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Contemporary Clinical Trials 26 (2005) 569–585

Contemporary Clinical Trials

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Design and baseline characteristics of the osteoporotic fractures in men (MrOS) study — A large observational study of the determinants of fracture in older men

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Received 17 September 2004; accepted 25 May 2005

Abstract

Very little information is available to direct the prevention or management of osteoporosis in men. The Osteoporotic Fractures in Men (MrOS) Study is a prospective cohort study designed to examine the extent to which fracture risk is related to bone mass, bone geometry, lifestyle, anthropometric and neuromuscular measures, and fall propensity, as well as to determine how fractures affect quality of life in men. The study is also designed to understand how osteoporosis is related to prostate disease.

At baseline, participants completed questionnaires regarding medical history, medications, physical activity, diet, alcohol intake, and cigarette smoking. Objective measures of anthropometric, neuromuscular, vision, strength, and cognitive variables were obtained. Skeletal assessments included DEXA, calcaneal ultrasound, and vertebral

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1551-7144/$ - see front matter
doi:10.1016/j.cct.2005.05.006

radiographs. Vertebral and proximal femoral QCT was performed on a subset (65%). Serum, urine, and DNA specimens were collected. After the baseline assessments, a questionnaire is mailed to participants every 4 months to ascertain incident falls, fractures, prostate cancer, and deaths. After an average of 4.5 years, participants are scheduled to return for a second comprehensive visit.

Men were eligible if ≥65 years. 5995 men enrolled with a mean (±SD) age of 73.7 (±5.9) years, 11% of which were minorities. Most rated their health as good/excellent. Few were current smokers, although 59% had smoked previously, and 35% reported no alcohol intake, while 47% consumed at least 2 drinks per week. The mean (range) body mass index was 26.9 kg/m^2 (17–56). A non-traumatic fracture after age 50 was reported by 17% of the cohort.

The MrOS cohort should provide valuable information concerning the determinants of fracture in men and should help set the stage for the development of effective methods to identify those at risk.

Keywords: Osteoporosis; Fractures; Men; Epidemiology

1. Introduction

Although osteoporosis is most commonly associated with postmenopausal women, fractures in men are also an enormous public heath problem. It was recently estimated that the care of fractures in men represents 20% of the annual economic burden of osteoporosis in the US (almost $14 billion) [1]. Bone mass measurements performed in NHANES III suggested that 1–2 million US men over the age of 50 have osteoporosis, and 8–13 million have osteopenia (low bone mass) [2]. The prevalence of the disease has major implications for older men. For instance, an observational study in the community of Dubbo, Australia found the lifetime risk of low trauma fracture in 60-year-old men to be 25.6% [3]. The majority of this risk comes after age 65, when vertebral and hip fracture rates begin an exponential increase in both men and women [4]. The number of fractures in US men is expected to double in the next 25 years, largely as a result of the increasing size of the elderly population [5]. The numbers of older men are projected to grow proportionately more than that of women. By the year 2050 there will be nearly five times as many people in the US over 85 as there were in 1980 [6,7]. The prevalence of osteoporosis associated with these demographic trends make the need to understand the risk factors for osteoporotic fractures in men an urgent national priority.

Despite the magnitude of the problem posed by fractures in men, there remains an impressive lack of information concerning male osteoporosis. Moreover, the current appreciation of osteoporosis is predicated on the character of the disease in women. Because of the current dearth of information, guidelines for the detection or care of osteoporosis in men are not evidence based. Trials designed to examine the effectiveness of drug therapies in men with established osteoporosis have been performed, but do little to enlighten us about the basis for disease. Especially lacking are prospective, longitudinal studies of the determinants of fracture risk in men. Without these data, it is difficult to design rational clinical and public health approaches for the diagnosis, evaluation, and prevention of osteoporosis in men. For instance, is the relationship between bone mass and fracture in men distinct from that in women? What lifestyle/medical variables are associated with fracture risk in men? Is the current interest in sex steroid action on the skeleton justified by their actual relationship to fracture risk? To what extent do fractures affect quality of life in men? In light of the known sex differences in skeletal physiology and fracture epidemiology it is clear that there is a need for male-specific data.

The Osteoporotic Fractures in Men (MrOS) Study is designed to address these questions and to provide comprehensive information concerning a host of putative risk factors for fracture in older men. It will provide a necessary foundation for the formulation of clinical algorithms for the identification of men at risk for fractures, and valuable information for the development of policies for osteoporosis detection and prevention in men. Finally, whereas the immediate goal is to establish a representative population of older men principally for the study of skeletal health, the founding of the cohort will also allow later studies to expand into related areas of investigation, and knowledge gained from the MrOS Study should have major implications for the understanding and management of several additional common problems of aging. Here we describe the goals of the MrOS study, the essential elements of its design, and the initial findings from the baseline clinical visit.

