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ORIGINAL ARTICLE

The potential impact of new National Osteoporosis Foundation guidance on treatment patterns

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Abstract
Summary This analysis of National Health and Nutrition Examination Survey III data describes the prevalence of risk factors for osteoporosis and the proportions of men and postmenopausal women age 50 years and older who are candidates for treatment to lower fracture risk, according to the new FRAX®-based National Osteoporosis Foundation Clinician's Guide.
Introduction Little information is available on prevalence of osteoporosis risk factors or proportions of US men and women who are potential candidates for treatment.
Methods The prevalence of risk factors used in the new National Osteoporosis Foundation (NOF) FRAX®-based Guide to the Prevention and Treatment of Osteoporosis was estimated using data from the third National Health and Nutrition Examination Survey (NHANES III). Risk factors not measured in NHANES III were simulated using World Health Organization cohorts. The proportion of US men and postmenopausal women age 50+ years who are treatment candidates by the new NOF Guide were calculated; for non-Hispanic white (NHW) women, the proportion eligible by the new NOF Guide was compared with that based on an earlier NOF Guide.
Results Twenty percent of men and 37% of women were potential candidates for treatment to prevent fractures by the new NOF Guide. Among NHW women, 53% were potential candidates by the previous NOF Guide compared with 41% by the new guide.

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Conclusions One fifth of men and 37% of postmenopausal women are eligible for osteoporosis treatment consideration by the new NOF Guide. However, fewer NHW women are eligible by the new guide than by the previous NOF Guide.

Keywords National Osteoporosis Foundation Clinician's Guide · Osteoporosis · Osteoporosis risk factors · Prevalence · Treatment eligibility ± population-based study

Introduction

Despite the fact that hip fracture incidence rates are declining in the USA [1, 2], demographic changes are expected to increase the actual number of hip fractures and other fractures in men and women age 50 and older by over 50% between 2005 and 2025 [3]. A revised National Osteoporosis Foundation (NOF) Clinician's Guide for the Prevention and Treatment of Osteoporosis, published in 2008 [4], makes recommendations about who should be considered for pharmacotherapy to lower the risk of future fractures. The guide is partly based on the World Health Organization (WHO) FRAX® algorithm, which employs clinical risk factors, along with bone mineral density (BMD) of the femoral neck, if available, to estimate 10-year fracture probability [5]. FRAX® results were combined with an economic analysis to determine the levels of risk at which it is cost effective to consider osteoporosis treatment [6]. However, the prevalence of the clinical risk factors used in FRAX® has not been assessed in the general US population, and the proportion of men and women in the USA expected to meet the new NOF Guide treatment thresholds is unknown. This information is important because the economic burden of osteoporotic fractures, which have a significant impact on both the delivery and cost of health care in the USA [3], must be balanced against the potential cost and benefits of fracture prevention.

Recommendations in the new guide [4] differ in several respects from those in a previous version [7]. The old NOF Guide, last updated in 2005, was based on an earlier cost effectiveness analysis that incorporated femoral neck BMD and the presence or absence of one or more clinical risk factors drawn from a long list of established risk factors for osteoporosis [8]. The old guide, which applied only to postmenopausal Caucasian women, indicated that it was cost effective to consider treating women with: (a) a prior vertebral or hip fracture, (b) a femoral neck T-score ≤−2.0 by dual-energy X-ray absorptiometry (DXA), or (c) low femoral neck BMD in the presence of one or more risk factors [7]. With the advent of additional data, the new guide could be extended to men age 50 years and older and to postmenopausal women of all races [4]. It indicates that it is cost effective to consider treatment in those with: (a) a vertebral or hip fracture, (b) a BMD T-score ≤−2.5 at the femoral neck or spine or (c) low bone mass (T-score −1 to −2.5, so-called "osteopenia") at the femoral neck or spine if the 10-year hip fracture probability is 3% or higher. The new guide also recommends treatment for osteopenic individuals with a 10-year probability of a major osteoporosis-related fracture of 20% or higher. Thus, for postmenopausal women, the old and new guides differ mainly with respect to which individuals with low bone mass (~osteopenia) should be considered for treatment.

The objectives of the present study were to describe the prevalence of risk factors for osteoporosis that are used in FRAX® (and the new guide) in older US adults as well as those used in the old guide; estimate the numbers of men and postmenopausal women age 50 years and older in the USA who meet the thresholds for treatment according to the new guide; and to compare the numbers and characteristics of white postmenopausal women in the USA who meet the treatment thresholds by the old and new NOF Guides, respectively. National Health and Nutrition Examination III (NHANES III) data, obtained from a representative sample of non-institutionalized civilians in the USA, contain femoral neck BMD measurements and information on most of the clinical risk factors used in the new and old guides. These data, augmented with simulations (provided by the WHO Collaborating Center) to fill in key risk factor gaps, were used to address these goals.

Methods

Definition of treatment eligibility

Postmenopausal (see below) women and men aged 50 years and older who met any of the following criteria were defined as eligible for treatment based on the new NOF Guide:

1. Had a self-reported hip or spine fracture after age 20 years
2. Had a femoral neck or spine BMD T-score ≤−2.5
3. Had a femoral neck T-score between −1 and −2.5 SD with a 10-year hip fracture probability ≥3% or major fracture probability ≥20%

The previous version of the NOF treatment guidelines pertained to white postmenopausal women only. For this analysis, these women were defined as postmenopausal non-Hispanic white women aged 50 years and older. Postmenopausal non-Hispanic white women in this age range were considered eligible for treatment under the old guide if they met the following criteria:

1. Had a self-reported hip or spine fracture after the age of 20 years

2. Had a femoral neck T-score ≤−2.0
3. Had a femoral neck T-score between −1.5 and −2.0 and at least one of the following: a personal history of wrist fracture after the age of 20 years; parental history of hip fracture; current cigarette smoker; body weight <127 lb; poor self-reported health status; early menopause; low lifetime milk intake; usually drinks 3+ units of alcohol on the days that alcohol was consumed; reduced vision; or fell 1+ times in the past year. The definitions of these variables are shown in the "Risk factors" section below.

