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Position Development Paper

Official Positions for FRAX® Clinical Regarding International Differences

From Joint Official Positions Development Conference of the International Society for Clinical Densitometry and International Osteoporosis Foundation on FRAX®

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Abstract

Osteoporosis is a serious worldwide epidemic. Increased risk of fractures is the hallmark of the disease and is associated with increased morbidity, mortality and economic burden.

FRAX® is a web-based tool developed by the Sheffield WHO Collaborating Center team, that integrates clinical risk factors, femoral neck BMD, country specific mortality and fracture data and calculates the 10 year fracture probability in order to help health care professionals identify patients who need treatment. However, only 31 countries have a FRAX® calculator at the time paper was accepted for publication. In the absence of a FRAX® model for a particular country, it has been suggested to use a surrogate country for which the epidemiology of osteoporosis most closely approximates the index country. More specific recommendations for clinicians in these countries are not available.

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In North America, concerns have also been raised regarding the assumptions used to construct the US ethnic specific FRAX® calculators with respect to the correction factors applied to derive fracture probabilities in Blacks, Asians and Hispanics in comparison to Whites. In addition, questions were raised about calculating fracture risk in other ethnic groups e.g., Native Americans and First Canadians.

In order to provide additional guidance to clinicians, a FRAX® International Task Force was formed to address specific questions raised by physicians in countries without FRAX® calculators and seeking to integrate FRAX® into their clinical practice. The main questions that the task force tried to answer were the following:

1. What is the evidence supporting ethnic and sex specific adjustments for fracture incidence rates in Blacks, Hispanics and Asians?
2. What data exist for other groups, e.g., Native Americans, First Nations Canadians?
3. Are there secular changes in fracture rates?
4. What are the requirements for the construction of a FRAX® calculator? And what are the desirable/optimal characteristics of the data?
5. What do I do if my country does not have a FRAX® calculator?

The Task Force members conducted appropriate literature reviews and developed preliminary statements that were discussed and graded by a panel of experts at the ISCD-IOF joint conference. The statements approved by the panel of experts are discussed in the current paper.

Key Words: FRAX; race/ethnicity; international variability; geographic variability; osteoporosis; fractures.

Introduction

Osteoporosis is a serious worldwide epidemic. Because life expectancy is increasing, the number of elderly individuals is expected to rise around the globe. With ageing societies and changing disease patterns worldwide, the human, social, and economic costs of osteoporosis will continue to rise *(1)*. Of particular concern is the associated increased numbers of hip fractures. The number of hip fractures is estimated to increase to 2.6 million by the year 2025, and to 4.5 million by the year 2050 *(2)*, thus an expected increase in their accompanying high toll in terms of morbidity, mortality, and economic burden in this era of limited health care resources *(3,4)*.

Reduced bone mineral density (BMD), age, and other clinical risk factors all increase fracture risk and can be utilized to identify individuals most likely to fracture*(5,6)*. The WHO Fracture Risk Assessment calculation Tool, FRAX® combines clinical risk factors, BMD and country-specific mortality and fracture data to calculate 10-year fracture probabilities in individual patients and provides a platform to assist clinicians and public health agencies in making rational treatment decisions*(7–10)*. Although the development of FRAX has been a major advance in the field of osteoporosis, its' clinical impact has been limited by lack of availability of country-specific fracture data. Despite a growing world-wide consensus that treatment decision paradigms should be based on absolute fracture probabilities, country-specific FRAX calculators are currently available for only 31 countries worldwide. Over 130 countries remain without this tool to help stem the growing tide of fractures.

In the US, ethnic-specific FRAX calculators are available for Whites, Blacks, Hispanics and Asians. These calculators were constructed using ethnic specific mortality rates (US 2005 mortality data by 5 year age categories, CDC Vital Statistics) and fracture rates derived by applying ethnic- and sex-specific correction factors to the fracture incidence observed in white women and men. For Blacks, the correction factor is 0.43 for women and 0.53 for men; for Asians, 0.50 for women and 0.64 for men; and for Hispanic: 0.53 for women and 0.58 for men *(11)*. The calculators also assume that the gradient of risk/ standard deviation (SD) change in BMD, body mass index (BMI) and other risk factors is the same in Whites and other ethnic groups (Eugene McCloskey, personal communication). The validity of these assumptions is important to the accuracy of FRAX calculations for individuals in these ethnic groups. Accuracy errors will affect the absolute probability of fracture reported by FRAX, and thus could have a significant impact on treatment decisions for individuals within these ethnic groups when thresholds of fracture risk are used for treatment decisions, as recommended by the National Osteoporosis Foundation Guidelines for the US *(12)*. In addition, there is uncertainty about which calculator should be used for other ethnic groups in the US and Canada who do not have their own ethnic-specific calculator.

The FRAX international Task Force consisted of a panel of experts, who addressed specific questions raised by physicians in countries without FRAX calculators who wish to integrate FRAX into their clinical practice and questions pertaining to the use of the ethnic-specific FRAX calculators in the US. The Task Force members conducted appropriate literature reviews and developed preliminary statements that were discussed and graded by a panel of experts at the ISCD-IOF FRAX Initiative joint conference, held in Bucharest November 12–14, 2010. The questions addressed by the International Task Force members and the statements approved by the panel of experts and their grading are discussed in the current paper.

Methodology & Data sources

- Dr. Eugene V. McCloskey of World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, UK provided Task Force members with information relevant to the development of country specific FRAX calculators.
- Data for countries with an-online FRAX calculator were provided to the Task Force members (see appendix II) by Dr. John A. Kanis and World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, UK in October 2010 (Please refer to Appendix II Tables 1 and 2 for details).
- For countries without an on-line FRAX calculator, the Global Subgroup Task Force members reviewed English language publications and sought to identify published and unpublished data to answer the following specific questions:
  a. What countries without a FRAX calculator have national or regional epidemiological data on fractures?
  b. What is the quality of the data and what are its limitations?
  c. Are there are major diverse ethnic groups within the country? If so, does the fracture data include these ethnic groups?
  d. Do these countries have age and gender specific fracture information available?
  e. Do cohort studies exist which could be used to validate the use of another country's FRAX calculator?
- In order to consider the benefits, challenges and disadvantages of constructing and using a ''region-specific'' FRAX calculator in circumstances when there are insufficient high quality national data to construct a country specific FRAX model, the world was divided into four large regions:
  - Asia/Oceania
  - Middle East/Africa
  - Latin America
  - Europe

195 countries were identified by the Global Subgroup. Medline search was implemented for 166 countries, excluding numerous small islands. Medline search for US and Canada was implemented by the North America Subgroup.

- World Health Organization data on mortality was used to provide age and gender specific mortality rates: ''http://www.who.int/healthinfo/statistics/mortality_life_tables/en/.''

The North American group also formed several subgroups to review the literature on race/ethnic specific fracture incidence, risk factors for fracture and the relationship between BMI and mortality across race/ethnicities.

Medline Search

The Medline OVID search was conducted for all four international regions by the American University of Beirut team (Ms Aida Farha and Rola El-Rassi) and for both subgroups, included publications between 1950 and May 10, 2010 (see Appendix III). The search utilized the various search options/techniques that the OVID interface allows using MeSH terms, explode functions, keyword searching in title, abstract, and subject headings, adjacency, and publication types, in addition to Boolean operators and truncation (and, or). All this was done to capture as many relevant articles as possible from Medline using key terms that were identified by task force members. The key words were divided into three main concepts through a reiterative technique the librarian performed using these key words. The three primary concepts were: Fracture, Incidence and the Country or their related terms. The three concepts were searched one at a time, and then merged together through the AND term, In order to obtain a thorough search, each concept was searched individually by entering the different MeSH terms and keywords. After conducting a search using all terms in one concept, they were included together into one search. After each concept search was completed, a final search was done that lumped together the three completed concept searches to come up with the final search results.

For North America separate Medline searches were run for each race/ethnic group and included publications until May 2010.

Additional relevant papers not identified through the above searches or in press identified by task force members were also taken into consideration.

Statements

Question:

What is the evidence supporting ethnic and sex specific adjustments for fracture incidence rates in Blacks, Hispanics and Asians in the United States?

What data exist for other groups, e.g., Native Americans, First Nations Canadians?