2. Study design and methods

2.1. General

MrOS is a multi-center prospective, longitudinal, observational study of risk factors for vertebral and all non-vertebral fractures in older men, and of the sequelae of fractures in men. The specific aims of the study include: (1) to define the skeletal determinants of fracture risk in older men, (2) to define lifestyle and medical factors related to fracture risk, (3) to establish the contribution of fall frequency to fracture risk in older men, (4) to determine to what extent androgen and estrogen concentrations influence fracture risk, (5) to examine the effects of fractures on quality of life, (6) to identify sex differences in the predictors and outcomes of fracture, (7) to collect and store serum, urine and DNA for future analyses as directed by emerging evidence in the fields of aging and skeletal health, and (8) define the extent to which bone mass/fracture risk and prostate diseases are linked.

Approval of the conduct of the MrOS study was obtained from the institutional review boards of the participating clinics and written informed consent was obtained from all study participants.

2.2. Study administration

MrOS is supported as a cooperative agreement (UO-1) by the National Institute of Arthritis, Musculoskeletal and Skin Disorders (NIAMS), the National Institute of Aging (NIA) and the National Cancer Institute (NCI). Its administrative structure is similar to that of other large, collaborative multi-center observational studies and clinical trials.

The primary administrative components of MrOS include the Administrative Center (Oregon Health and Science University), the Data Coordinating Center (University of California, San Francisco and California Pacific Medical Center Research Institute), and the six clinical sites in the United States [Birmingham, AL (University of Alabama at Birmingham); Minneapolis, MN (University of Minnesota); Palo Alto, CA (Stanford University); Pittsburgh, PA (University of Pittsburgh); Portland, OR (Oregon Health and Science University); San Diego, CA (University of California, San Diego)]. An additional administrative component is the MrOS Steering Committee, composed of principal investigators from the clinical sites, investigators at the Administrative and Coordinating Centers, other key investigators and representatives from NIAMS and NIA.

Overall scientific and study direction is provided by the study's Principal Investigator who acts as chair of the MrOS Steering Committee. In conjunction with the MrOS Steering Committee, the Administrative Center provides direction, sets scientific goals, and coordinates communication among clinical centers. The Data Coordinating Center provides study coordination, protocol development and the direction of data collection and collation. The Steering Committee is responsible for the primary oversight of the study and a subcommittee structure considers issues of publications, ancillary studies, specific research directions, and international collaborations.

2.3. Study population

The MrOS study population consists of community dwelling, ambulatory men aged 65 years or older. Inclusion criteria were designed to provide a study cohort that is representative of the broad population of older men. The inclusion criteria were: (1) ability to walk without the assistance of another, (2) absence of bilateral hip replacements, (3) ability to provide self-reported data, (4) residence near a clinical site for the duration of the study, (5) absence of a medical condition that (in the judgment of the investigator) would result in imminent death, and (6) ability to understand and sign an informed consent. To qualify as an enrollee, the participant had to provide written informed consent, complete the self-administered questionnaire (SAQ), attend the clinic visit, and complete at least the anthropometric, DEXA, and vertebral X-ray procedures. There were no other exclusion criteria.

The strategy for participant recruitment was intended to result in the enrollment of a population of men relatively representative of the communities involved. The effort was planned and coordinated by the Steering Committee, and relied primarily on the mailing of invitations to men living in the communities surrounding the clinical sites. For instance, men ≥ 65 years who resided in the 6 communities were identified from voter registrations, motor vehicle registrations, and HICFA listings, and received invitations to participate. Although most participants were enrolled as a result of these community-based mailings, the recruitment efforts were supplemented at some sites with community and senior newspaper advertisements, and presentations to community groups. Moreover, each of the 6 participating sites designed and customized these local strategies to enhance the recruitment of minority groups. Each clinical site had a recruitment goal of 950 men. Details of the MrOS recruitment strategies are published in the accompanying article [8].

2.4. Study events and timeline

The study enrolled participants and completed the initial baseline examination over a 25-month period from 3/2000 through 4/2002. A second comprehensive clinic visit is scheduled for 2005 after an average follow-up period of 4.5 years. At that time, most of the baseline measures will be repeated. During the intervening period, participants complete a Tri-Annual Questionnaire every four months that obtains information concerning the occurrence of incident falls and fractures, back pain and the occurrence of incident prostrate cancer and prostate biopsies. At the midpoint of the study (7/2002 to 12/2003) after 2–2.5 years of follow-up, each participant completed a more extensive mailed questionnaire designed to update much of the information obtained at baseline.