Study population

NHANES III was conducted by the National Center for Health Statistics (NCHS) to assess the health and nutritional status of a large representative sample of the non-institutionalized civilian US population. Data were collected via household interviews and standardized physical examinations conducted in specially equipped mobile examination centers [9]. The survey was designed to provide reliable estimates for three race/ethnic groups: non-Hispanic whites (NHW), non-Hispanic blacks (NHB), and Mexican Americans. Participants self-reported their race and ethnicity using census categories from Office of Management and Budget directives [10]. The NCHS Institutional Review Board approved all procedures in NHANES III, and all subjects provided written informed consent.

A total of 10,995 adults aged 50 years and older were eligible to participate in NHANES III. Of the eligible sample, 8,654 (79%) were interviewed, and 7,155 (65%) were examined. The present study was limited to men and postmenopausal women aged 50 years and older with available data for bone mineral density, height, and weight, since these variables are key factors in calculating FRAX® scores. The sample was limited to postmenopausal women because the NOF Guides do not apply to premenopausal women. The sample was also limited to those in whom spine T-score could be simulated, since this variable is used in the new NOF Guide to assess treatment eligibility. Of the 7,155 adults age 50 years and older who were examined in NHANES III, the following were excluded: 754 due to missing femur bone density data, 17 due to missing body weight, one due to missing height, and 32 due to missing simulated spine T-score data. Two hundred thirty-four premenopausal women were also excluded from the examined sample. The final analytic sample consisted of 6,117 men and postmenopausal women age 50 years and older, which represents 56% of the sample in this age range that was selected to participate in NHANES III, 71% of the sample that was interviewed, and 85% of the sample that was examined.

Risk factors

Bone mineral density Femoral neck BMD was measured by DXA (Hologic QDR 1000, Bedford, MA) [11]. Spine BMD was not measured in NHANES III but was estimated by simulation, as described below. Bone density T-scores were calculated as (Respondent's BMD−Reference group mean BMD)/Reference group standard deviation (SD). The reference group for the femoral neck consisted of 409 non-Hispanic white women aged 20–29 years from NHANES III [12]. The WHO cohorts were used as the reference group when calculating T-scores for the spine [5].

Anthropometry Body weight was measured to the nearest 0.01 kg using an electronic load cell scale, and standing height was measured with a fixed stadiometer. Body mass index (BMI) was calculated as body weight (kilograms) divided by height (square meters).

Previous fracture History of hip, spine, or wrist fracture was based on a self-reported fracture at these sites that occurred after age 20 years. Use of "fracture after age 40" gave FRAX® probabilities that differed by no more than 0.1 from those obtained when fracture after age 20 years was used. Fracture occurrence at other skeletal sites was estimated using the simulation approach described below.

Parental history of hip fracture Maternal history was based on self-report that the respondents' biological mother had fractured her hip. Data for paternal history of hip fracture was estimated using the simulation as described below.

Cigarette smoking and high alcohol intake Cigarette smokers were defined as respondents who self-reported that they currently smoked, while high alcohol users were defined as respondents who self-reported that they usually consumed three or more drinks per day when they drank alcohol.

Menopausal status As proposed by McKinlay [13], women were considered postmenopausal if they met at least one of the following conditions: (a) over 55 years of age, (b) had a hysterectomy, (c) had both ovaries removed, or (d) had no period in past 12 months and no pregnancy in the past 2 years. Postmenopausal women who reported cessation of menstrual periods before age 45 years were considered to have experienced early menopause.

Reduced vision Since visual acuity examinations were not performed, a self-report of being blind in at least one eye was taken as evidence of reduced vision.

Falling and poor health status These were defined as a self-report of falling ≥1 time in past year and self-reported poor health, respectively.

Low lifetime milk intake Milk intake was self-reported for selected life periods (childhood, adolescence, young adulthood, middle adulthood, and older adulthood for those ages 65+ years), and the frequency of consuming milk (times per day) during these periods was calculated. Low lifetime milk intake was defined as milk consumption ≤1 time per day for the majority of the applicable age periods (e.g., three of four periods for respondents <65 years of age and four of five periods for respondents age 65+ years).

Current and past long-term use of systemic glucocorticoids Respondents showed the containers for all current prescription medications to the interviewer, who recorded the name of the product and the reason and length of usage for each medicine. Medications were assigned the standard generic name and four-digit generic code using the Physicians' GenRx [14]. Drug class codes were assigned using the National Drug Code Directory [15] based on the medication's action and/or the health problem for which it was used. Unless drug class information indicated a topical or ocular form, the following drugs were considered to be systemic glucocorticoids in the present analysis: cortisone acetate, hydrocortisone, methylprednisolone, prednisolone, prednisolone acetate, prednisolone acetate and sodium phosphate, prednisone, and triamcinolone. Long-term use was defined as usage for 90 days or more. Past long-term use of systemic glucocorticoids was estimated using the simulation as described below.

