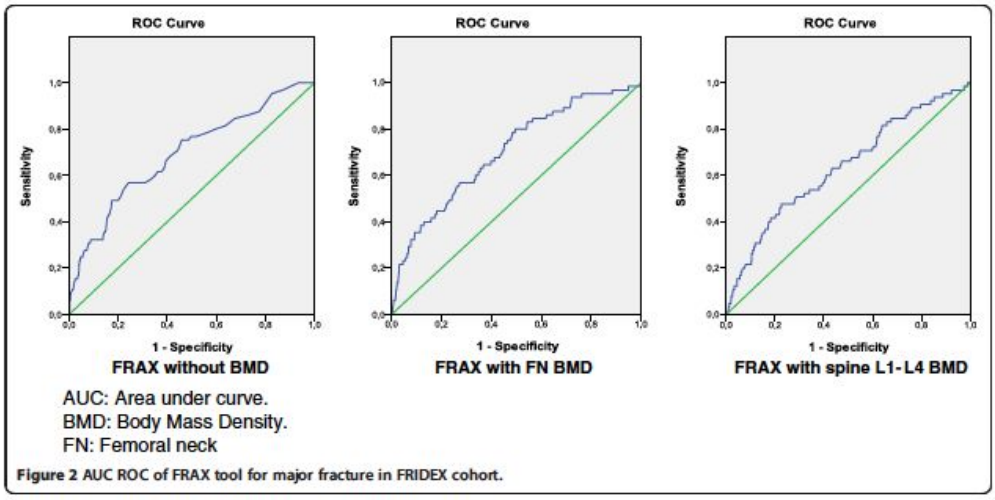


Figure 2 AUC ROC of FRAX tool for major fracture in FRIDEX cohort.

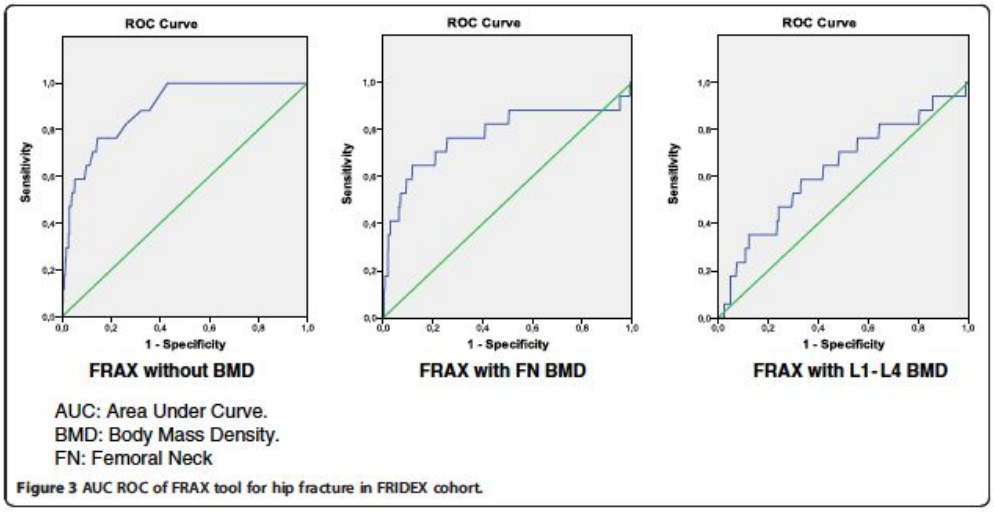


Figure 3 AUC ROC of FRAX tool for hip fracture in FRIDEX cohort.

they were one year older and more patients were on glucocorticoids. Thus, the participants in the study did not present worst conditions of the cohort.

Self-reported generally even structured interview 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.

The present study is centered on the discriminatory and predictive capacity of the FRAX. Analysis of the AUC-ROC was used to analyse the discriminatory capacity of this tool. As shown in (Table 4) the results of the FRAX without DXA values were greater than the AUC-ROC of BMD with values of the T-score of the femoral neck. Thus, these results demonstrate that the FRAX without the determination of BMD presents a discriminatory capacity not inferior to and even somewhat better than the DXA, according to the AUC-ROC. Analysis of the BMD with the DXA technique for the axial skeleton has traditionally been considered as the best predictive test known to determine fragility fractures [9,26,36] with the strategy of intervention for their prevention in medical practice having been based on this test in Spain [35] and in the remainder of the international scientific community until the appearance of the importance of other risk factors for fracture [27-33].