2.5. Measures

Information from study participants was obtained through several different means including a self-administered questionnaire, interviewer-administered questionnaire, and clinic examination. Numerous baseline assessments were made in order to have a comprehensive set of variables from study participants to relate to osteoporotic fractures risk in men or to the sequelae of fracture. The sections below describe these measurements in detail. A more comprehensive list of the individual measures obtained at baseline are provided in Appendix Table 1. The schedule of data collection throughout the study period is shown in Appendix Table 2.

2.5.1. Skeletal measures

To examine the association between fracture risk and skeletal parameters, bone mineral density (BMD) was measured at the total body, lumbar spine, and proximal femur using dual energy X-ray absorptiometry (DEXA) at baseline; with repeat measures scheduled for the second clinic visit. Due to resource restrictions and limitations on available participant time, radial BMD measures were not obtained. The total body BMD measurement should be a reasonable reflection of cortical bone density. Each U.S. clinical site used DEXA machines of the same model and manufacturer (QDR 4500, Hologic, Inc, Waltham, MA, USA). Quality assurance measures were incorporated into the DEXA protocols to optimize longitudinal measurement precision and comparability between DEXA machines at the six clinical sites. Central training of all DEXA technicians occurred before study measurements began. At each clinical site, phantoms were scanned daily to monitor machine performance. In addition, single sets of phantoms were scanned on all machines before the baseline visits to provide the cross-calibration data necessary for multi-site data analyses. The three cross-calibration phantoms used were the Hologic spine, hip, and linearity phantoms. A central quality control lab and standardized procedures for scanning were used to insure reproducibility of measurements. Spine and hip phantom scan results were assessed for longitudinal and cross-sectional quality control. The intra-clinic coefficients of variation (CV) for spine phantoms (0.34% to 0.42%) and hip phantoms (0.37% to 0.58%) were within acceptable limits. The inter-clinic CVs were 0.6% (spine) and 0.9% (hip), and the maximum difference between means was 1.4% (spine) and 2.2% (hip). To adjust for inter-clinic differences, statistical models included indicator variables for the individual scanners.

At baseline, BMD of the calcaneus was measured by ultrasound using machines of the same make and manufacturer (Hologic Sahara, Waltham MA, USA). Central training of ultrasound technicians occurred before the study began and two ultrasound calibration phantoms (one of normal density and one of low density) were circulated to all the clinical sites before the baseline visit for repeated measures on the ultrasound instruments.

Cross-calibration procedures will be repeated before the second visit when DEXA and ultrasound measures will again be obtained on all participants.

Quantitative computed tomography (QCT) scans were obtained at baseline to measure BMD of the lumbar vertebrae (L1, L2) and proximal femur along with parameters of skeletal geometry. In addition, a scan series through the L4 vertebral body was obtained to allow assessments of the abdominal aorta and abdominal body composition. On-site training of the radiological technicians occurred at all sites before study onset. To ensure consistency in this multicenter study, a single set of anthropomorphic spine and hip phantoms were scanned on all CT scanners at the beginning of the baseline visit and again halfway through the baseline visit. This provided inter-site standardization of

densitometric and geometric measures. Because of cost, QCT measures were obtained on only the first 65% of the cohort enrolled. In addition, QCT scans were obtained on all minority participants. Other than the minority make-up, the characteristics of the men who had CT scans were not different than those of the entire cohort.

2.5.2. Lifestyle, medical, and nutritional factors

To examine the association between fracture risk and lifestyle and medical characteristics, numerous aspects of personal and medical history were assessed at baseline. Information obtained by self-administered questionnaire included level of education and marital status, medical history, medications, prostate disease, diet history, physical activity, fall and fracture history (the specific circumstances of previous falls or fractures were not obtained), family history of fractures, back and joint health, plus tobacco use and alcohol consumption. Participants brought current prescription medications to the baseline clinic visit where study staff recorded the name and dose of all medications. Physical activity was quantified using the Physical Activity Scale for the Elderly (PASE) [9]. Additional physical activity measures addressed walking for exercise, time spent sitting or laying down, and volunteer or paid work. Aspects of usual diet in the past 12 months were assessed from a modified food frequency questionnaire developed specifically for MrOS by Block Dietary Data Systems while alcohol intake was assessed with specific questionnaire based inquiries, including the CAGE Questionnaire [10]. Several questions concerning back pain were included to examine the relationship of symptoms to vertebral fractures. Lower urinary tract symptoms were quantified using the American Urologic Association Symptom Index for Benign Prostatic Hyperplasia [11] at baseline, and in the mid-study questionnaire. It will also be obtained as part of the second clinic visit.