Rheumatoid arthritis Depending on the age of the respondent, rheumatoid arthritis (RA) was defined differently:

(A) For respondents age 60 years and older, clinically diagnosed RA was defined as described by Rasch et al. [16] for use with NHANES III data: Subjects who met three of six of the American College of Rheumatology (ACR) 1987 criteria (self-reported morning stiffness in hands for more than 1 h, presence of three separate types of joint swelling as determined by a physician's examination, presence of rheumatoid nodules as determined by a physician's examination, or a positive serum rheumatoid factor test) were classified as having RA. Data on morning stiffness were collected via questionnaire, while data on joint swelling were collected by a physician in the mobile examination center. Serum rheumatoid factor antibody was measured using the Singer–Plotz latex agglutination test [9].

(B) For respondents age 50–59 years, an indirect approach was used since data to define clinically diagnosed RA were not collected for persons <60 years of age in NHANES III:

1. The expected prevalence of RA for age 50–59 by sex was predicted from a logistic regression equation obtained by regressing clinically diagnosed RA (above) on age for NHANES III respondents aged 60 and older. The expected prevalences for ages 50–59 obtained by this approach was 1.3%, which was similar to observed results from Rochester, MN in this age group [17].
2. To obtain a weighted prevalence of 1.3%, as calculated in step 1, 23 individuals, ages 50–59 years, were required to be defined as having clinically diagnosed RA. These respondents were selected from the pool of 82 respondents in the analytic sample who self-reported that a doctor had told them they had RA, as described below:

(a) All those with self-reported RA who were currently taking disease-modifying antirheumatic prescription medications (aranofin, gold sodium thiomalate, methotrexate sodium, azathioprine, penicillamine, sulfasalazine, chloroquine phosphate, hydroxychloroquine sulfate, or any prescription medication assigned an ICD-9-CM code of 714) or glucocorticoids (as defined above) were defined as having clinically diagnosed RA. Ten respondents met this criterion.

(b) The remaining 13 respondents were then selected randomly from the remaining sample who self-reported that a doctor had told them they had RA.

Other secondary causes These were not included because they do not affect FRAX® scores when BMD is in the algorithm.

Estimated 10-year absolute fracture risk

Risk scores were calculated for hip fracture and for major osteoporotic fractures combined (hip, spine, shoulder, or wrist fracture) using the FRAX® algorithm, version 06/05/09 [5]. The algorithm employs a Poisson regression model to estimate 10-year fracture probability on the basis of the following risk factors included in the present study: age, femoral neck BMD T-score, BMI, personal history of prior fragility fracture, RA, parental history of hip fracture, long-term use (≥3 months) of systemic corticosteroids, high alcohol intake (≥3 units), and cigarette smoking. These risk factors were identified from an analysis of nine large prospective population-based study cohorts from around the world, and the FRAX® model was validated in an additional 11 study cohorts [18]. Death is taken into account as a competing risk in the Poisson model. The

algorithm is designed to provide absolute risk estimates (%) by sex and race/ethnicity (white, black, Hispanic, Asian).

The 10-year probability of hip fracture and major osteoporotic fractures was estimated for the present study using the algorithm that employs hip fracture incidence and death rates for the US population [19]. FRAX® estimates were calculated for non-Hispanic whites and non-Hispanic blacks using the algorithm for "whites" and "blacks," respectively. "Other Hispanics" were combined with Mexican Americans and analyzed as "Hispanic" in the FRAX® algorithm; the remaining "other races" category was analyzed as Asian since internally available NHANES III records on ancestry revealed that 80% were Asian. Asians and Other Hispanics were handled in this manner when calculating FRAX scores in order to obtain the best estimates of absolute fracture risk for these individuals. When performing all subsequent data analyses, Asians and Other Hispanics were defined as "Other Races" in order to be consistent with sampling domains used in the NHANES III survey. In addition, the Asian sample itself was too small to permit statistically reliable estimates.

Data simulations

Measured data on key risk factors that were missing from NHANES III (lumbar spine T-score, ever use of glucocorticoids, fractures at other skeletal sites, and paternal history of hip fracture) were available in the WHO cohorts from North America and Europe used to develop the FRAX® model [18]. Thus, data from the WHO cohorts were used to identify appropriate regression equations needed to generate data for missing key risk factors in the NHANES III sample. In particular, linear (for BMD) or logistic regression (for dichotomous risk factors) was used to examine the conditional probability of the association of the risk factor to be simulated for NHANES with age, sex, BMI, femoral neck BMD, glucocorticoid use, rheumatoid arthritis, parental history of a fracture, previous fracture at a skeletal site other than hip, wrist or spine, current smoking, and alcohol intake. Specifically:

For BMD at the lumbar spine, T-score at the femoral neck, age, BMI, and previous fracture were significant covariates in both men and women.

Ever use of glucocorticoids comprised those currently taking glucocorticoids (as measured in NHANES III) and an estimate of past use in the remaining cohort by simulation. Previous fracture and smoking were significant covariates of past use.

For fractures at other skeletal sites, age, BMI, smoking, femoral neck BMD, and previous fracture at the hip, forearm, or spine were significant covariates in women (age, current smoking, and previous fracture at the hip, forearm, or spine in men).

For paternal history of hip fracture, age, BMI, and maternal history were significant covariates in women (and BMD and maternal history of hip fracture in men).

The equations identified in the logistic regressions for the dichotomous risk factors were then applied to the measured risk factor data in the NHANES III sample to predict the probability of having a positive value for the missing key risk factor for each respondent. Next, a random number was generated using a computer program, which was then compared with the predicted probability for that variable for that respondent. If the random number was less than or equal to the predicted probability, the respondent was assigned a positive value for the risk factor. If the random number was less than the predicted probability, the respondent was assigned a negative value for the risk factor.

