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Clinical efficacy of FRAX®-based hybrid and age-dependent intervention thresholds in the Ecuadorian population

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Lopez Gavilanez E[1,2], Valdivieso Jara J[1,3], Imaicela Naula L[1,3], Cedeño German R[1,3]
1 AECE Research Group. The Association of Clinical Endocrinologists of Ecuador (Ecuador)
2 Endocrinology Service. Guayaquil National Police Teaching Hospital 2, Guayaquil (Ecuador)
3 Endocrinology Service. Hospital Abel Gilbert Pontón. Guayaquil (Ecuador)

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Summary

Objetive: To assess the clinical impact of FRAX-based intervention thresholds in Ecuadorian women. Also to test a combination of fixed and age-specific intervention thresholds to optimize the selection of women eligible for intervention.
Patients and methods: Transversal study in which 2,283 women aged 60 to 94 years were selected. We calculated the risk of major osteoporotic and femoral neck fractures with the Ecuadorian FRAX model (version 4.1), and calculated the proportion of individuals eligible for treatment and bone mineral density assessment applying age-specific thresholds of 60 to 94 years and a fixed threshold from 75 years.
Results: Applying age-specific thresholds, 2% of women qualified for treatment and 73.7% for bone mineral density assessment. Depending on age, women eligible for treatment ranged from 0.7 to 3.8% and those eligible for bone mineral density evaluation from 58.3 to 80.5%.
With the fixed threshold, 31% of women qualified for treatment and 76.3% for bone mineral density assessment. Depending on age, women potentially eligible for treatment ranged from 3.8% to 76.5%, and those eligible for bone mineral density assessment from 65.2% to 85.4%.
Conclusions: The proportion of women potentially eligible for treatment is low compared to countries with a high risk of fractures. Using a fixed threshold starting at age 75 optimizes the proportion of women eligible for treatment. In low to moderate fracture risk countries with limited resources, a hybrid model may be more appropriate.

Key words: FRAX, intervention threshold, hybrid threshold, fracture risk, Ecuador.

Introduction

Osteoporosis is a skeletal disorder characterized by compromised bone strength that predisposes to an increased risk of fracture[1]. Osteoporosis-related fractures are a major health problem and a significant economic and social burden worldwide. By 2050, 12.5% of hip fractures worldwide are projected to occur in the Latin American and Caribbean region[2]. Consequently, it is very important to recognize and treat people who are at high risk of fractures, for which several simple and inexpensive alternatives have been developed to identify and select people at risk who are candidates for treatment and evaluation of bone mineral density (BMD)[3].

The National Osteoporosis Foundation (NOF) recommends the FRAX tool for use in patients with osteopenia to identify subjects at high risk of osteoporotic fracture who are eligible for intervention[4]. On the other hand, the National Osteoporosis Guideline Group (NOGG) recommends the FRAX tool to identify the age-specific fracture risk in each country to choose treatment candidates and recommend BMD measurement[5].

Correspondence: Enrique Lopez Gavilanez (enrique_lopezg57@hotmail.com)

Fracture probability differs significantly in different regions of the world[6]. Thus, the FRAX model for a given country (or ethnic group) must be individualized based on the epidemiology of fractures and the population's life expectancy[7,8]. So it is important to establish appropriate intervention thresholds (treatment and recommendation to measure BMD) for each country or population[9]. In 2018, Clark et al. published FRAX-based intervention and evaluation thresholds for seven countries in the Latin American region: Argentina, Brazil, Chile, Colombia, Ecuador, Mexico, and Venezuela[10].

A FRAX model for Ecuador was released in 2012[11,12], but recently, the model has been revised and modified using more current fracture and mortality rates[13,14]. In 2019, the new age-specific evaluation and treatment thresholds for the population of Ecuador were announced[15].

The age-specific intervention thresholds obtained according to the NOGG strategy are hindered by underestimating the risk of fracture at older ages and overestimate it at younger ages[16]. As a means of overcoming this drawback, McCloskey proposed the use of alternative thresholds, which combine age-specific thresholds up to 70 years and thereafter a fixed threshold with a single probability of fracture in all age groups[16]. This strategy has also been implemented by other authors who have stated that the use of hybrid thresholds could be appropriate in countries where the incidence of hip fractures is low, as is the case in some countries in the Middle East, southern Europe and Latin America[17-19].