Official Position: Separate FRAX models are available for US Asians, Blacks, Hispanics because hip and major osteoporotic fracture rates are lower in these ethnic groups than in US Whites. Until additional data are available, the US Caucasian FRAX calculator should be used to assess fracture risk in US Native American women.

Grade: Fair, B, C.

Rationale

a. Blacks

Numerous publications show lower rates of hip fracture in Blacks compared to Whites. The rate of hip fracture among US Blacks is about 50−60% lower in women and 30−40% lower in Black men compared to Whites. Rates increase with age in both Whites and Blacks but rates of hip fracture among Black women age 80−84 are similar to hip fracture rates among White women age 70−74 *(13)*. Hip fracture rates are more similar in Black men and women but differ dramatically in White men and women. Six publications were identified that had information on hip fracture rates *(13−18)*. One study reported actuarial life time risk *(19)* and two studies reported rate ratios *(20)* or relative hazards *(21)* of hip

fracture compared to Whites. The publications with hip fracture incidence rates are quite old; rates are from the Medicare database for 1986−89 *(13)*, 1984−1987 *(14)*, 1992−1993 *(22)* and 1980−1982 *(23)*. Data from Tennessee Medicare enrollees was used to estimate hip fracture rates for 1987−1989 *(18)*. The most recent estimates of hip fracture rates in Blacks are from 1988−2002. Using hip fracture hospitalization rates in New York City (NYC), comparison of the risk of hip fracture in Blacks versus Whites ranged from 0.30−0.40 in women, with higher ratios in men ranging from 0.55 to 0.81 *(17)*. More recently, Curtis et al reported a rate ratio of 0.42 (95% CI, 0.40 to 0.44) for women and 0.64 (0.59, 0.69) for men *(15)*, Table 1.

Rates of non-hip fractures among Blacks in the US are about 50−70% lower in women and 20−50% lower in men *(13,15,18,20,24−27,29)*. The prevalence of vertebral fractures is about 33% lower in Black women compared to White women *(29)*. Four studies reported rates for all non-spine fractures *(18,24,27,30)*; several studies, all clinical fractures *(20,24,26)*, and one study, proximal humerus and distal forearm fractures *(13)*. The rate ratios for non-hip fractures comparing Blacks to Caucasians are summarized in Table 2. Across all studies, the incidence rate of fractures is 30−80% lower in Blacks compared to Whites with some variability across skeletal sites. This was true for both men and women.

b. Hispanics

Information on the incidence of hip fracture is available for Hispanics *(24,26,28,31−34)*. Information on Mexican Americans living in California (32,33) shows that the ratio of hip fracture compared to Whites is 0.35 in women and 0.45 in men, Table 3. The ratio of hip fracture rates using the Medicare data and assigning ethnicity by surname was considerably higher, 0.72 in women and 0.77 in men *(22)*. The data on hip fractures is quite old *(22,28,32)*. Zingmond and Silverman *(33)* updated their earlier paper and showed secular increases (doubling) in hip fracture rates in California Hispanics from 1983 to 2000. Results from a later study of hip fracture hospitalizations in NYC reported a rate ratio of 0.34 in women and 0.25 in men *(17)*. The Lauderdale paper *(22)* suggested some diversity within Hispanics showing higher rates in Mexican Americans compared to Cubans and Puerto Ricans. In the recent analysis of Medicare (2000−2005), hip fracture rate ratios were 0.67 (0.61, 0.73) in women and 0.73 (0.63, 0.84) in men *(15)*.

There is limited data on the incidence of other fractures in Hispanic men or women. Rate ratios of non-hip fractures were 35% lower in Hispanic women compared to White women in the WHI *(24)* and 23% lower in women enrolled in Medicare *(15)*. Major osteoporotic fractures were also 30% lower in Hispanic men compared to White men enrolled in Medicare *(15)*, Table 4. In NORA, multivariate models including adjustment for BMD T-score yielded a hazard ratio of fracture of 0.91 (95% CI, 0.72−1.16) in Hispanics versus Whites *(26)*. There is considerable variability in interstate incident hip fracture rates in Hispanics. The interstate variability of Hispanic fracture rates is greater than three-fold, while Whites stay relatively constant *(34)*. Part of this variability may well relate to the inclusion of Hispanic Blacks and Hispanic Whites. More recent data suggests that the rate ratio for both hip and non-hip fractures in Hispanics compared to whites may be higher than the FRAX assumption.

c. Asians

Hip fracture rates in Asians living in US are lower compared to Whites but the rate ratio varies markedly across studies and probably within different subgroups of the Asian population. Hip fracture incidence data are available for Asians in the state of California *(32)*, Medicare population *(16,22)*, Japanese in Hawaii *(35)* and from NYC hospital discharge data *(17)*. Rate ratios comparing Asians to Caucasians are summarized in Table 5 and vary markedly across study. This could reflect differences within Asians i.e., Japanese in Hawaii vs Chinese in NYC vs Hawaii vs California.

There is limited data on non-hip fractures in Asians. In WHI, the incidence of all clinical fractures in Asians was 1200 per 100,000 compared to 2000 per 100,000 in Whites. The relative hazard of fracture in Asians compared to Whites was 0.59 (95% CI, 0.53−0.65) *(24)*. In NORA, the relative hazard of fractures in Asian versus White women was 0.41 (95% CI, 0.21−1.79) in multivariate models, including BMD T-score *(26)*. In a later publication, holding HR for T-score constant for all ethnic groups, Asians had a significantly lower HR for fracture (HR=0.32, 95% CI, 0.15−0.66) *(31)*. For major osteoporotic fractures, unpublished data from Medicare reports rate ratios of 0.69 (0.64, 0.74) in Asian

Table 1
Rate Ratio of Hip Fracture in Blacks Compared to Whites. Ranges or 95% Confidence Intervals are shown

Author	Fracture Data Yrs	Women	Men
FRAX Assumption		0.43	0.53
Baron *(13)*	1986−89	0.32−0.42	0.54−0.75
Griffin *(18)*	1987−89	0.30−0.47	0.33−0.40
Jacobsen *(14)*	1984−87	0.38	0.56
Lauderdale *(22)*	1992−93	0.40	0.72
Fang *(17)*	1988−2002	0.30	0.50
Curtis *(15)*	2000−2005	0.42 (0.42−0.44)	0.64 (0.59−0.69)

Table 2
Summary of Rate Ratios (95% CI) of Incidence Rates of Non-hip Fracture in Blacks Compared to Whites. Ranges or 95% Confidence Intervals are shown

Author	Fracture Data Yrs	Site	Women	Men
FRAX Assumption			0.43	0.53
Baron *(13)*	1986−1990	Proximal humerus	0.25 (0.18−0.33)	0.49 (0.29−0.83)
		Other humerus	0.43 (0.33−0.55)	0.97 (0.68−1.40)
		Proximal radius/ulna	0.33 (0.22−0.50)	0.70 (0.37−1.32)
		Shaft radius/ulna	0.43 (0.34−0.54)	0.60 (0.39−0.92)
		Distal forearm	0.30 (0.27−0.33)	0.45 (0.36−0.57)
Griffin *(18)*	1987−1989	All non-vertebral	0.35−0.49	0.43−0.46
Cauley *(24)*	1996−2004	All non-vertebral	0.46−0.65	−
Mackey *(25)*	1997−2004	All non-vertebral	0.53	0.81
Barrett-Connor *(31)*	1998−2000	All clinical fractures	0.55 (0.48−0.62)	
Cauley *(27)*	1993−2005	All clinical fractures	0.51 (0.48−0.54)	
Cauley *(29)*	1986−1988	Prevalent vertebral fractures	0.33 (0.25−0.45)	
Kato *(20)*	1985−1999	All clinical fractures	0.44 (0.30−0.60)	
Curtis *(15)*	2000−2005	Major osteoporotic (FRAX)	0.34 (0.33−0.36)	0.53 (0.50−0.56)
		Hip	0.42 (0.40−0.44)	0.64 (0.59−0.69)
		Tibia/Fibula	0.84 (0.75−0.94)	1.02 (0.83−1.25)
		Distal radius/ulna	0.31 (0.28−0.33)	0.46 (0.38−0.56)
		Humerus	0.31 (0.28−0.34)	0.63 (0.53−0.74)
		Clinical spine	0.23 (0.21−0.25)	0.33 (0.29−0.37)

women and 0.61 (0.54, 0.70) in Asian men compared to White women and men *(15)*.