The linear equation for the mean (M) T-score of the lumbar spine (dependent on age, femoral neck T-score, etc) was used to generate a T-score of the lumbar spine for each individual. A normally distributed random number (X) with a mean of 0 and a SD=1was simulated by a computer program. To calculate the simulated spine T-score, the following equation was used:

$$\text{Simulated spine T score} = X \times \text{Standard deviation} + M.$$

The standard deviation was set to 1.0881 for men and 1.0191 for women, based on measured spine BMD data from the WHO cohorts.

Analysis

We used sample weights when calculating point estimates in order to provide estimates that are representative of the civilian, non-institutionalized US population at the time the survey was conducted; the weights also account for oversampling and nonresponse in the survey. Persons with missing measured BMD, height, or weight or missing simulated spine T-scores were excluded from the analytic sample. Persons with missing data for other risk factors used in the study were assumed not to have the risk factor in order to be consistent with the approach used by the University of Sheffield in calculating FRAX® scores. To perform the analyses, we used SUDAAN [14], a family of statistical procedures for analysis of data from complex sample surveys. Prevalence estimates for persons aged 50 years and older were age-standardized to 2000 US Census population estimates. Logistic regression was used to test the differences in prevalence of treatment-eligible individuals under the new guide by age, sex, and race/ethnicity. A t test was used to test significance of the difference in prevalence of treatment eligibility by the new versus old NOF Guides in postmenopausal women, with a Bonferroni correction for multiple comparisons.

Table 1 Prevalence of individual risk factors used in the new NOF Guide in men and postmenopausal women aged 50 years and older from NHANES III, 1988–1994

Risk factor and race/ethnicity	Men		Women	
Age (year)	% or *n*	SE	% or *n*	SE
Sample size				
Age 50+				
Non-Hispanic white	1,715	–	1,754	–
Non-Hispanic black	642	–	656	–
Mexican American	619	–	521	–
Non-Hispanic white				
50–59	393	–	336	–
60–69	473	–	454	–
70–79	444	–	551	–
80+	405	–	413	–
Femur neck T-score −1.0 to −2.5 (osteopenia)				
Age 50+ (age adjusted)[a]				
Non-Hispanic white	34.9	1.4	51.4	2.0
Non-Hispanic black	20.4	1.9	35.8	2.3
Mexican American	26.6	2.4	47.0	3.3
Non-Hispanic white				
50–59	27.4	2.6	47.3	3.2
60–69	34.6	2.1	53.3	3.3
70–79	41.5	2.7	58.1	2.7
80+	49.1	3.6	46.8	2.3
Femur neck T-score ≤−2.5 (osteoporosis)				
Age 50+ (age adjusted)[a]				
Non-Hispanic white	4.6	0.7	18.8	1.2
Non-Hispanic black	2.6	0.7	6.2	1.3
Mexican American	2.3[b]	0.8 [b]	15.5	1.9
Non-Hispanic white				
50–59	–	–	8.0	2.0
60–69	3.5 [b]	1.1 [b]	15.8	2.0
70–79	6.4	1.5	28.5	1.9
80+	16.6	2.3	47.4	2.7
Simulated lumbar spine T-score −1.0 to −2.5 (osteopenia)				
Age 50+ (age adjusted)[a]				
Non-Hispanic white	22.9	1.5	35.5	1.8
Non-Hispanic black	17.3	1.6	23.1	1.6
Mexican American	17.6	1.9	33.9	2.9
Non-Hispanic white				
50–59	28.0	2.9	35.0	3.5
60–69	20.5	2.0	35.1	2.8
70–79	18.4	2.1	39.7	2.5
80+	21.6	1.9	31.2	2.1
Simulated lumbar spine T-score ≤−2.5 (osteoporosis)				
Age 50+ (age adjusted)[a]				
Non-Hispanic white	4.2	0.6	9.0	0.8
Non-Hispanic black	2.4	0.7	5.0	0.7
Mexican American	–	–	7.6	1.8
Non-Hispanic white				
50–59	4.0	1.0	9.3	1.8
60–69	5.4	1.0	9.2	1.5
70–79	2.7 [b]	1.0 [b]	7.0	1.1
80+	3.9	1.0	10.7	1.6
Previous fracture at any skeletal site after age 20 years				
Age 50+ (age adjusted)[a]				
Non-Hispanic white	35.3	1.7	35.2	1.3
Non-Hispanic black	36.7	2.3	31.8	1.7
Mexican American	37.6	2.1	36.7	3.5
Non-Hispanic white				
50–59	37.5	2.9	29.8	2.0
60–69	35.6	2.2	37.0	2.3
70–79	30.4	2.4	36.9	2.0
80+	36.2	2.9	44.9	2.7
Current smoking				
Age 50+ (age adjusted)[a]				
Non-Hispanic white	20.0	1.2	16.0	1.1
Non-Hispanic black	34.4	1.6	21.8	2.2
Mexican American	20.5	2.4	11. 7	1.7
Non-Hispanic white				
50–59	29.5	3.1	20.7	2.9
60–69	19.2	2.4	18.4	1.8
70–79	11.9	1.6	9.2	1.0
80+	4.5	1.0	4.4	1.1
Alcohol intake ≥3 drinks/day				
Age 50+ (age adjusted)[a]				
Non-Hispanic white	16.7	1.7	4.9	0.7
Non-Hispanic black	25.8	1.9	5.7	0.8
Mexican American	23.3	2.1	5.2	1.4
Non-Hispanic white				
50–59	25.5	3.7	7.1	1.5
60–69	14.5	2.2	5.9	1.3
70–79	11.0	1.7	1.3 [b]	0.5 [b]
80+	5.0	1.1	–	–
Parental history of hip fracture[d]				
Age 50+ (age adjusted)[a]				
Non-Hispanic white	10.6	0.9	11.1	0.9
Non-Hispanic black	3.4	0.8	3.0	0.8
Mexican American	3.9	0.8	6.3	1.3
Non-Hispanic white				
50–59	10.5	2.0	9.1	1.5
60–69	10.9	1.2	11.7	1.7
70–79	11.0	1.5	14.7	1.6
80+	9.8	1.1	9.6	1.6
Previous hip or spine fracture after age 20				
Age 50+ (age adjusted)[a]				