In Latin America, the clinical efficacy of these thresholds to identify candidates for intervention in the respective populations has not been determined to date. In this study, we performed an analysis of the effectiveness with which the probability of fracture obtained with the Ecuadorian FRAX model (without BMD) identifies women who would be candidates for treatment for the calculation of FRAX probabilities in the absence. Additionally, we tested a combination of age-specific and fixed intervention thresholds to optimize the selection of women eligible for treatment and referral for BMD assessment.

Methods

Population

The present study used data from participants in the National Survey of Health, Well-being and Aging (SABE)[20]. This survey is a probability sample of households with at least one person aged 60 years or older residing in the Andean and coastal region of continental Ecuador (only the insular territory and the Amazon were excluded due to their lower population density, 4.4%), making it a representative sample of the Ecuadorian population. The data and the methodology of the survey (inclusion and exclusion criteria, sample size calculation, statistical methods), including the operation manuals, are freely accessible and available to the public at http://www.ecuadorencifras.gob.ec/encuesta-de-salud-bienestar-del-adulto-mayor/[20].

A total of 2,377 women over the age of 60 participated in the national SABE survey. Complete interview information was available for 2,283 women.

A structured questionnaire was used to collect information from all participants and was used to provide risk variables for the calculation of FRAX probabilities in the absence in the absence of BMD.

Age and sex were self-reported. Height in centimeters and weight in kilograms were measured and body mass index (kg/m^2) was calculated. Smoking status was classified as current, former and never. Mean alcohol consumption per week over the previous three months was classified as none, one day, or two or more days per week. Forearm and hip fractures within the past year were self-reported. In the SABE survey, participants were asked: Have you fallen in the last year? Have you suffered a fracture when you fell? Have you broken your hip in the last year? Have you broken your wrist in the last year? so we assumed that they were fragility fractures. Because the SABE[20] survey does not collect data on long-term use of glucocorticoids or family history of fractures, a negative response ("no") was entered in the FRAX questionnaire for both factors. Each participant provided informed consent prior to her inclusion in the survey[20]. The use of SABE survey data is freely accessible and, in accordance with local legislation, authorization is not required to use it, provided that the anonymity of the participants is preserved. The ethics committee of the "Abel Gilbert Pontón" hospital in Guayaquil, Ecuador, authorized the protocol and carrying out of this study.

Statistical analysis of the data was carried out with the EPIDAT Version 4.2 computer program[www.sergas.es/Saude-publica/EPIDAT].

Intervention thresholds

To establish intervention thresholds and assess bone mineral density (BMD), the methodology adopted by the NOGG in the FRAX-based guidelines for the United Kingdom was used[21].

The number of women aged 60 years or older who exceeded the intervention threshold (and would therefore be eligible for treatment) was calculated as a total and in 5-year age intervals using FRAX probabilities (BMD not included in the calculation).

As the NOGG considers a prior fracture to carry sufficient risk to recommend treatment, the threshold for intervention in women without a prior fracture was set at the 10-year (age-specific) probability of sustaining a major osteoporotic fracture (hip, spine, forearm, or humerus) equivalent to that of women with a previous fragility fracture using the Ecuadorian FRAX model (version 4.1). Body mass index was set at 25 kg/m^2.

Evaluation thresholds to recommend measuring BMD

Two evaluation thresholds were considered to formulate recommendations for the measurement of BMD[21]. Lower Evaluation Threshold (LET): Level of probability below which neither treatment nor a BMD test should be considered. Upper Evaluation Threshold (UET): Probability level above which treatment can be recommended regardless of BMD.

The lower evaluation threshold was established to exclude the requirement to measure BMD in women without clinical risk factors as indicated in the European guidelines[21]. An upper threshold was chosen to minimize the likelihood that an individual identified as being in a high-risk category (based solely on clinical risk factors) might, with additional BMD information, be reclassified into a low-risk category. The upper evaluation threshold was set at 1.2 times the intervention threshold[21].