d. Native Americans

In WHI, during a mean of 7.6 years, 5 of 417 (0.4%) American Indian women experienced a hip fracture. There is no other information on hip fractures in American Indians. There is limited data on non-hip fracture rates in Native Americans/American Indians. In WHI, the incidence of fracture was similar in American Indians compared to Caucasians: 2000 per 100,000 versus 2000 per 100,000. The age-adjusted relative hazard of fracture in American Indians was 1.03 (95% CI, 0.85−1.25) compared to Whites *(24)*. In NORA, the multivariable adjusted (including BMD) relative hazard of fractures comparing American Indians versus Caucasians women was 0.89 (95% CI, 0.59−1.34) *(26)*. To our knowledge there is no data on American Indian men or within different tribes of American Indians.

e. Canadian First Nations

Fracture rates were compared among First Nations people age 20+ (n = 32,692) using the Manitoba Administrative Health database (1987−1999) *(36)*. The Canadian First Nations people represent a large North American aboriginal group. Each First Nation person was randomly matched with 3 persons of the same sex and year of birth (n = 98076). Fracture rates were higher among First Nations, Table 6 .This population of First Nations should be a representative sample. These population based data suggest a greater than 2 fold higher fracture rate in First Canadians and thus, FRAX may underestimate their fracture risk. However these results are based on data from a single province in Canada and no changes are recommended at this time.

Table 3
Summary of Rate Ratios for Hip Fracture in Hispanics Compared to Whites. Ranges or 95% Confidence Intervals are shown

	Years	Women	Men
FRAX assumption		0.53	0.58
Silverman *(32)*	1983−84	0.35	0.45
Espino *(28)*	1998	0.92	1.11
Lauderdale *(22)*	1992−93	0.72	0.77
Fang *(17)*	1988−2002	0.21−0.34	0.33−0.42
Curtis *(15)*	2000−2005	0.67 (0.61−0.73)	0.73 (0.63−0.84)

Table 4
Summary of Rate Ratios for Non-Hip Fractures in Hispanics Compared to Whites. Ranges or 95% Confidence Intervals are shown

		Years	Women	Men
FRAX assumption			0.53	0.58
Siris *(26)*	All clinical fractures	1998−2000	0.91 (0.72−1.15)	—
Cauley *(24)*	All clinical fractures[+]	1993−2005	0.64 (0.59−0.70)	—
Curtis *(15)*	Major osteoporotic	2000−2005	0.77 (0.72−0.82)	0.69 (0.60−0.77)
	Tibia/Fibula		0.94 (0.73−1.20)	0.97 (0.63−1.48)
	Distal radius/Ulna		0.80 (0.80−1.01)	0.94 (0.70, 1.25)
	Humerus		0.75 (0.65−0.87)	0.69 (0.50, 0.94)
	Clinical vertebral		0.72 (0.65−0.80)	0.61 (0.51−0.73)

[+]Except fingers, toes, face, skull or sternum.

Question: Are there secular changes in fracture rates?

Official Position: Changing fracture and mortality rates and improved quality of data are expected. Therefore, periodic review of country-specific fracture rates used in the FRAX model is recommended.

Grade: Good, B, W

Rationale:

Recent data are preferred to older data because there may have been variously an increase, leveling off, or a decrease in age and sex specific incidence of fractures in many communities *(37)*. Indeed, the incidence rates have risen in many areas in the world *(2,38)*, and continue to rise in some countries in the East, but are starting to decrease at least in Whites in several countries including US *(39)* and Canada *(40)*. Older studies in Europe, North America and Oceana showed an increase whereas more recent studies showed a decrease in fracture rates. Conversely, fracture rates continues to rise in Asia. For example, in South Korea, a study conducted in 1991 showed an overall fracture rate of 34/100.000 in subjects aged 50 years and over *(41)*, whereas a national study conducted in 2004 showed rates ranging between 57/100.000 and 1331/100.000 in men, and between 37/100.000 and 1751/100.000 in women, according to the age group concerned *(42)*.

Within the US, recent data suggest increasing hip fracture rates in Hispanics. Zingmond and Silverman *(33)* showed secular increases (doubling) in hip fracture rates in California Hispanics from 1983 to 2000. This was not observed in other ethnic groups. The rate ratio for Hispanics compared to Whites was about 0.31 in 1983 compared to 0.61 in 2000. In addition, recent data from a 5% sample of Medicare enrollees reported a rate ratio of 0.67 (0.61−0.73) for hip fracture in Hispanic women and 0.73 (0.63−0.84) for hip fracture in Hispanic men *(15)*. For major osteoporotic fractures, the rate ratios were 0.77 (0.72−0.82) in Hispanic women and 0.69 (0.62−0.77) for Hispanic men. The Medicare data is based on 1,672,183 subjects and 60,354 fractures. Using the Medicare data, the rate ratio for individual fractures in Hispanic men and women in comparison to Whites is shown in Table 7.

Thus given secular changes in hip fracture rates in the US, Canada, Asia and possibly elsewhere, periodic review of country/ethnic specific fractures rates is warranted.

Table 5
Summary of Rate Ratios of Hip Fracture in Asians Compared to Whites. Ranges or 95% Confidence Intervals are shown

Author	Fracture Data Yrs	Women	Men
FRAX assumption		0.50	0.64
Silverman *(32)*	1983−84	0.61	0.54
Lauderdale *(16)*	1992		
Chinese		0.54−0.62	0.35−0.75
Japanese		0.62−1.03	0.47−0.50
Ross *(35)*	1991−95	0.34*	0.47*
Fang *(17)*	1998−2002	0.26−0.40	0.30−0.50
Curtis *(15)*	2000−2005	0.64 (0.58−0.72)	0.53 (0.44−0.65)

*Compared to US Caucasians on the mainland.

Table 6
Standardized Incidence Ratios (SIRs) and (95% Confidence Intervals) for Fractures in the First Nations Cohort Compared With Age-Matched Control Group *(36)*

Fracture	Men*	Women*	All**
Hip	2.13 (1.68−2.63)	1.75 (1.41−2.05)	1.88 (1.61−2.14)
Wrist	2.83 (2.29−3.39)	3.16 (2.68−3.79)	3.01 (2.63−3.42)
Spine	1.75 (1.54−2.08)	2.12 (1.88−2.51)	1.93 (1.79−2.20)
Craniofacial	4.89 (4.51−5.29)	5.48 (4.88−6.19)	5.07 (4.74−5.42)
Any	2.19 (2.12−2.27)	2.26 (2.20−2.36)	2.23 (2.18−2.29)

*adjusted for age only.
**Adjusted for age and sex.

Question: How do hip fracture rates vary internationally and how might this influence construction of a country specific FRAX model?

Official Position: There is significant variability in hip fracture rates throughout the world. The minimum requirements for construction of a country specific FRAX-model are hip fracture incidence data that are of high quality and representative of that country.

Grade: Good, A, W.

Rationale:

Variability of Hip Fracture Rates:

Worldwide the frequency of hip fracture cases varies greatly by race/ethnicity and geography *(38)*. The fracture rates vary by up to17-fold in women and up to 15-fold in men between countries *(43−45)*, Figure 1. Rates of hip fracture are highest in Northern European countries where the 10-year relative probability of hip fractures averaged for ages and gender, adjusted to probabilities of Sweden, is 1.24 in Norway compared to 0.62 in Singapore and 0.08 in Chile*(44)*. The 10-year probabilities of hip fractures are much lower in Asian countries, but there is considerable variability within that region too. For example it is 0.18 in Korea compared to 0.49 in Hong Kong and 0.72 in Taiwan *(44)*. Even within southern Europe, crude incidence rates are lowest in Turkey (2.3 to 6.2 per 10,000) and highest in Seville, Crete, and Portugal (9.8 to 37.0 per 10,000) *(45)*.