Table 1 (continued)

Risk factor and race/ethnicity	Men		Women	
Age (year)	% or *n*	SE	% or *n*	SE
Non-Hispanic white	3.5	0.5	3.9	0.5
Non-Hispanic black	2.1	0.6	1.1	0.3
Mexican American	6.1	1.6	2.7 [b]	0.8 [b]
Non-Hispanic white				
50–59	4.3	0.9	–	–
60–69	2.1 [b]	0.8 [b]	4.0	1.0
70–79	3.6	0.9	5.8	1.2
80+	5.1	0.9	7.9	1.2
Glucocorticoid use for ≥3 months[e]				
Age 50+ (age adjusted)[a]				
Non-Hispanic white	6.1	0.8	7.9	1.0
Non-Hispanic black	7.1	1.2	6.8	0.9
Mexican American	4.4	0.8	5.8	1.4
Non-Hispanic white				
50–59	5.3	1.2	8.2	2.1
60–69	6.3	1.6	8.2	1.2
70–79	6.1	1.3	5.8	1.3
80+	7.9	1.7	9.5	1.8
Rheumatoid arthritis				
Age 50+ (age adjusted)[a]				
Non-Hispanic white	1.5	0.4	2.1	0.5
Non-Hispanic black	1.0 [b]	0.5 [b]	1.8	0.5
Mexican American	–	–	2.3 [b]	0.7 [b]

[a] Age-standardized to the 2000 Census

[b] Estimates may be statistically unreliable, standard error/percent is 30–39%; – unreliable estimates, standard error/percent >40%

[c] Based on measured history of hip, wrist, or spine fracture after age 20 years and simulated history of fracture at other skeletal sites

[d] Based on measured maternal history of hip fracture and simulated paternal history of a hip fracture

[e] Based on measured current use of glucocorticoids for >90 days and simulated past use of glucocorticoids for >90 days

Results

The 6,117 participants in NHANES III who were aged 50 years and older and had data on BMD, height, weight, and simulated spine T-scores are included in this analysis. The prevalence of risk factors used in FRAX® and the new NOF Guide by sex and ethnic group and for non-Hispanic whites by age are shown in Table 1. The proportions of men and women with low bone mass (osteopenia) and osteoporosis of the femoral neck (measured in NHANES III) and spine (simulated data) are also shown in Table 1. The attenuated rise with age at the spine relative to the femoral neck is likely attributable to increasing artifacts in the anterior–posterior spine scan field (Table 1). The simulated data are indicated in the table; all other data were directly measured in NHANES III. Femoral neck osteopenia and previous fracture at any skeletal site were the most common risk factors overall, with age-adjusted prevalences >20% in both men and women in all three race/ethnic groups.

The proportions of men and women who would meet cost effectiveness thresholds for hip and major osteoporotic fractures in the new NOF guide are shown in Table 2, while Fig. 1 shows the adjusted odds ratios for treatment eligibility by sex, race/ethnicity, and age from multiple logistic regressions. As expected, the odds ratio for treatment eligibility based on fracture risk was higher in women than in men, rose markedly with age, and varied by race (Fig. 1) The odds ratio for treatment eligibility by the new guide was highest in non-Hispanic whites and intermediate in Mexican Americans when compared to

Table 2 Percent of men and postmenopausal women aged 50 years and older meeting 2008 NOF treatment thresholds by age, sex, and race/ethnicity from NHANES III 1988–1994

Race/ethnicity	Men			Women		
Age (year)	*n*	%	SE	*n*	%	SE
Non-Hispanic white						
50+ (age adjusted)[a]	1,715	21.8	0.8	1,754	40.5	1.3
50–59	393	10.7	1.4	336	18.4	2.6
60–69	473	16.0	1.7	454	33.0	2.1
70–79	444	30.9	1.9	551	67.9	2.4
80+	405	61.8	1.9	413	90.8	1.3
Non-Hispanic black						
50+ (age adjusted)[a]	642	7.3	1.3	656	12.1	1.0
50–59	195	7.2	1.9	205	7.2	1.5
60–69	253	3.2[b]	1.3[b]	254	7.6	1.8
70–79	147	11.5	3.1	143	11.1	2.2
80+	47	13.9[b]	5.0[b]	54	44.2	7.0
Mexican American						
50+ (age adjusted)[a]	619	12.7	1.7	521	24.9	2.7
50–59	155	9.5	2.3	106	12.9	3.0
60–69	294	8.5[b]	2.9[b]	276	15.2	2.8
70–79	123	14.2	4.2	101	38.7	8.2
80+	47	34.7	7.6	38	72.3	7.8
All races						
50+ (age adjusted)[a]	3,071	20.4	0.7	3,046	37.4	1.1
50–59	783	10.4	1.6	682	17.0	2.2
60–69	1,051	14.7	1.5	1,025	29.6	1.7
70–79	725	29.0	1.7	825	62.5	2.2
80+	512	57.1	2.1	514	87.5	1.5