Additional information on alcohol intake, physical activity, and social and economic status was obtained using an interviewer-administered questionnaire. Alcohol intake was quantified in terms of usual drinks per day. The MacArthur Subjective Status Scale was used to obtain information on perceived social and economic status [12].

2.5.3. Functional status and quality of life

To measure functional status and quality of life, we adapted items from several instruments, including a quality of life questionnaire used in the Study of Osteoporotic Fractures (SOF), the Medical Outcomes Study 12-Item Short Form (SF-12) [13], and the EuroQOL (EQ-5D) Questionnaire [14].

2.5.4. Physical and anthropometric measures

Information was obtained concerning current body weight, weight at age 25, change in weight since age 25, height, and body composition. All measures, with the exception of self-reported weight at age 25, were taken at baseline by an examiner using standard equipment, including a Harpenden stadiometer and balance beam scale. Body composition, including total fat and lean body mass, was measured using DEXA. QCT scans were obtained at the level of L4 to assess abdominal body composition. Additional physical measures included pulse and seated blood pressure obtained at both the arm and ankle.

2.5.5. Visual and neuromuscular function

At baseline, visual acuity (Bailey–Lovie Chart) [15], contrast sensitivity [16] (Vision Contrast Test System, Vistech Consultants Incorporation, Dayton OH, USA), and depth perception [17] (Frisby Stereo

Test, Richmond Products, Boca Raton FL) were assessed. Grip strength (both hands using a Jamar handheld dynamometer) [18] and lower extremity power (Nottingham Power Rig) [19,20] were used to assess muscle function in the extremities. Walking speed was determined by timing completion of a 6-m course performed at the participant's usual walking speed. The time to complete a tandem-walking course of 6 m × 20 cm was used to determine balance. Participants' ability to rise from a chair without using their arms along with their ability to complete five chair stands and the time required to complete the task were determined.

2.5.6. Cognition

To quantify cognitive function, participants completed both the Modified Mini-Mental Status (3MS) Examination [21] and Part B of the Trail Making Test [22].

2.5.7. Biochemical measures

Morning phlebotomy (most subjects were fasting) was performed at the baseline visit to obtain serum, plasma, and whole blood specimens. Second-voided morning urine was also obtained from each participant at the baseline visit. Blood and urine specimens were processed and stored (− 120 °C). DNA extraction is planned from stored whole blood specimens. In addition, whole blood was spotted on to paper blotters for DNA.

2.6. Adherence and retention

Retention of participants in the study is obviously important. In addition to the quarterly postcards and telephone follow-ups, other simple approaches are used to increase subject identification with the study including:

- Regular promotion and media stories that provide subjects with a sense of the study's importance
- Birthday and winter holiday greeting cards mailed to participants
- An annual study newsletter to keep participants informed about progress of the study and related medical updates. The newsletter also provides general information of interest to an older male population.

2.7. Incident event surveillance

Study participants receive a one-page Tri-Annual Questionnaire every four months. This instrument is used to update contact information and to ascertain the incidence of falls and fractures and back pain. Once per year, the questionnaire includes questions about recent prostate biopsies and newly diagnosed prostate cancers.

2.7.1. Non-vertebral and symptomatic vertebral fractures

If a participant reports a fracture, study staff conducts a follow-up telephone interview to determine the date and time the fracture occurred, a description of how the fracture occurred, the type of trauma that resulted in the fracture, the participant's location and activities at the time of the fracture, symptoms just before or coincident with the fracture, and source of medical care for the fracture. All reported fractures are verified by a physician adjudicator through medical records obtained from the participant's

physician. The Clinical Outcomes Committee adjudicates any uncertainties regarding the presence of a fracture.

2.7.2. Vertebral fractures

Lateral lumbar and thoracic radiographs were obtained at baseline and will be repeated at the second clinic visit. Morphometry, and semi-quantitative analyses by an experienced radiologist will be performed at a central site to ascertain both prevalent and incident vertebral fractures. Quality control procedures will be utilized to ensure consistency for each of these assessments.

Because incident vertebral fractures are one of the primary endpoints of the study, special effort is made to obtain X-rays on all surviving participants. For those participants who have moved out of the MrOS service area, X-rays will be obtained from their primary health care provider.

2.7.3. Prostate cancer/prostate symptoms

Once each year, the Tri-Annual Questionnaire requests information concerning recent prostate biopsies and newly diagnosed prostate cancers. Characteristics of the tumor (stage and grade) and type of treatment are obtained from medical records. The information concerning the diagnosis of prostate cancer is centrally reviewed and adjudicated.

2.7.4. Deaths

Vital status and cause of death during the study are verified through state death certificates.