Importance of High Quality Representative Data:

Fracture rates do not only vary between countries from the same region, they may also vary by up to three-fold within the same country. Indeed, fracture risk has been shown to vary within countries by latitude, socioeconomic and educational status and by rural versus urban locations. For example, in Croatia, a 6 year prospective study found a fracture rate that is 3 times higher in Istra district as compared to Padrovina district, namely in older ages *(46,47)*. Significant regional variation in hip fracture rates have also been noted in older ages in Brazil, possibly reflecting differences in ethnicity. Therefore, national hip fracture is preferred to data from smaller regional studies within a country *(48,49)*.

Fracture rates are known to vary by ethnicity /race as well. As detailed previously, within the US, for example, the rate ratio of hip fracture incidence rates compared to white women and men is 0.43 for black women and 0.53 for black men *(50−56)*, 0.53 for Hispanic women and 0.58 for men *(50,51,56,57)*; and, 0.50 for Asian women and 0.64 for men *(51,55,58)*. Within New Zealand, hip fracture rates among older Mauri women are approximately half that of other ethnic groups *(59)*. Little is known about ethnic differences in fracture incidence within other countries. In a study from Kuwait, the fracture rate was 5 times higher in Kuwaiti men as compared to non-Kuwaitis *(60)*. Within Israel, Jewish subjects of European and American origin had 1.5 to 2 times higher fracture rates than counterparts from Asia and Africa *(61)*. It may sometimes be desirable to examine fracture data separately for each major ethnic group in a country to determine whether the same calculator is appropriate for use for ethnic groups within that country.

In many countries, most, but not all, hip fractures are treated in the hospital. They are therefore more easily captured, thus allowing the determination of more accurate fracture rates, and better comparisons of such rates between countries/regions, than with other fractures. Nevertheless, such comparisons may be undermined if major methodologic differences are not minimized. This can be achieved

Table 7
Fracture Incidence Rate Ratio (95% CI) in Hispanics Compared to Whites *(15)*

	Hip	Tibia/Fibula	Distal Radius/Ulna	Humerus	Clinical spine
Men	0.73 (0.63−0.84)	0.97 (0.63−1.48)	0.94 (0.70−1.25)	0.69 (0.50−0.94)	0.61 (0.51−0.73)
Women	0.67 (0.61−0.73)	0.94 (0.73−1.20)	0.90 (0.80−1.01)	0.75 (0.65−0.87)	0.72 (0.65−0.80)

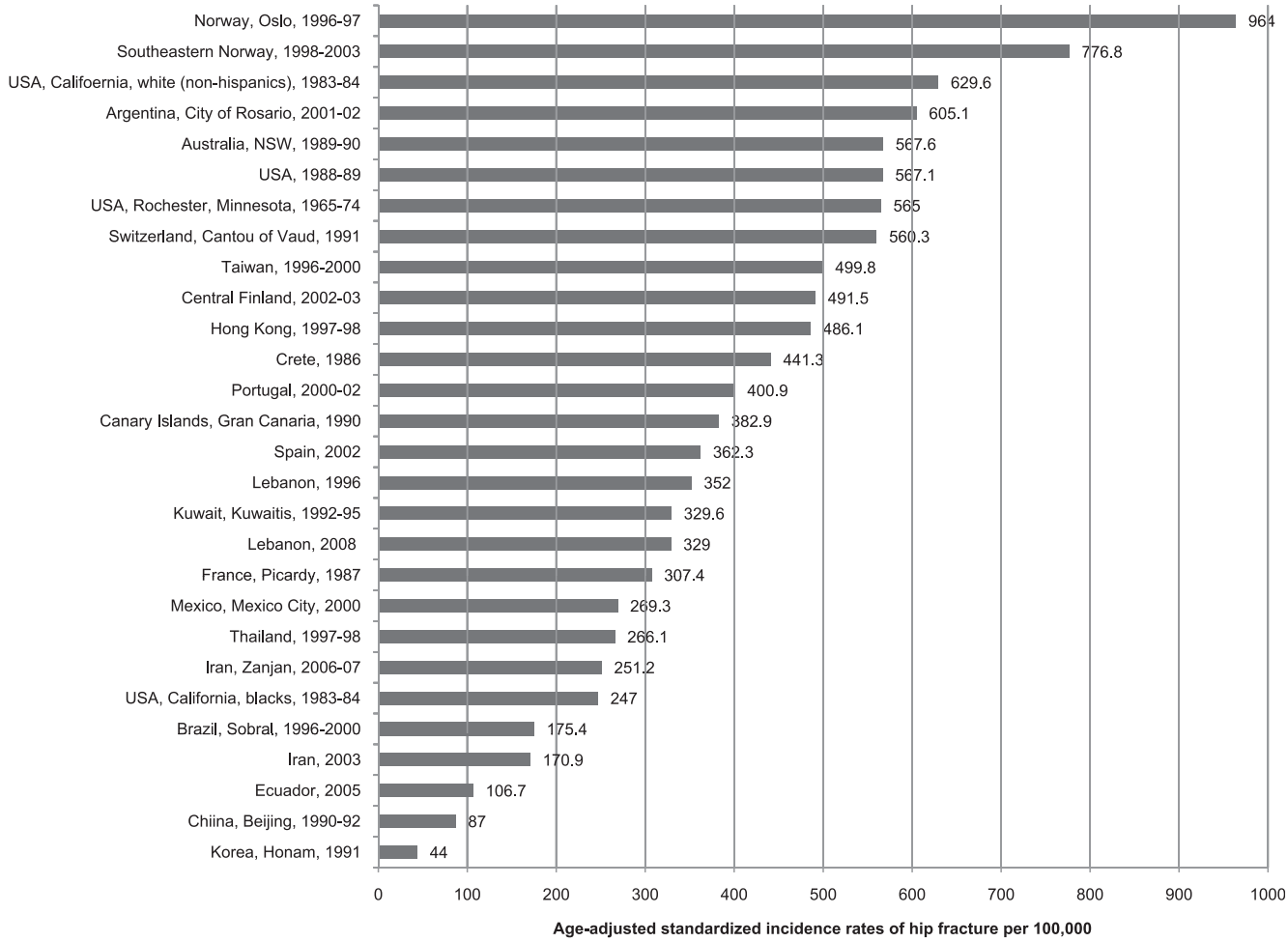

Fig. 1. Variability of Age Standardized Hip Fracture Rates among Females Worldwide. Adapted from Sibai et al, Osteoporos Int, 2010 (with permission).

by reviewing radiology reports and using hip fracture ICD codes, to minimize the risk of misclassification (for e.g., counting some strain and sprain injury, and hip dislocation as hip fracture in the emergency room). Because we are interested in fragility fractures and because the likelihood of a fracture depends largely on the level of trauma, excluding pathological fractures and high trauma fractures is also important. Indeed, in the same population, fracture rates may be up to 2 times higher when ICD codes are not used and when fractures resulting from both high and low trauma levels are included, compared to rates when ICD codes are used and only low trauma fractures are included *(62,63)*.

Ideally, the data provided should be that for the first fracture at a given site to avoid double counting of an incident fracture. In addition, estimates of the long-term risk of fracture in individuals who have not yet sustained a fracture require documentation of the incidence of the first fracture at a particular site. Second or subsequent fractures are more common, particularly in the spine, but also for other sites. The overestimate of the first fracture rates from unadjusted data on incidence varies from 0% to 58% depending on site and age *(64)*.

Question: How do major osteoporotic fracture rates vary internationally and how might this influence construction of a country specific FRAX model?

Official Position: The accuracy of FRAX models are improved by the inclusion of country, age- and sex-specific rates of other major osteoporotic fractures (clinical vertebral, humerus, distal forearm).

Grade: Good, B, W.