On analysing the role of the determination of BMD of L1-L4 in the different tests, it was found that the discriminatory capacity for major fracture using the AUC-ROC was lower than that of the determination of BMD with the T-score of the femoral neck, although statistical significance was maintained (Table 4). This inferiority was maintained for hip fracture but with no significant differences since the confidence interval integrates the value 0.50 which is the value of statistical significance for this test. Part of the debate on the possible

Table 5 Ratio of Observed fractures/Expected fractures by FRAX tool

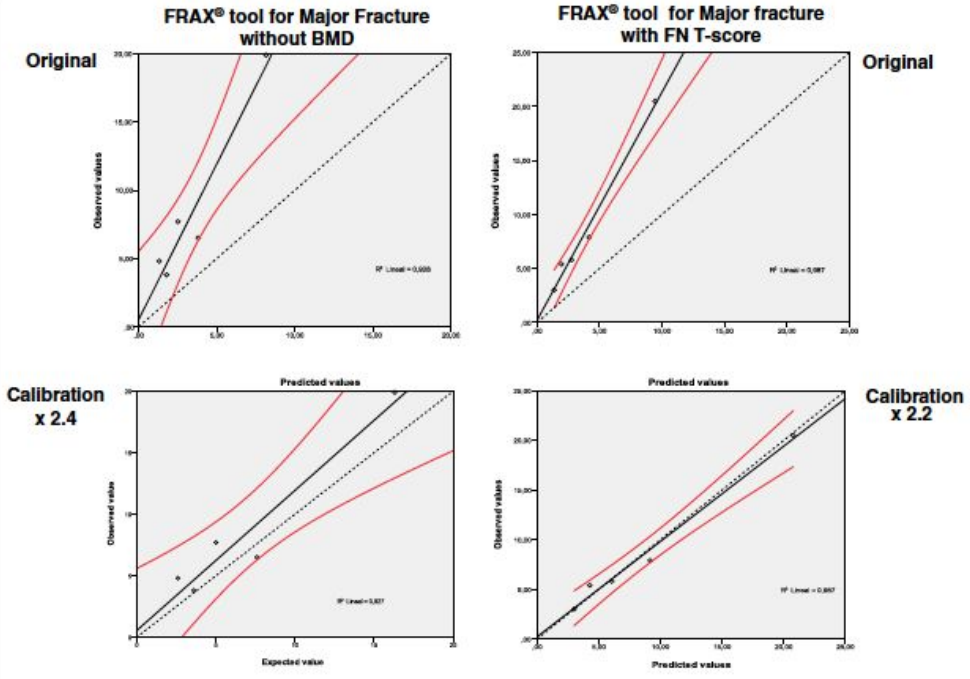
	MAJOR FRACTURES				HIP FRACTURES			
	Obs Fx	Exp Fx	Ratio Fx Obs/Exp	CI 95%	Obs Fx	Exp Fx	Ratio Fx Obs/Exp	CI 95%
FRAX without BMD	65	26.7	2.4	(1.9 - 3.1)	17	6.0	2.8	(1.7- 4.6)
FRAX with FN T-score	65	29.9	2.2	(1.7 - 2.8)	17	7.3	2.3	(1.4 - 3.8)

MAJOR FRACTURES (hip, vertebra, humerus, wrist). Fx: Fracture.
ObsFx: Observed fractures; ExpFx: Expected fractures; CI: Confidence Interval;
BMD: Bone Mineral Density; FN: Femoral Neck.

weaknesses of the FRAX has been centered on the lack of the BMD values of the lumbar spine in its algorithm. This criticism is based on the traditional consideration that the BMD of each area presents the best predictive capacity for fractures in the same area, especially for the vertebrae and the hip [36] and, thus, it has been argued that the prediction of vertebral fractures could be improved. The discriminatory capacity measured with the AUC-ROC worsened with the incorporation of the L1-L4 T-score in the algorithm of the FRAX for major or hip fractures (Table 4). This result is congruent, but on introducing the L1-L4 T-score value in the FRAX (as a simulation) to analyse what would happen with vertebral fracture, the result of the AUC-ROC for vertebral fracture worsened slightly with respect to that obtained with the FN T-score, although without significant differences. Thus, on introducing the values of the L1-L4 T-score in the FRAX in this study the result did not provide an improvement in the discrimination of vertebral fractures measured with the AUC-ROC. Although it has described that a correction can adapt the lumbar spine BMD and improve the prediction for major and vertebral fractures of FRAX [31] 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).