[a] Age-standardized to the 2000 Census

[b] Estimates may be statistically unreliable, standard error/percent is 30–39%

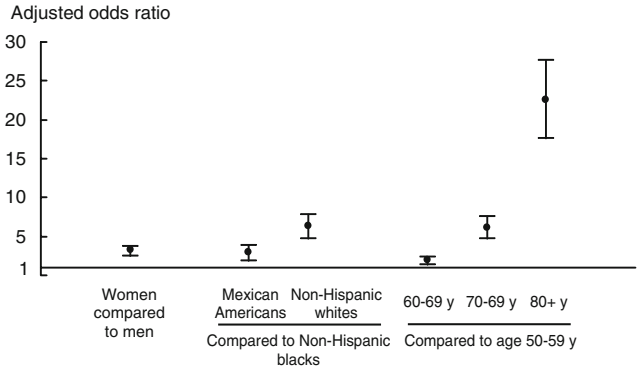

Fig. 1 Adjusted odds ratio (OR) for treatment eligibility under the new NOF guide by age, sex, and race/ethnicity. ORs for each demographic characteristic have been adjusted for the other characteristics shown in the figure

non-Hispanic blacks. This is reflected by the proportion of women and men, respectively, who were eligible for treatment: 41% and 22% among non-Hispanic whites, 25% and 13% among Mexican Americans, and 12% and 7% among non-Hispanic blacks (Table 2).

In participants with low bone mass (osteopenia) at the spine or hip but no prior spine or hip fracture (i.e., the group in whom treatment eligibility is dependent solely upon the FRAX® risk scores), 19% qualified for treatment on the basis of hip fracture probability alone, while 7% qualified on the basis of both hip and major fracture probability; only 2% qualified on the basis of major fracture probability alone. The corresponding age-adjusted proportions are shown for men and women by race (Fig. 2a); for non-Hispanic whites, the proportions are also shown by age category (Fig. 2b). Hip fracture risk (either alone or in combination with major fracture) was the predominant determinant of eligibility. The group in the "major fracture only" pool is small, is limited to non-Hispanic whites, and of these, mainly to women age 50–69 years.

The prevalence of the individual risk factors in the subset of 1,763 women with available data relevant to the old NOF Guide is shown in Table 3. Simulated data are designated in the table. The most prevalent risk factors in the old guide were menopause before age 45, low lifetime intake of milk, and a previous fracture after age 20 years.

The age-adjusted proportions of non-Hispanic white postmenopausal women meeting the treatment criteria by the old and new guides are shown in Table 4 and Fig. 3. Overall, 53% of women would meet the cost-effectiveness threshold by the old guide, whereas 41% meet criteria set forth in the new guide; this represents a significant decline ($P<0.05$). Among women with osteopenia (excluding those with a prior hip or spine fracture or osteoporosis at either site), 55% would be eligible by the old guide compared to 30% by the new guide. The age distribution of those eligible for treatment differed for the two guides, as shown in Table 4 and Fig. 3. Relative to the old guide, fewer younger women and more older women qualify for treatment by the new guide.

Discussion

One fifth of the men and 37% of the women aged 50 years and older in the USA are potential candidates for pharmacotherapy to prevent fractures according to the new NOF Clinician's Guide [4]. This, of course, does not mean that all can or should be treated, since the acceptance of therapy is based on shared decision-making between patient and physician [20] and is affected by many factors including patient preferences [21]. In actual practice, a

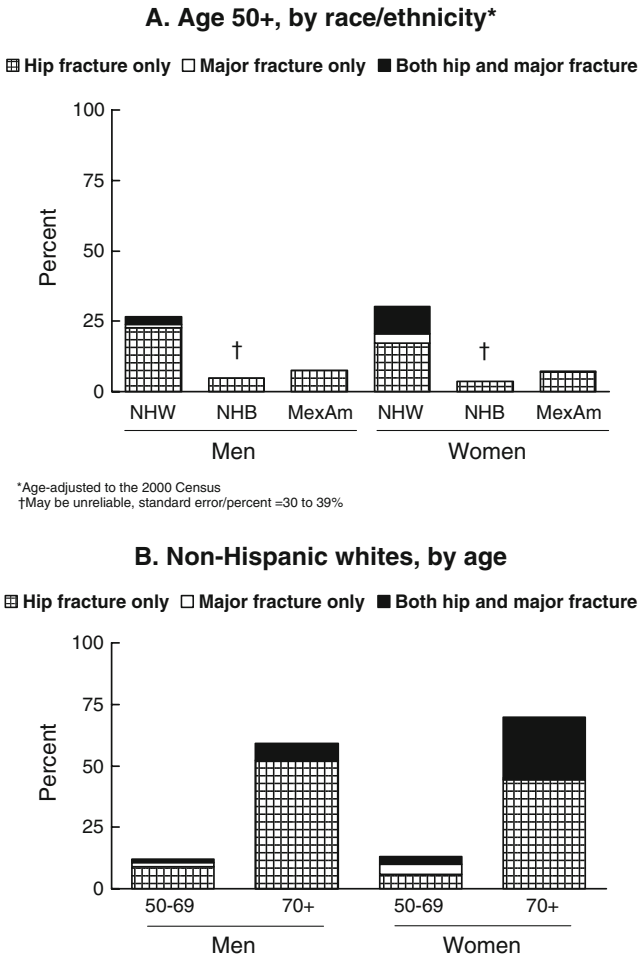

Fig. 2 **a** Percent of men and postmenopausal women aged 50 years or more with osteopenia and no prior spine or hip fracture who are candidates for treatment under the new NOF guide by hip fracture risk score only (*hatched bars*), by major osteoporotic fracture risk score (*open bars*), and by either hip or major fracture risk score (*black bars*), by race (non-Hispanic white [*NHW*], non-Hispanic black [*NHB*], and Mexican American [*MexAm*]). (**b**) The same data for non-Hispanic white men and women, by age categories