2.7.5. Participant safety

The safety of participants was of paramount importance. Meticulous attention was paid to ensure a safe experience for men during clinic visits, and in the process of any study procedure. Although most data and specimens were collated for later analysis, participants were provided with the results of any available measurements that were classified as abnormal. Specifically, men who had BMD measures that were unequivocally low (Z score less than -2.5, using male reference ranges from the DXA manufacturer) received a letter with those results and a suggestion that they consult their physician. Similarly, as the QCT scans were being collated, any potential abnormality that was incidentally noted was reviewed by a radiologist. If considered worth further clinical evaluation, the patient was notified and copies of the scan were provided to his physician. Serum and urine specimens were stored for future study, and no analysis results were available. In other ways, participants received their usual medical care after enrollment. Incident events noted during the study (e.g. fractures) did not prompt specific intervention from MrOS staff.

3. Results

3.1. Recruitment results

Recruitment began in January 2000 and the first clinic visit occurred in March 2000. Baseline visits were completed over a 25-month period with the last visit in April 2002. Recruitment goals were based on the demographics of the populations in the geographical areas of the clinical centers. A total of 5995 men completed the baseline measurements required for study enrollment, 5% more than the original

Table 1
Selected characteristics of MrOS participants at enrollment

Variable	Mean	Standard deviation
Height (cm)	174.1	6.8
Weight (kg)	83.2	13.3
BMI	27.4	3.9
Total calcium intake (mg/day)	1138.5	591.0
Dietary protein intake (g/day)	64.5	27.0
Walking pace (m/s)	1.25	0.23
Physical activity (PASE score)*	146.5	68.3

Variable	Number	Percent
Age (years)		
65–69	1769	30
70–74	1708	29
75–79	1447	24
≥80	1071	18
Race/ethnicity		
White non-Hispanic	5362	89
African American	244	4
Asian	191	3
Hispanic	127	2
Other	71	1
Self reported health		
Excellent	1769	34
Good	1708	52
Fair	760	13
Poor/very poor	97	2
Education		
Less than High School	393	7
High School/some college	2413	40
College/some graduate school	1727	29
Completed graduate school	1462	24
Cigarette smoking		
Current	206	3
Past	3539	59
Never	2249	38
Alcohol consumption		
0 drinks/week	2122	35
>0 to <2 drinks/week	1072	18
2 or more drinks/week	2794	47
Fall in last year	1268	21
History of fracture after 50 (yes)	1019	17
History of fracture in a parent		
Yes	1990	33
No	1717	29
Don't know	2288	38
Prostate symptom score		
None	141	2
Mild	3096	52
Moderate	2356	39
Severe	398	7

recruitment goal of 5700. An effort to over recruit men of older ages resulted in a greater number recruited than anticipated in the higher age ranges (age 65–69 years —89% of anticipated, 70–74 years —100%, 75–79 years —106%, ≥80 years —172%).

The goal of the MrOS Study was to recruit 285 men from ethnic and racial minority groups (5% of the cohort). Minority recruitment exceeded expectations, with 633 participants (11% of the cohort) reporting being a member of a racial/ethnic minority group (Table 1). Minority participation was similar in all age ranges (age 65–69 years —14%, 70–74 years —10%, 75–79 years —11%, ≥80 years —5%).

3.2. Participant characteristics

Selected characteristics of the study population are presented in Table 1. The average age was approximately 74 years. There are few current smokers but many previous smokers, and most participants ingest some alcohol. Seventeen percent reported a fracture after age 50 years, and one third recalled that a parent had suffered a fracture. The skeletal characteristics of the MrOS cohort are similar to those of the NHANES III cohort (Table 2), although the MrOS participants are slightly heavier and have slightly higher BMD than NHANES III participants of similar age.

Table 2
Mean unadjusted hip BMD measures by age among non-Hispanic white MrOS and NHANES III participants*

Region	*N*	MrOS	*N*	NHANES III**
		Mean (sd)		Mean (sd)
Femoral neck BMD				
60–69 years***	1520	0.806 (0.125)	241	0.790 (0.147)
70–79 years	2826	0.781 (0.126)	271	0.749 (0.123)
80+ years	1016	0.744 (0.122)	226	0.698 (0.149)
Trochanter BMD				
60–69 years***	1520	0.780 (0.123)	241	0.739 (0.140)
70–79 years	2826	0.767 (0.128)	271	0.705 (0.124)
80+ years	1016	0.740 (0.129)	226	0.667 (0.147)
Total hip BMD				
60–69 years***	1520	0.983 (0.135)	241	0.957 (0.163)
70–79 years	2826	0.957 (0.139)	271	0.910 (0.143)
80+ years	1016	0.912 (0.139)	226	0.842 (0.167)
Weight[&]				
60–69 years***	1520	87.1 (0.34)[#]	510	84.3 (0.71)
70–79 years	2826	83.7 (0.24)	524	79.6 (0.66)
80+ years	1016	77.7 (0.36)	560	72.3 (0.59)
BMI (kg/m^2)[%]				
60–69 years***	1519	28.1 (0.10)	510	27.5 (0.21)
70–79 years	2826	27.4 (0.07)	524	26.8 (0.20)
80+ years	1016	26.2 (0.11)	560	25.0 (0.18)