The adjusted predictive capacity of the FRAX analysed using the ObsFx/ExpFx ratio was far from the 1 value which would be the desired result in the case of good adjustment of the predictive capacity of the FRAX in our country. In our cohort this ratio was of 2.4 for major fracture and 2.8 for hip fracture. These values improved minimally on the introduction of the T-score of the femoral neck in the algorithm (2.2 and 2.3 respectively). Indeed, the FRAX predicted the risk of major fracture in 41.1% of the women and 35.5% for hip fracture without BMD, with these values improving only slightly with 46% and 42.8%, respectively on performing the BMD with DXA.

These data seem to coincide with the analysis recently carried out in two cohorts of French women with a



BMD: Body Mass Density.
FN: Femoral Neck

Figure 4 Hosmer-Lemeshow test. FRAX tool for Major Fracture.

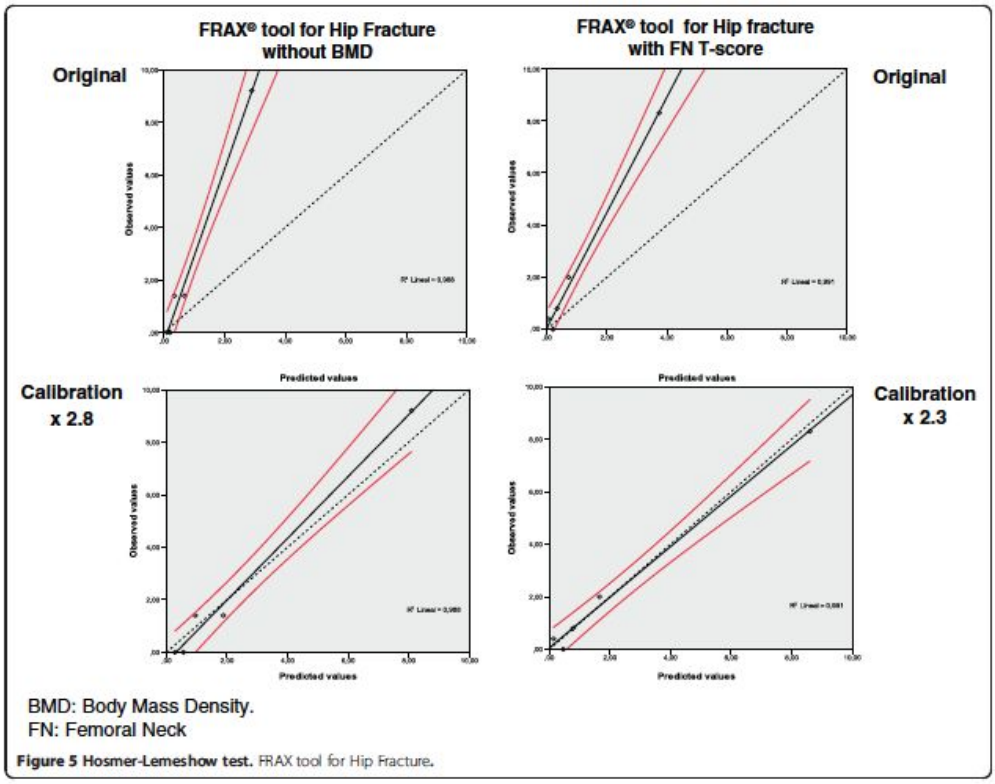


Figure 5 Hosmer-Lemeshow test. FRAX tool for Hip Fracture.