Rationale:

It has been suggested that there may be less racial/ethnic relative variability (lowest-highest rates) in vertebral fractures as compared to hip fractures worldwide *(38,65–70)*. Although vertebral fractures constitute an integral component of the osteoporotic syndrome, reliable information on their epidemiology in the general population is not as readily available as it is for hip fractures, and stems mostly from data generated in Europe and the US. Indeed, unlike hip fractures, the

Table 8
Prevalence of Morphometric Vertebral Fractures* within same Ethnicity (Caucasian Women)

	Lebanon *(66)* N = 291	LASA *(67)* N = 267	Mayo *(68)* N = 762	SOF *(70)* N = 9575	EPIDOS *(69)* N = 770
Age range	65−85	≥65	65−85	≥65	80(3)**
Prevalence (%)	19	19	23.9	20	22.8

*Same Method to identify fractures was used in all studies and mild fractures were excluded.
**Mean (SD).

assessment of the prevalence of vertebral fractures is not as clear, two-thirds are clinically silent *(71)*, and only 10% require hospital admission. Furthermore, such rates are dependent on the definition of such fractures, clinical versus morphometric vertebral fractures. Studies using the same methodology to define morphometric fractures showed similar prevalence within the same ethnic group of older Caucasian women in 5 different countries/regions of the world (America, Europe, Asia) *(66−70)*. Indeed, the prevalence of such fractures, excluding Grade I fractures in elderly women, from Lebanon, Amsterdam, France (EPIDOS) the US (Mayo and SOF), was between 19−23%, Table 8. Similar conclusions are reached when examining data from studies in elderly women from 5 different Latin American countries (Argentina, Brazil, Mexico, Columbia, Puerto Rico) partaking in the LAVOS study, where fractures varied between 17 and 22% in the 70−79 years old group *(65)*, Table 9.

Clinical vertebral fracture rates are, however, more variable. Indeed, when assessed using crude hospital discharge rates within Europe, it varied by 3−8 fold in women, being highest in the oldest subjects from northern European countries and lowest in Eastern Countries; variability in men was less pronounced *(72)*. These patterns are similar to that observed for hip fractures. Conversely, the highest variability in the prevalence of vertebral fractures is noted in studies from different regions and ethnicities, and was more pronounced in young ages (rate ratio reaching 15 folds) than older age groups (rate ratios between 1.5 and 3) *(38)*. When one considers the relatively limited data on ratios of hip to non-hip fractures incidence rates, there also appears to be ethnic and/or country related variability in these ratios, be it of hip to vertebral and possibly hip to other major osteoporotic fractures. Indeed, the ratios and correlations coefficients may vary by skeletal site used or gender. For example, the coefficient of correlation between age standardized risk for vertebral fractures and that for hip fractures in hospital discharge data in Europe was 0.83 ($p = 0.01$) in men and 0.64 (NS) in women, and the rate ratio of vertebral to non-hip fractures varied between countries, ranging between 7 and 20 in women and between 4 and 7 in men *(72)*. Whereas the calculated ratios of hip/non hip fractures in Malmo and the US were almost identical *(11,64)*, they differed by up to four folds in women using the a Swiss national data *(73)*, as compared to the Malmo study across age groups, Table 10; and varied by 1.5−2.8 folds (excluding a high calcium District in Yugoslavia) when comparing distal forearm to proximal fracture rate ratios in various countries worldwide *(74)*, Table 11. Similarly, it was shown recently that vertebral to hip fracture ratios varied widely being 2−5 fold higher in elderly Chinese from Hong-Kong or Japanese *(75,76)* compared to those from Malmo Sweden *(64)*. It is also important to note that these ratios are likely to change because of the secular trends in fracture rates in various regions. Therefore, country-specific data on age and gender specific incidences of other major fractures (forearm, proximal humerus and clinical spine fractures) per 100 000 is preferred and needed.

In the absence of these data, the ratio between hip fracture rate and major osteoporotic fracture rate from Malmö,

Table 9
Prevalence of Morphometric Vertebral fractures* in Women within same Region: Latin America

	LAVOS N = 1,902	Mexico N = 406	Argentina N = 420	Brazil N = 415	Colombia N = 261	Puerto Rico N = 400
50−59	6.9	7.7	10.4	6.7	3.6	5.3
60−69	10.2	13.8	13.7	7.6	7.9	8.2
70−79	18.0	18.0	16.8	17.7	22.0	16.8
80+	27.8	38.1	24.4	25.0	10.7	21.5

*Same method to define fractures was used in all studies: a fracture was defined if a reduction of 3 SD or more from the normal mean for the vertebral level of anterior-to-posterior or middle-to-posterior heights ratios were found. In addition, a vertebral body was defined as a fracture if the ratios of posterior-to-adjacent posterior and the anterior heights-to-adjacent anterior were reduced by 3 SD or more compared with normal values.
Adapted from Clark et al *(65)* with permission.

Table 10
Ratio of Annual Incidence of Major Osteoporotic to Hip Fracture (Spine, Humerus, Forearm and Hip) to Hip Fractures in Swedish (Malmo study), US, and Swiss Populations

Gender Age (years)	Sweden[a]	USA[b]	Switzerland[c]
Men			
50–54	4.6	7.9	7.8
55–59	4.1	4.6	5.9
60–64	6.3	6.4	6.6
65–69	3.4	3.4	4.0
70–74	3.1	2.6	3.6
75–79	2.0	1.9	2.6
80–84	1.6	1.4	3.6
85–89	1.8	1.6	1.7
Women			
50–54	11.2	13.9	17.6
55–59	13.0	12.4	8.6
60–64	5.5	10.3	14.1
65–69	4.9	5.9	8.1
70–74	4.0	4.4	8.7
75–79	2.5	2.4	7.1
80–84	1.9	1.9	7.3
85–89	1.7	1.6	3.6

[a]Calculated from the Malmo study, Kanis et al Osteoporos Int 2000.
[b]Ettinger et al *(11)* Osteoporos Int I 2010, revised discounted rates after by 10–20% depending on age group.
[c]Calculated from Lippuner et al *(73)* Osteoporos Int 2009 discounted rates by 10–20% depending on age group.

Sweden is applied to the hip fracture rate from the current country to estimate the risk for other major fractures *(64)*. Indeed, for countries with FRAX calculator, there were data on non-hip fractures in only 7 out of 31 countries, whereas in most countries, other fractures were imputed from Swedish epidemiology. Moreover, good quality data on non-hip fractures was missing for all countries without a FRAX calculator.

Question: What do I do if my country does not have a FRAX calculator? Can a surrogate country be used?

Official Position: In the absence of high quality, national hip fracture data, a country specific FRAX model can be built using hip fracture incidence rates from a surrogate country, but with incorporation of country specific mortality rates.

Grade: Fair, C, W.

Rationale:

Only 31 countries have a FRAX calculator. The majority of the countries without FRAX calculator (106 out of 137) have no fracture data at all, and the quality of the available data for hip fractures is poor to fair in most. Moreover,

Table 11
Ratio of Age-adjusted Incidence Rates (per 100 000 per year) of Distal Forearm Fractures to Hip Fractures in Different Populations of People Aged 35 Years or Older

	Women	Men
Oslo, Norway	1.80	0.88
Malmö, Sweden	1.90	0.74
Stockholm Sweden	1.90	0.68
Rochester, MN, USA	1.28	0.48
Trent, UK	1.37	0.57
Oxford-Dundee,UK	2.17	1.06
High calcium area	5.18	2.16
Low calcium area	1.86	1.17
Torroti, Japan	1.38	1.09
Singapore	1.40	0.86
Adebajo, Nigeria	3	1.33

Adapted from Melton LJ (*74*).

none of those has good quality data on non-hip fractures. The majority of countries without a FRAX calculator are located in the Middle East and Africa (n = 64), where FRAX calculator is available for two countries only: (Lebanon and Jordan), followed by Asia and Oceana (n = 23), Europe (n = 36) and Latin America (n = 14). It is likely that these countries do not, and will not have the resources to generate the robust data to derive a country specific calculator in the near future. Even if such resources were available, it is unclear that scarce national resources in many of these low-middle income countries will be allocated to generating such data. In view of the geographic location of many of these countries, and the known fracture rates in neighboring countries, it is anticipated that fracture risk would fall in the lower half of the spectrum for hip fracture rates worldwide. However, these are the areas registering the highest demographic growth, and anticipated to have the largest growth in the number of fractures and implementation of FRAX would optimize the targeting of scarce health resources in these countries. Thus, the need for FRAX models will continue to expand.