*MrOS measurements obtained from a Hologic QDR 4500; NHANES III measurements obtained with a Hologic QDR 1000.
**[24].
***MrOS participants in this category are ages 65–69.
[&]Average weight in NHANES computed with and without participants with BMD measures [25].
[%][26].
[#]Mean and standard error of the mean reported.

3.3. Adherence and retention

After an average 2.33 years of follow-up, response rates to the tri-annual questionnaire are high; 99.5% of all questionnaires have been completed and returned to the clinical centers. The rate of return of the mid-study questionnaire was similarly high (98.3%).

4. Discussion

Osteoporosis in men is a problem of enormous public health importance yet it is poorly understood compared to what is known about osteoporosis in women. MrOS is a large observational study of older men designed to supply essential information concerning the etiology of osteoporotic fractures and the influence of bone mineral density, bone structure, strength and activity, falls, and other variables that may be unique determinates of fractures in men. MrOS should provide not only a better understanding of the nature of osteoporosis but it should also allow for the development of more confident clinical guidelines for the detection and prevention of fractures in men. Because MrOS was designed to be similar to the Study of Osteoporotic Fractures, a large observational study of the determinants of fracture in older women [23], comparisons will facilitate studies of the impact of sex and sex specific variables on fracture risk (e.g. body composition, bone density, bone structure). Finally, MrOS will enhance our limited understanding of the impact of fractures on the quality of life in older men.

Although the assembly of a truly random sample of older men was not considered feasible, the recruitment approach utilized in MrOS was intended to result in the enrollment of men with characteristics similar to those in the general population. To a large extent this goal was accomplished. As shown in Table 2, MrOS participants are comparable to similarly aged men in NHANES, a cohort randomly selected from the U.S. population. Nevertheless, as a group of volunteers, the MrOS participants are on average in good health and generally well educated. Moreover, the mean levels of BMI and BMD are slightly higher than in NHANES, suggesting that MrOS should not be considered entirely representative of the overall population of older U.S. men and that care should be taken in generalizing results obtained from MrOS to all similarly aged men. With that caveat, the MrOS cohort represents an important opportunity to better understand the determinates of fracture, and of other common events, in many elderly men.

The cohort of US participants has been expanded to include 2000 men in Hong Kong and 3000 men recruited from three study sites in Sweden: Goteborg, Malmo, and Uppsala. Essentially identical recruitment criteria were used and very similar measurements have been obtained, allowing a wide array of ethnic and geographic comparisons. The characteristics of these cohorts will be described in subsequent communications. Thus, the MrOS cohort will include approximately 11,000 participants. The expansion of MrOS to include international collaborations is a unique feature of the study, which will allow us to examine the large ethnic and geographical differences in the character of bone and the epidemiology of fractures. Fracture rates in Sweden are one of the highest in the world, while in Hong Kong fracture rates are lower than those in Sweden or the United States. The large and diverse nature of the international MrOS cohort provides considerable power to examine common and uncommon risk factors. Few other studies of osteoporosis in men provide a comparable ability to explore the lifestyle, skeletal, biochemical, and genetic determinants of fracture and their ethnic and geographic variation.

Later assessments of factors that may be linked to the risk of osteoporotic fractures are planned. For example, the relation of sex steroids, including testosterone, estrodiol, and dihydrotestosterone, and

adrenal steroids, including dehydroepiandrosterone, to bone loss and osteoporotic fracture will be examined. Other potential biomarkers of mineral metabolism (calcium, phosphorus, creatinine, intact parathyroid hormone, 25(OH)D, and $1,25(OH)_2D$), markers of bone metabolism (e.g. bone specific alkaline phosphatase, collagen N-telopeptide), and growth factors (insulin-like growth factor-1 [IGF-1] and IGF-1 binding proteins) can be assessed in relation to bone loss and osteoporotic fracture risk using a case-cohort design. Toe and fingernail clippings were collected for the possible measurement of environmental exposures (e.g. fluoride, selenium, and heavy metals). Storing blood for DNA sets the stage for subsequent focused testing of the relationship of skeletal status and fracture risk to specific genetic loci. Bone density may be a marker for lifetime hormone status, and both androgens and estrogens promote prostate growth. Therefore, bone and hormone levels can be to used to examine the inter-relationships between sex hormones, bone mass, fracture, and risk of prostate disease.