similar overall discriminatory value for fracture and low overall sensitivity (48-50% for FRAX predictions) and better than BMD alone [33,37]. In Spain our group previously demonstrated that the FRAX has good capacity to detect densitometric osteoporosis but also with imbalance in the predictive capacity [38-40]. Nonetheless, a two recent studies in Spain had shown similar results to ours for major fractures with an ObsFx/ExpFx ratio of 3.1 (CI 95%: 2.8-3.5) and 0.8 (CI 95%: 0.7-1.1) for hip fracture [41]. Although the initial formation of the two cohorts followed very similar schemes, the method of follow up in our study was notably different. In the present study we only analysed fragility fractures reported by the women, which could be contrasted with electronic record or clinical reports. In the second study the results of ratio ObsFx/ExpFx were 0.66 and 1.10 for major and hip fracture respectively [34]. The most important methodological differences were that the study was carry out for a three years period, the authors do not included vertebral fractures [34].

The ROC curve has several problems. For analysis of sensitivity and specificity we have not a gold standard of FRAX for Spanish population. Moreover, ROC needs a gold standard of illness (fracture) and we do not have because of the electronic records are not completely reliable and we needed to make a double check (self-reported validate against records). On the other hand, the area under the ROC curve is important, since it measures the discrimination power of the model. Nevertheless, tests of discrimination alone are not sufficient for model evaluation, since they do not indicate whether calibration is also good [34,35,42].

In our study, on application of the Hosmer-Lemeshow test a good correlation was observed between the different quintiles of risk in all the simulation (Figures 4, 5) but with a line which groups the results of the regression deviated from the reference toward the values observed. This circumstance led us to carry out a calibration multiplying each of the values resulting from the prediction made by the FRAX by a constant based on the ObsFx/ExpFx ratio for major fracture and for hip fracture. As shown in the lower part (calibration) of Figures 4 and 5, on multiplication of the results of the FRAX by

the ObsFx/ExpFx ratios, the results with their CI 95% adjust perfectly to the diagonal of reference in the Hosmer-Lemeshow test.

The FRAX tool can therefore be considered to present with a poor discriminatory capacity for women to have major osteoporotic fractures within 10 years, with this capacity being good for hip fractures without the need of determining the BMD, although this improves somewhat with its determination. The FRAX tool shows a scarce predictive capacity of the risk of fracture and predicts less than 50% of those which occur. The reason for this underdiagnosis may be because the Spanish cohort introduced as the reference in the FRAX tool is not representative of the current female population since these women present significantly more fractures than those actually predicted by the FRAX tool.

We have excluded from the analysis of the cohort of women receiving active treatment for the bone at baseline of the study because of the FRAX has so defined, but we have not been excluded women who received treatment during the 10-year period. This can be a potential confounding factor, however exclude women would mean removing the greatest potential for fracture, but keep going who have received treatment can be reduced the all risk of new fractures observed. Other potential confounding factor can be the Calcium/Vit D supplement intake because we have not excluded at baseline or during the study period. There is important discussion in the literature about the role of these supplements in reducing the risk of fracture, except in a subgroup of patients taking bone active drugs for the potential hypocalcaemia or in patients admitted to nursing homes. These patients are not included in this study. Moreover there is no significant difference between Calcium/Vit D supplement intake between participants and no participants.

New epidemiological studies are needed in our country to compare these results on major and other fragility fractures which, although not severe, also affect the quality of life [43]. However, together with other authors in our country [6,10,34,38-41] we believe that there are sufficient data to promote the habit of investigating the risk factors of fragility fracture among Spanish physicians, especially in primary care, to determine the absolute risk and be able to propose changes in lifestyle in persons with a high risk as well as evaluate which patients should be referred for determination of the BMD by DXA [38]. In our opinion, the current state of the FRAX needs some adjustments such as those proposed in this study. Something similar to this need for adaptation and adjustments happened in Spain with the application of the first Framingham-type cardiovascular risk scales which required adaptations such as the REGICOR scale and others in our country [44-46].

We know that the promoters of the FRAX are committed to the adaptation of the tool to the different countries with the publication of new studies such as what has been done up to now. We also consider that with improvements this may be a very useful tool especially in the first level of care and this has been demonstrated by the important extension in its use worldwide [28,35].