For countries without a FRAX calculator, it has been suggested that, using the FRAX calculator of a surrogate country, is a reasonable alternative *(77)*. Because fracture hazards and death hazards both contribute to fracture probability (WHO Scientific Group Technical Report), and may vary between countries, the choice of a surrogate country should be based, to the extent possible, on both of these variables. The importance of choosing a country with similar mortality rate is illustrated in the following example. Whereas fracture rates in Kuwait are similar to those observed in Lebanon and somewhat to those in Spain, two countries with FRAX calculators, life expectancy in Kuwait is similar to that in Lebanon and differs from that in Spain. The 10 year probability of hip fracture for a 70 year old Kuwaiti woman with a T-score −1.7 and BMI 23.9 kg/m^2 and 3 risk factors, would be 11% if one were to use the Spain FRAX model and 3.5% if one uses the

Table 12
Point Estimates for Hip Fractures by Age Group in the Middle East, Asia and Latin America in Female Subjects*

Region/ Country	Reference	Level of evidence	Fracture rate/100.000	95% CI
ME Region				
≥ 50 years				
Kuwait	Memon (*60*)	Fair	152	125−178
Lebanon	Sibai (*43*)	Good	163	147−182
Oman	Shukla (*78*)	Fair	150	120−180
KSA	Al Nuaim (*79*)	Fair	100	NA
Asia				
70−74 years				
China	Schwartz (*85*)	Good	164	
Japan	Hagino (*54*)	Good	299	
Hong Kong	Lau (*50*)	Good	359	
Singapore	National data unpublished	Good	432	
Taiwan	Chie (*86*)	Good	459	
75−79 years				
China	Schwartz (*85*)	Good	141	
Japan	Hagino (*54*)	Good	620	
Hong Kong	Lau (*50*)	Good	820	
Singapore	National data unpublished	Good	896	
Taiwan	Chie (*86*)	Good	934	
Latin America				
60−69 years				
Argentina	Wittich (*80*)	Good	176	
Brazil	Castro Rocha (*81*)	Fair	74	
Mexico	Clark (*82*)	Good	76	
Columbia	Carmoma *83*)	Poor	65	
Ecuador	Orces (*84*)	Fair to good	29	
70−79 years				
Argentina	Wittich (*80*)	Good	554	
Brazil	Castro Rocha (*81*)	Fair	295	
Mexico	Clark (*82*)	Good	240	
Columbia	Carmoma (*83*)	Poor	192	
Ecuador	Orces (*84*)	Fair to good	84	

*Age ranges are shown as reported in the original publications referenced here-in.

Lebanon FRAX calculator. These probabilities would be 22% and 5.3% respectively, if the patient had 4 risk factors. This example highlights a major difference reflecting the importance of selecting the appropriate surrogate country with similar fracture rates and life expectancy. This approach is anticipated to be applicable to several countries in the Middle East where fracture rates and mortality rates are comparable, Table 12.

Question: What do I do if there is no hip fracture data for my country?

Official Position: In the absence of any hip fracture data, development of FRAX models based on broad categories of fracture risk (e.g., low, medium, high, adjusted for country specific mortality rates is recommended).

Grade: Fair, C, W.

Rationale:

Using a surrogate country is however only feasible in small regions with similar ethnic compositions, fracture rates and life expectancy across countries in that region. This may be feasible for the Middle East region where life expectancy is similar and the fracture rates are quite similar *(43,60,78,79)*, Table 12.

However, in some regions such as Latin America for example, marked variability in hip fracture rates was observed, with rate ratios up to 6 times between countries, possibly reflecting wide ethnic differences in that region of the world *(80−84)*. High rate ratios were also observed when comparing data from Asian countries*(50,54,85,86)*, Table 12. Other regions in the world (e.g., India and Indonesia) do not have data at all. Therefore, a regional calculator may not be a good alternative in such regions.

For these regions, creating FRAX models using broad categories of risk, which can then be adjusted for country specific mortality, may be an alternate option. It may indeed be possible to divide countries into broad categories of hip fracture risk (e.g., high, medium, low, very low) where within each category, there are several countries with FRAX models based on robust hip fracture data. The broad risk categories will include average point estimates for fracture risk with confidence intervals that are likely to include the anticipated fracture risks for the country of interest. The number of actual broad risk categories is best defined by implementing sensitivity analyses evaluating the impact of the change in number of risk categories on the actual risk assessment for a selective sample of potential illustrative countries of interest.

Summary

In summary, marked variability in hip fractures is noted across the world with highest rates in Northern European countries and lowest rates in selected Asian countries. There is also considerable variability in hip fracture rates by race/ethnicity within countries, in particular the US with 50% lower hip fracture rates among Blacks compared to Whites. Hip fracture rates are about 25% lower in Hispanics and Asians compared to US rates. Considerably less in known about variability in major osteoporotic fractures. Only six counties with a FRAX calculator have data on non-hip fractures and no countries without a FRAX calculator have data on non-hip fractures. The FRAX calculator assumes that the ratio of hip to non-hip fractures is the same in all countries as in Sweden.

The purpose of this task force was to address international implementation of FRAX. Questions addressed by the task force included examination of hip and other fractures by race/ethnicity and international variability. Only 31 countries have a FRAX calculator and we addressed what data is required to get a FRAX calculator and to make recommendations in situations where there is no FRAX calculator. Our task force makes the following recommendations:

1. Separate FRAX models are available for US Asians, Blacks, Hispanics because hip and major osteoporotic fracture rates are lower in these ethnic groups than in US Whites. Until additional data are available, the US Caucasian FRAX calculator should be used to assess fracture risk in US Native American women.
2. Changing fracture and mortality rates and improved quality of data are expected. Therefore, periodic review of country-specific fracture rates used in the FRAX model is recommended.
3. There is significant variability in hip fracture rates throughout the world. The minimum requirements for construction of a country specific FRAX-model are hip fracture incidence data that are of high quality and representative of that country.
4. The accuracy of FRAX models are improved by the inclusion of country, age- and sex-specific rates of other major osteoporotic fractures (clinical vertebral, humerus, distal forearm).
5. In the absence of high quality, national hip fracture data, a country specific FRAX model can be built using hip fracture incidence rates from a surrogate country, but with incorporation of country specific mortality rates.
6. In the absence of any hip fracture data, development of FRAX models based on broad categories of fracture risk (e.g., low, medium, high), adjusted for country specific mortality rates is recommended).

Additional Questions for Future Research

1. Secular changes in hip fracture rates have been observed with declining rates in Whites but increasing rates in Asians and Hispanics. The impact of these variations in hip fractures on FRAX estimates of risk warrants further study.
2. Are there Intra-ethnic variability in fracture rates?
3. Two of the most populous countries in the world, namely India and Indonesia, have no data on hip fractures. The need to fill this gap is pressing.
4. Only six countries in the world have data on non-hip fractures. Further research is needed to obtain high quality, national data on non-hip fractures to test if the assumption in FRAX regarding the ratio of hip to non-hip fractures holds across the world.
5. Little is known about ethnic variability in fracture rates outside the US. The US FRAX calculator is the only one that makes ethnic adjustments. Is this appropriate or should ethnicity be universally addressed across the world?
6. Can country specific FRAX models be simplified by using broad categories of risk and then adjust for country specific mortality rates?

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Appendix I. Position Conference Members

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Appendix II. Table 1
Countries with a FRAX Calculator?