Finally, the assembly of the MrOS cohort provides unique opportunities for the study of other diseases common in older men. Examples include obesity, diabetes, cardiovascular disease, sleep disorders, periodontal disease (and its relationship to skeletal events), neurocognitive abnormalities, osteoarthritis, and frailty. The support provided from the National Cancer Institute allows MrOS to supply unique information concerning prostate cancer and prostatic hypertrophy, and the relationship of these common disorders to bone metabolism. The extensive library of serum, blood, urine, and fingernails will allow analyses of a variety of new and emerging biochemical and genetic covariates of disease.

Acknowledgement

The Osteoporotic Fractures in Men (MrOS) Study is supported by the National Institutes of Health funding. The following institutes provided support: the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), the National Institute of Aging (NIA), and the National Cancer Institute (NCI), under the following grant numbers: U01-AR45647, AR45580, AR45614, AR45632, AR45654, AR45583, AG18197, and M01 RR000334. For information regarding MrOS contact Eric S. Orwoll, MD, OHSU. We would like to recognize the able assistance of Leah Williams for the preparation of this manuscript.

Appendix A

Appendix Table 1
Summary of baseline measurements

Category	Data points	Instruments and/or equipment (if applicable)
Self-Administered Questionnaire (SAQ)		
Contact information	Name, address, phone, email	
	Next-of-kin	
	Two personal contacts	
	Physician's name and address	
General characteristics	Age and date of birth	
	Social Security Number	
	Racial/ethnic background	

Appendix Table 1 (*continued*)

Category	Data points	Instruments and/or equipment (if applicable)
Self-Administered Questionnaire (SAQ)		
Social and lifestyle	Marital status	1998 Standard Occupational Classification System
	Living arrangement	
	Education level	
	Primary (longest) occupation	
Medical history	Diabetes	
	High thyroid, Grave's disease, or overactive thyroid	
	Low or underactive thyroid	
	Osteoporosis, thin or brittle bones	
	Stroke, blood clot in brain or bleeding in brain	
	Parkinson's disease	
	Hypertension or high blood pressure	
	Heart attack, coronary or myocardial infarction	
	Angina (chest pain)	
	Congestive heart failure or enlarged heart	
	Chronic obstructive lung disease, chronic bronchitis, asthma, emphysema, COPD	
	Prostatitis (inflammation or infection of the prostate)	
	Glaucoma	
	Cataracts	
	Abdominal surgery	
	Arthritis or gout	
	Kidney stones	
	Cancer	
	Dizziness	
	Birth weight	
	Height and weight at age 25 years	
	Highest adult weight	
Falls	Past 12 months	
Prostate health	Symptoms in past month	American Urologic Association Symptom Index for Benign Prostatic Hyperplasia
	Diagnosis of benign prostatic hyperplasia	
	Family history of prostate cancer	
	Current treatment for prostate symptoms	
Diet history	Special diet in past year	
Tobacco and alcohol use	Cigarette packs smoked in lifetime	
	Chewing tobacco or snuff, pipe or cigars	
	12 alcoholic drinks in lifetime	NHANES III tobacco questions, CAGE questionnaire
Physical activity	Past 7 days: sitting, walking, light, moderate, or strenuous sports or recreational activities	Physical Activity Scale for the Elderly (PASE) ©1991 New England Research Institute
	Strength or endurance exercises	
	Light or heavy housework	
	Other activities, work for pay or as a volunteer	
Lifestyle	Overall health	Study of Osteoporotic Fractures Quality of Life Questionnaire, Medical Outcomes Study, Short Form (SF-12)
	Problems with work or activity due to physical health	

(continued on next page)

Appendix Table 1 (*continued*)