Table 3 Prevalence of individual risk factors in the old NOF Guide in non-Hispanic white postmenopausal women ages 50+ years from NHANES III, 1988–1994

Risk factor and age	Number	Percent	SE
Reduced vision[a]			
50+ (age adjusted)[b]	1,754	1.4	0.3
50–59	336	–	–
60–69	454	–	–
70–79	551	—	–
80+	413	3.8	0.99
Fell ≥1 time in past year			
60+ (age adjusted)[b]	1,418	24.6	1.2
60–69	454	20.6	2
70–79	551	26.6	2.3
80+	413	29.8	2
Poor self-rated health			
50+ (age adjusted)[b]	1,754	4.1	0.6
50–59	336	–	–
60–69	454	4.2	1.1
70–79	551	7.1	1.2
80+	413	5.2	1.4
Body weight <127 lb			
50+ (age adjusted)[b]	1,754	21.4	1
50–59	336	14.6	2.1
60–69	454	20.9	1.8
70–79	551	26	2.7
80+	413	37.5	3
Low lifetime milk intake			
50+ (age adjusted)[b]	1,754	38.4	1.4
50–59	336	44.6	2.6
60–69	454	37.5	2.6
70–79	551	31.8	2
80+	413	32.2	3.2
Menopause <age 45 years			
50+ (age adjusted)[b]	1,754	34.6	1.7
50–59	336	41.1	3.1
60–69	454	32.3	2.6
70–79	551	31.2	2.7
80+	413	26.7	2.1
Alcohol intake ≥3 drinks/day			
50+ (age adjusted)[b]	1,754	4.9	0.7
50–59	336	7.1	1.5
60–69	454	5.9	1.3
70–79	551	1.3[c]	0.5[c]
80+	413	–	–
Parental history of hip fracture[d]			
50+ (age adjusted)[b]	1,754	11.1	0.9
50–59	336	9.1	1.5
60–69	454	11.7	1.7
70–79	551	14.7	1.6
80+	413	9.6	1.6
Previous fracture[e]			
50+ (age adjusted)[b]	1,754	35.2	1.3
50–59	336	29.8	2.0
60–69	454	37.0	2.3
70–79	551	36.9	2.0
80+	413	44.9	2.7
Currently smoke			
50+ (age adjusted)[b]	1,754	16.0	1.1
50–59	336	20.7	2.9
60–69	454	18.4	1.8
70–79	551	9.3	1.0
80+	413	4.4	1.1

[a] Blind in at least one eye

[b] Age-standardized to the 2000 Census; – unreliable estimate, standard error/percent >40%

[c] Estimates may be statistically unreliable, standard error/percent is 30–39%

[d] Based on measured maternal history of hip fracture and simulated paternal history of hip fracture

[e] Based on measured history of hip, wrist, or spine fracture after age 20 years and simulated history of fracture at other skeletal sites

Table 4 Percent of postmenopausal non-Hispanic white women aged 50 years and older who are candidates for pharmacotherapy under the old and new NOF Guidelines from NHANES III, 1988–1994

Age (year)	Number	Old guide		New guide	
		%	SE	%	SE
All NHW women					
50+ (age adjusted)[a]	1,754	52.7	1.7	40.5*	1.3
50–59	336	36.1	3.4	18.3*	2.6
60–69	454	51.0	2.5	33.0*	2.1
70–79	551	70.1	2.4	67.9	2.4
80+	413	83.4	1.7	90.8	1.3
NHW women with femur neck or lumbar spine osteopenia[b]					
50+ (age adjusted)[a]	876	55.3	2.5	30.3*	1.2
50–59	171	42.4	4.4	6.3*	1.9
60–69	231	56.6	3.7	18.8*	2.4
70–79	307	66.5	3.5	62.4	3.4
80+	167	74.6	4.0	91.3	2.6

*$P<0.05$

[a] Age standardized to the 2000 Census

[b] Excluding women with previous hip or spine fracture or who have osteoporosis at the femur neck or lumbar spine

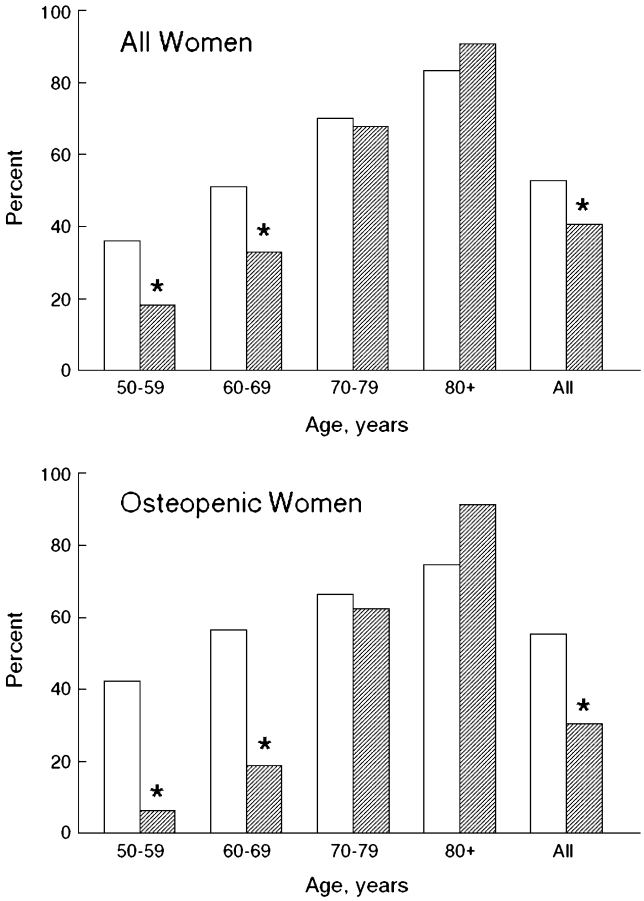

Fig. 3 Percent of postmenopausal non-Hispanic white women aged 50 years or more, by age category and overall, who are candidates for treatment under the old (*open bars*) and new (*hatched bars*) NOF guidelines in 1,754 women (*upper panel*) and in the subset of 882 women with osteopenia and no prior spine or hip fracture (*lower panel*). The total, "*All*" bars are age-adjusted to the 2000 Census