Conclusions

In summary, FRAX without BMD demonstrates a poor discriminative capacity for major fractures and a good discriminative capacity for hip fractures 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. On introducing the values of the L1-L4 T-score in the FRAX tool, the result did not provide an improvement in the discrimination of vertebral fractures measured with the AUC-ROC. Simple models based on age or BMD alone predicted 10-year risk of major and hip osteoporotic fractures, as well as more complex FRAX models.

We advise our Spanish colleagues to use the FRAX tool in clinical practice but weighing the resulting value of each individual case of the FRAX without BMD by a calibration value to obtain an absolute risk value of major o hip fracture at 10 years. New studies may allow a single value which is easier to remember in clinical practice. The result obtained will be more adjusted to the reality of the risk of fragility fracture in our country according to the results found in the present and other studies [34,38,41].

Study limitations and strengths

Our study has some strengths and limitations. We assumed that women in the FRIDEX cohort could have a higher risk of osteoporotic fractures than the general population because it is a population that had previously been selected to undergo a DXA scan for some reason. However it is important to know the profile of women who are selected to perform the DXA-scan by general practitioners and other specialists as may higher but close to the general population over 50 years. Fractures occurring in the participants were followed by an ad-hoc TQ taking into account the traditional low response rates by post in previous epidemiological studies conducted in Spanish population [36]. However, all fractures included were verified against patient records.

Other potential confounders and biases are that we excluded those who died during the follow-up, the collection of incident fractures is captured in retrospect, the validation records was only for patients with fractures and, as well, usually the electronic registers of fracture tends to be less records than actually occur. To minimize these potential biases we have verified all self-reported

fractures and not included in the study which did not fulfill both (self-reported and recorded). Therefore, this type of analysis tends to benefit the predicted fractures in the ratio ObsFx/ExpFx.

We are aware that the authors of the FRAX tool apply only the DXA value of the femoral neck because of the absence of improvement in the prediction of major fracture risk with the use of the lumbar spine T-score. This has been one of the main criticisms related to the FRAX tool.

As strengths of the study, 4 investigators were involved in the operating systems to verify the calculations of the values of FRAX and all hip fractures included in the analysis were contrasted. The FRIDEX study is a prospective population-based cohort study, being one of the first studies to follow Spanish women over a 10-year period to determine the incidence of fragility fractures.

Abbreviations

AUC: Area Under Curve; BMD: Bone Mineral Density; CRFs: Clinical risk factors; DXA: Dual-energy X-ray Absorptiometry; FN: Femoral neck; FRAX® and FRAX: Fracture Risk Assessment Tool; FRIDEX: Fracture Risk Factors and Bone Mass Density by DXA cohort; ISCD: International Society for Clinical Densitometry; NAHNES: National Health and Nutrition Examination Survey; NOGG: National Osteoporosis Guideline Group; ObsFx/ExpFx: Observed fractures/Expected fractures ratio; QRF: Questionnaire of Risk Factors; RF: Risk Factor; RR: Relative Risk; ROC: Receiver Operating Characteristics; REGICOR: Registre Gironí del Cor [http://www.regicor.org]; TQ: Telephone Questionnaire 10-year follow up; WHO: World Health Organization.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

RA is the principal investigator, project design and direction, preparation and review of the manuscript. GR coordination of field work, preparation and review of the manuscript. GE coordination and management of the cohort, review of the manuscript. AA coordination and analysis of the FRAX values, review of the manuscript. MI, NP, MZ, SG, PS, SS, VB, MR, MCG, FL-E, GL, JJA, GPL, JP-S and AP field work, calculation of the FRAX values and review of the manuscript. JCM statistical analysis and management of the database, review of the manuscript. EG, EC, YF, PT, DP-A and AD-P scientific support and methodological expert, review of the manuscript. All authors have read and approved the final manuscript.