Fracture probabilities
The probabilities in the next 10 years of suffering a major osteoporotic fracture (MOF) and a hip fracture were calculated using the Ecuadorian FRAX model (version 4.1)[15]. There was no confirmed diagnosis of secondary osteoporosis and rheumatoid arthritis (RA), so these data were recorded as "NO", following the recommendations of the FRAX questionnaire. Calculations did not include BMD. The upper age limit for probability calculation with FRAX is 90 years.

Evaluation strategy
The strategy for establishing BMD measurement and intervention thresholds followed the FRAX-based methodology, approved by the NOGG in the United Kingdom[22] and later recommended by the European guidelines[23].

Women with a prior fragility fracture are considered eligible for treatment without further assessment. In women without a previous fragility fracture, the strategy was based on the evaluation of the probability in the next 10 years of suffering a MOF. Women with probabilities below the lower assessment threshold were not considered eligible for treatment or BMD assessment. Women with probabilities above the upper evaluation threshold were considered eligible for treatment. Women with probabilities between the upper and lower limits of the assessment threshold would be referred for BMD measurement and re-assessment of fracture risk.

Results
A total of 2,377 women over the age of 60 participated in the SABE survey. 94 had a previous fracture and were excluded from the analysis. Complete interview information was available for 2,283 women.

The 2283 women (without previous fractures) had a mean age of 70.9 (7.9), and a body mass index (BMI) of 27.3 (7.8) kg/m^2; 61 (26.7%) were current smokers and 275 (12%) were former smokers; 16 (0.7%) drank alcohol 2 or more days per week.

Thresholds
The intervention and evaluation thresholds specific to the Ecuadorian population and the methodology used to obtain them have been described in a previous publication[15] and are presented in table 1 and figure 1.

The intervention threshold in women increased with age, from a 10-year probability of major osteoporotic fracture of 1.8% at age 60 years to 12% at age 90 years (table 1).

Table 1, figure 1 also provides age-specific upper and lower evaluation thresholds for recommending BMD measurement. At age 65, for example, BMD testing would not be recommended in an individual with a fracture probability of less than 1.3%. At the same age, a BMD test with a probability of fracture between 1.3 and 3.12% would be recommended. Treatment without the requirement of a BMD test would be recommended in individuals with a fracture probability greater than 2.6%.

FRAX score
The mean 10-year probability of having a MOF was 2.85 (2.3) but ranged from 0.92 (0.22) to 7.46 (1.25) depending on age; and the mean 10-year probability of a hip fracture was 1.21 (1.43), but ranged from 0.19 (0.15) to 4.25 (1.29) depending on age.

Impact
Age-Specific Intervention Thresholds
The proportion of women eligible for treatment was lower at older ages (80 years and older), and on average 2% of the female population aged 60 years or older exceeded the intervention threshold and were therefore eligible for treatment. Depending on age, the proportion of women potentially eligible for treatment ranged from 0.7 to 3.8%.

On average, the proportion eligible for evaluation with BMD is 73.7%, but it varied from 58.3 to 80.5% depending on age.

The impact of intervention and assessment thresholds (age-specific) is presented in table 2.

Fixed Intervention Threshold (hybrid or alternative)
Because the age-specific intervention threshold would be too high to include some older people, we also chose a fixed threshold, which was set at the 10-year probability of having an MOF of 6.8% for the population of 75 years and older (table 2, figure 2).

The proportion of the female population aged 75 years and older eligible for treatment was higher at older ages, and on average 31.4% of women aged 75 years and older exceeded the intervention threshold and were therefore eligible for treatment. Depending on age, the proportion of women potentially eligible for treatment ranged from 3.8 to 76.5%. On average, the proportion of women eligible for BMD evaluation is 76.3%, but ranged from 65.2 to 85.4% depending on age. The impact of fixed intervention and evaluation thresholds are shown in table 2 and figure 3.

Discussion
Our study establishes the efficiency with which the intervention thresholds obtained with the Ecuadorian FRAX model (version 4.1) allow us to quantify the proportion of subjects eligible for intervention in our population. In addition, we tested the use of a "fixed" (hybrid) threshold starting at age 75 to optimize treatment choice in older women.