much smaller proportion of the population is evaluated for osteoporosis [22]. Moreover, the estimated proportions meeting treatment thresholds, while large, are far lower than those for a similar chronic disease, hypertension: Among adults who are normotensive at age 55 years and who survive to the age of at least 80 years, the residual lifetime risk of becoming hypertensive is 86% for women and 81% for men [23]. These hypertension figures, like the fracture risk estimates used in FRAX®, have been adjusted for competing mortality.

When compared with the old NOF Guide, the proportion of postmenopausal US white women who are eligible for treatment by the new guide has declined significantly. The magnitude of the decline was 12.2 percentage units, which corresponds to a 23% decline in the group as a whole. Among women with osteopenia of the spine or hip and no prior spine or hip fracture, a group in whom eligibility is determined by their FRAX® scores, the magnitude of the decline was even greater, 25 percentage units or 45%. Moreover, the demographic profile of the women eligible for treatment by the new guide has shifted from a younger to an older age group. The shift in eligibility is most marked in women with osteopenia and no prior hip or spine fracture. In this group, eligibility declines from 42% to 6% for women in their 50s but increases from 75% to 91% for women aged 80 and older. Eligibility in white women age 65 and older in the Study of Osteoporotic Fractures, based on an earlier version of FRAX®, was found to be 72% [24]. With large proportions of older white women being eligible for treatment, by both the old and new guides, it remains a priority to know the extent to which treatment lowers fracture risk in this segment of the population.

Recent studies reveal that the overall proportion of postmenopausal women actually being treated is much lower than the proportion that is eligible by either the old or the new guide. For example, in a Medicare health maintenance organization (HMO) in the Boston area in 2002, bone medication use was <20% in women in all age groups [25]. In the Pennsylvania Medicaid population, age 50 and older, Lee et al. [26] found that the overall prevalence of anti-osteoporosis medication use was under 15% in December 2002. Further examination of these data revealed that the prevalence of anti-osteoporosis medication use was highest among women in their 50s and declined with each succeeding decade [26]. Some degree of under-treatment is to be expected among older women due to over-riding circumstances related to intercurrent illnesses, intolerance to medication, reduced life expectancy, etc [27, 28]. Nonetheless, there do appear to be important gaps in the appropriate use of such therapy in this age group [29]. Conversely, the study by Lee et al. [26] provides some evidence that, by the new NOF Guide criteria, younger postmenopausal women may be over-treated. The proportion of young postmenopausal women treated at the time of the Lee study was, however, still less than recommended by the old NOF Guide.

These analyses also highlight the magnitude of the osteoporosis problem in men. Among non-Hispanic white men, for example, 16% of those in their 60s, almost one third of those in their 70s, and over 60% of those aged 80 and older meet the treatment thresholds. However, prescribing patterns clearly indicate that older men are under-treated for osteoporosis. In a largely Caucasian (>98%) Medicare HMO population surveyed in 2002, only 2% of the men reported taking a prescription medication for osteoporosis [25]. Among men with a hip fracture (all of whom would qualify for treatment), use of prescription drugs has increased since 1995, but it remains low, with less than one third receiving therapy in the 6- to 12-month period after the fracture [30, 31].

This analysis provides estimates of the prevalence of specific risk factors for fracture by age, race, and sex in a

population-based sample in the USA. Use of a population-based sample large enough to analyze the impact of the new NOF Guide in different age segments for men and women is a major strength, as is the inclusion of multiple race groups. However, NHANES does not sample the institutionalized population and therefore misses an important group of at-risk individuals. Nonresponse bias may also be present in the estimates. Nonresponse bias due to refusal to participate in the interview or physical examinations in NHANES is reduced by a nonresponse adjustment factor included in the calculation of the sample weights for use with examinee data. However, about 15% of the NHANES III respondents age 50 years and older who came to the exam centers were excluded from the analytic sample due to missing data, and this nonresponse is not addressed by the sample weight adjustments. Another limitation is that some of the risk factor information needed was not present in NHANES III and had to be simulated. Finally, the NHANES III dataset is now 14 years old, and there may be secular changes in some of the risk factors. For instance, body mass index has been rising in the USA [32], and serum 25OHD levels have fallen slightly in men [33]. Nonetheless, these data may provide guidance in the development of targeted programs to reduce fractures and also in the assessment of the impact of life style intervention efforts on fracture risk.

In conclusion, this analysis of the US population in NHANES III describes the prevalence of risk factors used in the FRAX®-based NOF Guide to the prevention and treatment of osteoporosis. One fifth of the men and 37% of the women age 50 and older in the USA are at sufficient risk of fracture to warrant consideration for pharmacotherapy to lower their fracture risk according to the NOF Guide. However, fewer postmenopausal non-Hispanic white women are eligible for treatment by the new guide than by the previous NOF Guide.

Conflicts of interest None.

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