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doi:10.1186/1471-2474-13-204
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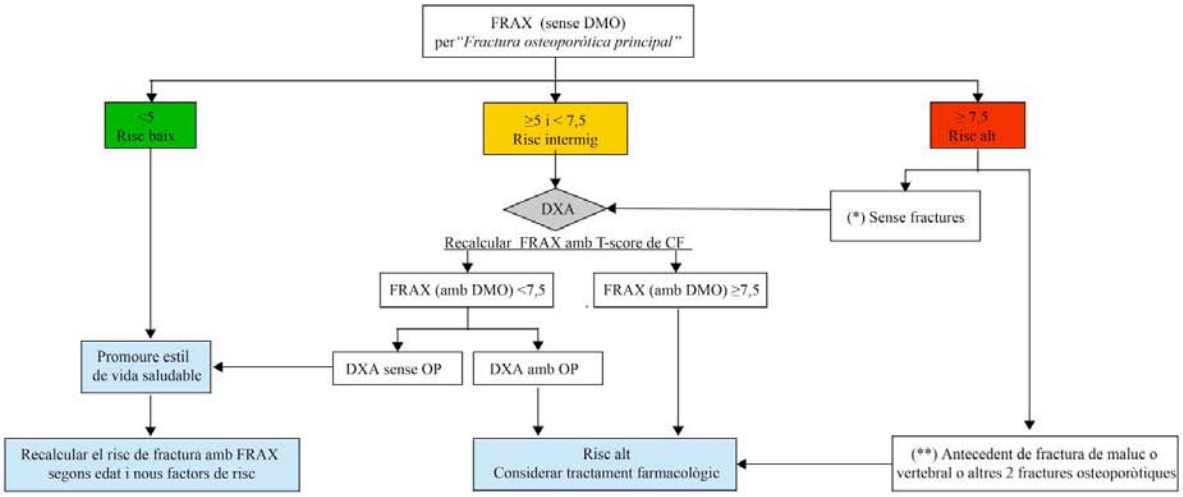
10.3. Annexe 3: Creació del model FRIDEX. Determinació i proposta dels llindars FRIDEX per la prevenció primària de fractures per fragilitat

Azagra R, Roca G, Martín-Sánchez JC, Casado, E, Encabo G, Zwart M, et al. Umbrales de FRAX® para identificar personas con alto o bajo riesgo de fractura osteoporótica en población femenina española. Med Clin (Barc). 2015;144(1):1-8.

10.4. Annexe 4. Diagrama de flux per determinar el risc de fractura osteoporòtica en la població femenina espanyola basat en els llindars FRIDEX de l'algoritme FRAX

Modificat amb permís d'Azagra et al. Med Clin (Barc). 2015;144(1):1-8. http://dx.doi.org/10.1016/j.medcli.2013.11.014



- FRAX®: Absolute risk of risk fracture: http://www.shef.ac.uk/FRAX/tool.jsp?lang=sp; "Fractura osteoporòtica principal" inclou cadera, columna vertebral, húmer i canell.
- DMO: Densitat mineral òssia.
- DXA: Densitometria axial per absorció dual de Rx.
- CF: Coll femoral.
- OP: Osteoporosi densitomètrica amb T-score ≤ -2.5 SD (WHO 1994), almenys a una de les següents 3 regions de la DXA: L1-L4, fèmur total o CF (ISCD 2007).
- (*): Opció cost-efectiva si no hi ha antecedent de fractura o una fractura que no sigui de cadera o de columna vertebral (clínica).
- (**): Tenint en compte consideracions d'altres associacions internacionals (CAROC 2010).

10.5. Annexe 5: Llistat alfabètic d'abreviatures

AUC	*Area Under the Curve*
BMD	*Bone Mineral Density*
CAROC	*Canadian Association of Radiologists and Osteoporosis Canada*
DE	Desviacions estandars
DMO	Densitat Mineral Òssia
DXA	*Dual-energy X-ray Absorptiometry*
FN	*Femoral Neck*
FRAX®	*Fracture Risk Assessment*
FRIDEX	Factors de RIsc de fractura i DEnsitometria dual de raigs X
GPC	Guies de Pràctica Clínica
IC 95%	Interval de Confiança 95%
95% CI	*95% Confidence Interval*
IMC	Índex de Massa Corporal
MAO	Medicaments AntiOsteoporòtics
Obs/Exp	Observada/Estimada
OMS	Organització Mundial de la Salut
ROC	*Receiver-Operating Characteristic*

10.6. Annexe 6: Agraïments

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