In a previous publication, we described the age-specific fracture probabilities based on the FRAX model, as well as the treatment thresholds and BMD evaluation for our country[15]. We used the intervention thresholds approach used by the NOGG in the United Kingdom[5,19], but applied to the Ecuadorian FRAX model[15].

The setting of intervention thresholds varies considerably around the world, with guidelines using fixed or age-specific thresholds and sometimes combining a probability threshold with BMD in the osteoporotic range[19,24,25].

The WHO suggests that each country determine its own intervention thresholds based on its own epidemiology and socioeconomic characteristics[26]. International clinical guidelines also take these epidemiological differences into account. Consequently, recommendations for treatment differ between countries. The only tool that considers these epidemiological differences between countries is FRAX, which is reflected in the calculation of the probability of fracture risk[8,28].

The age-specific intervention threshold, developed by the NOGG[22], is mainly used in the United Kingdom and varies according to age and sex, being higher in older ages[27] so inequalities arise in access to treatment, especially in older ages to 70 years[28]. An alternative threshold using a hybrid model reduces this disparity[19].

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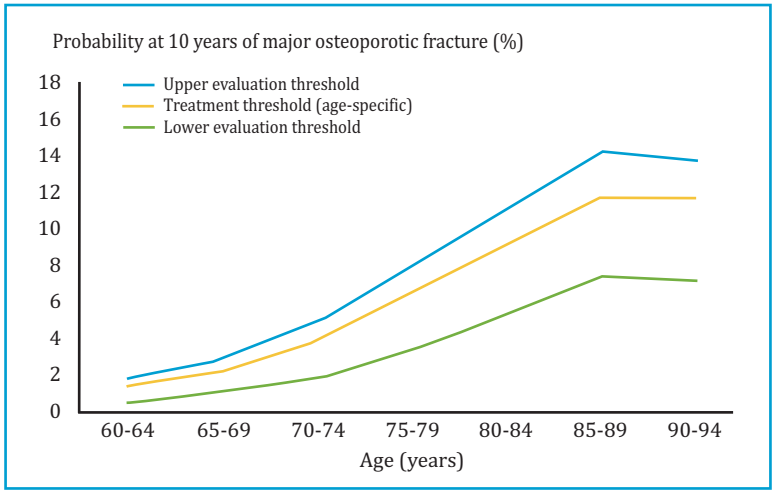
Table 1. Treatment thresholds and evaluation of BMD based on the Ecuadorian FRAX* model[15]

	Major fractures			Hip fractures		
Age group	Treatment threshold	Lower evaluation threshold	Upper evaluation threshold	Treatment threshold	Lower evaluation threshold	Upper evaluation threshold
50-54	1.2	0.6	1.4	0.2	0	0.2
55-59	1.4	0.6	1.7	0.2	0.1	0.2
60-64	1.8	0.8	2.1	0.4	0.1	0.48
65-69	2.6	1.3	3.1	0.7	0.3	0.8
70-74	4.3	2.2	5.16	1.3	0.6	1.56
75-79	6.8	3.7	8.16	2.4	1.3	2.9
80-84	9.5	5.7	11.1	4.0	2.6	4.8
85-89	12	7.6	14.4	5.9	3.8	7.0
90-94	12	7.3	14	5.6	3.6	6.7

BMD: bone mineral density; * Version 4.1.

Figure 1. Age-specific BMD intervention and evaluation thresholds in Ecuador. The yellow line represents the intervention threshold (age-specific). The blue and green lines represent the upper and lower evaluation thresholds[15]



In a systematic review, Kanis et al. describe the intervention thresholds of various populations, and observe significant differences between countries with different treatments and health cost reimbursement systems[19]. In the United Kingdom, the intervention threshold is globally 7%, although it varies with age[21]. The highest threshold corresponds to the USA, where it is 20% for a major osteoporotic fracture and 3% for a femoral fracture[19].