Country	Source of the hip fracture data used to construct the FRAX calculator*	Are data available re: other major fractures in the same cohort?**	Has this country's FRAX calculator been independently validated by a prospective fracture study?	Is there more than 1 major ethnic group in this country? If yes, does the hip fracture data used for FRAX include all major ethnic groups?	Comments
Argentina	Incidence of hip fracture in Rosario, Argentina (Supplementary information on Morosano et al, Ost Int 2005).	No, other fractures imputed from Swedish epidemiology.	No		Regional data
Australia	National Hospital Morbidity Database maintained at the Australian Institute of Health and Welfare.	No, other fractures imputed from Swedish epidemiology. Adequacy of assumption tested in Geelong study.	Partially in Geelong In progress elsewhere	Yes − data used for FRAX includes all ethnic groups	National data
Austria	Statistic Austria (which runs all healthcare-related databases) year 2001−2005.	No, other fractures imputed from Swedish epidemiology.	No		National data
Belgium	"The incidences of osteoporotic fractures in Belgium," Hiligsmann M and Reginster JY. Table 1 and Table 3. Incidence (rate/1000) of a fracture at the sites shown by age range in Belgian women/men (in 2006).	No, other fractures imputed from Swedish epidemiology.	In progress		National data
Canada	Risk of hip fracture comes from Canada 2005, personal communication with Bill Leslie.	No, other fractures imputed from US epidemiology.	Yes (In press)	Yes − data used for FRAX includes all ethnic groups	National data
China	Mean value of Beijing 1988−92, Beijing 1990/92, Shenyang 1994 and Tangshan 1994.	No, other fractures imputed from Swedish epidemiology.	No		Mean of 4 regional estimates

Chinese Taipei (Taiwan)	Ministry of Health Data in ''A nationwide seven-year trend of hip fracture in the elderly population of Taiwan'' in Bone 2008 by Shao C-J et al.	No, other fractures imputed from Swedish epidemiology.	No	National data
Colombia	Personal communication withJuan Jose Jaller. The source is six hospitals of the city Barranquilla, 2004−2006.	No, other fractures imputed from Swedish epidemiology.	No	Regional data
Denmark	From Bo Abrahamsen we got hip fracture incidence rates by age and sex, per 100 000 (S720, S721 and S722).	Yes for hip, humerus and forearm fracture For vertebral other fractures imputed from Swedish epidemiology.	Yes	National data
Finland	National research and development centre for welfare and health	No, other fractures imputed from Swedish epidemiology.	Yes	National data
France	''Osteoporotic fracture incidence in men & women aged $\geq$50 years in metropolitan France, 2004'', written by Pr. P.D. Delmas, Dr. Nansa Burlet, Dr. Anne-Marie Schott, Dr. Chantal Couris, Adeline Zamora & Antoine Beauvois.	No, other fracture imputed from Swedish epidemiology.	No	National data
Germany	''Trend of hip fracture incidence in Germany 1995−2004: a population-based study'' by A. Icks et al, Osteoporosis International 16 November 2007.	No, other fractures imputed from Swedish epidemiology.	No	National data
Hong Kong	Risk of hip fracture comes from Hong Kong 2000−2004.	No, other fractures imputed from Swedish epidemiology.	No	'National' data

(*Continued*)

Appendix II. Table 1 (Continued)

Country	Source of the hip fracture data used to construct the FRAX calculator*	Are data available re: other major fractures in the same cohort?**	Has this country's FRAX calculator been independently validated by a prospective fracture study?	Is there more than 1 major ethnic group in this country? If yes, does the hip fracture data used for FRAX include all major ethnic groups?	Comments
Hungary	Nationwide health insurance database, 1999−2003, Pentek, Horvath, et al. Ost Int 2008;19:243−249., Table 2.	No, other fractures imputed from Swedish epidemiology.	No		National sample
Italy	(Age > 65) is the mean value of Verona 2003 and 2004 per 100 from S. Adami. For ages below 65 it is a mean of Italy (Friuli Venezia) 1997, Italy (Sienna/ Rome/Parma) 1989 & Italy (Verona) 1997. The Italian figures are used from five regional estimates from Verona, Venezia (S, Adami, personal communications, 2000) and prospective data from Siena, Rome and Parma from Elffors I et al., ''The variable incidence of hip fracture in Southern Europe: The MEDOS study. OI 4:253−263.	No, other fractures imputed from Swedish epidemiology.	In progress		Mean of several regional estimates
Japan	Hagino et al., Bone 1999 24:265−270	Yes for hip, humerus and forearm fracture For vertebral other fractures imputed from Swedish epidemiology.	No		National data

Lebanon	Lebanese Ministry of Health	No, other fractures imputed from Swedish epidemiology.	No	NO	National data
Mexico	IMSS population using the mean incidence for the years 2000−2006. Fractures considered comprise the ICD codes S72.0, S72.1 and S72.2. Double admissions for hip fracture in each year are excluded.	Yes for hip, humerus and forearm fracture For vertebral other fractures imputed from Swedish epidemiology.	No		National sample
Netherlands	National Office for Statistics, CBS ''incident hip fractures were defined as events that were not preceded by a hip fracture in the 5 years before''	No, other fractures imputed from Swedish epidemiology.	No		National data
New Zealand	The burden of osteoporosis in New Zealand: 2007−2020, October 2007 by ''Osteoporosis New Zealand'' table 2 and 3:	No, other fractures imputed from Swedish epidemiology.	Yes	Yes − data used for FRAX includes whites only	National data
South Korea	''Incidences of hip fractures in Korea'' by Soo Lim et al, JBMM 2008;26:400−405.	No, other fractures imputed from Swedish epidemiology.	No		National data
Spain	Mean value of Barcelona 1984, Canaries 1990, Seville/Madrid 1989, Zamora 1991 and Ost Int 2006;7:464−70.	No, other fractures imputed from Swedish epidemiology.	No		Mean of regional samples
Sweden	Kanis et al 2000 OI 11:669−674.	Kanis et al. Ost Int 2000; 11:669−674.	No		National data
Switzerland	Fracture incidence is from Swiss Federal Office of Statistics (SFOS) year 2000.	Risk of other osteoporotic fracture is computed from Swiss Federal Office of Statistics (SFOS) year 2000 and from a not yet published database of fracture patients aged 50+ collected in different Swiss sites.	no		National sample

(*Continued*)

Appendix II. Table 1 (Continued)

Country	Source of the hip fracture data used to construct the FRAX calculator*	Are data available re: other major fractures in the same cohort?**	Has this country's FRAX calculator been independently validated by a prospective fracture study?	Is there more than 1 major ethnic group in this country? If yes, does the hip fracture data used for FRAX include all major ethnic groups?	Comments
Turkey	Istanbul 1988−9.	No, other fractures imputed from Swedish epidemiology.	No		Regional estimate
UK	Singer et al., 1998 JBJS 80B:234−238.	Singer et al., 1998 JBJS 80B:234−238.	Yes		
US (Asian)	Ratio from Caucasian.	Ratio from Caucasian.	No		National data
US (Black)	Ratio from Caucasian.	Ratio from Caucasian.	No		National data
US (Caucasian)	"Updated fracture incidence rates for the US version of FRAX." Ettinger B, Black DM, Dawson-Hughes B, Pressman AR, Melton LJ 3rd. Ost Int. 2010 Jan;21(1):25−33. Epub 2009 Aug 25.	"Updated fracture incidence rates for the US version of FRAX." Ettinger B, Black DM, Dawson-Hughes B, Pressman AR, Melton LJ 3rd. Ost Int. 2010 Jan;21(1):25−33. Epub 2009 Aug 25.	Yes		National data
US (Hispanic; Black; Asian)	Ratio from Caucasian	Ratio from Caucasian	No		National data

The task force received this information from Dr. JA Kanis.

Appendix II. Table 2
Incidence of Hip Fracture (per 100,000) by Country and Gender

	Men											
	Age (years)											
Region	40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79	80–84	85–89	90–94	95–99
Argentina	3.5	7.9	12.8	18.2	56.3	108.7	229.5	366.4	807.0*			
Australia‡												
Australia (Sanders 1999)			30	50	50	60	210	390	430	1930	2630 (90+)	
Austria‡												
Belgium			46	68	91	114	216	364	819	1252	2240	3198*
Canada	12.7	17.8	23.5	35.0	55.9	97.8	179.1	337.1	667.4	1484*		
China			25.8	41.7	71.2	83.6	122.1	167.7	281.7	625.0*		
Colombia‡												
Columbia (Carmona, 1999)			16.87		38.18		105.89		305.33 (80+)			
Denmark	17	38	67	90	148	236	367	742	1487	2745*		
Finland‡												
France‡												
Germany	30.3[a]		54.5[a]		89.2	119.5	214.0	379.5	785.9	1509.4	2024*	
Hong Kong			12.0	25.0	51.0	102.6	212.2	450.0	871.4	1654*		
Hungary			34	87	120	157	212	487	1129	2014[b]		
Italy			40	40	50	120	240	420	730	1720	2130*	
Japan	7.01	9.67	15.68	21.16	38.88	67.85	130.62	247.63	452.76	841.78	13221	18638
Lebanon‡												
Mexico‡												
Mexico (Clark, 2005)			20		52		162		688			
Netherlands‡												
New Zealand			19.9	39.5	43.9	81.1	155.2	357.3	823.0	1582.1	2641*	
S Korea	34.5[a]		62.1[a]		147.1[a]		346.2[a]		736.7[a]		1338*	
Spain			10	21.8	56.2	52.2	136.2	225.6	494.8	1022*		
Sweden	19	7	88	88	76	189	304	629	1474	1807	1852	5698
Switzerland			48	82	92	161	229	454	776	1488	2495	3584*
Taiwan						176.9	362.3	592.0	938.3	1530*		
Turkey			4.6	14.0	21.0	33.0	45.0	110	130	250		
UK			22	39	69	121	213	374	657	1115	2003*	
US Asian		10	16	24	40	69	122	239	506	973		
US Black		8	13	20	33	57	101	198	419	806		
US Caucasian		15	25	37	62	108	191	374	790	1521		
US Hispanic		5	15	22	36	63	111	217	458	882		