Category	Data points	Instruments and/or equipment (if applicable)
Self-Administered Questionnaire (SAQ)		
Lifestyle	Problems with work or activity due to emotions	
	Pain that interfered with normal activities	
	Emotions during past 4 weeks	
	Physical or emotional interference with social activities	
	Difficulty with activities of daily living	
Fracture history	Ever told broke or fractured a bone (age, circumstance, site)	
Family history	Natural mother and natural father: diagnosis with osteoporosis, broke or fractured hip, wrist or forearm, other still living or age at death	
	Number of living siblings	
	Number of living children	
Back and joint health	Back pain in past 12 months	
	Lower back pain	
	Pain, numbness, or tingling in buttock, hip, leg, foot, arm, or hand	
	Weakness, clumsiness in arm, hand or when walking	
	Limit activities because of back pain	
	Difficulty bending, lifting, reaching, dressing, getting into a car, standing, sitting	
	Hip or knee pain for more than a month	
Dietary intake	60 item food frequency questionnaire focusing of foods that might have an impact on bone health (e.g. calcium levels)	Block Dietary Data Systems Questionnaire
Medication log	Name and reason for use of prescription medications taken for at least one month	
Clinical Interview Questionnaire		
Alcohol use	Drinking pattern in past 12 months	
Social and economic status	Perceived status relative to others in community	
	Perceived status relative to others in the US	MacArthur Subjective Status Scale
Physical activity	Walk for exercise, number of blocks	
	Time spent sleeping, sitting upright	
	Time confined to bed or chair because of health	
	Volunteered or paid outside the home; job by category, hours, mode of transportation	
Current medication use	Current medications classified as: alpha-blocker, androgen, angiotensin converting enzyme (ACE) inhibitor; angiotensin II receptor antagonist, antiandrogen, urinary antispasmodic, aspirin, benzodiazepine, beta-blocker, calcium channel blocker, cholinergic agonist, inhaled cortocosteroid, oral cortocosteroid, cox-II inhibitor, loop diuretic, potassium-sparing diuretic, thiazine duiretci, gemfibrozil, histamine (h2) receptor antagonist,	

Appendix Table 1 (*continued*)

Category	Data points	Instruments and/or equipment (if applicable)
Clinical Interview Questionnaire		
Current medication use	HMG CoA reductase inhibitor (statin), hypoglycemic agents, narcotic analgesic, nitrate, nonbenzodiazepine anticonvulsant, nonsteroidal anti-inflammatory agent (NSAID), proton pump inhibitor, selective serotonin reuptake inhibitor (SSRI) sildenafil, thyroid hormone, trazodone, tricyclic (TCA)	
History of medication use	History of taking medication for the treatment of osteoporosis, Paget's or other bone disease Testosterone injections Current use of aspirin, NAIDS Participation in treatment clinical trials	
Clinical measurements		
Pulse	Radial pulse	
Anthropometric	Height in centimeter	Harpenden stadiometer
	Weight in kilograms	Balance beam scale
Blood pressure	Ankle–arm Index	8 megahertz Doppler probe
Cognitive function	Paper and pencil timed exercise	Trail Making Task B
	Memory, recall, response to instructions	Teng Mini Mental State Examination
Functional vision	Contrast sensitivity	Bailey–Lovie distance acuity chart,
	Depth perception	Pelli–Robson contrast sensitivity chart,
	High contrast acuity	Frisby stereo test, letter literacy card
Neuromuscular function	Single and repeated chair stand	Jamar hydraulic hand dynamometer
	Six meter usual pace and balance walk	Nottingham Power Rig
	20 cm narrow walk	
	Grip strength	
	Leg power	
Biochemical specimens		
Serum	Morning fasting draw followed by 2nd draw after 40 min	
DNA	Blood blotter	Whatman BFC180 3 × 3 bloodstain cards
Urine	Morning fasting	
Finger and toe nail clippings	Participant clip nails and bring to appointment	
Skeletal measures		
Bone mineral density	Dual energy X-ray absorptiometry of hip, spine, total body (with body composition)	Hologic QDR 4500 W Hologic Sahara Various QCTs
	Ultrasound of calcaneous	
	Quantitative computer tomography (L1, L2, proximal femur)	
Prevalent vertebral fractures	Thoracic spine X-ray	Various
	Lumbar spine X-ray	
Skeletal geometry	Quantitative computer tomography (L1, L2, proximal femur)	Various
Abdominal aorta	Quantitative computer tomography (L4)	Various

Appendix B

Appendix Table 2
Timing of Major Study Measurements

	Baseline visit 03/200–04/2002	Mid-Study Questionnaire 07/2002–12/2003	Second visit 01/2005–12/2005
Self-administered questionnaire			
Contact information	X	X	X
General characteristics	X		X
Social and lifestyle	X	X	X
Medical history	X	X	X
Fall and fracture history	X	X	X
Tobacco use	X	X	X
Quality of life	X	X	X
Physical activity	X	X	X
Prostate health	X	X	X
Back and joint health	X		
Medication inventory	X	X	X
Food frequency	X		
Kindreds		X	
Clinical visit			
Alcohol use	X		X
Anthropometric measures	X		X
Neuromuscular measures	X		
Functional status	X		
Cognitive function	X		
Visual function	X		
Radiographic visit			
DEXA (hip, spine, total body)	X		X
Vertebral X-rays	X		X
Calcaneous ultrasound	X		X
65% subset:			
QCT	X		
Biochemical specimens			
Serum	X		
DNA blood blotter	X		

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