In countries with low incidence rates of hip fractures, lower intervention thresholds have been described compared to other countries such as the United Kingdom, the United States, and Canada[6,17,29]. For example, in Lebanon, age-specific intervention thresholds (using an approach similar to NOGG), were low, barely exceeding 5% at age 65 and less than 10% up to age 70 in women.

Unlike countries such as the USA, Canada, Japan, Australia and the United Kingdom, in which fixed intervention thresholds are used, in Latin America it was shown that it was better to establish age-specific intervention thresholds for each country[10]. However, the impact or effect of these thresholds on decision-making about treatment and/or assessment of BMD in Latin American countries has not been established.

In the latest UK guidelines[22], the intervention threshold up to 70 years of age is set at a risk equivalent to that associated with a previous fracture, and fixed thresholds are applied from 70 years of age or older. Thus, the proportion of women potentially eligible for treatment increases from approximately 30 to 50% depending on age[16]. In Lebanon, using an approach similar to the NOGG, the proportion of women aged 50 to 85 years who are eligible for intervention ranged from 11 to 18% in women without prior fractures[17], and using a fixed hybrid model, less than 5% of postmenopausal women without fractures would be eligible for treatment at age 65, and between 13 and 17% thereafter[17]. In a population-based study in Turkey, approximately 13.6% of the female population aged 50 years or older without a previous fracture would be eligible for treatment[30].

In the Latin American countries that have FRAX, intervention thresholds range between 1.2% (Ecuador) and 27% (Argentina)[10] depending on age and are generally lower than in developed countries. Thus, for example, in

Table 2. Women potentially eligible for treatment and evaluation of BMD (without fractures)

	Age-specific treatment threshold					Fixed treatment threshold				
Age group		Above the TT		Between the ET			Above the TT		Between the ET	
	N	n	%	n	%	N	n	%	n	%
60-64	595	4	0.7	479	80.5					
65-69	538	12	2.2	393	73.0					
70-74	458	12	2.6	344	75.1					
75-79	313	12	3.8	221	70.6	313	12	3.8	221	70.6
80-84	226	5	2.2	155	68.6	226	88	38.9	193	85.4
85-89	115	0	0	67	58.3	115	88	76.5	75	65.2
90-94	38	0	0	24	63.2	38	29	76,3	32	84.2
≥60	2,283		2		73.7					
≥75						692		31.4		76.3
	100%					30.31%				

TT: treatment threshold; ET: BMD evaluation threshold; BMD: bone mineral density.

the 5 main countries of the European Union (United Kingdom, Spain, Italy, France, and Germany), they range between 6.3 and 32.5% depending on age[19].

In the present study, age-specific intervention thresholds were low, ranging from 1.8% at 60 years to less than 5% at 74 years. From 75 years of age, intervention thresholds increased from 6.8 to 12% depending on age. These results reflect the low age-adjusted incidence rates of hip fractures in Ecuador compared to the 5 main countries of the European Union[6]. The proportion of women between 60 and 94 years old who exceed the specific age thresholds and are therefore eligible for treatment is 1.96%, but it varied between 0.67 and 3.83% depending on age. At younger ages (60 to 74 years), FRAX overestimates the number of women eligible for treatment (n=28) and underestimates it in older women (n=17).

Some concerns have been raised regarding the use of fixed, age-specific thresholds: the NOGG guideline may overtreat very low-risk (<10%) young patients and undertreat the elderly[27,34], while the NOF guideline treats the majority of the elderly with a greater use of resources[18].

Hybrid thresholds have been used in some countries[16,17,31-35]. In 2015, a hybrid model using an age-specific threshold up to age 70 and a fixed threshold of 20% thereafter was evaluated in the UK, allowing a higher proportion of older women to be eligible for treatment compared to the previous NOGG model[16].