(*Continued*)

Appendix II. Table 2 (Continued)

	Women											
	40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79	80–84	85–89	90–94	95–99
Argentina	3.1	7.1	18.7	11.4	54.6	145.4	425.7	661.1	2947*			
Australia‡												
Australia (Sanders, 1999)			10	40	30	170	320	800	1380	3340	3750 (90+)	
Austria‡												
Belgium			46	57	171	205	512	797	1480	2397	3329	3869*
Canada	4.1	9.9	19.8	41.0	72.7	150.5	301.7	638.7	1275.5	2636.6*		
China			17.7	29.5	56.2	88.2	143.8	131.9	201.5	453.5*		
Colombia‡												
Columbia (Carmona, 1999)			20.36		65.41		192.26		661.74 (80+)			
Denmark	11	24	46	93	174	340	709	1339	2413	4560*		
Finland‡												
France‡												
Germany	13.4[a]		45.5[a]		92.5	158.5	363.6	789.5	1533.5	2735.7	3557.2*	
Hong Kong			8.8	23.6	68.0	156.0	364.4	830.8	1503.8	2837.6*		
Hungary			24	60	112	186	351	695	1845	3244[b]		
Italy			40	60	110	200	370	820	1470	2610	3070*	
Japan	4.18	7.28	18.21	30.99	55.82	128.61	264.40	597.91	1245.42	2069.29	3046.42	3578.54
Lebanon‡												
Mexico‡												
Mexico (Clark, 2005)			38		105		295		1137			
Netherlands‡												
New Zealand			11.9	32.8	58.1	121.1	277.6	654.3	1328.0	2424.4	3591.6*	
S Korea	13.6[a]		41.2[a]		159.4[a]		513.3[a]		1191.5[a]		1659.3*	
Spain			14.3	29.8	53.5	90.1	238.4	483.7	1108.3	2108.8*		
Sweden	0	26	55	56	192	315	556	1392	2348	4290	3998	3958
Switzerland			33	69	110	220	426	876	1877	3281	4314	4455*
Taiwan						247.5	511.3	991.0	1783.7	2745.5*		
Turkey			9	10	19	40	5.2	84	170	280*		
UK			30	57	107	201	379	713	1344	2532	4770*	
US Asian		7	14	26	49	93	184	368	702	1228		
US Black		6	12	22	42	80	158	316	604	1056		
US Caucasian		13	27	52	97	186	368	736	1404	2456		
US Hispanic		7	14	28	51	99	195	390	744	1302		

Data provided by John Kanis and the Please note that we deleted rates from countries that are considered confidential as per Dr. Kanis. Refer to Table 1 regarding the data source (hip & other major fractures, national or regional), validation of the calculator, and inclusion of all ethnic groups.

*≥age.

‡Please note that we deleted rates from countries that are considered confidential as per Dr. Kanis.

[a]decade.

[b]85–100 years.

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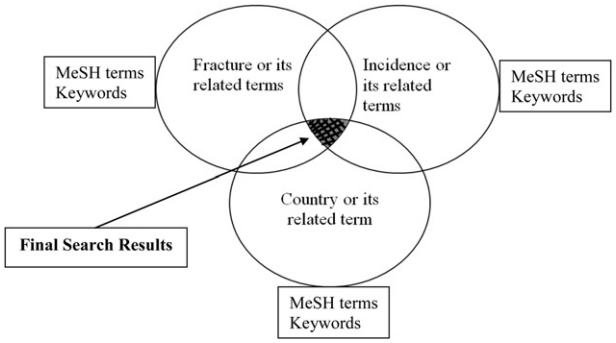
Appendix III. Medline Search Methodology

Research Concept

The search utilized the various search options/techniques that the OVID interface allows using MeSH[1] terms, explode functions, keyword searching in title, abstract, and subject headings, adjacency, and publication types, in addition to Boolean operators and truncation (and, or**).** All this was done to capture as many relevant articles as possible form Medline using key terms that were identified by task force members and exchanged by email. The key words were divided into three main concepts through a reiterative technique the librarian performed using these key words. The three primary concepts were: Fracture, Incidence and the Country or their related terms. The three concepts were searched one at a time, and then merged together through the AND term, as described in detail below.



In order to obtain a thorough search, each concept was searched individually by entering the different MeSH terms and keywords. After conducting a search using all terms in one concept, they were included together into one search. After each concept search was completed, a final search was done that lumped together the three completed concept searches to come up with the final search results.

[1]MeSH is used by the indexers at National Library Medicine to describe the content of an article. These MeSH terms are also organized in a hierarchy or tree structure, and this would allow users to explode a MeSH to ensure that narrower MeSH terms are also included in the search results.

For the **Fracture** concept, the following searches were done:
MeSH terms and keywords:

1 exp Fractures, bone/
2 exp Osteoporosis/ or Osteoporo*.ti,ab.
3 exp Bone density/ or (bone* adj2 (density or mass)).ti,ab.
4 FRAX.ti,ab. or ((fracture* adj2 risk*) and calculate*)
5 ((hip or vertebra* or spinal or spine or forearm* or bone* or femoral or femur) adj3 fracture*).ti,ab.
6 ((global adj2 fracture*) or (life adj time adj2 fracture*)).ti,ab.

All searches lumped together to get a final search result on the fracture concept.

When the above 6 searches were completed, the following search was run to lump them together to get a final search result on the fracture concept:

7 or/1−6

For the **Incidence** concept, the following searches were done:
MeSH terms and keywords:

8 exp Risk assessment/
9 exp Probability/
10 exp ''Predictive values of tests''/
11 exp Recurrence/
12 exp Incidence/
13 exp models, biological/ or exp models, statistical
14 exp Cohort studies/
15 exp Epidemiology/
16 exp Epidemiologic methods
17 exp Case-control studies/
18 exp Randomized controlled trial/
19 (risk$1 or inciden* or epidemiol*or recur* or predict* or probab* or occur*).ti,ab.
20 Epidemiology.fs.
21 Cohort*.ti,ab.
22 ((case* or study or studies or trial*) and control*).ti,ab.
23 (random* or placebo*).ti,ab,sh.
24 ((single or double* or triple* or treble*) and (blind* or mask*)).ti,ab,sh.
25 (prognost* adj3 model*).ti,ab.
26 Controlled clinical trial.pt.
27 Randomized controlled trial.pt.
28 exp Controlled clinical trial/

All searches lumped together to get a final search result on the incidence

When the above 21 searches were completed, the following search was run to lump them together to get a final search result on the fracture concept:

29 or/8−28

For the **Country** concept, the MeSH term of the country was used and **OR**ed with the truncated keyword (to include people originating from that country) for that country in title and abstract (ti,ab.).
For example, if *Lebanon* was the country of concern, the following search was run:

30 exp Lebanon/ or Leban*.ti,ab.

Finally the above three concept search results: **Fracture** + **Incidence** + **Country** were combined:

31 7 and 29 and 30

And the studies limited to humans to get the **Final Search Results** for *Lebanon*.

32 Limit 31 to humans

Please note that the star * is for truncation, and it is used to capture all words that start with a specific root; so inciden* would retrieve any word indexed in the Medline database that starts with the root inciden example incidence, incident, incidents, incidences etc… As for adj, it stands for adjacent i.e., the words are within maximum of n words in-between. The ti and ab stand for title and abstract respectively, thus we are searching for these particular terms in title and abstract.