Figure 2. Hybrid thresholds of treatment and evaluation of BMD. The yellow line represents the treatment threshold. Blue and green lines represent upper and lower evaluation thresholds

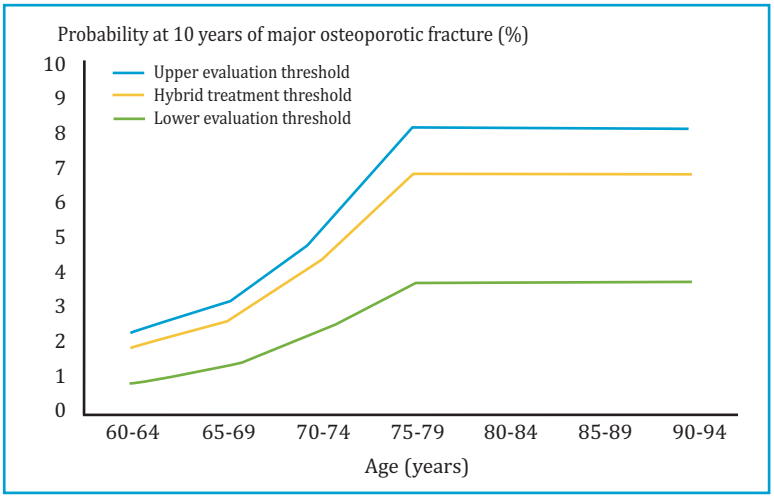
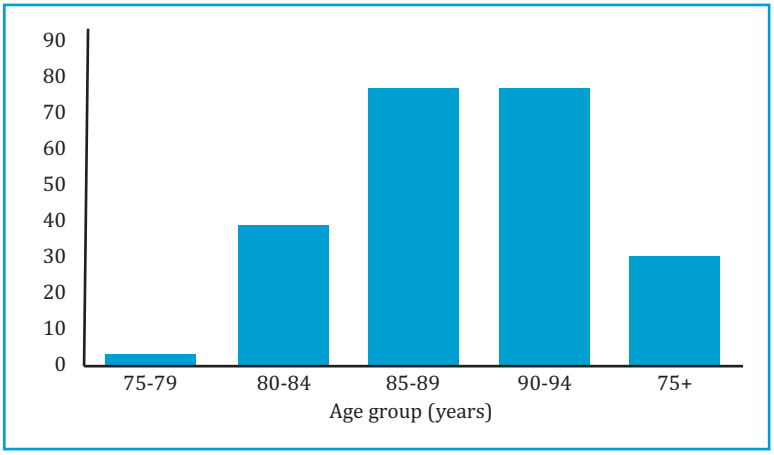


Figure 3. Proportion of women within each age group that would be recommended for treatment based on fixed thresholds



In Lebanon, the application of a hybrid model, a fixed threshold (10%) up to age 70 years and an age-specific threshold thereafter, avoids pharmacological treatment in a large proportion of younger subjects at low risk of fracture and directs it to elderly people at high risk[17].

The usefulness of the hybrid model has been suggested as potentially suitable for countries with low fracture rates, such as in the Middle East, southern Europe and Latin America[17,18]. For example, recently in a large clinical trial conducted in Latin American countries, the low incidence of fractures could not be explained exclusively by low BMD levels, but was consistent with low baseline FRAX scores[36,37].

Ecuador is a country with a low risk of fracture[13] similar to Brazil, Colombia, Chile and Venezuela in Latin America[37,38]. The low incidence of fracture is reflected in the low probabilities of fracture at 10 years calculated with FRAX described in this manuscript. Indeed, as we can see, the intervention thresholds are higher in the 5 main countries of the European Union (Spain, France, Italy, Germany and the United Kingdom) in which the incidence of hip fractures is higher[19], compared to the countries with a lower incidence of hip fractures[6,13].

The hybrid intervention threshold concept proposed in this study is similar to the application of the hybrid intervention threshold in the United Kingdom. However, in the present study, we found that a fixed intervention threshold was more suitable for participants older than 75 years, rather than 70 years. This fact is consistent with Kanis's suggestion that "fracture thresholds should be tailored individually on a country-by-country basis"[19].

In the SABE survey[20], 70% of women are under 75 years of age and 30% are 75 and over, so the decision to choose a new fixed intervention threshold was aimed at capturing the majority of women from 75 years and older[16]. In our analysis, the age-specific thresholds were very high from the age of 75 years and most of the patients could not reach them. The application of an age-specific threshold similar to that of NOGG up to 74 years, and a fixed threshold of 6.8% from 75 years, avoids the recommendation of pharmacological treatment in younger women at low risk, and directs them to favor of women at high risk. Consequently, it was decided that the intervention and evaluation thresholds would remain identical to those of the NOGG strategy until age 75 years, but thereafter a constant threshold would be maintained for older ages (i.e., the threshold at age 75 was applied to older ages)[16].

The NOGG guide establishes thresholds based on FRAX probabilities without BMD to select candidate patients to measure BMD[39], an upper evaluation threshold and a lower evaluation threshold. Those with intermediate probability values are referred for BMD evaluation. In general, use of the NOGG thresholds would identify between 6 and 20 percent of women as eligible for BMD measurement, depending on age[23].

Using age-specific thresholds, Ecuadorian women aged 60 years and older do not require BMD measurement if their probability of having an MOF at 10 years is less than 0.8%. Treatment (without BMD measurements) should be recommended if the 10-year MOF probability is greater than 1.8%. Finally, if this risk is 0.8 to 2.6%, additional BMD measurement and reassessment of fracture risk is required. With this approach, 58.3 to 80.5% (depending on age) of Ecuadorian women are eligible for BMD measurement. In the case of using the alternative threshold from 75 years of age, it turns out that 65.2 to 85.4% are eligible for BMD measurement.

The low values of the intervention thresholds in different developing countries, compared to the developed countries of the northern hemisphere, could be explained by the low incidence of hip fractures found among the former[6]. In a systematic review of the incidence of hip fractures worldwide, the 5 main countries of the European Union (United Kingdom, France, Italy, Germany and Spain) and the USA, are in the range of high risk of hip fractures. fractures according to the Kanis classification[38]. When comparing the probabilities of FRAX fracture (intervention thresholds) of these countries, it can be seen that in all of them they are higher than 15% (high risk)[5] than that of 7 countries in Latin America that have a FRAX model (Argentina, Brazil, Chile, Colombia, Ecuador, Mexico and Venezuela) with a lower incidence of hip fractures. Indeed, the 10-year probability of MOF in 4 of them is <10% and in another 2 it is <15% (Mexico and Chile), Argentina being the only exception with >15%[10,13,38].

This has also been described in countries in other regions, for example in Lebanon and Turkey where the results[17] reflect the low fracture incidence rates compared to other countries such as the UK, USA, and Canada[29,40]. This consideration could be applicable to other countries in the Middle East, with equally low fracture incidence rates[17].

Some limitations of the present study must be acknowledged. First, although the survey was large and representative of the Ecuadorian population, there were few women interviewed in the older age groups (17%), which could impair the accuracy of our estimates and therefore the number of women eligible for treatment.

BMD was not measured in the survey, which would have made it possible to improve the estimate of fracture risk, but this was not feasible in the context of the study. However, the probability of fracture calculated with and without BMD is the same as long as the population studied is truly representative of the general population[16]. The fractures were self-reported and were not confirmed by radiology, which could constitute a memory bias in the information collected. The SABE survey[20] only includes women of 60 years and older, so we do not cover the likelihood of fracture risk in people of younger ages (40-59 years).

We are unable to validate the FRAX-derived estimates with prospective data from Ecuadorian cohorts at this time. However, a systematic review of fracture risk prediction tools highlighted that the FRAX algorithm had the largest number of independent, externally validated studies, using Western and Asian cohorts[19]. A comparison of FRAX-based guidelines using prospective cohorts has only been implemented in a few countries[27].

In conclusion, the present study demonstrates that it is possible to apply FRAX-based assessment strategies using the same principles that have been applied in guidelines elsewhere, but adapted to the epidemiology of Ecuador.

This strategy has allowed us for the first time to ascertain the proportion of the female population with a high risk of fracture and therefore eligible for treatment according to the different age-specific thresholds and an

alternative threshold for older individuals. It is hoped that the application of these thresholds will avoid unnecessary treatment of people at low risk of fracture and direct treatment to people at high risk.

Although no model can universally fit the profile and needs of all countries, in countries with low to moderate risk of fracture, and with limited resources, a hybrid model may be the most appropriate.

Conflict of interests: The authors declare no conflict of interest.

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